The Significance of Duration and Amount of Sodium Reduction Intervention in Normotensive and Hypertensive Individuals: A Meta-Analysis[1,2]

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ABSTRACT

The purpose of this meta-analysis was to establish the time for achievement of maximal blood pressure (BP) efficacy of a sodium reduction (SR) intervention and the relation between the amount of SR and the BP response in individuals with hypertension and normal BP. Relevant studies were retrieved from a pool of 167 randomized controlled trials (RCTs) published in the period 1973–2010 and integrated in meta-analyses. Fifteen relevant RCTs were included in the maximal efficacy analysis. After initiation of sodium reduction (range: 55–118 mmol/d), there were no significant differences in systolic blood pressure (SBP) or diastolic blood pressure (DBP) between measurements at weeks 1 and 2 (ΔSBP: −0.18 mmHg/ΔDBP: 0.12 mmHg), weeks 1 and 4 (ΔSBP: −0.50 mmHg/ΔDBP: 0.35 mmHg), weeks 2 and 4 (ΔSBP: −0.20 mmHg/ΔDBP: −0.10 mmHg), weeks 2 and 6 (ΔSBP: −0.50 mmHg/ΔDBP: −0.42 mmHg), and weeks 4 and 6 (ΔSBP: 0.39 mmHg/ΔDBP: −0.22 mmHg). Eight relevant RCTs were included in the dose-response analysis, which showed that within the established usual range of sodium intake [<248 mmol/d (5700 mg/d)], there was no relation between the amount of SR (range: 136–188 mmol) and BP outcome in normotensive populations [ΔSBP: 0.99 mm Hg (95% CI: 2.12, 4.10), $P = 0.53$; ΔDBP: −0.49 mm Hg (95% CI: −4.0, 3.03), $P = 0.79$]. In contrast, prehypertensive and hypertensive populations showed a significant dose-response relation (range of sodium reduction: 77–140 mmol/d) [ΔSBP: 6.87 mmHg (95% CI: 5.61, 8.12, $P < 0.00001$); ΔDBP: 3.61 mmHg (95% CI: 2.83, 4.39, $P < 0.00001$)]. Consequently, the importance of kinetic and dynamic properties of sodium reduction, as well as baseline BP, should probably be considered when establishing a policy of sodium reduction. *Adv Nutr* 2015;6:169–177.

Keywords: dietary guidelines, meta-analysis, sodium, blood pressure, pharmacokinetics, pharmacodynamics, salt

Introduction

The need to define more precisely the efficacy of sodium reduction (SR)[9] for the general population has been brought into focus by conflicting Institute of Medicine (IOM) reports (1–3). One has defined a recommended upper sodium intake amount of 2300 mg/d (100 mmol/d) (1). In contrast, the most recent IOM report concluded that "Science was insufficient and inadequate to establish whether reducing sodium intake below 2300 mg/d either decreases or increases cardiovascular disease risk in the general population" (2). Furthermore, the 2300 mg/d recommendation is in conflict with the IOM's own rules on how to define adequate intake for a nutrient, which is "the approximate intake found in apparently healthy populations" (3). This is much higher than 2300 mg/d (4). The justification for the 2300 mg/d recommendation is based on the controversial association between sodium intake and blood pressure (BP) (5–8) and on modeling studies (9, 10). These use selected cross-sectional sodium intake data and BP data to create a sodium-dose–BP-response relation and successively apply this dose-response relation to BP mortality data. Disregarding side effects, these analyses predict millions of saved lives

(9, 10). However, these artificial data are in contrast to the outcome of real data from population studies, which indicate that both low and excessive sodium intake are associated with increased mortality, thus demonstrating a J-shape relation between sodium intake and outcome (11). The disagreement between the modeling studies and the observational studies could be because of incorrect premises for the modeling studies caused by a lack of knowledge of kinetic and dynamic consequences of a changed sodium intake. The purpose of the present supplementary analysis of a previous meta-analysis of randomized trials (8) was to clarify the significance of duration of SR and amount of SR by estimating *1*) the requisite time for establishing maximal BP efficacy in response to SR, and *2*) the dose-response relation between the reduction in sodium intake and the BP effect in normotensive and hypertensive subjects.

Methods

Relevant studies were retrieved from a pool of 167 randomized controlled trials (RCTs) published in the period 1973–2010 and identified in a Cochrane review in 2011 (8). Search methods for identification of these 167 studies are previously described in detail (8). The general eligibility criteria of the Cochrane review are described previously (8).

Inclusion criteria for estimation of maximal efficacy

Criteria for estimation of maximal efficacy were studies with at least 2 measurements of BP effects between week 1 and week 4 after initiation of SR intervention.

Inclusion criteria for estimation of dose-response relation

Criteria for estimation of dose-response relations were studies randomly allocating participants to at least 3 different amounts of SR.

Data extraction

Most data were retrieved as explained previously (8). Two authors independently retrieved additional data (NG and THG). The following data were recorded: *1*) mean baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) (millimeters of mercury); *2*) mean effect measurements (change in SBP and DBP in millimeters of mercury) obtained weekly until termination of study; *3*) effect measurements (change in SBP and DBP in millimeters of mercury) for different doses of SR; *4*) Cochrane risk of bias sources (12).

Because not all studies provided SE values for all intermediate measurements, we derived the SE values from SDs, CIs or figure graphs when necessary (12).

Risk of bias

The Cochrane Collaboration's tool for assessing risk of bias (12) was used to assess the risk of bias in the individual randomized trials. Funnel plots were used to estimate publication bias across studies.

Data synthesis

Review Manager (12, 13) was used to synthesize data and heterogeneity was estimated by I^2 (I^2 is the proportion of the total variability explained by heterogeneity and is expressed as a percentage) (12).

Time of maximal BP efficacy. Studies were integrated irrespective of baseline BP. The effect of SR on SBP and DBP (difference between BP at low sodium intake and higher sodium intake) was calculated for each week. In the comparison of week 1 vs. week 2, only those studies that had measurements at both week 1 and week 2 were included. The 2 summary estimates for weeks 1 and 2 were then compared. The same procedure was used for all week comparisons. For each week investigated, data were categorized as

generic inverse variance data and the mean difference for the week compared with baseline was calculated by means of the inverse variance method. The summary estimates (mean difference in SBP and DBP) for each week were then categorized as continuous data and compared by means of the inverse variance method (12, 13). Normotensive participants (BP <140/90) and hypertensive participants (BP ≥140/90) were combined in the analyses.

Dose-response relation. The mean usual sodium intake in 197 population samples from 45 countries was 159 mmol/d (3657 mg/d) and varied in the range of 90–248 mmol/d (2070–5700 mg/d) (4). We therefore categorized the sodium doses as follows: *1*) low (<90 mmol/d (2070 mg/d)) *2*) low usual [90–159 mmol/d (2070–3657 mg/d)], *3*) high usual [159–248 mmol/d (3657–5700 mg/d)], and *4*) high [>248 mmol/d (5700 mg/d)]. However, if a study had 2 groups within one category, we allowed the one closest to one of the cutoff values to be moved to the neighboring category. BPs at different sodium doses were recorded and depicted as a function of sodium intake. The effects of higher sodium intake categories (low usual sodium, high usual sodium, and high sodium) were compared with the low sodium category. Normotensive and hypertensive studies were integrated separately.

Normotensive participants (BP <140/90) and hypertensive participants (BP ≥140/90) were compared separately in Review Manager (13). Because there is general agreement about the effect of SR on BP in hypertensive participants (5, 6) but not in normotensive participants (5, 6), we classified mixed groups of participants with normal BP and hypertension as hypertensive, even if the mean BP was below 140/90, in order to be able to evaluate a clean normotensive population. The significance level was defined to be 5%.

Supplementary analyses

Sensitivity analyses were intended to investigate the importance of significant risk of bias factors and to explore sources of heterogeneity.

Results

Description of studies

Inclusion and exclusion criteria. Ten studies included healthy normotensive participants, 10 studies included hypertensive participants, and 3 studies included both. Eighteen studies specifically mentioned that participants with diseases were excluded. One study included regular drinkers (3 drinks/d) who were otherwise healthy. Five studies did not mention exclusion criteria.

Time to maximal efficacy. The 15 studies (14–28) of the 167 SR RCTs that were included in the "time to maximal efficacy" analysis are shown in Table 1. Seven studies included hypertensive participants, 7 included normotensive participants, and 1 (28) included both. Three studies included treated hypertensive participants (17, 20, 28). Eight studies used crossover design and 7 used a parallel design. Analysis of the individual studies showed that there were multiple BP measurements at weeks 1, 2, 4, and 6. Because of the few studies with measurements at weeks 3, 5, 7, 8, and beyond, separate analyses of these measurements compared with weeks 1, 2, 4, and 6 were not performed. In 2 studies that measured BP at weeks 1, 2, and 3 (26, 27), the week 3 measurement was included as a week 4 measurement. In one study that measured BP at weeks 2 and 5 (22), the week 5 measurement was included as a week 4 measurement. In another study that measured BP at weeks 2, 4, 8, 12, and 14 (28), the week 8 measurement was included as a week 6 measurement.

<table>

TABLE 1 Characteristics of studies included in maximal efficacy analysis[1]

Reference	Study design	SR method	Washout period	Order effect	Participants, n	Data source from reference	Exclusion of sick participants	Mean age, y	BMI, kg/m² or weight, kg	BP	Baseline SBP, mm Hg	Baseline DBP, mm Hg	Week of 24-hr urine sodium measurement
MacGregor et al. (14)	CO	T	No	No	19	Table 1	Yes	49	80 kg	HT	156	98	2, 4
Chalmers et al. (15)	P	T	—	—	100	Figure 2	Yes	53	N/A	HT	155	96	2, 4, 6
ANMMRC 89 (16)	P	T	—	—	103	Figure 2	Yes	58	N/A	HT	154	95	2, 4, 6
Parker et al. (17)	P	T	—	—	31	Figure 4	Yes	52	29 kg/m²	THT	138	85	1, 2, 3, 4
Mascioli et al. (18)	CO	T	Yes	No	48	Figures 3 and 4	Yes	52	27.6 kg/m²	NT	131	84	4
Cobiac et al. (19)	P	T	—	—	52	Figure 2	Yes	66	25 kg/m²	NT	132	77	2, 4
Sciarrone et al. (20)	P	T	—	—	91	Figure 3	Yes	54	25 kg/m²	THT	136	83	5 times[3]
Nestel et al. (21)	P	T	—	—	36	Tables 3 and 4	Yes	66	25 kg/m²	NT	125	73	2, 4, 6
Fotherby et al. (22)	CO	T	No	N/I	17	Tables 3 and 4	N/I	73	26 kg/m²	HT	184	100	5
Ruppert et al. (23)	CO	T	No	N/I	25	Table 3	Yes	46	70 kg	NT	112	73	1, 4
Schorr et al. (24)	CO	SW	Yes	N/I	16	Figure 1	Yes	64	26.1 kg/m²	NT	140	84	1, 4
Gates et al. (25)	CO	T	No	No	12	Figure 4	Yes	64	25.1 kg/m²	HT	148	84	1, 2, 3, 4
Palacios et al. (26)	CO	D	Yes	N/I	40	Table 3	Yes	13	22 kg/m²	NT	113	57	8 times[3]
Forrester et al. (27)[2]	CO	D + T	Yes	N/I	114	Figure 4	Yes	44	25.8 kg/m²	NT	119	75	3
Nowson et al. (28)	P	D	—	—	111	Figure 2	Yes	59	29.6 kg/m²	THT + NT	127	81	4, 8

</table>

[1] Abbreviations: ANHMRC, Australian National Health and Medical Research Council BP, blood pressure; CO, crossover; D, diet; DBP, diastolic blood pressure; HT, hypertension; N/A, not applicable; N/I, no information; NT, normotension; P, parallel; SBP, systolic blood pressure; SR, sodium reduction; SW, salt water; T, low-sodium diet followed by random assignment to salt or placebo tablets; THT, treated hypertension.

[2] Included only blacks.

[3] The precise time of the measurement was not specified.

Dose-response analysis. The 8 studies (9 dose-response relations) (7, 29–35) of the 167 studies included in the dose-response relation analysis are shown in Table 2. Four studies included hypertensive participants who were all untreated. All studies but one used a crossover design.

Descriptive data are shown in Tables 1 and 2 and the risk of bias sources are shown in **Supplemental Table 1**. None of the studies described the random assignment procedure. A main source of bias was lack of observer blinding (detection bias) in 5 of the maximal efficacy studies and 5 of the dose-response studies. The differences in 24-h urinary sodium excretions between the usual and low-sodium diets during the investigation period of the individual studies included in the maximal efficacy analysis are shown in **Supplemental Table 2**.

Outcomes

All single-week analyses included in the final comparison of different weeks are shown in **Supplemental Figures 1–8** and the dose-response analyses are shown in **Supplemental Figures 9–12**. Sample size, SE, and weight of the individual studies in each of the analyses appear in Supplemental Figures 1–12. In all but 5 of the analyses, there was no significance for heterogeneity and we therefore used the fixed effect model. We also calculated the effect sizes with the use of the random effect model for all analyses in which I^2 was bigger than 0. The results of the random effect models are also shown in Supplemental Figures 1–8, where applicable.

Comparisons of the effects of SR on SBP and DBP measured at week 1 vs. week 2 (number of studies = 4) and week 4 (number of studies = 6), week 2 vs. week 4 (number of studies = 13) and week 6 (number of studies = 5), and week 4 vs. week 6 (number of studies = 5) are shown in **Figure 1**. Weeks 1 and 6 were not compared, because there was no paired measurement for these time points.

The numbers of participants with paired measurements are shown in **Supplemental Table 3**. All but 3 studies (18, 22, 27) measured 24-h urinary sodium at each BP measurement and these measurements were stable (Table 1, Supplemental Table 2). None of the comparisons were statistically significant, with *P* values varying between 0.52 and 0.92.

The individual study data used in the dose-response analysis are shown in **Supplemental Table 4**. Nine dose-response relations extracted from 8 studies are shown in **Figure 2**. Baseline BP varied significantly between the studies, with SBP ranging from 110 mm Hg to 160 mm Hg and DBP ranging from 65 mm Hg to 95 mm Hg. Figure 2 indicates that in studies in which participants' baseline BP was below 130/80 mm Hg, there was no dose-response relation until the intervention exceeded the upper limit for usual sodium intake (248 mmol/d). In the 3 studies (31, 33, 34) in which the upper limit of the intervention was greater than the upper limit of usual

human sodium intake, an increase in BP was observed. In 4 studies (7, 30, 31, 35) with a BP above 130/80 mm Hg (4 upper studies in Figure 2), a dose-response relation is suggested across the entire range of sodium intake. Three of these studies (30, 31, 35) include only hypertensive participants, whereas the fourth included a mixture of borderline hypertensive and hypertensive participants with a mean baseline BP of 135/86 mm Hg (7).

Normal BP. There was only one study that measured SBP at the low usual sodium dose (90–159 mmol/d) (Figure 2) (29). Therefore, no statistical calculations were performed for the low usual dose.

Compared with the low sodium dose, there was no significant increase in SBP at the high usual sodium dose [159–248 mmol/d (3657–5700 mg/d)] [ΔSBP: 0.99 mmhg; (95% CI: 2.12, 4.10, $P = 0.53$)], or at the high sodium dose [>248 mmol/d (5700 mg/d)] [ΔSBP: 3.06 mmHg (95% CI: −1.47, 7.60), $P = 0.19$] (29, 31, 33, 34) (Supplemental Figure 9).

Compared with the low sodium dose, there was no significant increase in DBP when sodium intake was increased at the low usual sodium intake [ΔDBP −0.49 mmHg (95% CI: −4.00, 3.03), $P = 0.79$], or the high usual sodium dose [ΔDBP −1.67 mmHg (95% CI: −4.17, 0.82), $P = 0.19$]. There was no change at the high sodium dose [ΔDBP: 0.38 mmHg (95% CI: −4.03, 4.79), $P = 0.87$] (29, 31–34) (Supplemental Figure 10).

Hypertension. As mentioned, we included 1 study of borderline hypertensive and hypertensive participants (7) in the hypertensive group. Compared with the low sodium dose, there was a significant increase in SBP at the low usual sodium dose [ΔSBP: 4.65 mmHg (95% CI: 3.39, 5.91), $P < 0.00001$], at the high usual sodium dose [ΔSBP: 6.87 mmHg (95% CI: 5.61, 8.12), $P < 0.00001$], and at the high dose [ΔSBP: 10.03 mmHg (95% CI: 4.12, 15.95), $P = 0.0009$] (7, 30, 31, 35) (Supplemental Figure 11).

Compared with the low sodium dose, there was a significant increase in DBP at the low usual sodium dose [ΔDBP: 2.44 mmHg (95% CI: 1.57, 3.31), $P = 0.00001$], at the high usual sodium dose [ΔDBP: 3.61 mmHg (95% CI: 2.83, 4.39), $P = 0.00001$], and at the high dose [ΔDBP: 5.55 mmHg (95% CI: 1.53, 9.56), $P = 0.007$] (7, 30-31, 35) (Supplemental Figure 12).

Supplementary analyses

Funnel plots (**Supplemental Figures 13 and 14**) for SBP and DBP were not obviously asymmetric.

Because lack of blinding was the most obvious source of bias, we performed separate maximal efficacy analyses of 10 studies with blinded blood pressure measurements. Eight of the studies were double blind. These analyses (**Supplemental Figure 15**) were in accordance with the main analysis (Figure 1). Exclusion of the week 1 and week 3 results (26, 27) from the week 1 vs. wk 4 analysis (Supplemental Figure 4) did not change the result.

TABLE 2 Characteristics of studies included in dose-response analysis[1]

Reference	Study design	SR method	Washout period	Order effect	Participants, n	Data source from reference	Exclusion of sick participants	Mean age, y	BP	Baseline SBP, mm Hg	Baseline DBP, mm Hg	Week of 24-h urine sodium measurement
Sachs et al. (7)	CO	D	No	N/I	192	Figure 1	Yes	49	HT	135	86	4
Fuchs et al. (29)	CO	T	Yes	N/I	17	Table1	Yes	21	NT	117	68	1
MacGregor et al. (30)	CO	T	No	No	20	Table	Yes	57	HT	163	100	
Bruun et al. (31)	CO	T	Yes	N/I	10	Table1	N/I	46	NT	110	65	1
Bruun et al. (31)	CO	T	Yes	N/I	12	Table 2	N/I	47	HT	148	98	1
Gow et al. (32)	CO	D	Yes	N/I	9	Page 636	N/I	—	NT	120	68	1
Heer et al. (33)	P	D	No	N/I	32	Page F592	Yes	25	NT	109	67	1
Burnier et al. (34)	CO	D	No	N/I	15	Table 2	Yes	23	NT	126	75	1
Johnson et al. (35)	CO	T	Yes	N/I	40	Tables1 and 2	N/I	69	HT	159	84	2

[1] BP, blood pressure; CO, crossover; D, diet; DBP, diastolic blood pressure; HT, hypertension; N/I, no information; NT, normotension; P, parallel; SBP, systolic blood pressure; SR, sodium reduction; T, low-sodium diet followed by random assignment to salt or placebo tablets.

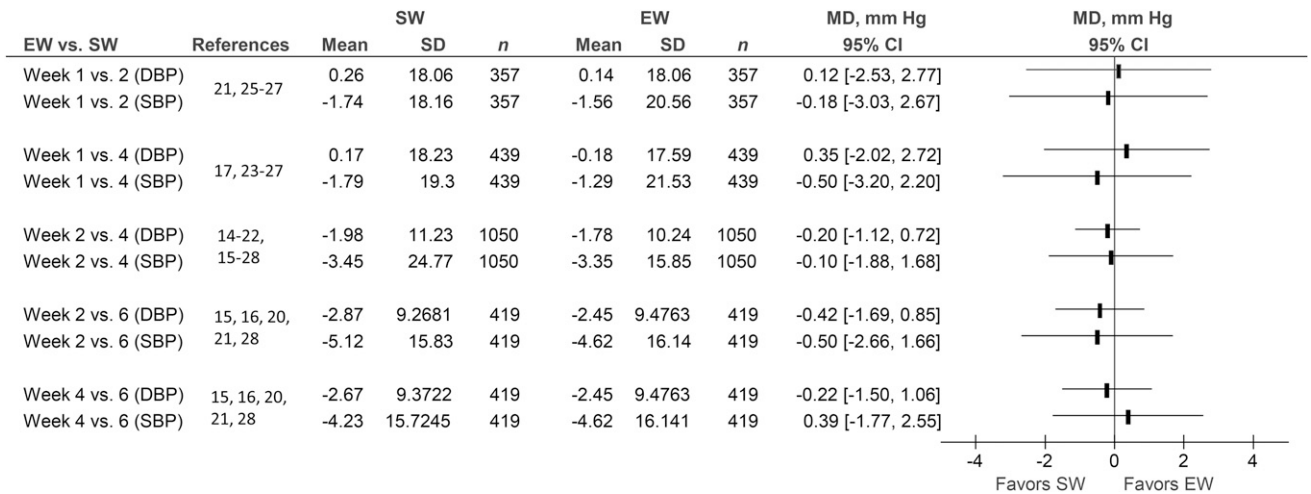| EW vs. SW	References	SW Mean	SD	n	EW Mean	SD	n	MD, mm Hg 95% CI	MD, mm Hg 95% CI
Week 1 vs. 2 (DBP)	21, 25-27	0.26	18.06	357	0.14	18.06	357	0.12 [-2.53, 2.77]	
Week 1 vs. 2 (SBP)		-1.74	18.16	357	-1.56	20.56	357	-0.18 [-3.03, 2.67]	
Week 1 vs. 4 (DBP)	17, 23-27	0.17	18.23	439	-0.18	17.59	439	0.35 [-2.02, 2.72]	
Week 1 vs. 4 (SBP)		-1.79	19.3	439	-1.29	21.53	439	-0.50 [-3.20, 2.20]	
Week 2 vs. 4 (DBP)	14-22,	-1.98	11.23	1050	-1.78	10.24	1050	-0.20 [-1.12, 0.72]	
Week 2 vs. 4 (SBP)	15-28	-3.45	24.77	1050	-3.35	15.85	1050	-0.10 [-1.88, 1.68]	
Week 2 vs. 6 (DBP)	15, 16, 20,	-2.87	9.2681	419	-2.45	9.4763	419	-0.42 [-1.69, 0.85]	
Week 2 vs. 6 (SBP)	21, 28	-5.12	15.83	419	-4.62	16.14	419	-0.50 [-2.66, 1.66]	
Week 4 vs. 6 (DBP)	15, 16, 20,	-2.67	9.3722	419	-2.45	9.4763	419	-0.22 [-1.50, 1.06]	
Week 4 vs. 6 (SBP)	21, 28	-4.23	15.7245	419	-4.62	16.141	419	0.39 [-1.77, 2.55]	

FIGURE 1 Paired comparisons of BP responses obtained at successive weeks (1, 2, 4, and 6) after initiation of sodium reduction in otherwise healthy normotensive and hypertensive individuals. (Individual study data are shown in Supplemental Figures 1–8). BP, blood pressure; DBP, diastolic blood pressure; EW, early week; MD, mean difference; SBP, systolic blood pressure; SW, successive week.

Exploration of heterogeneity

Five analyses showed significant heterogeneity [Supplemental Figure 5 (weeks 2 and 4), Supplemental Figure 6 (week 2), and Supplemental Figure 7 (weeks 2 and 4)]. In all 5 analyses, heterogeneity disappeared when separate analyses of participants with untreated hypertension and participants with a baseline BP below 140/90 (normotensive and treated hypertensive participants) were performed.

Discussion

Our review of 167 RCTs of the effect of SR on BP showed that the vast majority only measured the effect on BP 1 time during the observation period, and with only 1 amount or 1 target level of SR. However, the longitudinal and randomized nature of the limited amount of data from the 23 studies addressing the objectives of this study is more reliable than the cross-sectional meta-regression data obtained in studies biased in favor of study populations with
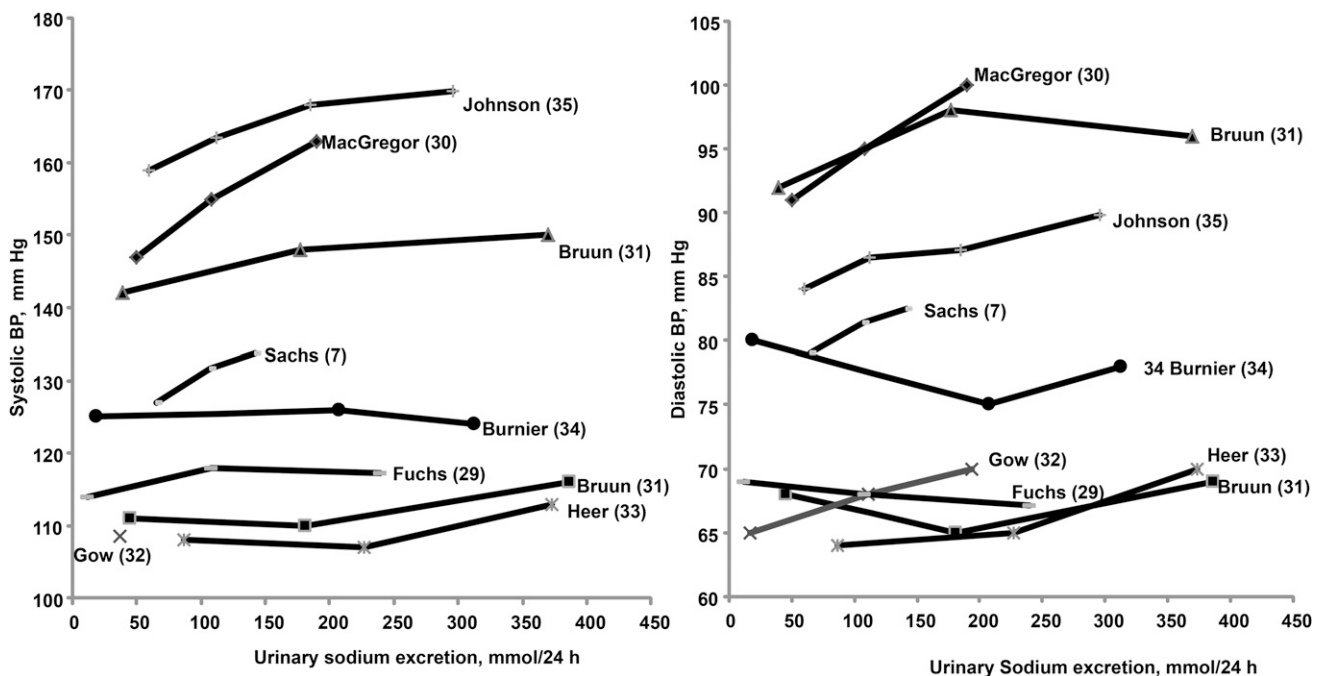

FIGURE 2 Individual study diastolic and systolic BP response to increasing changes in sodium urinary excretion (as a measure of sodium intake) in otherwise healthy normotensive and hypertensive individuals. (Individual study data are shown in Supplemental Figures 9–12 and Supplemental Table 4.) The study by Gow et al. (32) presented data only on diastolic BP. BP, blood pressure.

high BP (9, 10). The present study provides evidence to indicate that the maximal efficacy of SR on BP may be evident and stable after 1 wk. The statistically strongest comparison between SBP and DBP involving 2192 BP measurements in 853 participants measured at weeks 2 and 4 showed no difference between the 2 values (Figure 1, Supplemental Table 3). The CI for this comparison is reasonably narrow, but many of the other CIs were broader; for instance, the one comparing week 1 with week 4 (Figure 1). This indicates that the existing data are not sufficient to firmly establish that maximal efficacy is achieved at 1 wk. However, the identical patterns found for all other pairwise comparisons during the first 6 wk, including comparisons of weeks 1 and 2 and weeks 1 and 4 (Figure 1, Supplemental Figures 1–8), indicate that at least there are no scientific data to support the assumption that more than 1 wk is required to achieve maximal efficacy. In addition, the results could not be explained by variation in dose or adherence, because the 24-h excretions were relatively stable at all measurements (Supplemental Table 2). Furthermore, there were no borderline significant effects to indicate that a true difference may have been overlooked (P values between 0.52 and 0.92) and separate analyses of blinded studies (Supplemental Figure 15) were in accordance with the main analysis. Finally 18 of 23 studies specifically excluded sick individuals (apart from hypertension), and in the remaining 5 there is no indication that such individuals were included. It is therefore reasonable to assume that the included studies were relatively homogeneous. The paucity of studies does complicate an interpretation of the funnel plots (Supplemental Figures 13 and 14), but at a minimum they did not reveal obvious bias. If a publication bias does exist, it should favor a significant result, but because our analyses were nonsignificant, the potential elimination of publication bias would strengthen, rather than weaken, our findings. Therefore, the finding that SR has its full effect after 1 wk is a reasonable conclusion with no scientific evidence supporting the notion that the achievement of maximal efficacy requires more than 1 wk.

To consider the dose-response relation, we categorized sodium intake in relation to usual sodium intake (4) for which there is general agreement between critics (4) and advocates (10) of SR. Our analysis indicates that there is no relation between sodium dose and BP in subjects whose BP is <130/80. However, there was a significant dose-response relation in 4 studies that included hypertensive individuals or both borderline and hypertensive individuals with a mean baseline BP >130/80, consistent with the assumption that the effect of SR on BP is proportional to baseline BP. This was further emphasized by our analysis to explore the reason for heterogeneity in 5 of the intermediate analyses [Supplemental Figure 5 (weeks 2 and 4), Supplemental Figure 6 (week 2), and Supplemental Figure 7 (weeks 2 and 4)], which showed that heterogeneity disappeared when studies of hypertensive and normotensive participants were analyzed separately. In general, baseline BP was high in the included studies. In the maximal efficacy analysis, 12 of 15 studies included participants with an SBP that was higher than the mean of the population (119 mm Hg) (36), and 14 of 15 included participants with a DBP that was higher than the mean of the population (71 mm Hg) (36). The fact that the majority of RCTs were carried out in subjects with a BP higher than those of the general population likely explains why effects of SR on SBP up to 5.12 mm Hg (Supplemental Figure 8) were identified in the present analyses (Supplemental Figures 1–8), but should not be taken as representative of the BP response to SR that would be expected in subjects with a BP corresponding to the mean of the general population, i.e., normotensive subjects. The reason for the larger effect size in hypertensive patients is probably general sensitivity to BP-lowering interventions, rather than specific sodium sensitivity.

Recently, it was found that total body sodium fluctuates in an infradian rhythm that is independent of sodium intake and BP (37). This complicates the understanding of the assumed association between body sodium content and BP and is in contrast to the frequent association between the physiologic steady state of a drug and the time of maximal efficacy of the drug. This, however, does not prevent the possibility of defining the time of maximal efficacy or a dose-response relation. A potential limitation of our analysis is that only 8 of 16 crossover studies used washout periods between treatment interventions. Because our analysis documented that maximal efficacy is reached in 1 wk and all studies lasted for at least 1 wk, it is unlikely that this limitation influenced our results. This is confirmed by the fact that 3 of the studies, which did not use washout periods, found no order effect.

Inaccurate assumptions concerning the significance of the duration of an intervention, i.e., the time of maximal efficacy and the dose-response relation, can lead to biases in meta-analyses (6, 38) and modeling projections of the effect of SR on BP to effects on mortality (9, 10). Advocates of SR have used the putative difference between the 2 Cochrane Reviews (8, 38) as justification to accept the findings of the meta-analysis that excluded RCTs with an SR duration <4 wk (38). A detailed analysis of the mean baseline BP of included RCTs indicates that, at entry, the study populations' BP was ~130/80 (38), a baseline BP significantly higher than the mean BP in the all-inclusive, larger meta-analysis (8) and substantially higher than the mean BP of the general population (36). Consequently, baseline BP, rather than duration of RCTs, seems to be the determinant of the apparent difference in effect size between these 2 frequently quoted meta-analyses.

In addition He and MacGregor showed a significant sodium-dose–BP-response relation, which was based on a cross-sectional meta-regression analysis (6). However, 9 of 12 studies in the "normotensive" analysis included borderline hypertensive participants, the dose-response data were not linearly distributed, and the statistical significance of the dose-response relation depended on 1 study of overweight, borderline hypertensive participants (7). In contrast, a later update of the large meta-analysis, which included 167

studies (8), confirmed the findings from the first version (5). In addition, both large meta-analyses (5, 8) showed significant adverse effects from SR on hormones and lipids. In spite of this, the 2 modeling studies (9, 10) did not include adverse effects in the statistical model. The first (9) is based on a dose-response analysis of the borderline hypertensive meta-analysis (6) and the borderline hypertensive Dietary Approaches to Stop Hypertension study (7). In the second analysis (10), the authors borrowed their literature search from the Cochrane Review of 167 studies (8) and performed a cross-sectional sodium dose–blood pressure response meta-regression analysis on 107 of the 167 studies without revealing precisely which studies or how the data were extracted. Furthermore, individual study data were not shown. The authors found a dose-response relation of 3.7 mm Hg/100 mmol in 50-y-old participants (10) based on selected studies drawn from the large Cochrane Review (8). The regular meta-analysis had shown this effect to be ~1.2 mm Hg in all studies of normotensive participants (8) and ~1.4 mm Hg in studies of normotensive participants with a mean age between 40 and 60 y (39). On the basis of the modeling analysis of indirectly associated sodium intake data and mortality data, which were not documented, the authors projected millions of saved lives in stark contrast to an observational study in the same journal issue that showed that sodium intake simultaneously was inversely associated with mortality (40) and directly associated with BP (41) by means of genuine scientific data directly linking sodium intake with mortality.

Other variables influenced by SR, such as renin, aldosterone, noradrenalin, adrenalin, cholesterol, and TGs, have also been shown to change within 1 wk after the introduction of SR (5, 8). Despite the claim that it takes time for BP to adapt to SR (6), it has been maintained that hormones and lipids only change for a short time after SR and then regress to original concentrations (6). Thus, the question is whether the duration of the physiologic effects of SR differs among variables. Concerning renin and aldosterone, there is scientific evidence that these hormones are permanently increased in individuals on a low sodium diet (42, 43). In the case of catecholamines and lipids, there is evidence that these variables increase in short-term studies up to 2 wk (5, 8), but little evidence that these changes are permanent. Conversely, there is also no evidence to support the claim that these variables revert to normal.

The present findings, like those from the 2013 IOM Report (2), several population studies (40, 44–48), and a meta-analysis of population studies (11), raise valid concerns about whether there is any benefit from SR in individuals whose BP is below 130/80, i.e., the normotensive general population. Recently, advocates of SR, in rejecting the findings of the 2013 IOM Report and the 25 reports of health outcomes (11), argued that the body of evidence linking sodium to elevated BP was a "robust" basis for the recommendations of a population-wide policy of SR (49). This postulate is in contrast to the population studies linking SR to increased all-cause mortality (11, 40, 44, 45, 47, 48). The

remarkably limited data addressing the kinetic and dynamic properties of SR indicate that the assumption of a robust link between sodium and BP is questionable, in particular for normotensive subjects across the usual range of sodium intake.

In conclusion, the present data may be considered to be insufficient to definitively answer the question on the time of maximal efficacy of SR and the dose-response relation. The acknowledgment of such a conclusion by policymakers instead of the present acceptance of flawed dose-response meta-regression analyses would be appropriate progress. Although available data are limited, our analysis indicates that the effect of SR is evident primarily in persons with borderline BP elevation and hypertension. Specifically, the effect of SR on BP appears to reach maximal efficacy at 1 wk and remain stable over subsequent time intervals. At present, it is reasonable to assert that there is no statistically significant evidence to show that the time of maximal efficacy requires more than 1 wk to be established. In normotensive individuals, the effect of SR is not evident within the range of sodium intake consumed by 95% of the population. An effect of SR in normotensive participants was only evident when sodium intake was reduced from an intake >248 mmol/d (5600 mg/d), an amount consumed by <2% of individuals worldwide (50). On the population level, it is important that the baseline BP distribution of studies to be included in meta-analyses corresponds to the distribution of BP in the population and that the chosen amount of SR is relevant, i.e., within the level of 95% of usual intake. Finally, the fact that SR has been so widely touted without knowledge of these simple and fundamental kinetic and dynamic properties merits thoughtful consideration vis-a-vis the appropriateness of the current population-wide recommendation of sodium restriction. This conclusion echoes that of the editorial (51) accompanying recent reports that presented divergent conclusions with respect to the impact of SR on cardiovascular disease events and mortality (10, 40, 41).

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