

## ORIGINAL ARTICLE

# Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials

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The objective of the study was to assess the blood pressure response to changes in sodium and potassium intake and examine effect modification by age, gender, blood pressure, body weight and habitual sodium and potassium intake. Randomised trials of sodium reduction or potassium supplementation and blood pressure were identified through reference lists of systematic reviews and an additional MEDLINE search (January 1995–March 2001). A total of 40 sodium trials and 27 potassium trials in adults with a minimum duration of 2 weeks were selected for analysis. Data on changes in electrolyte intake and blood pressure during intervention were collected, as well as data on mean age, gender, body weight, initial electrolyte intake and initial blood pressure of the trial populations. Blood pressure effects of changes in electrolyte intake were assessed by weighted metaregression analysis, overall and in strata of trial population characteristics. Analyses were repeated with adjustment for potential confounders.

Sodium reduction (median: –77 mmol/24 h) was associated with a change of –2.54 mmHg (95% CI: –3.16, –1.92) in systolic blood pressure and –1.96 mmHg (–2.41, –1.51) in diastolic blood pressure. Corresponding values for increased potassium intake (median: 44 mmol/24 h) were –2.42 mmHg (–3.75, –1.08) and –1.57 mmHg (–2.65, –0.50). Blood pressure response was larger in hypertensives than normotensives, both for sodium (systolic: –5.24 vs –1.26 mmHg,  $P < 0.001$ ; diastolic: –3.69 vs –1.14 mmHg,  $P < 0.001$ ) and potassium (systolic: –3.51 vs –0.97 mmHg,  $P = 0.089$ ; diastolic: –2.51 vs –0.34 mmHg,  $P = 0.074$ ). In conclusion, reduced intake of sodium and increased intake of potassium could make an important contribution to the prevention of hypertension, especially in populations with elevated blood pressure.

*Journal of Human Hypertension* (2003) 17, 471–480.  
doi:10.1038/sj.jhh.1001575

**Keywords:** blood pressure; sodium; potassium; sodium sensitivity; randomised trials; metaregression analysis

## Introduction

Hypertension is a major risk factor for cardiovascular disease and is highly common in Western societies. It has been estimated that a shift in the population blood pressure distribution to a 5 mmHg lower level may prevent one-thirds of strokes and one-fifth of coronary events.<sup>1</sup> Sodium and potassium have been implicated in the aetiology of hypertension.<sup>2,3</sup> Meta-analyses of randomised trials found blood pressure falls of 3–5 mmHg systolic and 1–2 mmHg diastolic for sodium reduction in hyper-

tensives, and reductions half this size in normotensives.<sup>4–12</sup> For potassium supplementation, blood pressure reductions of more than 3 mmHg systolic and 2 mmHg diastolic have been reported.<sup>13–16</sup> Blood pressure response to sodium (and possibly also potassium) could be related to initial blood pressure level, age, gender, race, and genetic factors.<sup>2,17–19</sup> Effect modifiers (eg, hypertension) could underly the selection of study populations in blood pressure trials. Therefore, blood pressure estimates from meta-analyses of randomised trials may not be applicable to the population as a whole. More insight into the blood pressure effects of sodium and potassium in specific population subgroups is therefore warranted.

We examined blood pressure response to changes in sodium and potassium intake, overall and in relevant segments of the population. Multivariate metaregression analysis of randomised blood

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Received 24 November 2002; revised 18 March 2002; accepted 18 March 2003

pressure trials was performed in strata of age, gender, blood pressure, body weight, and habitual sodium and potassium intake.

## Methods

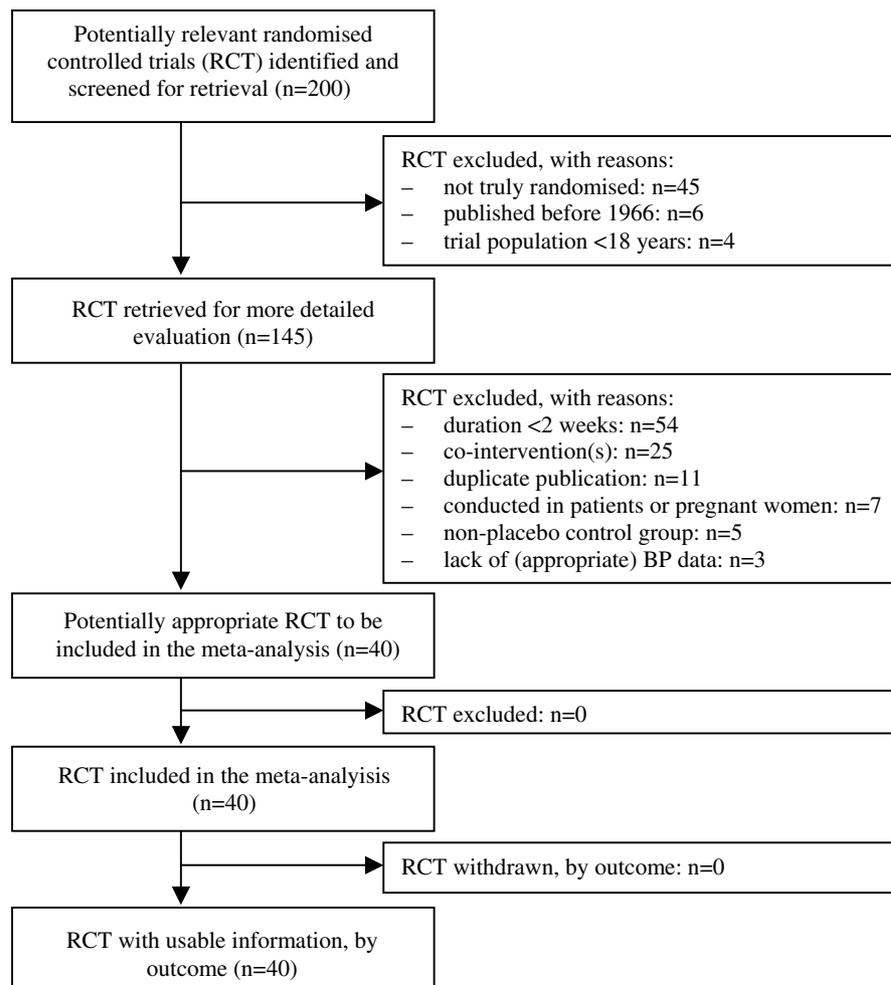
### Selection of randomised trials

Trials of the effect of sodium reduction or potassium supplementation on blood pressure were identified using tables and references lists from meta-analysis papers and quantitative reviews.<sup>4–16</sup> An additional MEDLINE search for publications of sodium and potassium trials between January 1995 and March 2001 was performed. Eligibility criteria were (1) randomised design, (2) adult study population (mean age of 18 years or above), and (3) publication date after 1966. A total of 145 trials out of 200 sodium trials and 47 out of 58 potassium trials that were identified fulfilled these criteria (list of all identified trials available from the authors). We subsequently excluded 105 sodium trials and 19 potassium trials for the following reasons: (1) over-

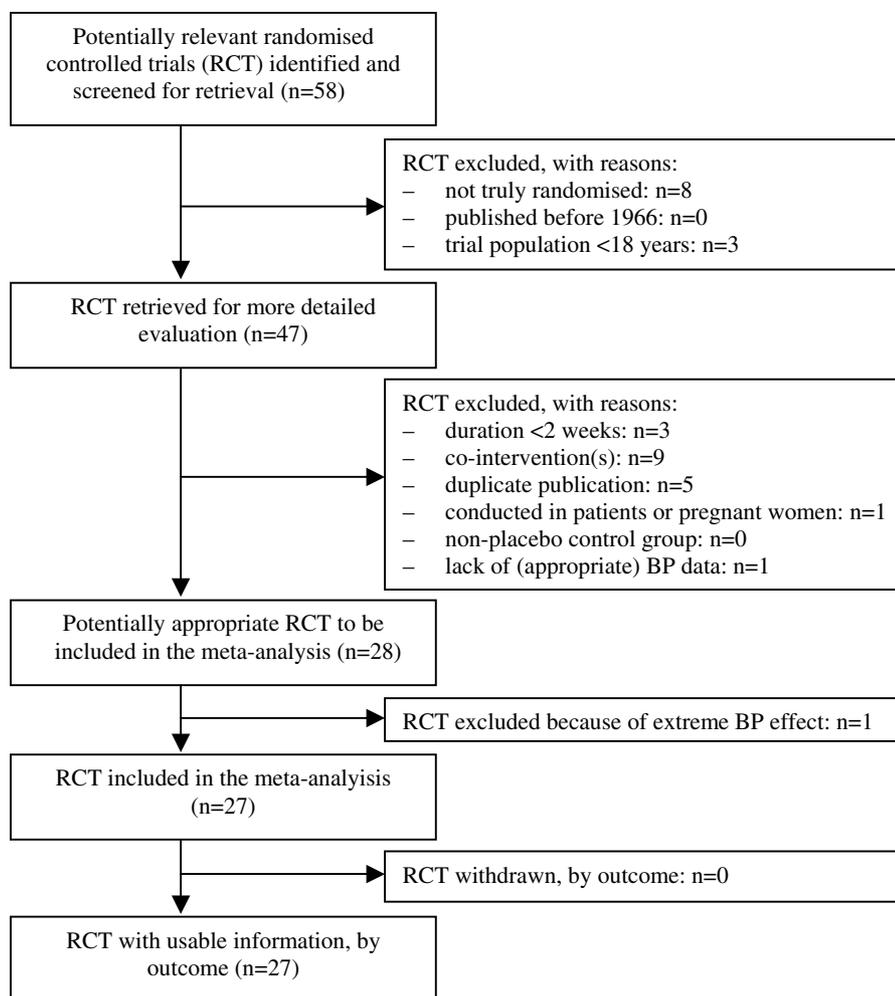
lap with trial(s) already selected for this study ( $n=16$ ), (2) lack of blood pressure data ( $n=4$ ), (3) cointervention from which the effect of sodium or potassium could not be separated ( $n=34$ ), (4) diseased study population (eg, renal, diabetic patients;  $n=8$ ) (5) nonplacebo control group ( $n=5$ ), and (6) less than 2 weeks of intervention ( $n=57$ ). In addition, one potassium trial was excluded because of markedly outlying blood pressure reductions ( $-41/-17$  mmHg).<sup>20</sup> A total of 40 trials of sodium and blood pressure (47 relevant strata)<sup>21–60</sup> and 27 trials of potassium and blood pressure (30 relevant strata)<sup>23,33,35,37,40,61–82</sup> remained for the present analysis (flow diagrams given in Figures 1 and 2, respectively).

### Data extraction

For trials that entered the study, the original papers or abstracts were retrieved and data were abstracted on changes in blood pressure and urinary sodium and potassium excretion during intervention. In addition, data were collected on trial design (paral-



**Figure 1** Flow diagram for meta-regression analysis of sodium–blood pressure trials.



**Figure 2** Flow diagram for meta-regression analysis of potassium-blood pressure trials.

lel vs cross-over), number of participants, mean age, proportion of males, initial blood pressure levels, initial 24 h-urinary sodium and potassium excretions, initial body weight and change in body weight during intervention. With regard to blood pressure, measurements in sitting position were used. If not available, supine blood pressure, standing blood pressure or mean daytime ambulatory blood pressure was taken in that order. A database was created with individual trials (or relevant trial strata) as the units of observation. A number of imputations for missing data were performed, that is, for age (one trial in middle-aged adults; imputed value: 45 year),<sup>40</sup> proportion of males (two trials in mixed populations; imputed value: 0.50),<sup>28,40</sup> initial systolic blood pressure (two trials; imputed values: 140/90 mmHg for population described as ‘mildly hypertensive’ and 160/95 mmHg for population described as ‘hypertensive’),<sup>40,73</sup> initial urinary sodium excretion (four trials; imputed values: population-specific data from the Intersalt study<sup>83</sup>)<sup>56,57,70,72</sup> and initial urinary potassium excretion (10 trials; imputed values: Intersalt data<sup>82</sup>).<sup>21,22,24,30,49,51,56,57,70,72</sup>

Data on body weight (initial level and change) of the trial population could not be retrieved for 11 sodium trials (28%)<sup>21,22,24,28,30,35,40,41,46,57,58</sup> and 7 potassium trials (26%)<sup>35,40,61,66,67,73,76</sup> Data on body mass index were missing for 80% of the trials and could therefore not be taken into account in the analysis.

### Statistical analysis

Pooled blood pressure estimates with 95% confidence intervals (95% CI) were obtained for sodium reduction and potassium supplementation separately using meta-regression analysis weighted for trial sample sizes.<sup>84,85</sup> Adjustments were made for trial design (parallel vs crossover), duration (week), age (year), proportion of males (range 0–1), initial blood pressure (mmHg), initial urinary sodium and potassium excretion (mmol/24 h), and change in urinary sodium and potassium excretion during intervention (mmol/24 h). The analysis was repeated with additional adjustment for initial body weight and change in body weight during intervention in a

subset of 49 trials for which complete data were available. For the study of effect modification, the analyses were repeated in strata of mean age ( $\leq 45$  vs  $> 45$  years), gender ( $< 50\%$  vs  $\geq 50\%$  men), initial blood pressure level ( $< 140/90$  vs  $\geq 140/90$  mmHg), initial sodium excretion (according to the median in sodium trials:  $< 150$  vs  $\geq 150$  mmol/24h), initial potassium excretion (according to the median in potassium trials:  $< 60$  vs  $\geq 60$  mmol/24h), and size of intervention (according to the median:  $\leq 77$  vs  $> 77$  mmol/24 h for sodium,  $\leq 44$  vs  $> 44$  mmol/24h for potassium). Stratified analyses for initial body weight included 29 sodium trials (35 strata) and 20 potassium trials (24 strata) for which data were available. For this purpose, the distribution of initial body weight in all trials combined was adjusted for age, sex and race (asian vs non-asian), and subsequently divided according to the median ( $\leq 76$  vs  $> 76$  kg). Statistical analyses were performed using SPSS 10.0.5 for Windows.

## Results

Characteristics of sodium and potassium trials included in the study are presented in Table 1. The average, unweighted blood pressure change in sodium trials was  $-4.1/-2.5$  mmHg for a mean sodium reduction of 91 mmol/24h (median:

77 mmol = 1.8 g Na = 4.5 g NaCl). For potassium, blood pressure changes were  $-3.3/-2.1$  mmHg for a mean increase of 51 mmol/24h (median: 44 mmol = 1.7 g). The median change in body weight during intervention was  $-0.5$  kg in sodium trials (range  $-3.0$  to  $+4.5$  kg) and  $-0.2$  kg in potassium trials (range  $-1.0$  to  $+1.6$  kg).

Metaregression analysis of sodium trials, weighted for trial sample sizes, yielded an average systolic blood pressure change of  $-2.54$  mmHg (95% CI:  $-3.16$ ,  $-1.92$ ) and a diastolic blood pressure change of  $-1.96$  mmHg ( $-2.41$ ,  $-1.51$ ). Adjustment for age, proportion of males, initial blood pressure, initial urinary sodium and potassium, and changes in urinary sodium and potassium excretion during intervention ('full model') did not change the overall blood pressure estimates (Table 2). Trial design and duration showed no significant relation to blood pressure response. Therefore, these variables were left out of the model.

Sodium reduction was associated with significantly larger systolic and diastolic blood pressure responses at older compared to younger age (cutoff: 45 years) in univariate, weighted regression analysis. For systolic blood pressure, the interaction with age was attenuated after adjustment for confounders ( $-3.07$  mmHg above 45 years vs  $-1.77$  mmHg below 45 years,  $P=0.10$ ). For diastolic blood pressure, increased sensitivity at older age reached borderline statistical significance in the full model ( $-2.36$  mmHg above 45 years vs  $-1.38$  mmHg below 45 years;  $P=0.054$ ). Blood pressure decreases during sodium reduction were significantly larger in hypertensive than normotensive individuals, and these differences in response persisted in the full model (systolic:  $-5.24$  vs  $-1.26$  mmHg,  $P<0.001$ ; diastolic:  $-3.69$  vs  $-1.14$  mmHg,  $P<0.001$ ). Larger blood pressure reductions were also observed for large compared to mild sodium reduction (cutoff: 77 mmol/24h), but this difference was no longer statistically significant after adjustment for confounders (Table 2).

Potassium supplementation was associated with a mean change in systolic blood pressure of  $-2.42$  mmHg ( $-3.75$ ,  $-1.08$ ) and a mean change of  $-1.57$  mmHg ( $-2.65$ ,  $-0.50$ ) in diastolic blood pressure using the full model weighted for trial sample sizes (Table 3). Blood pressure response to potassium supplementation was stronger in hypertensive compared to normotensive trial populations, which was borderline significant in the full model (systolic:  $-3.51$  vs  $-0.97$  mmHg,  $=0.089$ ; diastolic:  $-2.51$  vs  $-0.34$  mmHg,  $P=0.074$ ). Systolic blood pressure reductions during potassium supplementation tended to be increased at older age ( $-3.30$  mmHg for age  $> 45$  years vs  $0.01$  mmHg for age  $\leq 45$  years;  $P=0.11$ ). The potassium-related change in blood pressure was also larger in trial populations with a relatively high age-, sex- and race-adjusted body weight (cutoff: 76 kg; systolic:

**Table 1** Characteristics of randomised blood pressure trials of sodium reduction or potassium supplementation

	Sodium	Potassium
No. of trials (no. of strata)	40 (47)	27 (30)
Duration (week) <sup>a</sup>	4 (2–156)	6 (2–114)
Age (year)	48 $\pm$ 15	45 $\pm$ 12
Men (%)	61 $\pm$ 23	60 $\pm$ 35
Initial body weight (kg) <sup>b</sup>	76 $\pm$ 6	75 $\pm$ 8
Change in body weight (kg) <sup>a,b</sup>	-0.5 (-3.0 to 4.5)	-0.2 (-1.0 to 1.6)
<i>Initial urinary electrolyte excretion (mmol/24 h)</i>		
Sodium	153 $\pm$ 33	157 $\pm$ 30
Potassium	66 $\pm$ 11	60 $\pm$ 11
<i>Change in urinary electrolyte excretion (mmol/24 h)</i>		
Sodium	-91 $\pm$ 52 <sup>c</sup>	3 $\pm$ 16
Potassium	-0.5 $\pm$ 5	51 $\pm$ 26 <sup>d</sup>
<i>Initial blood pressure (mmHg)</i>		
Systolic	144 $\pm$ 17	143 $\pm$ 21
Diastolic	88 $\pm$ 12	89 $\pm$ 14
<i>Change in blood pressure (mmHg)</i>		
Systolic	-4.1 $\pm$ 4.1	-3.3 $\pm$ 4.0
Diastolic	-2.5 $\pm$ 2.9	-2.1 $\pm$ 3.6

<sup>a</sup>Value is median with range in parentheses.

<sup>b</sup>Data on body weight were missing for 11 sodium trials and seven potassium trials.

<sup>c</sup>Median difference:  $-77$  mmol/24 h; 1 mmol Na equals 23 mg.

<sup>d</sup>Median difference: 44 mmol/24 h; 1 mmol K equals 39 mg.

Na: sodium, K: potassium; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Values are mean  $\pm$  s.d., unless indicated otherwise.

**Table 2** Weighted mean blood pressure changes during sodium reduction, stratified by population characteristics and size of intervention

	Unadjusted		Adjusted <sup>a</sup>	
	SBP	DBP	SBP	DBP
Overall (n=47 strata)	-2.54 (-3.47, -1.60)	-1.96 (-2.56, -1.36)	-2.54 (-3.16, -1.92)	-1.96 (-2.41, -1.51)
Age				
≤45 years (n=17)	-0.68 (-1.97, 0.61)	-1.31 (-2.23, -1.64)	-1.77 (-2.88, -0.65)	-1.38 (-2.13, -0.62)
>45 years (n=30)	-3.82 (-4.90, -2.75)	-2.41 (-3.17, -1.64)	-3.07 (-4.00, -2.18)	-2.36 (-2.98, -1.74)
	<i>P</i> <0.001	<i>P</i> =0.070	<i>P</i> =0.10	<i>P</i> =0.054
Gender				
<50% men (n=13)	-3.95 (-6.42, -1.48)	-1.49 (-3.11, 0.12)	-3.33 (-5.39, -1.26)	-0.95 (-2.37, 0.47)
≥50% men (n=34)	-2.31 (-3.31, -1.30)	-2.03 (-2.69, -1.38)	-2.41 (-3.13, -1.69)	-2.12 (-2.62, -1.63)
	<i>P</i> =0.22	<i>P</i> =0.54	<i>P</i> =0.42	<i>P</i> =0.14
Hypertension <sup>b</sup>				
No (n=19)	-1.19 (-2.09, -0.29)	-1.06 (-1.62, -0.49)	-1.26 (-2.08, -0.43)	-1.14 (-1.76, -0.51)
Yes (n=28)	-5.38 (-6.69, -4.07)	-3.86 (-4.68, -3.04)	-5.24 (-6.56, -3.93)	-3.69 (-4.69, -2.69)
	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001
Initial body weight <sup>c</sup>				
≤76 kg (n=17)	-1.77 (-2.95, -0.59)	-1.50 (-2.20, -0.80)	-2.13 (-2.96, -1.30)	-1.68 (-2.19, -1.17)
>76 kg (n=18)	-4.12 (-7.21, -1.03)	-2.03 (-3.87, -0.19)	-1.62 (-4.10, 0.85)	-0.80 (-2.32, 0.72)
	<i>P</i> =0.16	<i>P</i> =0.59	<i>P</i> =0.70	<i>P</i> =0.29
Initial 24 h-Na excretion <sup>d</sup>				
≤150 mmol (n=23)	-3.75 (-5.10, -2.41)	-2.24 (-3.15, -1.32)	-2.85 (-3.97, -1.73)	-2.25 (-3.09, -1.42)
>150 mmol (n=24)	-1.60 (-2.78, -0.42)	-1.74 (-2.55, -0.94)	-2.30 (-3.25, -1.35)	-1.73 (-2.44, -1.02)
	<i>P</i> =0.020	<i>P</i> =0.42	<i>P</i> =0.50	<i>P</i> =0.40
Initial 24 h-K excretion <sup>e</sup>				
≤60 mmol (n=14)	-3.14 (-4.72, -1.55)	-1.52 (-2.54, -0.50)	-2.94 (-4.21, -1.67)	-2.15 (-3.13, -1.18)
>60 mmol (n=33)	-2.22 (-3.38, -1.06)	-2.19 (-2.94, -1.45)	-2.32 (-3.18, -1.46)	-1.85 (-2.50, -1.21)
	<i>P</i> =0.35	<i>P</i> =0.29	<i>P</i> =0.47	<i>P</i> =0.65
Decrease in 24 h-Na excretion <sup>f</sup>				
≤77 mmol (n=25)	-2.00 (-2.97, -1.03)	-1.73 (-2.38, -1.08)	-2.31 (-3.05, -1.57)	-1.81 (-2.35, -1.28)
>77 mmol (n=22)	-5.03 (-7.12, -2.94)	-3.03 (-4.43, -1.62)	-3.60 (-5.44, -1.75)	-2.64 (-3.92, -1.37)
	<i>P</i> =0.011	<i>P</i> =0.099	<i>P</i> =0.22	<i>P</i> =0.25

<sup>a</sup>Adjusted for age, proportion of males, initial blood pressure, initial 24 h urinary sodium and potassium excretions and changes in 24 h urinary sodium excretion during the trial.

<sup>b</sup>SBP ≥140 mmHg and/or DBP ≥90 mmHg.

<sup>c</sup>According to the median of the age-, sex- and race-adjusted body weight distribution in sodium and potassium trials combined; data on initial body weight were available for 29 sodium trials (35 strata).

<sup>d</sup>According to the median of the distribution in sodium trials; 1 mmol Na equals 23 mg.

<sup>e</sup>According to the median of the distribution in potassium trials; 1 mmol K equals 39 mg.

<sup>f</sup>According to the median of the distribution in sodium trials.

Na: sodium; K: potassium; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Values are mean blood pressure changes with 95% confidence intervals, weighted for trial sample sizes. *P*-values are given for the difference in blood pressure response between strata.

-4.21 vs -1.26 mmHg, *P* = 0.14; diastolic: -2.62 vs -0.56 mmHg, *P* = 0.13). The interactions with gender, initial sodium or potassium intake, and size of intervention were not statistically significant (Table 3).

## Discussion

The pooled findings from randomised trials provide evidence for an increased blood pressure sensitivity to sodium and potassium in hypertensives. The

**Table 3** Weighted mean blood pressure changes during potassium supplementation, stratified by population characteristics and size of intervention

	Unadjusted		Adjusted <sup>a</sup>	
	SBP	DBP	SBP	DBP
Overall (n=30 strata)	-2.42 (-3.65, -1.18)	-1.57 (-2.56, -0.59)	-2.42 (-3.75, -1.08)	-1.57 (-2.65, -0.50)
<i>Age</i>				
≤45 years (n=11)	-0.65 (-2.95, 1.64)	-0.75 (-2.65, 1.15)	0.01 (-3.25, 3.27)	-1.04 (-3.70, 1.62)
>45 years (n=19)	-3.06 (-4.45, -1.67)	-1.88 (-3.02, -0.73)	-3.30 (-4.98, -1.63)	-1.77 (-3.17, -0.37)
	<i>P</i> =0.077	<i>P</i> =0.31	<i>P</i> =0.11	<i>P</i> =0.66
<i>Gender</i>				
<50% men (n=10)	-2.44 (-3.93, -0.94)	-1.61 (-2.80, -0.42)	-2.58 (-5.38, 0.21)	-1.44 (-3.67, 0.79)
≥50% men (n=20)	-2.37 (-4.68, -0.06)	-1.49 (-3.33, 0.35)	-2.35 (-4.03, -0.66)	-1.63 (-2.98, -0.28)
	<i>P</i> =0.96	<i>P</i> =0.91	<i>P</i> =0.89	<i>P</i> =0.89
<i>Hypertension<sup>b</sup></i>				
No (n=11)	-1.38 (-3.22, 0.46)	-0.78 (-2.25, 0.69)	-0.97 (-3.07, 1.14)	-0.34 (-2.04, 1.36)
Yes (n=19)	-3.20 (-4.81, -1.60)	-2.18 (-3.46, -0.90)	-3.51 (-5.31, -1.72)	-2.51 (-3.96, -1.06)
	<i>P</i> =0.14	<i>P</i> =0.15	<i>P</i> =0.089	<i>P</i> =0.074
<i>Initial body weight<sup>c</sup></i>				
≤76 kg (n=13)	-1.81 (-3.51, -0.11)	-0.75 (-1.88, 0.38)	-1.26 (-3.09, 0.58)	-0.56 (-1.87, 0.75)
>76 kg (n=11)	-2.83 (-5.24, -0.43)	-2.04 (-3.64, -0.44)	-4.21 (-7.33, -1.10)	-2.62 (-4.79, -0.45)
	<i>P</i> =0.48	<i>P</i> =0.19	<i>P</i> =0.14	<i>P</i> =0.13
<i>Initial 24 h-Na excretion<sup>d</sup></i>				
≤150 mmol (n=12)	-2.14 (-4.01, -0.27)	-1.11 (-2.59, 0.36)	-1.76 (-4.12, 0.61)	-0.63 (-2.41, 1.16)
>150 mmol (n=18)	-2.64 (-4.33, -0.95)	-1.95 (-3.28, -0.62)	-2.95 (-5.03, -0.88)	-2.35 (-3.93, -0.77)
	<i>P</i> =0.69	<i>P</i> =0.40	<i>P</i> =0.49	<i>P</i> =0.18
<i>Initial 24 h-K excretion<sup>e</sup></i>				
≤60 mmol (n=14)	-3.09 (-4.99, -1.18)	-1.69 (-3.23, -0.15)	-2.70 (-5.60, 0.21)	-2.16 (-4.62, 0.30)
>60 mmol (n=16)	-1.93 (-3.55, -0.30)	-1.49 (-2.81, -0.17)	-2.21 (-4.52, 0.10)	-1.15 (-3.09, 0.79)
	<i>P</i> =0.35	<i>P</i> =0.84	<i>P</i> =0.83	<i>P</i> =0.59
<i>Increase in 24 h-K excretion<sup>f</sup></i>				
≤44 mmol (n=16)	-1.79 (-3.13, -0.26)	-1.60 (-2.85, -0.34)	-1.68 (-3.44, 0.09)	-1.51 (-2.93, -0.10)
>44 mmol (n=14)	-3.51 (-5.52, -1.50)	-1.54 (-3.19, 0.12)	-3.70 (-6.11, -1.30)	-1.68 (-3.61, 0.25)
	<i>P</i> =0.17	<i>P</i> =0.95	<i>P</i> =0.20	<i>P</i> =0.89

<sup>a</sup>Adjusted for age, proportion of males, initial blood pressure, initial 24 h urinary sodium and potassium excretions and changes in 24 h urinary potassium excretion during the trial.

<sup>b</sup>SBP ≥140 mmHg and/or DBP ≥90 mmHg.

<sup>c</sup>According to the median of the age-, sex- and race-adjusted body weight distribution in sodium and potassium trials combined; data on initial body weight were available for 20 potassium trials (24 strata).

<sup>d</sup>According to the median of the distribution in sodium trials; 1 mmol Na equals 23 mg.

<sup>e</sup>According to the median of the distribution in potassium trials; 1 mmol K equals 39 mg.

<sup>f</sup>According to the median of the distribution in potassium trials.

larger blood pressure response to changes in sodium and potassium intake that we observed in hypertensive trial populations remained after adjustment for age, gender (% men), and habitual sodium and potassium intake (estimated from 24 h urinary excretion). We observed a tendency towards an increased blood pressure sensitivity to sodium and potassium at older age which could not be explained by higher blood pressure levels, as shown by multivariate analyses.

The effect of sodium and potassium intake on blood pressure was estimated from randomised trials. Trials in which sodium and potassium intakes were altered at the same time were excluded. The blood pressure estimates that we obtained by meta-regression analysis are therefore likely to be causal and fully attributable to either sodium or potassium intake. Acute blood pressure effects of alterations in electrolyte intake (<2 weeks) were not included in the study. The weighted blood pressure

increases of 2.5 mmHg systolic and 2.0 mmHg diastolic that we observed for sodium (median reduction of 77 mmol, or 1.8 g) is in line with other meta-analyses.<sup>3–12</sup> For potassium (median increase of 44 mmol, or 1.7 g), our estimates of 2.4 mmHg for systolic blood pressure and 1.6 mmHg for diastolic pressure are somewhat conservative compared to the meta-analyses by Whelton *et al*<sup>15</sup> (3/2 mmHg) and Cappuccio and MacGregor<sup>16</sup> (6/3 mmHg). The exclusion of short-term trials (<2 week) from our study may explain part of this discrepancy.

The method of metaregression analysis that we used has been shown a valid approach for aggregating quantitative data in systematic reviews.<sup>84,85</sup> The findings from this study suggest that blood pressure sensitivity both to sodium and potassium is increased in hypertensives. For sodium, larger blood pressure reductions in hypertensives were also observed in subgroup analyses of the DASH-Sodium trial.<sup>86</sup> Expected decreases in blood pressure in hypertensive populations may be as large as 5/4 mmHg for sodium reduction, and 4/3 mmHg for potassium supplementation. A large part of the effect may already be achieved with mild to moderate changes in intake.

It has been suggested that women are more sensitive to sodium intake than men.<sup>18</sup> Our findings, however, which were adjusted for age, blood pressure level, and other potential confounders, provide no evidence for strong effect modification by gender. This study provides some support for the hypothesis of an increased blood pressure responsiveness to sodium at older age,<sup>18</sup> after adjustment for gender and blood pressure level. Potential effect modification of the potassium–blood pressure relation by age and body weight, which may not have reached statistical significance in our study because of limited power, warrants further investigation.

Sodium and potassium are likely to interact in blood pressure regulation.<sup>87</sup> The renal handling of sodium and potassium is closely related, which argues for a concomitant consideration of these electrolytes when studying their effect on blood pressure. We achieved a large reduction in blood pressure (8/3 mmHg) in 100 mildly hypertensive older subjects when both electrolytes were altered at the same time by using a mineral salt.<sup>88</sup> In metaregression analysis, we found a three- to four-fold, but nonsignificant, increase in diastolic blood pressure response to potassium supplementation in subjects with a high habitual sodium intake (–2.35 vs –0.63 mmHg). Blood pressure sensitivity to sodium, on the other hand, was not modulated by habitual potassium intake. For the study of sodium–potassium interaction, blood pressure changes resulting from simultaneous changes in these electrolytes should be compared to the effect of single interventions within the same study population. However, the number of randomised trials of combined sodium–potassium interventions is limited and there was insufficient power to

address sodium–potassium interaction in the present study.

In conclusion, reduced sodium intake and increased potassium intake could make a substantial contribution to the prevention of hypertension, especially in populations where blood pressure is already elevated.

## Acknowledgements

This work was supported by an unrestricted grant from the Factors Affecting Hypertension Task Force of the European Branch of the International Life Sciences Institute (ILSI Europe; E-mail: info@ilsieurope.be). Industry members of this task force are Frito Lay (PepsiCo), Kellogg, RHM Technology, Unilever, and Valio. The opinions expressed herein are those of the authors and do not necessarily represent the views of ILSI Europe.

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