



## Original Contribution

### Relation of Urinary Calcium and Magnesium Excretion to Blood Pressure

#### The International Study of Macro- and Micro-Nutrients and Blood Pressure and the International Cooperative Study on Salt, Other Factors, and Blood Pressure

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Data indicate an inverse association between dietary calcium and magnesium intakes and blood pressure (BP); however, much less is known about associations between urinary calcium and magnesium excretion and BP in general populations. The authors assessed the relation of BP to 24-hour excretion of calcium and magnesium in 2 cross-sectional studies. The International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP) comprised 4,679 persons aged 40–59 years from 17 population samples in China, Japan, the United Kingdom, and the United States, and the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) comprised 10,067 persons aged 20–59 years from 52 samples around the world. Timed 24-hour urine collections, BP measurements, and nutrient data from four 24-hour dietary recalls (INTERMAP) were collected. In multiple linear regression analyses, urinary calcium excretion was directly associated with BP. After adjustment for multiple confounders (including weight, height, alcohol intake, calcium intake, urinary sodium level, and urinary potassium intake), systolic BP was 1.9 mm Hg higher per each 4.1 mmol per 24 hours (2 standard deviations) of higher urinary calcium excretion (associations were smaller for diastolic BP) in INTERMAP. Qualitatively similar associations were observed in INTERSALT analyses. Associations between magnesium excretion and BP were small and nonsignificant for most of the models examined. The present data suggest that altered calcium homeostasis, as exhibited by increased calcium excretion, is associated with higher BP levels.

blood pressure; calcium; magnesium

Abbreviations: BP, blood pressure; INTERMAP, International Study of Macro- and Micro-Nutrients and Blood Pressure; INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure.

Adverse blood pressure (BP) levels remain a major cause of cardiovascular morbidity and mortality worldwide (1). Elevated BP has been consistently related to both high dietary sodium intake and high urinary sodium excretion, which reflects dietary intake of sodium (2, 3). In contrast, calcium intake and urinary calcium excretion have shown conflicting associations with BP. Inverse associations between calcium intake and BP are now well established

(4–7). However, some observational studies have reported direct associations between urinary calcium excretion and BP, and elevated urinary excretion of calcium has been reported in hypertensive individuals compared with nonhypertensive individuals (8–10). Disturbances in calcium metabolism have also been reported in patients who are obese or have kidney stone disease; both conditions are associated with elevated BP (11, 12). Magnesium intake has also been

found to be inversely associated with BP (6, 13); however, the relation between urinary magnesium excretion and BP, as well as a possible interaction between calcium and magnesium excretion in relation to BP, are largely unexplored (14–16). We investigated associations between BP and timed 24-hour urinary calcium and magnesium excretion in the cross-sectional population-based International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP) and the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT).

## MATERIALS AND METHODS

### Population samples and field

The methods used in INTERMAP (1996–1999) and INTERSALT (1985–1987) have been described in detail elsewhere (17, 18). The INTERMAP population comprised 4,680 men and women aged 40–59 years from Japan (4 samples), the People's Republic of China (3 samples), the United Kingdom (2 samples), and the United States (8 samples); the INTERSALT population comprised 10,079 men and women aged 20–59 years from 52 samples around the world. Both general-population and workforce samples were included. Whenever possible, individuals were selected randomly from population lists and stratified by age and gender to obtain approximately equal numbers; however, in INTERSALT, some target populations were so small (e.g., populations from a remote village) that the entire adult population was recruited. In INTERMAP, each participant attended the research clinic on 4 occasions: 2 visits on consecutive days, followed by a gap that averaged 3 weeks, and then 2 further consecutive visits. In INTERSALT, each participant attended the research clinic on a single occasion, returning the following day only to complete the timed 24-hour urine collection; 8% were selected at random to return to the clinic for repeat BP measurements and timed 24-hour urine collection.

Blood pressure was measured twice at each clinic visit in INTERMAP (8 measurements in total) and in INTERSALT with a random-zero sphygmomanometer. Measurements were taken when the participant was seated and after he or she had emptied his/her bladder and rested for at least 5 minutes. Korotkoff sounds I and V were used for systolic and diastolic BP. We measured height and weight and obtained questionnaire data regarding daily alcohol intake over the past 7 days (twice for INTERMAP) and other possible confounders.

Two timed 24-hour urine specimens were obtained from all INTERMAP participants; for all INTERSALT participants except the 8% of patients who had repeat clinic visits, a single timed 24-hour urine specimen was collected. The participants with a repeat clinic visit also provided a second urine sample. Collections were started at the research center and completed there the following day. Urine aliquots were stored at  $-20^{\circ}\text{C}$  before being shipped frozen to the central laboratory, where analyses were performed with internal and external quality control. Urinary sodium and potassium concentrations were measured by using emission flame photometry; calcium and magnesium concentrations were

measured by using atomic absorption flame photometry; and creatinine concentration was measured by using the Jaffé method (17). Individual 24-hour excretion values were calculated as the product of concentrations in the urine and urinary volume corrected to 24 hours.

For INTERMAP participants, dietary data were collected at each visit by a trained interviewer using the in-depth multipass 24-hour recall method. All food and drink consumed in the previous 24 hours, including supplements, were recorded. Quality-control measures were extensive (19).

INTERMAP participants were excluded if they did not participate in all 4 clinic visits, their dietary data were considered unreliable, their energy intake from any 24-hour recall was below 500 kcal or above 5,000 kcal (for women) or 8,000 kcal (for men), 2 urine specimens were not available, or data on other variables were incomplete or indicated protocol violation. In total, 215 INTERMAP participants were excluded. INTERSALT participants were excluded if urine specimens or BP measurements were incomplete. A total of 569 INTERSALT participants were excluded. INTERMAP and INTERSALT received institutional ethics committee approval for every collaborating site, and all participants gave informed consent to participate.

### Statistical methods

The main analyses were performed with INTERMAP data; reproducibility of results was assessed with INTERSALT data. Primary analysis was preferred for INTERMAP because of the larger number of potential confounders available and because availability of repeated measurements of 24-hour urinary calcium and magnesium excretion in all participants reduced regression dilution bias.

**INTERMAP.** Food data were converted into nutrients (83 nutrients) through the use of country-specific food composition tables that were updated and standardized across countries by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota (20). For nutrients that supplied energy, intake was calculated as the percentage of total energy and amount per 24-hour increment; for other nutrients, intake was calculated as intake per 1,000 kcal and as amount per 24-hour increment. Nutrient and BP variables were averaged across the 4 visits, and urinary excretion levels were averaged across the two 24-hour collections. One participant with missing urinary calcium and magnesium data was excluded.

Reliability of urinary calcium, magnesium, and creatinine excretion data (mean of 2 collections) was estimated using the formula  $1/[1 + (\text{ratio}/2)] \times 100$ , where the ratio is intra-individual variance divided by the interindividual variance, estimated separately for 8 gender/country strata and pooled by weighting each stratum-specific estimate by sample size minus 1. This gives a first approximation of the effect of random error (day-to-day variability) on the reliability of the urinary cation association with BP; the statistic represents the estimated size of an observed coefficient as a percentage of theoretical coefficient in univariate regression analysis (21–24).

We computed partial Pearson correlations (adjusted for age, gender, and population sample) of urinary mineral excretion with nutrients pooled across countries, weighted

by sample size. We assessed associations of urinary calcium and magnesium excretion with BP by multiple linear regression analyses. Adjustment for possible confounders was done sequentially. Model 1 was adjusted for age, gender, sample, weight, and height; model 2 was adjusted for the variables in model 1 plus reported special diet, physical activity level, doctor-diagnosed heart attack or stroke, family history of hypertension, and smoking; model 3 was adjusted for the variables in models 1 and 2 plus alcohol intake (questionnaire on alcohol intake over the past 7 days administered at 2 different visits), and 24-hour urinary excretion of sodium and potassium; model 4 was adjusted for the variables in models 1, 2, and 3 plus dietary cholesterol, total saturated fatty acid, and total polyunsaturated fatty acid intakes; and models 5a, 5b, and 5c were adjusted for the variables in all other models and calcium intake, magnesium intake, and animal protein intake, respectively, in separate models to avoid multicollinearity. Regression models were fit by country; coefficients were pooled across countries and weighted by the inverse of variance. Cross-country heterogeneity of regression coefficients was tested by using chi-squared analysis.

Regression analyses were done for all 4,679 participants, as well as for males and females separately. Sensitivity analysis entailed regression analyses limited to nonhypertensive participants (those with a systolic BP <140 mm Hg and a diastolic BP <90 mm Hg who were not taking antihypertensive drugs) and to nonintervened participants (those not eating a special diet, not consuming dietary supplements, not diagnosed with cardiovascular disease or diabetes, and not taking drugs for high BP, cardiovascular disease, or diabetes). In addition, we did analyses using censored normal regression to adjust for potential antihypertensive treatment bias, as well as analyses that excluded participants with high day-to-day variation in urinary, dietary, and/or BP variables. Interactions were assessed for age, gender, and urinary calcium and magnesium levels. We examined nonlinearity by testing a quadratic term in the regression models; there was no evidence of significant nonlinearity in any of the models examined.

**INTERSALT.** The 2 BP measurements were averaged. Twelve INTERSALT participants with incomplete urinary cation excretion or questionnaire data were excluded. Associations between urinary calcium and magnesium excretion and BP were assessed by using multiple linear regression analyses with nondietary confounders similar to what was done in the INTERMAP analyses (see the Results section for a complete set of confounders). Regression analyses were done separately for all 10,067 participants, males, females, people aged 20–39 years, and people aged 40–59 years. Analyses were also conducted 1) using censored normal regression to adjust for potential antihypertensive treatment bias (25) and 2) limiting the data to include nonhypertensive participants only. We examined interaction with age only in INTERSALT participants, as the age range was much wider than in INTERMAP. Regression models were fitted by population sample, with coefficients pooled across samples and with weighting by the inverse of the variance.

Regression coefficients are presented as differences in BP for a +2 standard deviation difference in urinary excretion of calcium or magnesium. For comparability, BP differences

presented for both INTERMAP and INTERSALT were calculated based on +2 standard deviations in urinary excretion of calcium and magnesium obtained in INTERMAP.

Analyses were done by I. J. B. and I. T. using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina). Two-tailed  $P < 0.05$  was considered statistically significant.

## RESULTS

### INTERMAP

Descriptive characteristics of the INTERMAP study population samples are provided in Web Table 1 (available at <http://aje.oxfordjournals.org/>). Mean systolic BP ranged from 117.2 mm Hg (Japan) to 121.3 mm Hg (China); mean diastolic BP ranged from 73.2 mm Hg (China) to 77.3 mm Hg (United Kingdom). Mean urinary calcium excretion ranged from 4.0 mmol (161.8 mg) per 24 hours (United Kingdom) to 4.5 mmol (179.3 mg) per 24 hours (China); and mean urinary magnesium excretion ranged from 3.2 mmol (78.3 mg) per 24 hours (Japan) to 4.2 mmol (103.3 mg) per 24 hours (United States). Mean dietary calcium intake ranged from 149.3 mg/1,000 kcal (China) to 445.2 mg/1,000 kcal (United Kingdom), and dietary magnesium intake ranged from 134.4 mg/1,000 kcal (Japan) to 154.6 mg/1,000 kcal (China).

Univariate estimates of the reliability of urinary calcium and magnesium excretion data, based on mean values from two 24-hour urine collections per participant (mmol per 24 hours) were as follows: 81.3% of theoretical coefficient for calcium and 72.6% for magnesium. These were similar for men and women and across the 4 countries.

The Pearson partial correlation (adjusted for sample, age, and gender) between urinary calcium and magnesium excretion was 0.4 and between urinary calcium or magnesium excretion and urinary sodium or potassium excretion was 0.2–0.5 (Table 1). Positive correlations (0.2 or smaller) were observed between urinary calcium excretion and intake of calcium, animal protein, and phosphorus, as well as between urinary magnesium excretion and intakes of calcium, magnesium, fiber, phosphorus, and potassium (Table 1).

Urinary calcium excretion showed consistent positive and statistically significant associations with BP across all analyses (Table 2). Associations were smaller for diastolic BP than for systolic BP. In model 3 (adjusted for multiple possible confounders, including urinary sodium and potassium levels and weight), a difference of +2 standard deviations in urinary calcium excretion (4.1 mmol per 24 hours; equivalent to 163.1 mg per 24 hours) was associated with a difference in systolic BP of 1.9 mm Hg ( $P < 0.001$ ) and with a difference in diastolic BP of 0.9 mm Hg ( $P < 0.001$ ). Associations with systolic BP remained statistically significant after adjustment for dietary calcium, magnesium, or animal protein intakes. Associations were direct in gender-specific analyses; they were consistently larger in women than in men (Web Tables 2 and 3). Interaction terms for urinary calcium excretion and gender were significant for most models (Web Table 4).

Magnesium excretion showed weak, mostly inverse and nonsignificant, associations with BP (Table 2). Interaction

**Table 1.** Pearson Partial Correlation Coefficients, Adjusted for Age, Gender, and Population Sample and Pooled by Country, Between Timed 24-Hour Urinary Mineral Excretion and Dietary Variables for the 4,679 Participants in the International Study of Macro- and Micro-Nutrients and Blood Pressure, 1996–1999

Variable	Urinary Magnesium Excretion	Urinary Calcium Excretion	Urinary Sodium Excretion	Urinary Potassium Excretion
Alcohol intake per 24 hours over a 14-day period, g	−0.01	0.07	0.00	0.00
Vegetable protein intake, % kcal	0.14	−0.04	0.03	0.14
Animal protein intake, % kcal	0.00	0.12	0.09	0.11
Total protein intake, % kcal	0.07	0.11	0.11	0.18
Calcium intake, mg/1,000 kcal	0.16	0.15	0.00	0.29
Magnesium intake, mg/1,000 kcal	0.21	0.03	0.00	0.35
Phosphorus intake, mg/1,000 kcal	0.16	0.12	0.04	0.31
Potassium intake, mg/1,000 kcal	0.19	0.02	0.00	0.46
Sodium intake, mg/1,000 kcal	0.04	0.07	0.32	0.06
Fiber intake, g/1,000 kcal	0.18	−0.05	0.00	0.32
Cholesterol intake, mg/1,000 kcal	−0.05	0.09	0.10	−0.05
Total polyunsaturated fatty acid intake, g/1,000 kcal	0.04	0.02	0.06	−0.03
Total saturated fatty acid intake, g/1,000 kcal	0.00	0.10	0.06	−0.04
Height, m	0.17	0.07	0.14	0.19
Weight, kg	0.14	0.16	0.32	0.18
Body mass index <sup>a</sup>	0.07	0.14	0.28	0.11
Urinary potassium, mmol per 24 hours	0.48	0.21	0.38	1.00
Urinary sodium, mmol per 24 hours	0.34	0.34	1.00	
Urinary calcium, mmol per 24 hours	0.39	1.00		
Urinary magnesium, mmol per 24 hours	1.00			

<sup>a</sup> Body mass index was calculated as weight in kilograms divided by height in meters squared.

terms between urinary calcium and magnesium excretion were not significant (Web Table 5).

Positive associations between urinary calcium excretion and BP were qualitatively similar to the foregoing for subcohorts of 3,671 nonhypertensive and 2,038 nonintervened participants and were statistically significant in most models (Web Tables 7 and 8) and after exclusion of participants with high day-to-day variation in urinary, dietary, and/or BP variables (Web Table 9). Censored normal regression to adjust for potential antihypertensive treatment bias yielded positive associations qualitatively similar to the abovementioned; associations for urinary calcium with BP were statistically significant in all models (Web Table 10).

## INTERSALT

Results qualitatively similar to those seen in the INTERMAP population were observed in the INTERSALT population. Mean levels of 24-hour urinary calcium and magnesium excretion in population samples from Japan, China, the United Kingdom, and the United States in INTERSALT (see reference 18) were compatible with the

findings in INTERMAP participants some 15 years later. Associations between urinary calcium excretion and BP were positive but smaller than those observed in comparable regression models for INTERMAP (Table 3) based on a single 24-hour urine collection from each individual in INTERSALT (2 in INTERMAP). Associations between urinary calcium excretion and BP were stronger in women than in men (interaction terms were statistically significant) and stronger in analyses restricted to nonhypertensive individuals (Web Tables 13–18).

## DISCUSSION

Our main findings were direct associations between 24-hour urinary calcium excretion and BP. Associations prevailed in sequential regression models that were controlled for multiple confounders, both nondietary and dietary, including variables previously demonstrated to relate to BP (e.g., 24-hour excretion of sodium and potassium, weight standardized for height, and calcium intake) (3–6). Importantly, direct associations were also observed for nonhypertensive individuals, which suggested that high levels

**Table 2.** Estimated Differences in Systolic and Diastolic Blood Pressure Associated With Differences of +2 Standard Deviations in Urinary Calcium or Magnesium Excretion for 4,679 Participants in the International Study of Macro- and Micro-Nutrients and Blood Pressure, 1996–1999

Variable (2 Standard Deviations)	Model <sup>a</sup>	Systolic Blood Pressure		Diastolic Blood Pressure	
		Difference	95% CI	Difference	95% CI
Urinary calcium, mmol per 24 hours (4.07)	1	1.62	0.84, 2.41***	0.67	0.14, 1.20*
	2	1.69	0.91, 2.47***	0.70	0.17, 1.23*
	3	1.86	1.04, 2.68***	0.91	0.35, 1.47**
	4	1.81	0.99, 2.63***	0.88	0.31, 1.44**
	5a	2.08	1.25, 2.91***	1.05	0.48, 1.62***
	5b	1.82	0.99, 2.64***	0.87	0.30, 1.43**
	5c	1.84	1.02, 2.67***	0.88	0.32, 1.45**
	5d	1.94	1.12, 2.77***	0.96	0.40, 1.53***
Urinary magnesium, mmol per 24 hours (2.69)	1	-1.00	-1.81, -0.18*	-1.08	-1.63, -0.52***
	2	-0.98	-1.80, -0.17*	-1.04	-1.59, -0.49***
	3	-0.14	-1.05, 0.78	-0.54	-1.17, 0.09
	4	-0.12	-1.03, 0.80	-0.54	-1.17, 0.08
	5a	-0.02	-0.94, 0.89	-0.48	-1.11, 0.15
	5b	-0.12	-1.04, 0.79	-0.55	-1.17, 0.08
	5c	0.01	-0.92, 0.93	-0.52	-1.15, 0.12
	5d	-0.04	-0.95, 0.88	-0.49	-1.12, 0.14

Abbreviation: CI, confidence interval.

\*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

<sup>a</sup> Model 1 was adjusted for age, gender, sample, weight, and height; model 2 was adjusted for the variables in model 1 plus reported special diet, physical activity level, physician-diagnosed heart attack or stroke, family history of hypertension, and smoking; model 3 was adjusted for the variables in models 1 and 2 plus alcohol intake (questionnaire on alcohol intake over the past 7 days administered at 2 different visits) and 24-hour urinary excretion of sodium and potassium; model 4 was adjusted for the variables in models 1, 2, and 3 plus dietary cholesterol, total saturated fatty acid, and total polyunsaturated fatty acid intakes; and models 5a, 5b, and 5c were adjusted for the variables in all other models and calcium intake, magnesium intake, and animal protein intake, respectively. No significant cross-country heterogeneity was observed,  $P < 0.05$ .

of urinary calcium excretion might not be secondary to the development of hypertension.

Higher magnesium intake has been associated with lower BP levels; urinary magnesium excretion has been inconsistently shown to be inversely associated with BP in some

studies (6, 14–16). In agreement with those findings, we report weak inverse nonsignificant associations between magnesium excretion and BP. Numerous observational studies and clinical trials (4–7) have shown inverse associations between calcium intake and supplementation and BP;

**Table 3.** Estimated Differences in Systolic and Diastolic Blood Pressure Associated With Differences of +2 Standard Deviations in Urinary Calcium or Magnesium Excretion for 10,067 Participants for International Cooperative Study on Salt, Other Factors, and Blood Pressure, 1985–1987

Variable (2 Standard Deviations)	Model <sup>a</sup>	Systolic Blood Pressure		Diastolic Blood Pressure	
		Difference	95% CI	Difference	95% CI
Urinary calcium, mmol per 24 hours (4.07)	1	0.49	-0.05, 1.03	0.08	-0.30, 0.46
	2	0.48	-0.06, 1.02	0.10 <sup>b</sup>	-0.28, 0.48
	3	0.45	-0.13, 1.03	0.33	-0.09, 0.74
Urinary magnesium, mmol per 24 hours (2.69)	1	-0.14	-0.63, 0.34	-0.69 <sup>b</sup>	-1.04, -0.34***
	2	-0.16	-0.65, 0.32	-0.63	-0.99, -0.28***
	3	0.14	-0.42, 0.70	-0.38 <sup>b</sup>	-0.79, 0.02

Abbreviation: CI, confidence interval.

\*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

<sup>a</sup> Model 1 was adjusted for age, gender, sample, weight, and height; model 2 was adjusted for the variables in model 1 plus reported special diet, physical activity level, physician-diagnosed heart attack or stroke, family history of hypertension, and smoking; and model 3 was adjusted for the variables in models 1 and 2 plus alcohol intake (questionnaire on alcohol intake over the past 7 days administered at 2 different visits) and 24-hour urinary excretion of sodium and potassium.

<sup>b</sup> Cross-sample heterogeneity was significant  $P < 0.05$ .

however, we and others (4–7) found that calcium intake is positively correlated with urinary calcium excretion, and thus the direct association between urinary calcium excretion and BP observed in this and previous studies (8, 14–16) seems conflicting.

Hypertensive individuals may have altered renal handling of calcium, which could lead to increased calcium excretion (9), and the use of loop diuretics in treating hypertension may also increase urinary calcium excretion. As noted above, however, increased urinary calcium was also directly associated with BP among nonhypertensive individuals, which suggested that increased urinary calcium excretion could precede the onset of hypertension. Nonetheless, causality could not be inferred because of the cross-sectional nature of the present study. A primary renal “leak” of calcium has been proposed as an underlying pathophysiologic factor in hypertension (26). Two widely studied rat models of hypertension, the spontaneously hypertensive rat and the Milan hypertensive strain, are known to be hypercalciuric and to have increased renal sodium reabsorption mediated by the thiazide-sensitive sodium-chloride cotransporter (27, 28). When this mechanism of sodium reabsorption is blocked or disturbed, as with intake of a thiazide diuretic or in Gitelman’s syndrome, renal calcium excretion is reduced, magnesium excretion is increased, and BP is decreased (29). Thus, it is possible that the link between elevated urinary calcium excretion and elevated BP is related to a primary increase in thiazide-sensitive sodium-chloride cotransporter-mediated renal sodium retention, with increases in urinary calcium excretion that occur as an indirect result of the consequent increase in extracellular fluid volume expansion (30).

Calcium is the main component of most renal stones, and urinary calcium excretion/concentration is one important factor in the formation of renal stones (31). Some investigators have also noted an association between renal stones and hypertension in some animal models, such as spontaneously hypertensive rats (see above), and in humans (32). Data from population-based studies suggest that renal stone disease is a risk factor for the development of hypertension (33–35), as is a low urinary magnesium level (36). Others have reported an increased risk of renal stones in hypertensive individuals compared with normotensive individuals (37). Although speculative, the increase in renal calcium excretion could be related to underlying sodium retention, and thiazide diuretics are commonly used to treat hypercalciuria in stone formers.

The observed associations between urinary calcium and BP were higher in women than in men. Associations between sodium intake or sodium excretion and BP have also been shown to be stronger in women, and some evidence indicates higher blood pressure response to dietary sodium intervention in women (38, 39). In the Dietary Approaches to Stop Hypertension-Sodium Trial, systolic BP reduction associated with lower versus higher sodium intakes was higher in females than in males among persons on the Dietary Approaches to Stop Hypertension diet (40). Physiologic studies have suggested that female hormones might explain the observed differences through influences in renal sodium excretion (39, 41). Potential mechanisms to explain differences

in the relation of sodium and calcium excretion to BP in women compared with men warrant further research.

Strengths of the present study include the large sample size, as well as standardized collection of high-quality BP and nutrition data, with use in INTERMAP of four 24-hour dietary recalls and two 24-hour timed urine collections to enhance reliability of data and reduce regression-dilution bias. Limitations include the fact that the data are cross-sectional, and thus the long-term influences of mineral excretion on BP may be underestimated, and that causality cannot be inferred. Despite adjustment for multiple confounders, the possibility of residual confounding by dietary or other variables remains; such misclassification would probably reduce observed associations between urinary cations and BP. Associations were larger in the INTERMAP population than in the INTERSALT population. This could be explained at least in part by reduced regression dilution bias in INTERMAP analyses, which had two 24-hour urine collections for each individual versus the 1 collection in INTERSALT, as well as the 8 BP measurements in INTERMAP compared with 2 in INTERSALT.

In contrast to inverse relations of dietary calcium with BP, we observed urinary calcium to have consistent, direct associations with BP in 2 large, standardized, international population-based studies. These data are consistent with previous findings that alterations in calcium metabolism, reflected in increased calcium excretion or calcium-to-magnesium imbalance, are associated with higher BP levels. These changes seem to point to a defect in renal handling of these divalent cations that may be related to subtle but important changes in distal nephron transport function. Further research should be aimed at elucidating the mechanisms linking renal calcium handling with BP; meanwhile, recommendations for an adequate intake of calcium and magnesium, as components of an optimal nutrition program for preventing high BP, and in managing renal stone disease, remain relevant.

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