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International Study of Macro- and Micro-Nutrients and Blood Pressure

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***Abstract*—**Raised blood pressure is a leading cause of morbidity and mortality worldwide; improved nutritional approaches to population-wide prevention are required. Few data are available on dietary phosphorus and blood pressure and none are available on possible combined effects of phosphorus, magnesium, and calcium on blood pressure. The International Study of Macro- and Micro-Nutrients and Blood Pressure is a cross-sectional epidemiologic study of 4680 men and women ages 40 to 59 from 17 population samples in Japan, China, United Kingdom, and United States. Blood pressure was measured 8 times at 4 visits. Dietary intakes were obtained from four 24-hour recalls plus data on supplement use. Dietary phosphorus was inversely associated with blood pressure in a series of predefined multiple regression models, with the successive addition of potential confounders, both nondietary and dietary. Estimated blood pressure differences per 232 mg/1000 kcal (2 SD) of higher dietary phosphorus were −1.1 to −2.3 mm Hg systolic/−0.6 to −1.5 mm Hg diastolic (n=4680) and −1.6 to −3.5 mm Hg systolic/−0.8 to −1.8 mm Hg diastolic for 2238 "nonintervened" individuals, ie, those without special diet/nutritional supplements or diagnosis/treatment for cardiovascular disease or diabetes. Dietary calcium and magnesium, correlated with phosphorus (partial r=0.71 and r=0.68), were inversely associated with blood pressure. Blood pressures were lower by 1.9 to 4.2 mm Hg systolic/1.2 to 2.4 mm Hg diastolic for people with intakes above versus below country-specific medians for all 3 of the minerals. These results indicate the potential for increased phosphorus/mineral intake to lower blood pressure as part of the recommendations for healthier eating patterns for the prevention and control of prehypertension and hypertension. **(*Hypertension*. 2008;51:669-675.)**

Key Words: blood pressure ■ dietary phosphorus ■ calcium ■ magnesium ■ population study ■ primary prevention

Raised blood pressure (BP) commonly affects middle- and older-aged adults and is a major contributor to the high rates of coronary heart disease and stroke worldwide.[1] Data from epidemiological studies[2,3]; randomized, controlled trials[4–13]; and studies of migrants[14,15] show the importance of dietary factors in the primary prevention and control of high BP. Mineral intakes are important, especially sodium and potassium,[2–9] possibly also calcium and magnesium,[10–13] but little attention has been paid to the possible effects of phosphorus intake on BP,[16–18] despite its role in cellular structure and function,[19] calcium turnover, and regulation.[20] We report here multivariate data from the International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP Study) on the independent relationship of dietary phosphorus to BP and on estimated combined influences of higher versus lower intakes of phosphorus, calcium, and magnesium.

Methods

The INTERMAP Study includes men and women ages 40 to 59 years, from 17 diverse population samples in Japan (4 samples), People's Republic of China (3 samples), United Kingdom (2 samples), and United States (8 samples).[21,22] Each participant attended 2 visits (consecutive days) and an additional 2 visits on average 3 weeks later. At each of the 4 visits, seated BP after ≥5 minutes of rest was measured twice with a random zero sphygmomanometer; amounts of all foods, drinks, and dietary supplements consumed in the previous 24 hours (from multiple-pass 24-hour recalls) were recorded by trained interviewers,[22] aided by food and drink models, measuring devices, and photographs.[22] Measurements of height, weight, and data on daily alcohol consumption (previous 7 days) were obtained at the first and third visits. Data on possible confounders included education, occupation, physical activity, smoking, medical and family history, current special diet, and medication use.[21] In the United States, dietary data were entered directly into a computerized system (online Nutrition Data System version 2.91), containing information on the nutrient composition of 17 000 foods, beverages, ingredients, and supplements. In the other countries, data

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were entered onto standard forms, coded, and computerized (a random 10% of recalls were recoded and re-entered with staff blinded to original entries).[21] Timed 24-hour urine collections were started at the first and third visits and completed at the research center the next day; measurements included urinary creatinine, sodium, and potassium corrected to 24 hours. Eight percent of urine samples were split at the field center for estimation of laboratory precision.[23]

There were 215 exclusions (4.4%) among 4895 initially surveyed: 110 did not attend all 4 visits; 7 had diet data that was considered unreliable by diet interviewer and site nutritionist; 37 had energy intake from any 24-hour dietary recall <500 kcal/d or >5000 kcal/d for women or 8000 kcal for men; 37 had 2 complete urine collections not available; and 24 had data on other variables incomplete, missing, or indicative of protocol violation. Thus, 4680 people (2359 men and 2321 women) are included. The response rate averaged over the 4 countries was 49%. Institutional review board/ethics approval was obtained for each site; all of the participants gave written consent.

Statistical Methods

Individual dietary intakes from foods and beverages were converted into nutrients (83 total) with the use of specially enhanced and comparable country-specific food tables.[24] These were computed as nutrient densities (percentage of kilocalories or milligrams per 1000 kcal) and also for the sum of foods and beverages plus dietary supplements. To improve precision, measurements for each participant were averaged across visits.[25,26]

Per the previous analysis plans, analyses were done for individuals, not across samples/countries. Analyses for dietary phosphorus were part of preplanned exploratory analyses of micronutrients to BP. Partial correlation (adjusted age, gender, or sample) and multiple regression were used. We examined relationships of phosphorus intake (milligrams per 1000 kcal) with BP for all 4680 people and, to reduce possible bias, for 2238 "nonintervened" individuals, ie, those without special diet/nutritional supplements or diagnosis/treatment for cardiovascular disease or diabetes.[27] Potential confounders were added sequentially to regression models, without and with height, with weight included, because they can influence nutrient-BP associations,[2,3,28] leading possibly to overadjustment; also, their high precision of measurement compared with dietary variables can impact estimates of dietary-BP relations.[25] Also, weight adjusted for height appears to relate more strongly to BP than body mass index.[29] Adjustments were sample, age, and gender (model 1), plus reported special diet, dietary supplement intake, moderate or heavy physical activity (hours per day), history of cardiovascular disease/diabetes, and family history of hypertension (model 2), plus 24-hour urinary sodium, potassium, and 7-day alcohol intake[2,3] (model 3), plus dietary saturated and polyunsaturated fatty acids and cholesterol[30] (model 4). Given high-order intercorrelations, models 5a through 5c separately added dietary vegetable protein, calcium, and magnesium. Interaction terms were tested for gender/age and quadratic terms to assess departures from linearity.

Phosphorus-BP regression coefficients were obtained by country and pooled (weighted by the inverse of variance) across countries to obtain study-wide estimates of association. Coefficients were expressed as differences in BP (millimeters of mercury) for a 2-SD difference in phosphorus intake, ie, 232 mg/1000 kcal (approximate amount from a 250-g serving of roast chicken for a person consuming 2500 kcal/24 hour). We used the *Z* score, ie, regression coefficient divided by its SE, to assess statistical significance, and χ^2 tests of heterogeneity to assess differences in the size or direction of country-specific phosphorus-BP regression estimates for individuals.

To assess the sensitivity of primary findings, additional analyses were done including the following: (1) phosphorus intake from foods plus dietary supplements; (2) inclusion of energy intake (kilocalories) in nutrient density regression models[31]; (3) the use of body mass index instead of height and weight; (4) the use of grams-per-day intakes adjusted for energy (instead of nutrient densities); (5) exclusion from the nonintervened group of people reporting any medication use; and (6) exclusion of people with predefined high day-to-day variability of nutrient intakes or BP.[21] A model was also run for all of the participants that included all of the covariates.

To identify food sources of phosphorus, food items in the US database were assigned automatically to predefined food groups by Nutrition Data System software.[24] For Japan, People's Republic of China, and United Kingdom, food items were manually assigned to groups based on Nutrition Data System classification. The amount of phosphorus, as well as calcium and magnesium, provided by each food item was summed by food group.

We also examined associations of calcium and magnesium with BP. To estimate combined effects on BP of higher versus lower intakes of phosphorus, magnesium, and calcium (milligrams per 1000 kcal), the mean BP difference comparing individuals above and below country-specific medians of each of these nutrients was computed by ANCOVA with adjustment for country, age, gender, and additional variables as per models 3 and 5a described above, without or with height and weight adjustment.

Analyses were conducted in SAS version 8.02 (SAS Institute). The study sponsors had no role in study design; collection, analysis, and interpretation of data; or writing of the report.

Results

Descriptive Statistics and Partial Correlations

Mean systolic pressure ranged from 117.2 (Japan) to 121.3 mm Hg (People's Republic of China), mean diastolic pressures from 73.2 (People's Republic of China) to 77.3 mm Hg (United Kingdom), and mean dietary phosphorus intake from 439 (People's Republic of China) to 662 mg/1000 kcal (United Kingdom; supplementary Table S1, please see http://hyper.ahajournals.org). Largest partial correlations were for dietary phosphorus with calcium (0.71) and magnesium (0.68), magnesium with vegetable protein (0.56), and calcium with magnesium (0.46).

All Participants (n=4680)

Associations of phosphorus with BP were all inverse. Estimates ranged from −1.13 to −2.31 mm Hg for systolic pressure and −0.59 to −1.47 mm Hg for diastolic pressure per +232 mg/1000 kcal (2 SD) of phosphorus intake (Table 1). There was heterogeneity between countries in size or direction of the phosphorus-BP regression coefficients: for People's Republic of China, United Kingdom, and United States, all 14 of the associations were inverse; for Japan, both inverse and direct associations (*Z*: −0.53 to +1.17) were observed. There was no longer significant heterogeneity with Japan excluded. Quadratic terms (for nonlinearity) and interactions with age or gender were nonsignificant.

Nonintervened Subcohort (n=2238)

Associations of phosphorus with systolic pressure were larger (inverse) than for all 4680 participants; this was the case also for 5 (of 7) analyses for diastolic pressure. Estimates ranged from −1.64 to −3.51 mm Hg for systolic and −0.79 to −1.77 mm Hg for diastolic pressure per +232 mg/1000 kcal (2 SD) of phosphorus intake (Table 2). Again there was evidence of between-country heterogeneity reflecting inverse and direct associations in Japan, whereas all of the associations were inverse in the other 3 countries. With Japan excluded, there was no longer significant heterogeneity except for systolic BP with adjustment for calcium, height, and weight (model 5b), where associations were larger (inverse)

Table 1. Estimated Mean Difference in BPs With Dietary Phosphorus Intake Higher by 2 SDs Using Sequential Regression Models for All Participants (n=4680)

		Systolic BP				Diastolic BP			
		Not Adjusted for Height and Weight		Adjusted for Height and Weight		Not Adjusted for Height and Weight		Adjusted for Height and Weight	
Model	Variables Added Sequentially*	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score
1	Sample, age, gender	−2.13†	−4.95	−2.05†	−5.06	−1.43†	−4.91	−1.41†	−5.02
2	Special diet, supplement intake, CVD/DM diagnosis, physical activity, family history of high BP	−2.31†	−5.36	−2.15†	−5.24	−1.47	−4.98	−1.39	−4.89
3	Urinary Na, urinary K, alcohol	−1.77	−3.87	−1.36	−3.10	−1.20	−3.82	−0.94	−3.09
4	Cholesterol, SFA, PFA	−2.23	−4.67	−1.69	−3.71	−1.37	−4.17	−1.02	−3.24
5a	Vegetable protein or	−1.75	−3.49	−1.47	−3.07	−1.05	−3.05	−0.86	−2.59
5b	Calcium or	−1.52	−2.10	−1.20	−1.74	−0.80	−1.63	−0.59	−1.25
5c	Magnesium	−1.13	−1.76	−1.48	−2.41	−1.08	−2.45	−1.26	−2.94

Z score ≥1.96: uncorrected $P \leq 0.05$; ≥2.58: uncorrected $P \leq 0.01$. CVD/DM indicates cardiovascular disease/diabetes mellitus; SFA, saturated fatty acids; PFA, polyunsaturated fatty acids. Two SD difference is 232.0 mg/1000 kcal for phosphorus.

*Variables listed are added to previous model so that model 5a combines all the variables listed in model 4 as well as vegetable protein. Models 5b and 5c similarly add sequentially to model 4.

†Test for cross-country heterogeneity significant at $P<0.05$.

in the People's Republic of China and United Kingdom than in the United States. Interaction with gender was significant (*Z*: 1.98 to 2.70); regression coefficients were larger (inverse) for men than women (data not shown).

Sensitivity Analyses

Sensitivity analyses showed consistent inverse phosphorus-BP associations (Table 3). With all of the covariates included, estimates per 2-SD higher dietary phosphorus were −0.62 mm Hg (*Z*: 0.71) for systolic and −0.75 mm Hg (*Z*: 1.24) for diastolic BP. BP differences were larger (inverse) for the nonintervened group with the additional exclusion of people taking any medication.

Sources of Dietary Phosphorus

Five food groups contributed most of the dietary phosphorus in each country (65% to 81%; Table 4). The leading source of dietary phosphorus by country was as follows: Japan, fish and shellfish (22%); People's Republic of China, pasta, rice, and noodles (25%); and United Kingdom and United States, milk and cheese (22%). Meats and poultry/vegetable groups contributed together another 22% (Japan) to 30% of dietary

Table 2. Estimated Mean Difference in BPs With Dietary Phosphorus Intake Higher by 2 SDs Using Sequential Regression Models for Nonintervened Participants (n=2238)

		Systolic BP				Diastolic BP			
		Not Adjusted for Height and Weight		Adjusted for Height and Weight		Not Adjusted for Height and Weight		Adjusted for Height and Weight	
Model	Variables Added Sequentially*	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score
1	Sample, age, gender	−2.47†	−3.52	−2.44†	−3.61	−1.27†	−2.61	−1.40†	−2.99
2	Physical activity, family history of high BP	−2.63†	−3.74	−2.54†	−3.75	−1.46†	−2.99	−1.54†	−3.27
3	Urinary Na, urinary K, alcohol	−1.90†	−2.53	−1.64†	−2.27	−1.20†	−2.29	−1.13†	−2.25
4	Cholesterol, SFA, PFA	−2.80†	−3.54	−2.34†	−3.06	−1.65	−2.99	−1.44	−2.71
5a	Vegetable protein	−2.36	−2.82	−2.02†	−2.49	−1.25	−2.13	−1.13	−2.01
5b	Calcium	−3.51	−3.06	−2.99	−2.71	−1.77	−2.27	−1.51	−2.01
5c	Magnesium	−1.92	−1.81	−2.12	−2.08	−0.79	−1.06	−1.00	−1.40

Z score ≥1.96: uncorrected $P \leq 0.05$; ≥2.58: uncorrected $P \leq 0.01$. SFA indicates saturated fatty acids; PFA, polyunsaturated fatty acids. Nonintervened participants: individuals not on a special diet, not consuming nutritional supplements, not with diagnosed cardiovascular disease/diabetes mellitus, and not taking medication for high BP/cardiovascular disease/diabetes mellitus. Two SD difference is 232.0 mg/1000 kcal for phosphorus.

*Variables listed are added to previous model so that model 5a combines all the variables listed in model 4 as well as vegetable protein. Models 5b and 5c similarly add sequentially to model 4.

†Test for cross-country heterogeneity significant at $P<0.05$.

Table 3. Sensitivity Analyses: Estimated Mean Difference in Blood Pressure for Dietary Phosphorus Intake (Milligrams per 1000 kcal) Higher by 2 SDs

	Systolic BP				Diastolic BP			
	Model 3		Model 5b		Model 3		Model 5b	
Analyses	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score
(a) Milligrams per 1000 kcal of phosphorus from foods plus dietary supplements (n=4680)	−1.25	−2.96	−1.37	−2.60	−0.90	−3.07	−0.91	−2.49
(b) Milligrams per 1000 kcal adjusted for energy intake (kcal/24 h; n=4680)	−1.28	−2.87	−1.13	−1.61	−1.00	−3.24	−0.67	−1.39
(c) Milligrams per 1000 kcal adjusted for body mass index (kg/m^2) instead of height and weight	−1.37	−3.15	−1.20	−1.74	−0.96	−3.17	−0.61	−1.29
(d) Milligrams per 24 hours adjusted for energy intake (kcal/24 h; n=4680)	−1.61	−2.33	−1.11	−1.02	−1.02	−2.12	−0.52	−0.70
(e) Milligrams per 1000 kcal with exclusion from nonintervened subcohort of people taking any medication (n=1732)*	−2.01†	−2.34	−3.93	−3.03	−1.59	−2.67	−1.94	−2.22
(f) Milligrams per 1000 kcal with exclusion of people with high day-to-day variability of systolic BP, diastolic BP, and/or nutrient intakes (n=3473)	−1.07†	−2.13	−1.07	−1.31	−0.60	−1.73	−0.08	−0.14

Z score ≥1.96: uncorrected $P \leq 0.05$; ≥2.58: uncorrected $P \leq 0.01$. Nonintervened participants: individuals not on a special diet, not consuming nutritional supplements, not with diagnosed cardiovascular disease/diabetes mellitus, and not taking medication for high BP/cardiovascular disease/diabetes mellitus. Model 3 is controlled for sample, age, gender, height, weight, special diet, supplement use, cardiovascular disease/diabetes mellitus diagnosis, physical activity, family history of high BP, urinary Na, urinary K, alcohol, except c, where height and weight are replaced by body mass index. Model 5b is controlled for variables of model 3+cholesterol, saturated fatty acids, polyunsaturated fatty acids, and dietary calcium. Unless otherwise stated 2 SD differences (men and women combined) for phosphorus are 232.0 mg/1000 kcal (analyses of a through c, e, and f) and 763.6 mg/24 hours (analysis of d).

*Regressions not controlled for special diet, supplement use, or cardiovascular disease/diabetes mellitus diagnosis.

†Test of cross-country heterogeneity significant at $P<0.05$.

phosphorus (United Kingdom and United States). Milk and cheese in the United Kingdom and United States were also important sources of dietary calcium, as were vegetables in People's Republic of China. Vegetable intake contributed importantly to dietary magnesium (Table 4).

Calcium, Magnesium, and Their Combined Influences With Phosphorus on BP

Both calcium and magnesium were inversely associated with BP. For all 4680 individuals, estimated BP differences for dietary calcium higher by 240 mg/1000 kcal (2 SD) ranged from −1.0 to −2.4 mm Hg for systolic pressure and −0.7 to −1.5 mm Hg for diastolic pressure (Table S2). For dietary magnesium higher by 75.6 mg/1000 kcal (2 SD), they ranged from −0.2 to −3.3 mm Hg systolic and +0.4 to −1.7 mm Hg diastolic (Table S3). Table 5 shows estimated mean differences in systolic and diastolic pressures for 1352 people with dietary intakes above their country-specific medians for all 3 of the minerals (phosphorus, magnesium, and calcium) compared with 1368 people with intakes below the medians, with adjustment for country, age, gender, and multiple other variables, without and with height and weight. These differences ranged from −1.9 to −4.2 mm Hg systolic and −1.2 to −2.4 mm Hg diastolic.

Discussion

We found significant inverse relationships of dietary phosphorus intake with BP. Until now, this possible association has been largely unexplored. High intercorrelation with other minerals, especially calcium, limits the ability to assign a possible BP-lowering effect to phosphorus. Nonetheless, the inverse association in different countries with differing dietary sources of phosphorus tends to strengthen the inference that phosphorus may be playing an etiologic role.

One animal study found a significant BP-lowering effect of dietary phosphorus in spontaneously hypertensive and normotensive rats.[32] To our knowledge, there are no clinical trial data, and the few available epidemiologic data are inconsistent, based on weak study design, without control for possible dietary confounders. A direct association was reported from the National Health and Nutrition Examination Survey I, based on a single 24-hour recall,[17,18] whereas the Honolulu Heart Study (also with a single 24-hour recall) reported 3/2 mm Hg lower systolic/diastolic pressures for the top compared with bottom quartile (≈2.2 SDs) of phosphorus intake (milligrams per day), with adjustment for age and body mass index.[16] In a comparable analysis (model 1, milligrams per day adjusted for height, weight, and energy), we found similar BP differences: −2.8/−1.8 mm Hg per 2 SD of difference in phosphorus intake. Unlike these other studies, we used dietary data from 4 dietary recalls over 4 visits to increase precision[25,26] and assessed the potential confounding in depth.

We reaffirmed inverse associations of calcium and magnesium with BP. Concerning calcium, meta-analyses of

Table 4. Five Food Groups (Excluding Supplements) Contributing Most of the Dietary Intake of Phosphorus Among INTERMAP Participants and the Contribution of Each Group to Dietary Intakes of Calcium and Magnesium, by Country

	Japan (n=1145)			People's Republic of China (n=839)			United Kingdom (n=501)			United States (n=2195)		
Rank	Food Source	Milligrams per 24 h	Percentage	Food Source	Milligrams per 24 h	Percentage	Food Source	Milligrams per 24 h	Percentage	Food Source	Milligrams per 24 h	Percentage
1	Fish and shellfish	P 245.1	21.6	Pasta, rice, and noodles	P 223.6	25.4	Milk and cheese	P 300.7	21.6	Milk and cheese	P 285.8	22.1
		Ca 87.0	14.3		Ca 18.4	6.1		Ca 381.0	40.8		Ca 350.2	44.3
		Mg 38.6	14.4		Mg 82.5	26.8		Mg 31.2	9.8		Mg 29.6	9.8
2	Pasta, rice, and noodles	P 148.2	13.1	Cereals	P 202.9	23.1	Meats and poultry	P 264.2	19.0	Meats and poultry	P 258.1	19.9
		Ca 17.9	3.0		Ca 0.01	0.0		Ca 31.5	3.4		Ca 18.8	2.4
		Mg 26.1	9.7		Mg 0.03	0.0		Mg 29.2	9.1		Mg 29.4	9.2
3	Vegetables	P 133.9	11.8	Vegetables	P 175.5	20.0	Bread, rolls, and biscuits	P 216.8	15.6	Vegetables	P 134.7	10.4
		Ca 81.0	13.4		Ca 135.0	44.6		Ca 163.0	17.5		Ca 71.4	9.0
		Mg 27.9	10.4		Mg 65.7	21.3		Mg 55.4	17.3		Mg 58.1	18.2
4	Milk and cheese	P 116.0	10.2	Meats and poultry	P 63.8	7.3	Vegetables	P 151.6	10.9	Bread, rolls, and biscuits	P 106.7	8.2
		Ca 129.2	21.3		Ca 3.6	1.2		Ca 57.7	17.5		Ca 78.6	9.9
		Mg 11.5	4.3		Mg 7.6	2.5		Mg 51.7	16.2		Mg 28.9	8.1
5	Meats and poultry	P 110.3	9.7	Cakes, puddings, cookies, and other sweet snacks	P 46.0	5.2	Cakes, puddings, cookies, and other sweet snacks	P 95.3	6.8	Nonalcoholic beverages	P 59.9	4.6
		Ca 5.7	0.9		Ca 17.1	5.7		Ca 83.2	8.9		Ca 59.5	7.5
		Mg 12.1	4.5		Mg 13.1	4.2		Mg 19.1	6.0		Mg 43.1	13.5

Percentage is of the total intake for 24 hours.

randomized, controlled trials yielded an inverse association[10,11]; the most recent[12] estimated reduction in systolic/diastolic pressure was −1.9/−1.0 mm Hg for calcium supplementation averaging 1200 mg/d based on 23 trials (764 participants) of hypertensive and 27 trials (1728 participants) of nonhypertensive individuals. For magnesium, a meta-analysis of randomized clinical trials reported a reduction in systolic/diastolic BP of −0.6/−0.8 mm Hg for magnesium supplementation averaging 375 mg/d,[13] based on 14 trials (467 participants) of hypertensive and 6 trials (753 participants) of nonhypertensive individuals.

An increase in dietary phosphorus from an estimated 940 to 1481 mg (at 2100 kcal) was a component of the Dietary Approaches to Stop Hypertension combination diet[7,8]; it also involved increases in dietary calcium, magnesium, and other micronutrients.[33] Compared with control, the Dietary Approaches to Stop Hypertension diet lowered average systolic/diastolic pressures by 5.5/3.0 mm Hg.[7] In the Optimal Macronutrient Intake Trial for Heart Health Study, compared with carbohydrate diet, a diet increased in protein further decreased mean systolic/diastolic BP by 1.4/1.1 mm Hg; the protein diet involved an 8% increase in urinary phosphorus excretion.[34] Because changes in phosphorus intakes and other mineral compositions with these combination diets were part of multiple dietary modifications, their separate impact on BP cannot be estimated from the above studies. In our study, higher compared with lower intakes of all 3 of the minerals, phosphorus, calcium, and magnesium, were associated with BPs lower by ≤4.2 mm Hg systolic and 2.4 mm Hg diastolic.

Our study has limitations. Nutrient intakes and BPs were assessed cross-sectionally in middle age, whereas the rise in BP begins during young adulthood; thus, we may be underestimating true effects if lifelong exposures are important.[35] We used the multiple-pass 24-hour recall method for the collection of dietary data; like all of the dietary assessment methods, it depends on participant reporting and is subject to possible systematic and nonsystematic errors.[36] We attempted to minimize bias by an extensive program for training dietary interviewers and coders and to improve precision by the inclusion of 4 dietary recalls.[26] We enhanced the 4 food tables to achieve state-of-the-art standardized calculation of nutrients in the different countries.[21,24] We adopted a careful model-building approach to deal with problems of high-order multicollinearity[37] among the minerals and with dietary vegetable protein.

The main dietary sources of phosphorus were milk, cheese, meats, and poultry in Western samples and pasta, rice, noodles, fish, and shellfish in Chinese and Japanese samples. Although milk and cheese also provided a high proportion of calcium intake, this was not the case for meats and poultry. Vegetables also contributed importantly to phosphorus and magnesium intakes. Phosphorus is most commonly found in nature as phosphate, ie, in its pentavalent form in combina-

Table 5. Estimated Mean Difference in BP Between Individuals With Higher (n=1352) Compared With Lower (n=1368) Intakes Each of Phosphorus, Magnesium, and Calcium (Milligrams per 1000 kcal)

		Systolic BP				Diastolic BP			
		Not Adjusted for Height and Weight		Adjusted for Height and Weight		Not Adjusted for Height and Weight		Adjusted for Height and Weight	
Model	Variables Added Sequentially*	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score	Difference, mm Hg	*Z* Score
1	Country, age, gender	−4.17	−7.56	−3.20	−6.03	−2.40	−6.33	−1.85	−5.03
3	Special diet, supplement intake, physical activity, CVD/DM diagnosis, family history of high BP, urinary Na, urinary K, alcohol	−2.93	−4.71	−1.90	−3.15	−1.91	−4.46	−1.22	−2.92
5a	Cholesterol, SFA, PFA, vegetable protein	−2.71	−4.08	−1.91	−2.98	−1.69	−3.67	−1.17	−2.60

Z score ≥1.96: uncorrected $P \leq 0.05$; ≥2.58: uncorrected $P \leq 0.01$. CVD/DM indicates cardiovascular disease/diabetes mellitus; SFA, saturated fatty acids; PFA, polyunsaturated fatty acids. Higher/lower-mineral–intake consumers are defined as those with higher/lower than country-specific median intakes each of dietary phosphorus, magnesium, and calcium. Medians for phosphorus intake (mg/1000 kcal) are: Japan, 550.7; People's Republic of China, 422.8; United Kingdom, 648.3; and United States, 572.0. Medians for magnesium intake (mg/1000 kcal) are: Japan, 132.5; People's Republic of China, 154.1; United Kingdom, 149.1; and United States, 142.5. Medians for calcium intake (mg/1000 kcal) are: Japan, 287.3; People's Republic of China, 139.8; United Kingdom, 430.6; and United States, 334.4. Country-age-gender-adjusted mean differences in mineral intake (mg/1000 kcal) for high vs low mineral consumers were 226.0 for phosphorus, 66.5 for magnesium, and 205.9 for calcium.

*Variables listed are added to each previous model, so that model 5a contains all of the variables listed in model 3, as well as cholesterol, SFA, PFA, and vegetable protein.

tion with oxygen. Food phosphate is a mixture of inorganic and organic forms; phosphorus absorption occurs mainly as inorganic phosphate. Most food sources exhibit good bioavailability of phosphorus, with the exception of plant seeds (beans, peas, cereals, and nuts).[38] Phosphates are also found in foods as food additives in the form of various inorganic phosphate salts. Phosphorus-containing food additives are estimated to contribute >30% of adult phosphorus intake in the United States, where there has been increasing use of phosphorus-containing food additives.[39]

The critical importance of phosphorus in cellular structure and function could have profound effects on BP regulation through its role in plasma membrane structure (phospholipids), energy production and storage (adenosine triphosphate, creatine phosphate, and other phosphorylated compounds), enzyme activation, cellular messengers such as G-proteins, and acid-base regulation.[19] Phosphorus is also intimately involved in calcium regulation[20]; calcium has a membrane stabilizing effect[40] with a key role in vascular smooth muscle function.[41] Sodium loading raises intracellular calcium levels,[42] increasing contractility, whereas calcium loading decreases these levels, presumably via calcium-regulating hormones.[43] Magnesium also plays an important role in transmembrane calcium transport and the regulation of vascular tone and endothelial function.[44]

Perspectives

Elevated BP is a leading preventable cause of cardiovascular morbidity and mortality worldwide.[1] Improved diet and nutrition are critical to the goal of reducing BPs and associated morbidity/mortality in populations. Dietary/lifestyle modifications that lower BP include reduced salt intake, increased potassium intake, more exercise, improved weight control, and moderation by drinkers in alcohol intake.[45] Other dietary factors possibly lowering BP include higher intakes of omega-3 polyunsaturated fatty acids,[27] vegetable protein,[28] and fiber,[30] as well as calcium[10–12,46] and magnesium.[13,47] Our data highlight a largely unrecognized possible role for increased phosphorus intake, which (with intake of other minerals) may be a contributor to the achievement of lower BP. This may have importance for prevention and control of prehypertension and hypertension. Further work is needed to assess the possible BP lowering of added phosphorus (as inorganic phosphate) in randomized, controlled trials.

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Disclosures

None.

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Correction

An incomplete version of the *Hypertension* article by Elliott et al (Elliott P, Kesteloot H, Appel LJ, Dyer AR, Ueshima H, Chan Q, Brown IJ, Zhao L, Stamler J; for the INTERMAP Cooperative Research Group. Dietary phosphorus and blood pressure. International Population Study on Macro- and Micro-Nutrients and Blood Pressure. *Hypertension*. 2008;51:669–675) was incorrectly posted at http://hyper.ahajournals.org/cgi/content/abstract/HYPERTENSIONAHA.107.103747v1 on February 4. The correct pdf is now available online at http://hyper.ahajournals.org/cgi/content/abstract/HYPERTENSIONAHA.107.103747v3.

The publisher regrets this error.

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HYPERTENSION/2007/103747 ONLINE SUPPLEMENTARY TABLES

DIETARY PHOSPHORUS AND BLOOD PRESSURE: INTERMAP STUDY

Short title: Dietary Phosphorus and Blood Pressure

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Table S1. Mean and Standard Deviation (sd) or Number and Percent (%), Study Variables by Country, Men and Women Combined: INTERMAP, 1996-1999

	JAPAN (n=1,145)		**P.R.CHINA (n=839)**		**UK (n=501)**		**USA (n=2,195)**	
Variable	**Mean**	**(sd)**	**Mean**	**(sd)**	**Mean**	**(sd)**	**Mean**	**(sd)**
Age (years)	49.4	(5.3)	49.0	(5.8)	49.1	(5.6)	49.1	(5.4)
Systolic BP (mm Hg)	117.2	(13.8)	121.3	(17.4)	120.4	(14.6)	118.6	(13.9)
Diastolic BP (mm Hg)	73.6	(10.3)	73.2	(10.2)	77.3	(9.9)	73.4	(9.7)
Height (m)	1.61	(0.09)	1.59	(0.08)	1.69	(0.09)	1.68	(0.10)
Weight (kg)	61.2	(10.2)	58.9	(10.0)	78.2	(15.3)	82.3	(19.6)
Body Mass Index (kg/m^2)	23.4	(2.9)	23.1	(3.4)	27.5	(4.6)	28.9	(5.9)
Moderate and heavy physical activity (hours/24hr)	2.5	(3.6)	6.0	(3.8)	2.2	(2.4)	3.2	(3.1)
Dietary Energy (kcal/24hr)	2038.6	(449.0)	2035.8	(576.8)	2167.8	(631.8)	2244.2	(698.7)
Dietary Phosphorus (mg/1000kcal)	562.6	(94.4)	438.9	(113.2)	661.6	(126.1)	591.0	(124.6)
Dietary Magnesium (mg/1000kcal)	134.4	(25.2)	154.6	(46.6)	153.3	(35.0)	148.1	(40.0)
Dietary Calcium (mg/1000kcal)	305.6	(108.7)	149.3	(56.2)	445.2	(118.7)	363.0	(142.0)
Dietary Vegetable Protein (%kcal)	7.1	(1.1)	9.9	(1.3)	6.1	(1.4)	5.2	(1.6)

Dietary SFA (%kcal)	6.6	(1.8)	5.0	(2.0)	12.1	(3.3)	10.7	(2.8)
Dietary PFA (%kcal)	6.4	(1.5)	5.8	(2.2)	6.2	(1.9)	7.0	(2.2)
Dietary Cholesterol (mg/1000kcal)	197.2	(66.9)	89.0	(85.9)	120.4	(48.3)	131.4	(58.8)
7-Day Alcohol (g/24hr)	17.0	(22.6)	8.6	(21.4)	14.7	(19.2)	6.9	(13.7)
Urinary Sodium (mmol/24hr)	198.3	(56.2)	227.5	(100.3)	145.2	(49.1)	162.6	(59.4)
Urinary Potassium (mmol/24hr)	48.9	(13.6)	38.3	(12.7)	68.2	(20.1)	57.7	(20.9)
	n	(%)	n	(%)	n	(%)	n	(%)
Hypertensive*	153	(13.4)	145	(17.3)	116	(23.2)	595	(27.1)
Current Alcohol Drinkers	1039	(90.7)	382	(45.5)	444	(88.6)	1533	(69.8)
Special Diet: weight loss, weight gain, vegetarian, salt reduced, diabetic, fat modified or any other	76	(6.6)	45	(5.4)	106	(21.2)	401	(18.3)
Taking dietary supplements	243	(21.2)	34	(4.1)	191	(38.1)	1136	(51.8)
Taking antihypertensive, other cardiovascular disease† or diabetes medication	124	(10.8)	86	(10.3)	98	(19.6)	644	(29.3)
History of heart attack, other heart								

disease, stroke or diabetes		131	(11.4)	59	(7.0)	54	(10.8)	343	(15.6)
Family history of hypertension in any									
first degree relative	– Yes	528	(46.1)	298	(35.5)	242	(48.3)	1491	(67.9)
	– Unknown	406	(35.5)	188	(22.4)	188	(37.5)	489	(22.3)

BP Blood Pressure SFA Saturated fatty acids PFA Polyunsaturated fatty acids 1 kcal = 4.184 kJ

* SBP ≥140 mm Hg or DBP ≥90 mm Hg or on antihypertensive medication

† Includes lipid lowering medication

Table S2. Estimated Mean Difference in Blood Pressure (mm Hg, Z-score), Calcium (mg/1000kcal) Higher by Two Standard Deviations*, Sequential Regression Models, All Participants (n = 4,680)

Model		Systolic Blood Pressure				Diastolic Blood Pressure			
		Not Adjusted for Height and Weight		Adjusted for Height and Weight		Not Adjusted for Height and Weight		Adjusted for Height and Weight	
		Difference mm Hg	(Z-score)	Difference mm Hg	(Z-score)	Difference mm Hg	(Z-score)	Difference mm Hg	(Z-score)
1	Sample, Age, Gender	-2.24	(-5.40)	-2.02	(-5.15)	-1.41	(-4.96)	-1.29	(-4.75)
2	Special Diet, Supplement Intake, CVD/DM Diagnosis, Physical Activity, Family History of High BP	-2.42	(-5.85)	-2.15	(-5.48)	-1.48	(-5.20)	-1.33	(-4.86)
3	Urinary Na, Urinary K, Alcohol	-1.78	(-4.07)	-1.35	(-3.24)	-1.15	(-3.79)	-0.88	(-3.01)
4	Cholesterol, SFA, PFA	-1.98	(-4.42)	-1.48	(-3.46)	-1.29	(-4.17)	-0.97	(-3.26)
5a	Vegetable Protein or	-1.78	(-3.92)	-1.37	(-3.16)	-1.14	(-3.63)	-0.88	(-2.90)
5b	Phosphorus or	-1.24	(-1.78)	-0.95	(-1.43)	-0.88	(-1.86)	-0.72	(-1.56)
5c	Magnesium	-1.28	(-2.57)	-1.24	(-2.61)	-1.01	(-2.94)	-0.98	(-2.95)

Z-score ≥1.96: uncorrected p≤0.05; ≥2.58: uncorrected p≤0.01 SFA Saturated fatty acids PFA Polyunsaturated fatty acids

CVD/DM Cardiovascular disease/diabetes mellitus

*Two standard deviation difference is 240.2 mg/1000kcal for calcium

All tests for cross-country heterogeneity non-significant.

Table S3. Estimated Mean Difference in Blood Pressure (mm Hg, Z-score), Magnesium (mg/1000kcal) Higher by Two Standard Deviations*, Sequential Regression Models, All Participants (n = 4,680)

Model		Systolic Blood Pressure				Diastolic Blood Pressure			
		Not Adjusted for Height and Weight		Adjusted for Height and Weight		Not Adjusted for Height and Weight		Adjusted for Height and Weight	
		Difference mm Hg	(Z-score)	Difference mm Hg	(Z-score)	Difference mm Hg	(Z-score)	Difference mm Hg	(Z-score)
1	Sample, Age, Gender	-3.20	(-7.07)	-2.20	(-5.08)	-1.69	(-5.54)	-1.17	(-3.96)
2	Special Diet, Supplement Intake, CVD/DM Diagnosis, Physical Activity, Family History of High BP	-3.33	(-7.27)	-2.28	(-5.16)	-1.72	(-5.54)	-1.15	(-3.80)
3	Urinary Na, Urinary K, Alcohol	-2.79	(-5.63)	-1.49	(-3.09)	-1.43	(-4.24)	-0.66	(-2.00)
4	Cholesterol, SFA, PFA	-2.68	(-5.11)	-1.51	(-2.98)	-1.29	(-3.62)	-0.61	(-1.75)
5a	Vegetable Protein or	-2.09	(-3.30)	-1.18	(-1.94)	-0.72	(-1.69)	-0.21	(-0.51)
5b	Phosphorus or	-1.67	(-2.33)	-0.21	(-0.30)	-0.42	(-0.85)	0.41	(0.87)
5c	Calcium	-2.09	(-3.59)	-0.95	(-1.69)	-0.81	(-2.06)	-0.16	(-0.42)

Z-score ≥1.96: uncorrected p≤0.05; ≥2.58: uncorrected p≤0.01 SFA Saturated fatty acids PFA Polyunsaturated fatty acids

CVD/DM Cardiovascular disease/diabetes mellitus

*Two standard deviation difference is 75.6 mg/1000kcal for magnesium

All tests for cross-country heterogeneity non-significant.