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Relationship of Dietary Cholesterol to Blood Pressure: The INTERMAP Study

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Abstract

Objective—A direct relationship of dietary cholesterol to blood pressure of men has been reported in a few observational studies from the United States. It is not clear whether this association prevails consistently, e.g., in populations with varied dietary habits, across ethnic groups, genders. Cross-sectional data from the International Study of Macro/Micro-nutrients and Blood Pressure (INTERMAP) were used to assess relations of dietary cholesterol intake to blood pressure in men and women from four countries.

Methods—Data include 83 nutrients from four multi-pass 24-h dietary recalls and two timed 24-h urine collections; eight blood pressure readings; and questionnaire data, for 4680 participants ages 40–59 years from 17 population samples in Japan, People's Republic of China, United Kingdom, and United States of America.

Results—With sequential models to control for multiple possible confounders (dietary, other), linear regression analyses showed that dietary cholesterol was directly related to systolic blood pressure for all participants and for non-hypertensive individuals, but not to diastolic blood pressure. With adjustment for 12 variables, estimated systolic blood pressure differences with 2 standard deviation higher cholesterol intake (131.0 mg/1,000kcal) were 0.9 mmHg ($p < 0.05$) for all participants, and 1.1 mmHg ($p < 0.01$) for non-hypertensive individuals, findings attenuated with addition of height and weight to the model.

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CONFLICT OF INTEREST DISCLOSURES None.

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Conclusion—INTERMAP found a low-order, positive relationship of dietary cholesterol intake to SBP with control for multiple possible confounders. Reduction of dietary cholesterol intake may contribute to prevention and control of adverse blood pressure levels in general populations.

Keywords

Blood pressure; nutrition; dietary cholesterol; population study

INTRODUCTION

Limited research has been done on the association between dietary cholesterol and blood pressure (BP) [1,2]. This is in marked contrast to the extensive investigations (clinical, epidemiologic, animal-experimental) over decades on relations of dietary cholesterol to serum cholesterol and the atherosclerotic cardiovascular diseases [3,4,5]. Given the massive positive findings in the latter area, it is a reasonable hypothesis that cholesterol intake is one among many dietary factors that in combination have major impact on BP [6].

The Multiple Risk Factor Intervention Trial (MRFIT) reported a significant independent cross-sectional relation of dietary cholesterol to BP [1]. The Western Electric Study, in prospective analyses of relations of nutrient intakes to change of BP through 9 years, found that dietary cholesterol intake was positively and significantly related to average annual increase in BP [2]. These previous studies were on American men. Per capita dietary cholesterol intake varies across populations, due mainly to amount of egg consumption, e.g., higher in Japan and lower in China compared to the United States (USA) [7]. It is not clear whether the association between dietary cholesterol and BP prevails consistently, across populations with varied dietary habits, ethnic strata, genders.

The population-based International Study of Macro/Micro-nutrients and Blood Pressure (INTERMAP) was designed to elucidate relations of multiple dietary factors to BP [8,9]. Its basic premises are: multiple nutrients have small independent influences on BP of individuals that in combination summate to sizable effects. To detect impact of single nutrients on BP of individuals, it is essential to collect standardized, high-quality data on large samples of diverse populations. Accordingly, INTERMAP surveyed in-depth 4,680 men and women ages 40–59 from 17 population samples in Japan, Peoples Republic of China (PRC), United Kingdom (UK), and USA. The data enable INTERMAP to address unanswered questions on dietary cholesterol intake and BP. INTERMAP hypothesized that dietary cholesterol intake of individuals is directly related to their blood pressure. Findings are reported here.

METHODS

Population Samples, Field Methods (1996–1999)

INTERMAP included men and women ages 40–59 years from 17 random population samples in Japan (four samples), PRC (three), UK (two), and USA (eight) [8]. Participants were selected randomly from population lists, stratified by age/gender (4 strata). Staff were trained and certified for BP measurement by international/national senior colleagues based on a common standardized protocol [8]. Each participant attended four times, visits 1 and 2 on consecutive days, visits 3 and 4 on consecutive days on average 3 weeks later. For BP measurement, each participant -- having emptied his/her bladder -- was seated comfortably for five minutes, feet flat on the floor, in a quiet room, with no physical activity in the preceding half hour. Korotkoff sounds I and V were criteria for systolic BP (SBP) and diastolic BP (DBP). BP was measured twice at each visit with a random zero sphygmomanometer; BP at each visit was the average of the two readings. Measurements of

height and weight, and questionnaire data on daily alcohol consumption over the previous seven days were obtained at two visits (14 days total). Dietary data were collected at each visit by a trained certified interviewer with use of the in-depth multi-pass 24-hr recall method [1]. All foods and drinks consumed in the previous 24 hours, including dietary supplements, were recorded. Questionnaire data were obtained on demographic and other possible confounders. Quality control throughout field surveys was on-going and extensive at international, national, and local levels [8,9].

Each participant provided two 24-hour urine collections, start and end timed at the research center (visits 1–2 and 3–4); measurements included urinary volume, sodium, potassium, creatinine [8]; 8% of urine samples were split locally and sent blind to the Central Laboratory to estimate technical error.

Individuals were excluded if they did not attend all four visits; diet data were considered unreliable; energy intake from any 24-hour dietary recall was below 500 or greater than 5,000 kcal/day for women, 8,000 kcal for men; two urine collections were not available; data on other variables were incomplete or indicated protocol violation (total exclusions: 215 people).

The study received institutional ethics committee approval for each site; all participants gave written informed consent.

Statistical Methods

Food data of individuals were converted into nutrients (83 nutrients) with use of country-specific food tables, enhanced and standardized across countries by the Nutrition Coordinating Center, University of Minnesota [9,10]. For nutrients supplying energy, intake was calculated as percent total energy; for others, as intake/1000 kcal; nutrients were calculated also as amounts/24 hours. Food data were used to assess main food groups supplying dietary cholesterol. Urinary values/24 hours were calculated as products of urinary concentrations and timed volume standardized to 24 hours. Measurements/person were averaged, for BP and nutrient variables across the four visits, and for urinary excretions across the two collections. For descriptive statistics, means and standard deviations, numbers and percentages were calculated by country and study-wide. Approximations of reliability of SBP, DBP, and dietary nutrient intakes were estimated from the mean of the four visits using the formula $1/[1+(\text{ratio}/4)] \times 100$, where the ratio is intra-individual variance/inter-individual variance, estimated separately for 8 gender/country strata and pooled by weighting each stratum-specific estimate by sample size minus one. This gives a first approximation of reliability, i.e., an estimate of the size of an observed coefficient as a per cent of the theoretical coefficient in a univariate regression analysis [11,12]. It is limited due to its univariate focus, its similar handling of values one day and three weeks apart, and its dealing only with regression dilution bias due to random variation, i.e., it cannot address systematic (nonrandom) bias. Reliability of urinary sodium and potassium excretion from the mean of the two measurements was similarly estimated from the formula $1/[1+(\text{ratio}/2)] \times 100$.

Associations among nutritional variables were explored by partial correlation, adjusted for sample, age, gender; pooled across countries, weighted by sample size. Multiple regression analyses were used to examine relationships of dietary cholesterol (mg/1,000 kcal) of individuals to their SBP and DBP. These analyses were done for all 4,680 participants; also for 2,238 “non intervened” persons not on a special diet, not consuming nutritional supplements, no diagnosed CVD/diabetes, not taking medication for high BP, high cholesterol, cardiovascular disease or diabetes, i.e., exclusion of people whose data might bias the dietary cholesterol-BP relationship; 3,671 non-hypertensive participants, to assess

whether any observed overall relation of dietary cholesterol to BP prevailed throughout the population; and for 2,038 non-hypertensive, non-intervened participants. Analyses were also done for all 1,103 U.S. men and 717 U.S. higher risk men, to evaluate comparability of INTERMAP results with those from the MRFIT and the Western Electric Studies of U.S. men [5,12]. Higher risk was defined as any one or more of the following: systolic BP $\geq$ 140mmHg, diastolic BP $\geq$ 90mmHg, BMI $\geq$ 30.0 kg/m², current smoker, history of CVD or diabetes, diabetic diet, or taking antidiabetic/antihypertensive/lipid-lowering/cardiovascular-influencing drugs. Adjustment for possible confounders was done sequentially: for sample, age, gender, special diet (Yes/No), supplement intake (Yes/No), CVD-DM diagnosis (Yes/No), physical activity (medium + heavy, hours/day), family history of high BP (Yes, No, or Unknown), urinary Na and urinary K (mmol/24h), 14-day alcohol (g/24h) (Model A); plus saturated fatty acids (SFA) and PFA (%kcal) (Model B); plus each of several stipulated other nutrients (expressed per 1,000 kcal or percent kcal) (Model C1–C11).

Sensitivity analyses involved: use of nutrient densities adjusted for energy; urinary sodium/creatinine ratio and potassium/creatinine ratio instead of sodium and potassium (mmol/24-h); use of mg/day intake of dietary cholesterol; exclusion of pre-identified people with marked intra-individual variability in nutrient intake and/or SBP, DBP (n=3,473) [8]; censored-normal regression to control for potential antihypertensive treatment bias [13].

Regression models were fit separately by country and coefficients pooled across countries, weighted by inverse of variance, to estimate overall association; cross-country heterogeneity was tested; interactions were assessed for age and gender; lowess regression analyses [14] and quadratic terms were used to assess linearity of cholesterol-BP relations. Regression coefficients were expressed as mm Hg for two standard deviation (SD) differences in dietary cholesterol, from pooled within-country standard deviations weighted by sample size.

Analyses were with SAS version 9.1 (SAS Institute, Cary, North Carolina, USA) and Stata/SE 10.1 (StataCorp, College Station, Texas, USA) by Ian J. Brown and Queenie Chan.

RESULTS

Descriptive Statistics

Average SBP ranged from 117.2 (Japan) to 121.3 mmHg (PRC); average DBP, from 73.2 (PRC) to 77.3 (UK) mmHg (Supplemental Table S1). Mean BMI was lower for Japanese (23.4 kg/m²) and PRC participants (23.1 kg/m²), highest for American (28.9 kg/m²). Mean cholesterol intake (mg/1,000 kcal) was highest in Japan (197.2 mg/1,000 kcal) and lowest in PRC (89.0 mg/1,000 kcal). Main food groups supplying cholesterol were eggs (59%, PRC; 44%, Japan; 37%, USA; 21%, UK) and meat (37%, UK; 36%, USA; 31%, PRC; 11%, Japan).

Reliability Estimates

Univariate estimate for reliability of cholesterol intake (mg/1,000 kcal) by individuals, based on means of four 24-hour recalls, yielded an observed coefficient 50.1% of theoretical coefficient for all 4,680 participants (Supplemental Table S2). This estimate was similar across countries, ranging from 41.1% (UK) to 58.0% (PRC). BP reliability estimates were 94.3% for SBP, 93.0% for DBP, uniformly high in each country.

Partial Correlation Data

Dietary cholesterol (mg/1000 kcal) correlated directly with total fat (partial $r=0.38$), saturated and monounsaturated fatty acids (SFA, MFA) (0.37), animal protein (0.55), and BMI (0.10); inversely with available carbohydrate (−0.46), starch (−0.30), sugars (−0.21),

vegetable protein (−0.35). Correlations were small with total energy, calcium, magnesium, phosphorus, urinary sodium and potassium.

Relation of Dietary Cholesterol to Blood Pressure

In all 4,680 participants, dietary cholesterol was directly related to SBP in all twelve multivariate models, with Z-scores in the range 1.96–3.05 in six of the twelve models (Table 1). Quantitative estimates of the difference in SBP with 2 SD higher cholesterol intake (131.0 mg/1,000 kcal) were in the range 0.6 to 1.4 mmHg. Results were similar to the foregoing in sensitivity analyses, with SBP differences in the range 0.8 to 1.8 mmHg (Table 2). In corresponding analyses adjusted for height and weight, these positive cholesterol-SBP relations were smaller, e.g., SBP differences in the range 0.3 to 0.8 mmHg (detailed data not tabulated). In all analyses, DBP differences were low order and Z-scores small (Tables 1 and 2).

In the non-intervened subcohort (n = 2,238), results were similar to the foregoing -- e.g., SBP differences 0.6–1.1 mmHg (Table 3). In the non-hypertensive subcohort (n = 3,671), the dietary cholesterol-SBP relation tended to be slightly stronger than for all participants -- e.g., Z-scores 2.94 to 3.75 despite smaller sample size (SBP differences 1.1–1.5 mmHg). In gender-specific analyses, the dietary cholesterol-SBP relation was significant for women (SBP differences 1.8 to 2.5 mmHg, Z-scores 2.7 to 3.7), but not for men (Z-scores for gender-cholesterol interaction 2.9 to 3.1). Correspondingly, for all U.S. men (n=1,103) and in U.S. higher risk men (n=717), there were no significant relationships between dietary cholesterol and BP (Table 3). Findings were similar with after adjustment of the model also for lipid-lowering medication use or with exclusion of participants who used lipid lowering medication (data not shown).

All tests for cross-country heterogeneity were non-significant. Lowess regression analyses with use of three of the multivariate models (Model B, C1 and C2 as in Table 1) indicated little deviation from the linear prediction (data not tabulated/graphed). Quadratic tests for nonlinearity of the dietary cholesterol-BP relationship were also non-significant.

DISCUSSION

Main finding of this population-based study on dietary cholesterol of individuals and their blood pressure is a low-order independent relation of dietary cholesterol to SBP, prevailing also in non-intervened and in non-hypertensive persons; estimated effect size about 1.0 mmHg SBP with 2 SD higher cholesterol intakes (131.0 mg/1,000kcal), significantly stronger for women than men -- findings attenuated with inclusion of height and weight in multiple regression models.

Among the few previous epidemiologic studies on dietary cholesterol intake and BP, MRFIT found a positive cross-sectional relation with SBP and DBP [1]. Coefficients for regression of BP on dietary cholesterol (mg/1,000 kcal) for pooled data from trial years 1–6 were in the range 0.0015–0.0039, Z score 1.12–2.46 for SBP (most Z scores significant); 0.0025–0.0034, Z score 3.17–3.93 for DBP. In 8-year follow-up of the Western Electric Study cohort [2], dietary cholesterol was significantly associated with change over the years of SBP (Z score 2.73); annual increase in SBP was estimated to be 2.1 mmHg greater for 100mg/1,000kcal higher intake of dietary cholesterol. Both these data sets were on US men; findings are sparse for women and for non-Western ethnic groups with different dietary habits. In the present study with female and male participants from four countries including two East Asian countries, dietary cholesterol was positively associated with SBP without cross-country heterogeneity, stronger for women than men. Overall SBP difference was approximately 1.0 mmHg with 2SD (131.0mg/1,000kcal) higher dietary cholesterol intake,

results consistent with those of the two previous studies [1,2]. Attenuation of this finding with inclusion of height and weight in the INTERMAP models may reflect over-adjustment (partial r for BMI and dietary cholesterol = 0.1) and/or influence of a variable measured with very high reliability (height and weight, or BMI) on regression coefficients of a variable measured with much lower reliability (dietary cholesterol) [15,16].

A dietary intervention study reported that a vegetarian diet, high in polyunsaturated fat, dietary fiber, vegetable protein, potassium, magnesium, and with less total fat, saturated fat and dietary cholesterol, lowered BP, especially SBP [17]. Another randomized trial found that a reduced-fat (25% of energy), low-cholesterol (< 150 mg/day) diet with or without additional fiber intake lowered BP in hyperlipidemic patients [18]. The two DASH feeding trials, with reduced dietary cholesterol as one of multiple dietary modifications with the DASH combination diet, reduced BP in both prehypertensive and hypertensive adults [19,20]. Results of these trials are concordant with the concept that reduction of dietary cholesterol contributes to BP reduction, but it is not possible to elucidate the independent effect of reduced dietary cholesterol on BP in these trials with multifactorial dietary modifications.

In our INTERMAP analyses, the relationship between dietary cholesterol and SBP was slightly stronger in the non-hypertensive subcohort. It is possible that individuals detected as having adverse cardiovascular risk factors, including high BP, tend to decrease dietary cholesterol intake to reduce serum cholesterol level and to prevent atherosclerosis. These behaviors would cause underestimation of a positive relationship between dietary cholesterol intake and BP.

Possible mechanisms to account for a relationship between dietary cholesterol and blood pressure are dietary cholesterol related endothelial dysfunction and arterial stiffness. Serum cholesterol is strongly associated with endothelial dysfunction and reduced nitric oxide bioavailability [21–23], which may lead to functional arterial stiffening. In cholesterol-fed rabbits, increased oxidative stress has been found, attributable to endothelial dysfunction [24]. Oxidative stress reduces the function of renal dopamine receptors in rats, leading to sodium retention and high blood pressure [25].

Limitations of the INTERMAP findings include: their cross-sectional nature, but they are the only available set of extensive, high-quality international population-based data on dietary cholesterol and BP of women and men; underestimation of effect size due to limited reliability in measurement of nutrients (regression dilution bias), despite multiple standardized state-of-the-art measurements; inadequate sample size, i.e., statistical power to assess the dietary cholesterol -BP relation in substrata, e.g., U.S men and U.S. high risk men; limited ability fully to control for higher-order collinearity, consequently limited ability to address definitively the matter of a causal relation of cholesterol intake with BP.

If intake of dietary cholesterol influences BP for people in the general population, effect size is apparently small, based on our results. This finding, anticipated by INTERMAP [8], needs to be kept in perspective: First, with multiple nutrients having “small” independent influences, the combined effect becomes sizable, i.e., improved nutrition is capable of preventing or lowering unfavorable BP levels for most people, as the INTERMAP, as well as DASH and OmniHeart feeding trial, results indicate [19,20,26]. Second, long-term BP effects of habitual eating patterns, from early life into middle-age, may be greater, as data on salt intake and BP indicate [16,27]. Third, lowering of population average SBP by “small” amounts (e.g., 2 mm Hg) is estimated to reduce mortality rates 6% for stroke, 4% for CHD [27]. Fourth, reduced cholesterol intake from animal products may decrease risk of CHD/CVD not only by modestly lowering BP, also by favorably influencing serum cholesterol

level [28–30]. Fifth, INTERMAP data also indicate low-order independent favorable influences on BP of food omega-3 and omega-6 PFA, vegetable protein, calcium, phosphorus, magnesium, non-heme iron, potassium, and other nutrients on BP, as well as lower sodium intake, avoidance of heavy alcohol consumption and overweight/obesity -- adding up to estimated sizable combined effect for general populations [6,9,11,31–38].

In conclusion, in agreement with limited data available from other studies, INTERMAP found a low-order, positive relationship of dietary cholesterol intake to SBP with control for multiple possible confounders, a finding attenuated with control also for height and weight. Population-wide reduction of dietary cholesterol intake may also contribute – with multiple other improvements in nutrition-- to prevention and control of adverse blood pressure levels in general populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MRFIT	Multiple Risk Factor Intervention Trial
CHD	coronary heart disease
CVD	cardiovascular disease
INTERMAP	International Study of Macro/Micro-nutrients and Blood Pressure
DASH	Dietary Approaches to Stop Hypertension
PFA	polyunsaturated fatty acids
SFA	saturated fatty acids
MFA	monounsaturated fatty acids

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Table 1

Estimated mean difference in blood pressure (mmHg), dietary cholesterol (mg/1,000kcal) higher by two standard deviations ^a, sequential regression models

Model	Variable added sequentially	Systolic blood pressure		Diastolic blood pressure	
		Difference (mm Hg)	Z-score	Difference (mm Hg)	Z-score
A		0.94	2.25 ^b	0.24	0.87
B	Total SFA and total PFA	0.94	2.08 ^b	0.09	0.29
C1	Phosphorus	1.42	3.05 ^c	0.37	1.16
C2	Calcium	0.88	1.96 ^b	0.06	0.21
C3	Magnesium	0.87	1.93	0.06	0.20
C4	Iron	1.02	2.26 ^b	0.14	0.45
C5	Fiber	0.75	1.64	0.00	-0.01
C6	Vegetable protein	0.58	1.26	-0.17	-0.54
C7	MFA	0.74	1.64	0.18	0.58
C8	Animal protein	0.60	1.13	-0.20	-0.20
C9	Total carbohydrate	0.57	1.16	0.02	-0.13
C10	Starch	0.82	1.78	-0.03	-0.22
C11	Estimated total sugars	0.94	2.06 ^b	0.14	-0.06

SFA, saturated fatty acids; PFA, polyunsaturated fatty acids; MFA, monounsaturated fatty acids.

Model A: Controlled for sample, age, gender, special diet (yes/no), supplement intake (yes/no), CVD-DM diagnosis (yes/no), physical activity (medium+heavy, hours/day), family history of high BP (yes, no, or unknown), urinary Na and urinary K (mmol/24-h), 14-day alcohol (g/24h).

Model B: Model A variables + total SFA and total PFA (%kcal).

Model C1-C6: Controlled for model B variables + each stipulated nutrient (C1-C6, expressed per 1,000 kcal; C7-C11, expressed per %kcal). Model C7 (MFA) not controlled for SFA.

All tests for cross-country heterogeneity were non-significant (p<0.05).

^aTwo standard deviation difference is 131.0 mg/1,000kcal for dietary cholesterol.

^bp<0.05

^cp<0.01.

Estimated mean difference in blood pressure (mm Hg), dietary cholesterol (mg/1000kcal) higher by two standard deviations^a, sequential regression models, sensitivity analyses

Table 2

Variable added sequentially	Systolic blood pressure		Diastolic blood pressure	
	Difference (mm Hg)	Z-score	Difference (mm Hg)	Z-score
Adjusted for total energy (kcal) (n=4,680)				
B	1.00	2.22 ^b	0.09	0.30
C1 Phosphorus	1.45	3.11 ^c	0.36	1.15
C2 Calcium	0.93	2.06 ^b	0.05	0.18
Adjusted for urinary Na/Cr ratio and K/Cr ratio (mmol/mmol) instead of urinary Na and K (mmol/24-h) (n=4,680)				
B	0.84	1.88	0.03	0.11
C1 Phosphorus	1.13	2.42 ^b	0.19	0.59
C2 Calcium	0.83	1.85	0.03	0.10
Dietary cholesterol expressed as mg/day (instead of mg/1,000 kcal)* (n=4,680)				
B	0.98	1.86	0.13	0.37
C1 Phosphorus	1.44	2.62 ^c	0.38	1.03
C2 Calcium	0.93	1.76	0.11	0.31
Excluding participants with high day-to-day variability in nutrients and/or BP (n = 3,473)				
B	1.11	2.07 ^b	0.15	0.40
C1 Phosphorus	1.56	2.79 ^c	0.41	1.09
C2 Calcium	1.07	2.00 ^b	0.15	0.42
Censored-normal regression to control for potential antihypertensive treatment bias (n = 4,680)				
B	1.30 ^d	2.57 ^b	0.34	0.99
C1 Phosphorus	1.83 ^d	3.48 ^c	0.63 [§]	1.78
C2 Calcium	1.23 ^d	2.44 ^b	0.30	0.88

Model B includes sample, age, gender, special diet (yes/no), supplement intake (yes/no), CVD-DM diagnosis (yes/no), physical activity (medium+heavy, hours/day), family history of high blood pressure (yes, no, or unknown), urinary Na and urinary K (mmol/24h), 14-day alcohol (g/24h), total SFA and total PFA (% kcal). Total energy (kcal/24h) was also included in the model with dietary cholesterol expressed as mg/day.

Model C1, C2: Controlled for model B variables + each stipulated nutrient (expressed per 1,000 kcal).

^aTwo standard deviation difference is 131.0 mg/1,000kcal or 324.7 mg/day for dietary cholesterol.

^b $p < 0.05$ ^c $p < 0.01$.^d Cross-country heterogeneity detected, $P < 0.05$.

Table 3

Estimated mean difference in blood pressure (mm Hg), dietary cholesterol (mg/1,000kcal) higher by two standard deviations^a in non-intervened participants, non-hypertensive participants, all U.S. men and U.S. higher risk men, sequential regression models, sensitivity analyses

Variable added sequentially	Systolic blood pressure		Diastolic blood pressure	
	Difference (mmHg)	Z-score	Difference (mmHg)	Z-score
Non-intervened participants (n = 2,238)				
B	0.71	1.17	0.18	0.43
C1 Phosphorus	1.07	1.70	0.39	0.90
C2 Calcium	0.63	1.04	0.15	0.35
Non-hypertensive participants (n = 3,671)				
B	1.14	3.03 ^b	0.47	1.67
C1 Phosphorus	1.46	3.75 ^b	0.66	2.29
C2 Calcium	1.11	2.94 ^b	0.46	1.65
All U.S. men (n = 1,103)				
B	0.09	0.10	-0.42	-0.60
C1 Phosphorus	0.53	0.55	-0.21	-0.29
C2 Calcium	-0.03	-0.03	-0.46	-0.65
U.S. higher risk men (n = 717)				
B	-0.69	-0.58	-0.73	-0.84
C1 Phosphorus	-0.52	-0.43	-0.62	-0.70
C2 Calcium	-0.74	-0.63	-0.75	-0.85

Model B includes sample, age, gender, special diet (yes/no), supplement intake (yes/no), CVD-DM diagnosis (yes/no), physical activity (medium-heavy, hours/day), family history of high blood pressure (yes, no, or unknown), urinary Na and urinary K (mmol/24h), 14-day alcohol (g/24h), total SFA and total PFA (% kcal). For non-intervened participants, Model B is not adjusted for special diet, supplement intake, or CVD-DM diagnosis. For U.S. higher risk men, Model B is not adjusted for gender, or CVD-DM diagnosis.

Model C1, C2: Controlled for model B variables + each stipulated nutrient (expressed per 1,000 kcal).

All tests for cross-country heterogeneity were non-significant in non-intervened participants and non-hypertensive participants (p>0.05).

^aTwo standard deviation difference is 131.0 mg/1,000kcal or 324.7 mg/day for dietary cholesterol.

^bp<0.01.