Association Between Protein Intake and Blood Pressure

The INTERMAP Study

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Background: Findings from epidemiological studies suggest an inverse relationship between individuals' protein intake and their blood pressure.

Methods: Cross-sectional epidemiological study of 4680 persons, aged 40 to 59 years, from 4 countries. Systolic and diastolic blood pressure was measured 8 times at 4 visits. Dietary intake based on 24-hour dietary recalls was recorded 4 times. Information on dietary supplements was noted. Two 24-hour urine samples were obtained per person.

Results: There was a significant inverse relationship between vegetable protein intake and blood pressure. After adjusting for confounders, blood pressure differences associated with higher vegetable protein intake of 2.8% kilocalories were -2.14 mm Hg systolic and -1.35 mm Hg diastolic ($P < .001$ for both); after further adjustment for height and weight, these differences were -1.11 mm Hg systolic ($P < .01$) and -0.71 mm Hg diastolic

($P < .05$). For animal protein intake, significant positive blood pressure differences did not persist after adjusting for height and weight. For total protein intake (which had a significant interaction with sex), there was no significant association with blood pressure in women, nor in men after adjusting for dietary confounders. There were significant differences in the amino acid content of the diets of persons with high vegetable and low animal protein intake vs the diets of persons with low vegetable and high animal protein intake.

Conclusions: Vegetable protein intake was inversely related to blood pressure. This finding is consistent with recommendations that a diet high in vegetable products be part of healthy lifestyle for prevention of high blood pressure and related diseases.

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DESPITE PROGRESS IN THE DETECTION, evaluation, and treatment of hypertension, most of the adult population has prehypertensive or high blood pressure levels, with a consequent increase in cardiovascular risk.^{1,2} To combat this, populationwide efforts are needed to modify adverse lifestyles leading to high blood pressure levels.³ Current recommendations emphasize reduced salt intake and increased potassium intake, avoidance or correction of excess alcohol and calorie consumption, and adoption of the Dietary Approaches to Stop Hypertension combination diet, shown to contribute significantly to further blood pressure reduction.³⁻⁵

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Findings of higher blood pressure among meat eaters compared with vegetarians⁶ suggest that high dietary protein intake may be detrimental to blood pressure. This view was challenged by epidemiological and

experimental evidence indicating that total dietary protein intake is inversely related to blood pressure,⁷⁻¹³ which has practical and theoretical implications for medical care and public health. Accordingly, the initial hypothesis of the INTERMAP Study on macronutrients, micronutrients, and blood pressure, involving 17 diverse population samples in 4 countries, was that total protein intake is inversely related to blood pressure.¹⁴ In the present study, we report results on the association of vegetable, animal, and total protein intake with blood pressure.

METHODS

The INTERMAP Study methods have been reported in detail.^{14,15} They are summarized herein.

POPULATION SAMPLES AND FIELD SURVEYS

The INTERMAP Study included men and women, aged 40 to 59 years, from 17 randomly selected population samples in Japan (4 samples), the People's Republic of China (3

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samples), the United Kingdom (2 samples), and the United States (8 samples). The mean participation rate was 49% (45% in Japan, 83% in the People's Republic of China, 22% in the United Kingdom, and 44% in the United States).

Each participant had 2 study visits on consecutive days, with 2 additional study visits on consecutive days 3 to 6 weeks later. Measurements included systolic and diastolic blood pressure (2 measurements per study visit, for a total of 8 measurements), height and weight (on the first and third study visits), and dietary intake based on multiple-pass 24-hour recalls (at each study visit).^{15,16} All foods and beverages consumed in the previous 24 hours, including dietary supplements, were recorded. Because single 24-hour recalls are generally inadequate for assessing diets of individuals,¹⁷ 4 dietary recalls per person were obtained, yielding greater precision on the associations between nutrient intake and blood pressure of 0.06.¹⁸

Questionnaire data on demographics and other possible confounders were obtained by interview, including 2 histories of 7-day alcohol intake, medical and family histories, medication use, special diets, and physical activity.

Two 24-hour urine samples, started at the research center (on the first and third study visits) and completed the next day, were obtained from each participant. Urine aliquots were stored at -20°C for shipment to the Central Laboratory, Leuven, Belgium. For external estimation of laboratory precision, a random 10% of samples were split locally and sent to the Central Laboratory with different identification numbers. Urinary measurements included sodium, potassium, urea, creatinine, calcium, and magnesium.¹⁴

Quality control was extensive, with local, national, and international checks on the completeness and integrity of non-dietary¹⁴ and dietary¹⁵ information. In the United States, dietary data were entered directly into a computerized database (Nutrition Data System, version 2.91; University of Minnesota, Minneapolis). This system contains information on the nutrient composition of 17 000 foods, beverages, ingredients, and supplements. In the other countries, data were entered onto standard forms, coded, and computerized; a random 10% of dietary recalls were recoded and reentered (with the staff blinded to the original entries). Nutrient intake was calculated using country-specific food tables, which were standardized for consistency across countries by the Nutrition Coordinating Center at the University of Minnesota.¹⁹

Of 4895 individuals initially surveyed, 215 were excluded as follows: 110 persons who did not attend all 4 study visits, 7 individuals for whom the diet data were considered unreliable, 37 persons for whom the calorie intake from any 24-hour dietary recall was less than 500 kcal/d (2100 kJ/d) or was greater than 5000 kcal/d (21 000 kJ/d) for women or greater than 8000 kcal/d (33 600 kJ/d) for men, 37 individuals for whom 2 complete urine samples were unavailable, and 24 persons with other data that were incomplete, missing, or indicating a protocol violation. Therefore, 4680 participants (2359 men and 2321 women) were included in the analysis.

The study was designed to have sufficient power to test prior hypotheses at the 1% level. With a sample size of 4680, the power is greater than 90% at the 1% level to detect partial correlations between nutrient intake of 0.06 (that is, true correlations of 0.10 or more because, with 4 dietary recalls and 8 blood pressure measurements, correlations could be attenuated by 40% or more due to daily variability in nutrient intake and blood pressure). A true correlation of 0.10 indicates that 1 SD above vs 1 SD below the group mean of daily protein intake is associated with a mean difference of 20% of the standard deviation in blood pressure, corresponding to about 3 mm Hg systolic and 2 mm Hg diastolic.

The study received institutional review board or ethics committee approval at each site. All participants gave written informed consent.

STATISTICAL ANALYSIS

The dietary data of individuals were converted to macronutrient and micronutrient intake, including 18 amino acids.¹⁵ Data were based on intake of foods and beverages, including dietary supplements. Dietary protein was divided into animal protein and vegetable protein (including grains, legumes, and other nonanimal sources). Nutrients supplying energy were calculated as the percentage of total energy; other dietary variables were calculated per 1000 kcal (4200 kJ). Measurements for each individual were averaged across study visits. Means, standard deviations, numbers, and percentages were calculated by country.

Associations among nutritional variables were explored by partial correlation analysis and were adjusted for sample, age, and sex by pooling cross-country correlations weighted by sample size. Multiple regression analysis was used to examine associations between individuals' vegetable, animal, and total protein intake (percentage of kilocalories or kilojoules) and their blood pressure. Potential confounders were added sequentially to the regression models, calculated with and without adjustment for height and weight because of known associations among vegetarianism, lighter body weight, and lower blood pressure⁶ (the overadjustment problem) and because height and weight affected associations, possibly because of their high precision of measurement compared with dietary variables.¹⁷ Adjustments were made for 5 models, with each successive model repeating the adjustments of the previous model, as follows: *model 1* (adjustment for sample, age, and sex), *model 2* (plus adjustment for special diet, history of cardiovascular disease or diabetes mellitus, family history of hypertension, moderate or heavy physical activity [usual hours per day], and dietary supplement intake), *model 3* (plus adjustment for 24-hour urinary sodium and potassium excretion and 7-day alcohol intake²⁰), *model 4* (plus adjustment for calcium, saturated fatty acid, polyunsaturated fatty acid, and dietary cholesterol intake^{11,21}), *model 5a* (plus adjustment for dietary magnesium intake), and *model 5b* (plus adjustment for fiber intake).^{13,22} Model 5a and model 5b were considered separately because of multicollinearity.²³ Interaction terms were included for age and sex. Because of significant interaction with sex, results for total protein intake are presented separately for men and women. Additional analyses used 24-hour urinary urea as a marker of total protein intake, adjusted (as in the INTERSALT study¹⁰) for sample, age, 7-day alcohol intake, body mass index (calculated as weight in kilograms divided by the square of height in meters), and urinary sodium, potassium, calcium, and magnesium excretion¹⁰ separately by sex because of significant interaction with sex.

To check linearity, associations between protein intake and blood pressure were plotted by country (mean systolic and diastolic blood pressure by country-specific quartiles of protein intake), and the significance of adding a quadratic term for protein intake was assessed for each regression model. These analyses did not indicate a need for nonlinear models.

Regression models were fit separately by country, and coefficients were pooled across countries, weighted by the inverse variance of each coefficient, to obtain an overall estimate of association. To assess interactions in the size and direction of country-specific regression estimates, homogeneity was tested. Overall regression coefficients were expressed as millimeters of mercury for a 2-SD difference in protein intake (ie, 1 SD below the mean to 1 SD above the mean) from pooled within-country standard deviations (1-way analysis of variance).

To assess the sensitivity of primary findings, additional analyses were performed. These included calorie intake in all models,²⁴ nutrient intake from foods and dietary supplements, intake (in grams per day) adjusted for calories (instead of nutrient densities), separate exclusions of participants taking antihypertensive or other cardiovascular disease medications, individuals with history of cardiovascular disease or diabetes melli-

Table 1. Study Variables by Country*

Variable	Japan (n = 1145)	People's Republic of China (n = 839)	United Kingdom (n = 501)	United States (n = 2195)
Age, y	49.4 ± 5.3	49.0 ± 5.8	49.1 ± 5.6	49.1 ± 5.4
Blood pressure, mm Hg				
Systolic	117.2 ± 13.8	121.3 ± 17.4	120.4 ± 14.6	118.6 ± 13.9
Diastolic	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†	23.4 ± 2.9	23.1 ± 3.4	27.5 ± 4.6	28.9 ± 5.9
Moderate or heavy physical activity, h/d	2.5 ± 3.6	6.0 ± 3.8	2.2 ± 2.4	3.2 ± 3.1
Calorie intake, kcal/d	2038.6 ± 449.0	2037.2 ± 577.2	2168.2 ± 631.8	2244.2 ± 698.7
Protein, % kcal				
Total	16.0 ± 2.3	12.4 ± 1.9	15.8 ± 3.1	15.5 ± 3.2
Vegetable	7.1 ± 1.1	10.0 ± 1.3	6.1 ± 1.4	5.2 ± 1.6
Animal	8.9 ± 2.1	2.5 ± 2.4	9.8 ± 3.3	10.2 ± 3.2
Fat, % kcal				
Total	24.9 ± 5.0	20.0 ± 6.1	32.8 ± 6.5	32.9 ± 6.9
Saturated fatty acids	6.6 ± 1.8	5.0 ± 2.0	12.1 ± 3.3	10.7 ± 2.8
Polyunsaturated fatty acids	6.4 ± 1.5	5.8 ± 2.2	6.2 ± 1.9	7.0 ± 2.2
Dietary cholesterol, mg/1000 kcal	197.2 ± 66.9	88.9 ± 85.9	120.4 ± 48.3	131.4 ± 58.8
Total available carbohydrate, % kcal	54.2 ± 7.3	65.0 ± 10.0	47.4 ± 7.1	49.5 ± 8.1
Dietary calcium, mg/1000 kcal	305.6 ± 108.7	150.6 ± 56.0	445.4 ± 118.7	363.0 ± 142.0
Dietary magnesium, mg/1000 kcal	134.4 ± 25.2	154.9 ± 46.6	153.8 ± 35.2	148.1 ± 40.0
Fiber intake, g/1000 kcal	7.9 ± 2.3	14.2 ± 3.8	12.2 ± 3.8	9.0 ± 3.4
Alcohol intake, g/d	17.0 ± 22.6	8.6 ± 21.4	14.7 ± 19.2	6.9 ± 13.7
Urinary urea nitrogen, g/24 h	9.2 ± 2.2	7.8 ± 2.2	9.0 ± 2.5	9.6 ± 3.1
Urinary sodium, mmol/24 h	198.3 ± 56.2	227.5 ± 100.3	145.2 ± 49.1	162.6 ± 59.4
Urinary potassium, mmol/24 h	48.9 ± 13.6	38.3 ± 12.7	68.2 ± 20.1	57.7 ± 20.9
Current alcohol drinkers	1039 (90.7)	382 (45.5)	444 (88.6)	1533 (69.8)
Special diet for weight loss, weight gain, vegetarianism, reduced salt, diabetes mellitus, fat modification, or other	76 (6.6)	45 (5.4)	106 (21.2)	401 (18.3)
History of heart attack, other heart disease, stroke, or diabetes mellitus	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)
Taking dietary supplements	243 (21.2)	34 (4.1)	191 (38.1)	1136 (51.8)

SI conversion factor: To convert kilocalorie to kilojoules, multiply by 4.2.

*Data are given as mean ± SD or as number (percentage).

†Calculated as weight in kilograms divided by the square of height in meters.

tus, individuals on special diets, and those with high daily variability of nutrient intake and blood pressure.¹⁴

To examine possible differences in the amino acid content of diets, participants were assigned to quartiles of vegetable and animal protein intake within each country. The amino acid content of diets among participants in the top quartile of vegetable protein intake and bottom quartile of animal protein intake was compared with those among participants in the bottom quartile of vegetable protein intake and top quartile of animal protein intake (analysis of covariance with adjustment for country, age, and sex). Analyses were conducted using SAS version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS

DESCRIPTIVE STATISTICS

The mean±SD systolic blood pressure ranged from 117.2±13.8 mm Hg (in Japan) to 121.3±17.4 mm Hg (in

the People's Republic of China) (**Table 1**). The mean body mass index, caloric intake, and animal protein intake (caloric percentage) were lowest in the People's Republic of China and highest in the United States. The mean vegetable protein intake was lowest in the United States and highest in the People's Republic of China.

PARTIAL CORRELATION ANALYSIS

Vegetable protein intake and animal protein intake (adjusted for sample, age, and sex) were inversely correlated ($r=-0.36$) (**Table 2**). High correlations were found between vegetable protein intake and total fiber intake ($r=0.64$), between vegetable protein intake and dietary magnesium intake ($r=0.56$), between animal protein intake and cholesterol intake ($r=0.55$), and between dietary magnesium intake and total fiber intake ($r=0.71$).

Table 2. Partial Correlation Analysis Between Caloric Intake, Nutritional Variables, Physical Activity, Weight, and Height, Adjusted for Sample, Age, and Sex

Variable	Energy Intake	Vegetable Protein	Animal Protein	Total Protein	Urinary Sodium	Urinary Potassium	Alcohol Intake	Dietary Calcium	Cholesterol	Total SFA	Total PFA	Dietary Magnesium	Total Fiber	Physical Activity
Total protein	-0.18													
Vegetable protein	-0.18													
Animal protein	-0.09	-0.36												
Urinary sodium	0.24	0.03	0.09	0.11										
Urinary potassium	0.18	0.14	0.11	0.18	0.38									
Alcohol intake	0.16	-0.20	0.04	-0.05	-0.01	0.00								
Dietary calcium	-0.07	0.17	0.22	0.32	0.00	0.29	-0.07							
Cholesterol	0.00	-0.35	0.55	0.41	0.10	-0.05	0.03	0.00						
Total SFA	0.15	-0.39	0.23	0.04	0.06	-0.04	-0.10	0.09	0.37					
Total PFA	0.08	0.01	0.00	-0.01	0.06	-0.03	-0.08	-0.05	0.10	0.21				
Dietary magnesium	-0.19	0.56	0.08	0.38	0.00	0.35	-0.02	0.46	-0.14	-0.28	-0.02			
Total fiber	-0.19	0.64	-0.18	0.13	0.00	0.32	-0.15	0.27	-0.26	-0.32	-0.05	0.71		
Physical activity	0.10	-0.01	-0.05	-0.06	0.05	0.01	0.03	-0.05	-0.04	-0.04	-0.02	-0.05	-0.04	
Weight	0.16	-0.08	0.13	0.09	0.32	0.18	-0.01	-0.01	0.10	0.11	0.06	-0.07	-0.09	-0.08
Height	0.16	-0.03	0.01	0.00	0.14	0.19	0.03	0.02	0.02	0.05	0.04	0.02	0.01	-0.04

Abbreviations: PFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

Table 3. Estimated Blood Pressure Differences Associated With 2-SDs Higher Vegetable Protein Intake and With 2-SDs Higher Animal Protein Intake

Model*	Systolic Blood Pressure				Diastolic Blood Pressure			
	Unadjusted for Height and Weight		Adjusted for Height and Weight		Unadjusted 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
Vegetable Protein Intake								
1	-2.72†	-6.81‡	-1.95	-5.10‡	-1.67	-6.20‡	-1.22	-4.67‡
2	-2.88†	-6.88‡	2.05	-5.08‡	-1.73	-6.11‡	-1.23	-4.47†
3	-2.14†	-4.99‡	-1.11	-2.67§	-1.35	-4.61‡	-0.71	-2.48
4	-1.70	-3.44‡	-0.90	-1.90	-1.11	-3.30‡	-0.63	-1.93
5a	-1.23	-2.07	-0.95	-1.67	-1.22	-3.02§	-1.03	-2.65†
5b	-1.29	-2.05	-1.01	-1.68	-1.12	-2.64§	-0.95	-2.32
Animal Protein Intake								
1	1.55	3.76‡	0.31	0.78	0.68	2.41	-0.07	-0.25
2	1.23	3.02§	0.15	0.39	0.59	2.12	-0.06	-0.27
3	1.03	2.53	0.20	0.51	0.49	1.76	-0.02	-0.07
4	1.15	2.27	0.26	0.53	0.78	2.23	0.24	0.70
5a	1.28	2.52	0.32	0.65	0.85	2.42	0.26	0.76
5b	0.96	1.88	0.22	0.44	0.70	1.97	0.25	0.73

*Variables were added sequentially in the models per the "Statistical Analysis" subsection of the "Methods" section. Values of 2 SDs of vegetable and animal protein are given in the "Results" section.

†Test of homogeneity significant at $P < .05$.

‡ $P < .001$.

§ $P < .01$.

|| $P < .05$.

MULTIPLE REGRESSION ANALYSES

Vegetable Protein Intake and Blood Pressure

With adjustment for sample, age, and sex (model 1), blood pressure differences for higher vegetable protein intake by 2.80% kilocalories (ie, 2 SD of vegetable protein intake) were -2.72 mm Hg systolic and -1.67 mm Hg diastolic; with additional adjustment for height and weight,

these values were -1.95 mm Hg systolic and -1.22 mm Hg diastolic ($P < .001$ for all) (**Table 3**). With further adjustment (model 3), blood pressure differences without adjustment for height and weight were -2.14 mm Hg systolic and -1.35 mm Hg diastolic ($P < .001$ for both); with additional adjustment for height and weight, these values were -1.11 mm Hg systolic ($P < .01$) and -0.71 mm Hg diastolic ($P < .05$). Significant heterogeneity in systolic blood pressure differences was found among countries

Table 4. Sensitivity Analyses of Estimated Blood Pressure Differences Associated With Higher Vegetable Protein Intake

Analysis*	Systolic Blood Pressure				Diastolic Blood Pressure			
	Unadjusted for Height and Weight		Adjusted for Height and Weight		Unadjusted 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
Model 2								
A	-2.72†	-6.43‡	-1.98	-4.84‡	-1.72	-5.99‡	-1.28	-4.59‡
B	-3.91	-6.22‡	-2.90	-4.77‡	-2.42	-5.71‡	-1.83	-4.44‡
C	-2.72†	-6.43‡	-1.99	-4.91‡	-1.71	-5.99‡	-1.29	-4.67‡
D	-4.07	-6.37‡	-2.94	-4.86‡	-2.49	-5.85‡	-1.81	-4.51‡
E	-2.88†	-6.57‡	-2.23†	-5.27‡	-1.77	-5.91‡	-1.32	-4.57‡
F	-2.99	-6.79‡	-2.11	-5.00‡	-1.79	-5.99‡	-1.24	-4.30‡
G	-2.49	-5.29‡	-1.81	-4.00‡	-1.43	-4.44‡	-1.00	-3.21§
H	-2.93	-5.96‡	-2.17	-4.59‡	-1.62	-4.90‡	-1.16	-3.63‡
Model 3								
A	-2.05†	-4.70‡	-1.06	-2.50	-1.37	-4.60‡	-0.76	-2.63§
B	-2.90	-4.47‡	-1.38	-2.21	-1.81	-4.34‡	-1.00	-2.31
C	-2.07†	-4.78‡	-1.06	-2.53	-1.40	-4.68‡	-0.76	-2.67§
D	-2.94	-4.56‡	-1.36	-2.25	-2.04	-4.41‡	-0.90	-2.34
E	-2.14†	-4.74‡	-1.24	-2.85§	-1.45	-4.70‡	-0.86	-2.86§
F	-2.28†	-5.06‡	-1.21	-2.79§	-1.42	-4.63‡	-0.75	-2.52
G	-1.67	-3.45‡	-0.76	-1.63	-0.98	-2.94§	-0.39	-1.21
H	-2.16	-4.25‡	-1.23	-2.52	-1.20	-3.51‡	-0.61	-1.91
Model 5a								
A	-1.25	-2.10	-0.99	-1.72	-1.24	-3.06§	-1.06	-2.72§
B	-1.31	-1.46	-1.02	-1.16	-1.54	-2.49	-1.31	-2.22
C	-1.54	-2.90	-0.98	-1.90	-1.20	-3.35‡	-0.87	-2.48
D	-2.04	-2.42	-1.13	-1.44	-1.58	-2.77§	-0.90	-1.91
E	-1.49†	-2.43	-1.38†	-2.34	-1.37	-3.26§	-1.26	-3.11§
F	-1.61	-2.55	-1.37	-2.27	-1.37	-3.18§	-1.19	-2.90§
G	-0.63	-0.94	-0.64	-1.00	-0.82	-1.78	-0.79	-1.79
H	-1.23	-1.73	-1.18	-1.73	-1.11	-2.32	-1.09	-2.34

*A indicates vegetable protein (in percentage of kilocalories) with inclusion of caloric intake (in kilocalories per 24 hours) (n = 4680); B, vegetable protein (in grams per day) adjusted for caloric intake (in kilocalories per 24 hours) (n = 4680); C, vegetable protein (in percentage of kilocalories) with nutrients from foods and dietary supplements (n = 4680); D, vegetable protein (in grams per day) adjusted for caloric intake (in kilocalories per 24 hours) with nutrients from foods and dietary supplements (n = 4680); E, vegetable protein (in percentage of kilocalories) with exclusion of those taking antihypertensive or other cardiovascular disease medications (n = 3930); F, vegetable protein (in percentage of kilocalories) with exclusion of participants with a history of heart disease, stroke, or diabetes mellitus (n = 4093); G, vegetable protein (in percentage of kilocalories) with exclusion of participants on a special diet (n = 4052); and H, vegetable protein (in percentage of kilocalories) with exclusion of participants with high daily variability of nutrient intake and blood pressure (n = 3473).

†Test of homogeneity significant at $P < .05$.

‡ $P < .001$.

§ $P < .01$.

|| $P < .05$.

for models 1, 2, and 3 unadjusted for height and weight, with the largest differences (inverse) in the United States and the smallest differences in the United Kingdom. Adjusted for other dietary variables (models 4 and 5), systolic blood pressure differences remained significant in models unadjusted for height and weight. All models were significant or borderline significant for diastolic blood pressure differences. There were no significant age or sex interactions.

Multiple sensitivity analyses (models 2, 3, and 5a) showed blood pressure differences associated with higher vegetable protein intake that were generally similar to those for the main analyses. An exception was observed for persons on a special diet (**Table 4**).

Based on computerized data (see the "Methods" section), foods contributing to vegetable protein intake could be assessed for the 2195 participants from the United States,

which had the largest inverse relationship between vegetable protein intake and blood pressure. Of 1647 food items consumed by US participants, 978 (59%) contained vegetable protein. The following 4 food groups supplied 75% of the vegetable protein intake: breads, rolls, and biscuits (33%); vegetables (16%); soy and soy products (15%); and rice and pasta (11%). Four other food groups supplied an additional 20% of vegetable protein intake as follows: beans, excluding soy (7%); nuts, nut butters, and seeds (6%); fruit and fruit juices (5%); and cereals (2%).

Animal Protein Intake and Blood Pressure

Unadjusted for height and weight, there was a significant association (direct) in most models between higher animal protein intake (by 2 SDs equal to 5.84% kilocalories) and systolic and diastolic blood pressure. Adjusted

Table 5. Estimated Blood Pressure Differences Associated With 2-SDs Higher Total Protein Intake

Model*	Systolic Blood Pressure				Diastolic Blood Pressure			
	Unadjusted for Height and Weight		Adjusted for Height and Weight		Unadjusted 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
	Men							
1	-0.67	-1.20	-1.56	-2.92†	-0.44	-1.06	-1.11	-2.87†
2	-0.89	-1.60	-1.61	-3.04†	-0.50	-1.33	-1.22	-2.81†
3	-0.55	-0.99	-0.95	-1.80	-0.32	-0.79	-0.67	-1.69
4	-0.17	-0.29	-0.64	-0.99	-0.11	-0.24	-0.49	-1.04
5a	0.42	0.59	-0.44	-0.64	0.13	0.26	-0.53	-1.07
5b	-0.03	-0.05	-0.58	-0.90	-0.05	-0.11	-0.49	-1.05
Women								
1	1.06	1.68	0.22	0.38	0.17	0.39	-0.22	-0.58
2	0.61	0.97	-0.01	-0.02	0.17	0.41	-0.12	-0.32
3	0.61	1.00	0.33	0.55	0.22	0.54	0.11	0.28
4	0.44	0.62	0.12	0.17	0.54	1.13	0.45	0.96
5a	1.17	1.47	0.21	0.28	0.82	1.57	0.39	0.82
5b	0.77	1.03	0.21	0.29	0.72	1.46	0.50	1.06

*Variables were added sequentially in the models per the "Statistical Analysis" subsection of the "Methods" section. Value of 2 SDs of total protein is given in the "Results" section.

† $P < .01$.

for height and weight, the blood pressure differences were smaller and nonsignificant (Table 3).

Total Protein Intake and Blood Pressure

Given the significant ($P < .01$) interactions with sex, the results for the association between total protein intake and blood pressure are given by sex in **Table 5**. For men, the associations unadjusted for height and weight were nonsignificant; adjusted for height and weight, the blood pressure differences were inverse (significant only in models 1 and 2). For women, no associations were significant.

Based on 24-hour urinary urea nitrogen excretion (in grams per 24 hours) as an index of dietary total protein intake,¹⁰ blood pressure differences for higher urinary urea nitrogen by 5.34 g per 24 hours (ie, 2 SDs) were small and nonsignificant. These blood pressure differences were -0.77 mm Hg systolic and -0.40 mm Hg diastolic for men and -1.11 mm Hg systolic and -0.41 mm Hg diastolic for women.

AMINO ACID CONTENT OF DIETS (HIGH VEGETABLE AND LOW ANIMAL PROTEIN INTAKE VS LOW VEGETABLE AND HIGH ANIMAL PROTEIN INTAKE)

Overall, 491 individuals in the country-specific top quartiles of vegetable protein intake and bottom quartiles of animal protein intake consumed 9.1% (95% confidence interval, 9.0%-9.1%) of their total calories from vegetable protein and 4.3% (95% confidence interval, 4.2%-4.4%) from animal protein. For 471 individuals in the country-specific bottom quartiles of vegetable protein intake and top quartiles of animal protein intake, the corresponding percentages were 5.4% (95% confidence interval, 5.3%-5.5%) of their total calories consumed from

vegetable protein and 12.0% (95% confidence interval, 11.9%-12.2%) from animal protein. Blood pressure differences between these 2 diet groups (adjusted for sample, age, and sex) were -4.15 mm Hg systolic ($P < .001$) and -2.15 mm Hg diastolic ($P < .01$). For 18 amino acids, the percentage of total protein intake was compared between the 2 diet groups (**Table 6**), ranked by T score (most positive to most negative). There were significant between-group differences for 17 amino acids. Individuals with high vegetable and low animal protein intake consumed greater proportions of glutamic acid, cystine, proline, phenylalanine, and serine, and they consumed smaller proportions of the other 13 amino acids compared with persons with lower vegetable and higher animal protein intake.

COMMENT

Our main finding was an inverse relationship between individuals' vegetable protein intake and their blood pressure. For animal protein intake, significant direct associations with blood pressure did not persist after adjustment for height and weight. Among women, there was no significant association between total protein intake and blood pressure; among men, the associations were not significant after adjusting for dietary confounders.

Investigators from previous epidemiological cross-sectional and prospective studies²⁵⁻²⁷ reported inverse relationships between vegetable protein intake and blood pressure. Regarding possible inverse relationships between total protein intake^{9,11,28} or animal protein intake^{8,29,30} and blood pressure, the INTERMAP Study found no significant independent relationships, consistent with the results of other cross-sectional³¹⁻³³ and prospective^{34,35} studies. Specifically, we did not replicate the INTERSALT Study¹⁰ and

Table 6. Amino Acid Intake in Individuals With High Vegetable and Low Animal Protein Diets Compared With Individuals With Low Vegetable and High Animal Protein Diets, Adjusted for Sample, Age, and Sex*

Amino Acid	% of Total Protein Intake		Difference in %	T Score†
	High Vegetable and Low Animal Protein Diet (n = 491)	Low Vegetable and High Animal Protein Diet (n = 471)		
Glutamic acid	22.67 ± 0.11	18.28 ± 0.11	4.39 ± 0.14‡	30.27
Cystine	1.72 ± 0.01	1.51 ± 0.01	0.21 ± 0.01‡	24.50
Proline	7.14 ± 0.06	5.49 ± 0.07	1.66 ± 0.08‡	19.64
Phenylalanine	4.64 ± 0.01	4.44 ± 0.01	0.20 ± 0.01	17.02
Serine	4.62 ± 0.01	4.48 ± 0.01	0.14 ± 0.02	9.11
Tryptophan	1.25 ± 0.00	1.27 ± 0.00	-0.01 ± 0.01	-1.68
Leucine	7.59 ± 0.02	7.76 ± 0.02	-0.17 ± 0.02	-7.06
Arginine	5.44 ± 0.03	5.78 ± 0.03	-0.34 ± 0.04	-9.31
Valine	5.09 ± 0.01	5.32 ± 0.01	-0.22 ± 0.02	-11.69
Aspartic acid	8.34 ± 0.04	9.02 ± 0.04	-0.68 ± 0.05	-12.53
Tyrosine	3.33 ± 0.01	3.52 ± 0.01	-0.19 ± 0.10	-13.18
Glycine	4.95 ± 0.02	4.5 ± 0.02	-0.53 ± 0.03‡	-18.59
Isoleucine	4.24 ± 0.01	4.49 ± 0.01	-0.25 ± 0.01	-23.22
Alanine	4.50 ± 0.02	5.13 ± 0.02	-0.63 ± 0.03‡	-23.63
Histidine	2.57 ± 0.01	2.90 ± 0.01	-0.33 ± 0.01‡	-26.77
Threonine	3.56 ± 0.01	4.01 ± 0.01	-0.45 ± 0.01‡	-33.84
Methionine	1.91 ± 0.01	2.30 ± 0.01	-0.38 ± 0.01‡	-40.56
Lysine	5.09 ± 0.02	6.76 ± 0.03	-1.68 ± 0.03‡	-50.68

*Data are given as mean ± SE unless otherwise indicated.

†Based on 955 *df* in the analyses of variance across the 2 combinations of vegetable and animal protein intake.

‡Difference greater than 10% of the mean of the 2 values.

MRFIT Study¹¹ findings of an inverse relationship between total protein intake and blood pressure.

The reasons for these differences in results may be differences in study methods or populations. The INTERSALT Study¹⁰ included 52 population samples in 32 countries, with 24-hour urine sample analysis as a marker of dietary intake. The INTERMAP Study, carried out in 4 countries, included 4 direct measures of dietary intake from 24-hour dietary recalls. Although the MRFIT Study¹¹ results were based on a mean of 4 or 5 measures from 24-hour dietary recalls, these were conducted annually during 5 to 6 years, not 3 to 6 weeks apart as in the INTERMAP Study. In addition, the MRFIT Study included only men at high risk of coronary heart disease.

Given the high correlations among vegetable protein intake, total fiber intake, and dietary magnesium intake, it is difficult to assess whether vegetable protein intake, these other variables, or their combination is responsible for the inverse relationship between vegetable protein intake and blood pressure.^{36,37} Vegetarians have lower blood pressure and lighter body weight than nonvegetarians⁶; their lower blood pressure may, in part, reflect their higher vegetable protein intake. If so, the INTERMAP Study inclusion of body weight as a confounder of vegetable protein intake may be an overadjustment. After controlling for body weight, an association between blood pressure reduction and vegetable protein intake was found in randomized trials of vegetarian diets^{37,38} and of soy protein supplement use.³⁹

In part, because heavier individuals consume more food on average, body weight correlates more strongly with

nutrient intake expressed as amounts per day than as caloric density. Although we expressed dietary variables as percentages of kilocalories, adjustment for height and weight still had a marked effect on the extent of the associations between protein intake and blood pressure, possibly reflecting greater precision of measurement for body mass than for dietary variables.¹⁷

In the Dietary Approaches to Stop Hypertension trials,⁴⁵ the recommended combination diet emphasized fruits, vegetables, and low-fat or fat-free dairy products; included whole grains, poultry, fish, and nuts; and reduced the intake of red meats, fats, and sweets. In the first Dietary Approaches to Stop Hypertension trial,⁴ total protein intake was moderately increased in the group receiving the combination diet (17.9%) compared with the control group (13.8%), sodium intake across the groups was similar by design, and alcohol intake was low or nil. The isocaloric diet increased the intake of fiber, potassium, phosphorus, calcium, and vitamins; improved the polyunsaturated fat-saturated fat ratio; and decreased the intake of total fat, saturated fat, cholesterol, and all sugars. Compared with the control group fed a usual American diet, mean systolic and diastolic blood pressure among the combination diet group was significantly lowered by 5.5/3.0 mm Hg.⁴ Because this combination diet entailed multiple dietary modifications, no conclusion is possible as to contributions of specific nutrients to the blood pressure reduction.

Regarding animal protein intake, a small study⁴⁰ reported increased systolic blood pressure with 250 g of beef per day added to the diets of normotensive vegetarians for 4 weeks. However, other similar small studies^{41,42} found no effect on blood pressure.

If a causal relationship exists between vegetable protein intake and blood pressure, a potential mechanism is the action of constituent amino acids, several of which have been implicated.⁴³⁻⁴⁶ We found significant differences in the amino acid content of diets predominating in vegetable protein compared with those predominating in animal protein, possibly contributing to the opposing blood pressure effects of vegetable vs animal protein. Other components of diets high in vegetable protein (eg, magnesium) may interact with amino acids to lower blood pressure. Further work is needed to assess such concepts.

The epidemiological approach in the INTERMAP Study has limitations. These include the lack of a gold standard for dietary assessments, which are dependent on reporting by participants (subject to systematic and non-systematic errors); variation among food tables in different countries; variability in daily dietary intake, with consequent attenuation of associations between nutrient intake and blood pressure^{17,18}; use of cross-sectional data to make inferences about long-term dietary effects on blood pressure; and intercorrelations and nonindependence among dietary variables,²³ limiting the ability to clarify causal relationships.

We attempted to minimize dietary reporting errors through extensive quality control procedures.¹⁵ The problem of variability in daily dietary intake was addressed through the use of repeated dietary recalls^{11,17} and 24-hour urine samples, rather than statistical corrections, given the complex underlying statistical assumptions.¹⁷ Despite the use of repeated measures, the effects of vegetable protein intake on blood pressure may still be underestimated. Finally, we standardized the food tables¹⁹ and used urinary biomarkers for sodium, potassium, and protein (urinary urea) excretions to verify dietary intake.¹⁵

Cross-sectional data probably underestimate the true effects if lifelong dietary exposures are important and if people modify their diets because of health concerns. We addressed these problems by controlling for participants on a special diet in regression models. Regarding dietary intercorrelations and potential overfitting of statistical models, we adopted a parsimonious approach and limited inclusion of highly correlated variables in the same model.

CONCLUSIONS

We found an inverse relationship between individuals' vegetable protein intake and their blood pressure. We did not confirm previous epidemiological findings of an inverse relationship between total protein intake and blood pressure.^{9-11,28} Our results are consistent with current recommendations that a diet high in vegetable products be part of a healthy lifestyle for prevention of high blood pressure and related chronic diseases.³ Definitive ascertainment of a causal relationship between vegetable protein intake and blood pressure awaits further data from randomized controlled trials, especially regarding the effect of constituent amino acids on blood pressure.

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