A Nutrient-Wide Association Study on Blood Pressure

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Background—A nutrient-wide approach may be useful to comprehensively test and validate associations between nutrients (derived from foods and supplements) and blood pressure (BP) in an unbiased manner.

Methods and Results—Data from 4680 participants aged 40 to 59 years in the cross-sectional International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) were stratified randomly into training and testing sets. US National Health and Nutrition Examination Survey (NHANES) four cross-sectional cohorts (1999–2000, 2001–2002, 2003–2004, 2005–2006) were used for external validation. We performed multiple linear regression analyses associating each of 82 nutrients and 3 urine electrolytes with systolic and diastolic BP in the INTERMAP training set. Significant findings were validated in the INTERMAP testing set and further in the NHANES cohorts (false discovery rate <5% in training, $P<0.05$ for internal and external validation). Among the validated nutrients, alcohol and urinary sodium-to-potassium ratio were directly associated with systolic BP, and dietary phosphorus, magnesium, iron, thiamin, folacin, and riboflavin were inversely associated with systolic BP. In addition, dietary folacin and riboflavin were inversely associated with diastolic BP. The absolute effect sizes in the validation data (NHANES) ranged from 0.97 mm Hg lower systolic BP (phosphorus) to 0.39 mm Hg lower systolic BP (thiamin) per 1-SD difference in nutrient variable. Inclusion of nutrient intake from supplements in addition to foods gave similar results for some nutrients, though it attenuated the associations of folacin, thiamin, and riboflavin intake with BP.

Conclusions—We identified significant inverse associations between B vitamins and BP, relationships hitherto poorly investigated. Our analyses represent a systematic unbiased approach to the evaluation and validation of nutrient-BP associations. **(*Circulation*. 2012;126:2456-2464.)**

Key Words: blood pressure ■ diet ■ epidemiology ■ nutrition assessment

Dietary habits have long been related to complex diseases, such as cancer and cardiovascular diseases, but the role of many nutrients and food groups in disease merits further investigation despite intensive research efforts.[1–3] Epidemiological studies often test associations of single nutrients with disease or examine food patterns (eg, the Mediterranean diet), which are often difficult to characterize. Recently, a study design analogous to genome-wide association studies (GWAS), the environment-wide association study, has been proposed to search for and analytically validate environmental factors associated with complex diseases.[4,5] Instead of testing 1 only or a few associations at a time, an environment-wide association study evaluates multiple environmental factors for association, with proper adjustment for multiplicity of comparisons. The emerging significant associations are then validated across different datasets, as is commonly done in GWAS.[4,5]

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Here, we extend the environment-wide association study approach to evaluate multiple associations between a wide range of nutrients and blood pressure (BP). We used data

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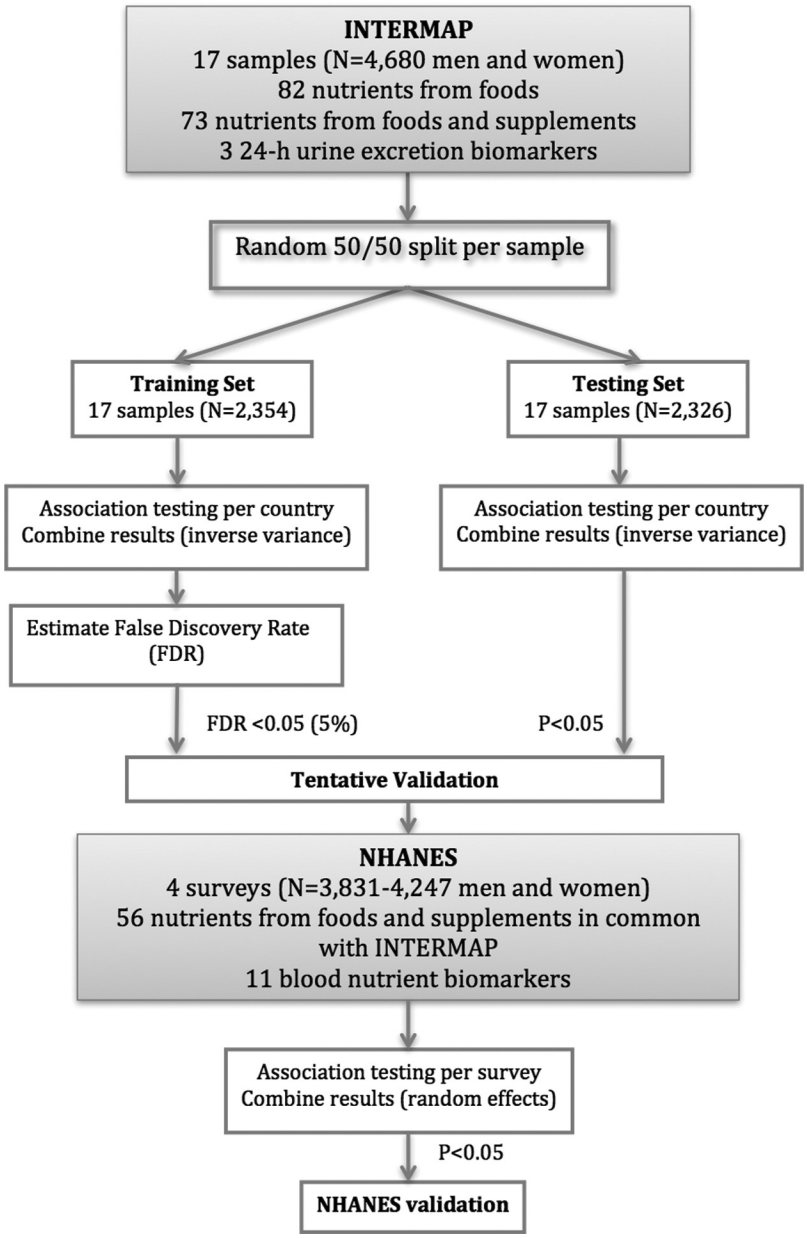

Figure 1. Procedure to systematically associate nutrients with blood pressure.

from the population-based INTERnational Collaborative Study on Macro-/Micronutrients and Blood Pressure (INTERMAP) and subsequently systematically validated our findings using independent datasets from the US National Health and Nutrition Examination Survey (NHANES).

Methods

The analytic procedure is summarized in Figure 1.

INTERMAP

INTERMAP methods have been described in detail.[6] This cross-sectional study consists of 4680 individuals (2359 men and 2321 women) aged 40 to 59 years from 17 population samples: Japan (4 samples), the People's Republic of China (3 samples), the United Kingdom (2 samples), and the United States (8 samples). Participants attended the research clinic 4 times with 2 consecutive visits, a gap averaging 3 weeks, and 2 more consecutive visits. BP, seated, was measured at each visit twice with a random zero sphygmomanometer.

An in-depth interview administered multipass 24-hour diet recall at each of the 4 visits. We recorded all foods and drinks, including supplements, consumed in the previous 24 hours. Two timed 24-hour urine collections were done to measure a range of analytes including 24-hour urinary sodium, potassium, calcium, and magnesium. At 2 visits height and weight were measured and questionnaire data were obtained on daily alcohol intake over the past 7 days and on possible confounders. Quality control measures were extensive.[6] Participants gave written informed consent.

We did a random 50:50 split of each of the INTERMAP population samples, one half for training (n=2354) and the other for testing (n=2326).

NHANES

NHANES is a cross-sectional, biannual, representative health survey of the United States population.[7] We used data from four surveys (1999–2000, 2001–2002, 2003–2004, and 2005–2006). For a proportion of individuals (n=3831–4247 per survey) 1 (in person, 1999–2000 and 2001–2002 surveys) or 2 (1 in person and 1 by telephone; 2003–2004 and 2005–2006 surveys) 24-hour food recall

questionnaires were administered using the United States Department of Agriculture (USDA) and US Department of Health and Human Services (DHHS) food recall questionnaires. Self-reported data were also collected for supplement intake, diabetes mellitus, or cardiovascular disease status, family history of hypertension, and fitness level coded as metabolic equivalent of task (MET).[8] Height, weight, and 3 to 4 seated systolic and diastolic BP measurements were also administered.

Statistical Analyses

INTERMAP

Measurements per person were averaged, for BP and nutrients, across the 4 visits; for urinary excretions, across the 2 collections. We calculated nutrient intakes from foods only and from foods plus supplements. For nutrients from foods, we systematically screened for associations of 82 nutrients and 3 urinary electrolytes/electrolyte ratio with systolic and diastolic BP using linear regression models adjusted for the following: age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease or diabetes mellitus, family history of hypertension, height, weight, and total energy intake. We also examined the associations with systolic and diastolic BP of 73 nutrients derived from both foods and supplements using the same models. We fitted each model per country and combined coefficients across countries weighted by inverse of their variance. Cross-country heterogeneity measures were computed using the I^2 statistic (proportion of between-survey over the sum of between-survey and within-survey variance).[9]

We estimated the false discovery rate to account for multiple comparisons using the training set, and we tentatively validated the most significant associations (defined as those with false discovery rate [FDR] <5%) in the INTERMAP testing set ($P<0.05$; Figure 1). The FDR is the ratio of the number of false-positive to total number of positive associations, or the percentage of findings that are drawn from the null distribution at a given significance level.[10] We use an analytic method to compute the FDR that estimates the expected number of false-positive results through permutations of the dataset and the number of total positive results by the number of dietary variables found to be significant at a specified level of significance. The procedure is as follows:

In the training cohort, the following steps were used:

(1) Screen for all dietary variables (82 nutrients and 3 urinary electrolytes/electrolyte ratio) associated with BP and collect all probability values corresponding to the coefficient of each dietary variable. Briefly, for each dietary variable, model systolic or diastolic BP as a function of the dietary variable and the other covariates included in the regression models. Then, compute the pooled per-center coefficients and probability values. Call these probability values P_{real}.
(2) Permute the phenotype per country, and redo (1) and collect probability values.
(3) Do (2) 1000 times. The set of probability values collected from (2) and (3) is P_{null}.
(4) Estimate the FDR for a given significance level. For example, for 0.05, $FDR(0.05)=((\#P_{null}< 0.05)/1000)/(\#P_{real}< 0.05)$.

For tentatively validated nutrients (FDR <5% in the training set, $P<0.05$ in the testing set), we performed a sensitivity analysis excluding individuals on special diet and recalculating coefficients as mentioned above.

We estimated statistical power to detect effects observed in this study. We assumed that variance of BP explained by the dietary variables ranged from 0.1% to 2% after adjustment for covariates documented above. At FDR <5%, we concluded that power was low to moderate (20%–80%; see Figure I in the online-only Data Supplement).[11]

We also performed multivariable analysis fitting a linear regression model in the INTERMAP training set using all dietary variables that achieved FDR <5%, adjusting for all covariates, as previously documented. We then used a stepwise method based on Akaike Information Criterion (AIC) to select dietary variables from this larger set using the INTERMAP training data and the step function in R.[12]

Pearson correlation coefficients (adjusted for age, sex, and sample) were calculated for nutrients and visualized with a heatmap, where variables are arranged using a hierarchical clustering algorithm.[13] The larger the correlation between a pair of variables, the closer in proximity they appear in the heatmap.

NHANES

We then attempted to validate in NHANES dietary variables tentatively identified as related to BP in INTERMAP and having a corresponding similar measurement in NHANES. For each tentatively validated dietary variable, we fitted a per-NHANES survey linear model estimating systolic or diastolic BP as a function of the dietary variable adjusted for a comparable set of confounders: age, sex, ethnicity, diabetes mellitus, physical activity, total energy intake, use of dietary supplements, family history of cardiovascular disease, height, and weight. Information on special diet was not available in NHANES. Where 2 data values were available for nutrient intake (2003–2004 and 2005–2006 surveys), the mean value was used for analysis. Similarly, the mean of the BP values (3–4 measurements) was used for analysis. We computed an overall estimate of nutrient–BP associations by combining coefficients from each survey using a random-effects meta-analytic method.[14] Heterogeneity measures were computed using the I^2 statistic.[9] A heatmap with correlation coefficients was plotted between nutrients using the same clustering as in INTERMAP to allow comparability of results between the 2 cohorts.

All analyses were performed using the R project software.[15]

Results

INTERMAP

Descriptive characteristics of the INTERMAP and NHANES populations are shown in Tables I and II (in the online-only Data Supplement). Figure 2 shows the distribution of probability values and effect sizes for association with systolic and diastolic BP of nutrients and urinary electrolytes in the training INTERMAP population set (a volcano plot). Twenty nutrients and 2 urinary variables were significantly associated with systolic BP (FDR <5%); 13 of them (11 nutrients and 2 urinary variables) were tentatively validated ($P<0.05$) in the INTERMAP testing dataset. These comprised positive associations with alcohol intake, 24-hour urinary sodium-to-potassium excretion ratio, and 24-hour urinary calcium, and inverse associations with non-heme iron, vegetable protein, fiber, magnesium, phosphorus, riboflavin, folacin (folic acid), glutamic acid, thiamin, and copper (Figure 2A; Table 1). For diastolic BP, 6 factors were tentatively validated (Figure 3A and Table 2). Sensitivity analysis excluding individuals on special diet showed qualitatively similar results (Table III in the online-only Data Supplement).

To ascertain independent effects, we fitted multivariable models considering multiple nutrients and potential confounders described above. Using the INTERMAP training data, we first fitted a multivariable model with all variables that were significant (FDR <5%) in our systematic scan (Figure 2 and 3). Second, again with the INTERMAP training data, we chose the nutrients which best predicted BP using the AIC selection criteria. Third, we assessed the AIC-selected model in the INTERMAP test dataset. For systolic BP, 30 dietary variables along with 10 potential confounders documented above, entered the initial model. Of these 30, 11 were selected by the AIC

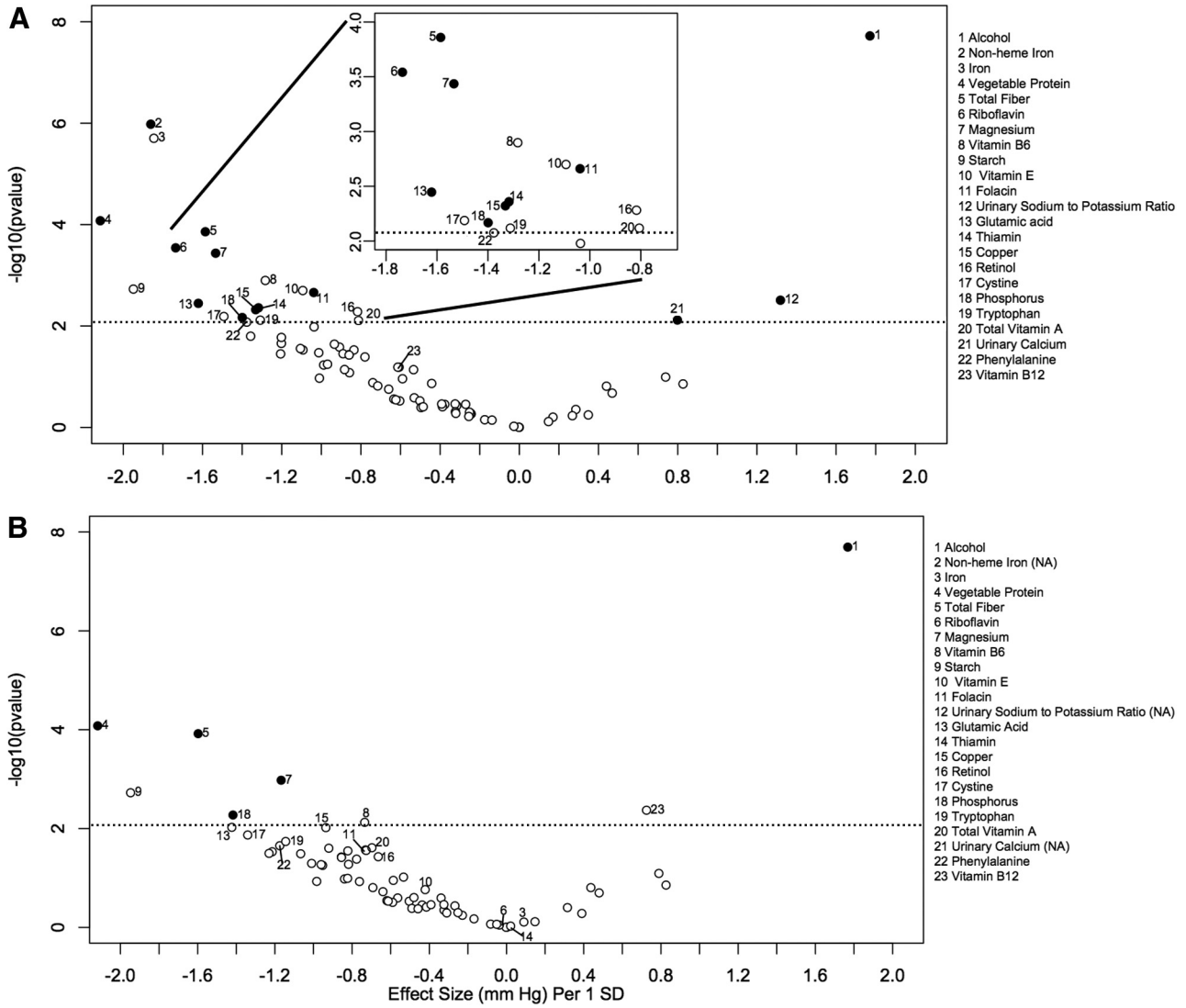

Figure 2. Volcano plot graphic showing the nutrient-wide associations with systolic blood pressure levels in INTERMAP training set for nutrients received from foods and urine excretion markers (**A**) and for nutrients received from foods and supplements (**B**). *y* axis indicates −log10(*P* value) of the adjusted linear regression coefficient for each of the nutrients. Horizontal (dotted) line represents the level of significance corresponding to FDR less than 5%, and the *x* axis shows the effect sizes (mm Hg) per 1 SD change in the nutrient variable. Filled marks represent tentatively validated nutrients in the INTERMAP testing set ($P<0.05$). Analyses are adjusted for age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease or diabetes mellitus, family history of hypertension, height, weight, and total energy intake. INTERMAP indicates International Collaborative Study on Macro-/Micronutrients and Blood Pressure. FDR indicates false discovery rate.

criterion. In the INTERMAP test dataset, only 3 of these 11 were nominally significant ($P<0.05$): alcohol, urinary calcium, and urinary sodium-to-potassium ratio (Table IV in the online-only Data Supplement). For diastolic BP, 40 dietary or supplement variables entered the initial model, and 10 were selected by AIC (Table IV in the online-only Data Supplement). In the INTERMAP test dataset, only alcohol intake retained nominal significance. Thus, although we have evidence pointing to some independent effects of nutrients for systolic BP, multivariable estimates were attenuated or lost significance compared with their main effects documented above (Figures 2 and 3).

The absolute effect sizes (INTERMAP testing set) ranged from 2.06 mm Hg lower systolic BP (phosphorus) to 0.81 mm Hg lower systolic BP (non-heme iron) per 1-SD difference in nutrient variable. The effect sizes between the INTERMAP training set and testing set were not systematically different (5 estimates were higher and 8 were lower for systolic BP). The effect sizes between nutrients obtained from foods or from food and supplements combined were similar in some cases (eg, phosphorus, magnesium, fiber; Tables 1 and 2), though for some tentatively validated nutrients from foods (eg, folacin, riboflavin, and thiamin) effect sizes incorporating supplemental and food intake were attenuated and no longer reached the FDR 5% threshold (FDR 10%, 94%, and 97% for folacin, riboflavin, and thiamin, respectively for systolic BP (Figures 2B and 3B).

NHANES

Tables 1 and 2 show the associations between the tentatively validated dietary factors with systolic BP and diastolic BP across

Table 1. Adjusted Estimated Differences in Systolic Blood Pressure Associated With Nutrients Higher by 1SD in Training, Testing and External Validation Sets

	INTERMAP Training Set		INTERMAP Testing Set		NHANES External Validation*	
Dietary Variable	Difference–mm Hg (95% CI)	*P* Value/FDR+ %	Difference–mm Hg (95% CI)	*P* Value	Difference–mm Hg (95% CI)	*P* Value
Nutrient from foods						
Alcohol	1.77 (1.15, 2.39)	2×10^{-8}/0.01	1.69 (1.07, 2.30)	7×10^{-8}	0.84 (0.43, 1.2)	5×10^{-5}
Vegetable protein	−2.12 (−3.17, −1.06)	8×10^{-5}/0.2	−1.85 (−2.92, −0.77)	7×10^{-4}	NA	NA
Riboflavin	−1.74 (−2.67, −0.78)	3×10^{-4}/0.5	−1.51 (−2.44, −0.58)	0.001	−0.89 (−1.5, −0.28)	0.004
Non-heme iron♯	−1.86 (−2.61, −1.11)	1×10^{-6}/0.01	−0.81 (−1.59, −0.03)	0.04	−0.51 (−0.92, −0.09)	0.02
Total fiber	−1.59 (−2.41, −0.77)	1×10^{-4}/0.3	−1.04 (−1.83, −0.25)	0.009	−0.66 (−1.5, 0.16)	0.1
Thiamin	−1.32 (−2.22, −0.41)	0.004/4	−0.86 (−1.6, −0.13)	0.02	−0.39 (−0.76, −0.02)	0.04
Glutamic acid	−1.62 (−2.71, −0.53)	0.004/4	−1.21 (−2.26, −0.15)	0.03	NA	NA
Magnesium	−1.53 (−2.38, −0.69)	4×10^{-4}/0.6	−1.64 (−2.48, −0.80)	1×10^{-4}	−0.97 (−1.9, 0.002)	0.05
Phosphorus	−1.40 (−2.41, −0.39)	0.007/5	−2.06 (−3.05, −1.07)	5×10^{-5}	−0.97 (−1.9, −0.07)	0.03
Copper	−1.33 (−2.26, −0.41)	0.005/4	−1.18 (−2.16, −0.19)	0.02	−0.19 (−0.57, 0.19)	0.3
Folacin	−1.04 (−1.70, −0.37)	0.002/2	−1.12 (−1.77, −0.47)	8×10^{-4}	−0.4 (−0.68, −0.13)	0.004
Urinary excretion						
Calcium	0.79 (0.21, 1.37)	0.008/5	0.97 (0.39, 1.55)	0.001	NA	NA
Sodium to potassium ratio‡	1.31 (0.44, 2.18)	0.003/3	1.96 (1.05, 0.35)	2×10^{-5}	0.61 (−0.11, 1.3)	0.1
Nutrient from foods and supplements						
Alcohol	1.77 (1.15, 2.39)	2×10^{-8}/0.01	1.68 (1.07, 2.3)	7×10^{-8}	…	…
Vegetable protein	−2.12 (−3.17, −1.06)	8×10^{-4}/0.2	−1.85 (−2.92, −0.77)	7×10^{-4}	…	…
Total fiber	−1.60 (−2.41, −0.78)	1×10^{-4}/0.3	−1.06 (−1.85, −0.27)	0.008	−0.69 (−1.5, 0.08)	0.08
Phosphorus	−1.42 (−2.41, −0.42)	0.005/4	−1.93 (−2.91, −0.95)	1×10^{-4}	−0.81 (−1.8, 0.22)	0.1
Magnesium	−1.17 (−1.87, −0.47)	0.001/2	−0.99 (−1.72, −0.26)	0.008	−0.74 (−1.7, 0.18)	0.1

Only variables that were tentatively validated in INTERMAP testing set are shown. Analyses are adjusted for age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease and diabetes mellitus, family history of hypertension, height, weight, and total energy intake (INTERMAP) and age, sex, ethnicity, diabetes mellitus, physical activity, total energy intake, supplement intake, family history of CVD, height, and weight (NHANES). INTERMAP indicates International Collaborative Study on Macro-/Micronutrients and Blood Pressure; NHANES, National Health and Nutrition Examination Survey.

*Variables that were not available in NHANES (eg, vegetable protein) were not tested. NA indicates not available.

†FDR indicates false discovery rate %.

‡Non-heme iron was not available in NHANES; total dietary iron was used as proxy. Urinary sodium-to-potassium ratio was not available in NHANES; dietary sodium-to-potassium was used as proxy.

The SDs for each variable are listed in Table I in the online-only Data Supplement.

the NHANES cohorts. Data on 5 tentatively validated variables (vegetable protein, non-heme iron, glutamic acid, 24-hour urinary calcium, and 24-hour urinary sodium-to-potassium ratio) were not available in NHANES, thus external validation for those was not possible. We used dietary sodium-to-potassium ratio and total iron as proxies for the urinary sodium-to-potassium ratio and non-heme iron, respectively. We also tested serum iron, phosphorus, and folacin as serum biomarkers of these nutrients; serum biomarkers were not available in INTERMAP. Associations of systolic BP with dietary alcohol, magnesium, phosphorus, iron, folacin, riboflavin, and thiamin were externally validated ($P<0.05$ for random effects estimate across 4 cohorts) in NHANES analyses adjusted for similar confounders as in INTERMAP (Table 1). Results for B vitamins (riboflavin, folacin) were externally validated also for diastolic BP (Table 2). The absolute effect sizes in the validation data (NHANES) ranged from 0.97 mm Hg lower systolic BP (phosphorus) to 0.39 mm Hg lower systolic BP (thiamin) per 1-SD difference in nutrient variable. Heterogeneity across cohorts was low or modest for most analyses with only fiber and magnesium showing high heterogeneity across cohorts ($I^2=78\%$; Tables V, VI, and VII in the online-only Data Supplement). Effect sizes were attenuated in the external validation sets, sometimes substantially. Among the 10 dietary variables that were assessed in both INTERMAP and NHANES for associations with systolic BP, the geometric mean of the absolute value of the coefficients was 1.49 mm Hg in the INTERMAP training set, 1.39 mm Hg in the INTERMAP testing set, and 0.64 mm Hg in NHANES.

Serum markers of dietary intake showed results in the same direction of association as for dietary variables; in some cases, the strength of association was attenuated. Phosphorus and folacin higher by 1 SD were associated with −0.32 mm Hg (95% confidence interval [CI], −0.74 to −0.10; $P=0.04$) and −0.20 mm Hg (CI, −0.61 to 0.23; $P=0.4$) differences in systolic BP, and −0.38 mm Hg (CI, −0.70 to −0.07; $P=0.02$) and −0.61 mm Hg (CI, −0.97 to −0.25; $P=0.001$) differences in diastolic BP, respectively, whereas 1 SD higher serum iron

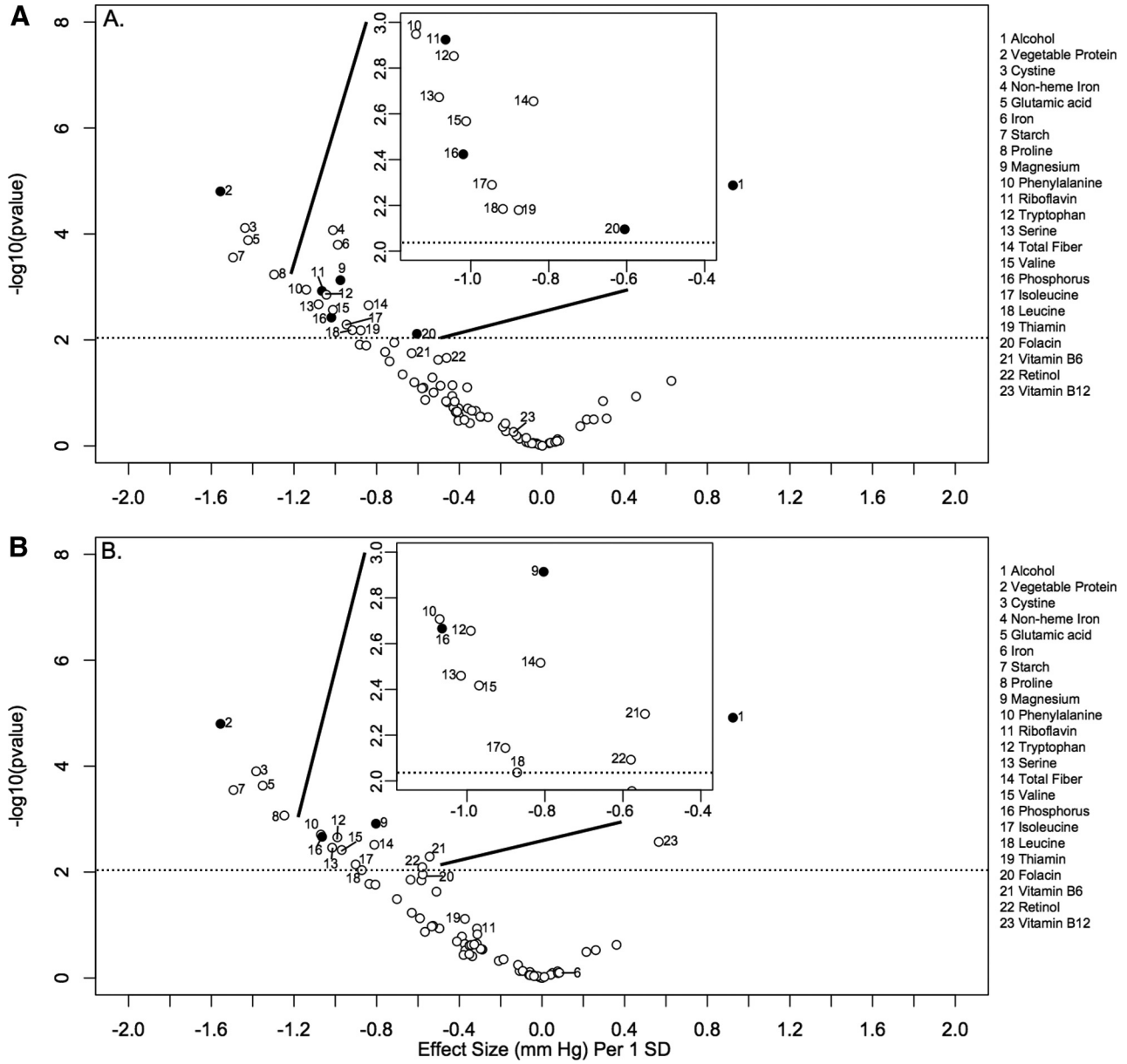

Figure 3. Volcano plot graphic showing the nutrient-wide associations with diastolic blood pressure levels in INTERMAP training set for nutrient received from foods and urine excretion markers (**A**) and for nutrients received for foods and supplements (**B**). *y* axis indicates −log10(*P* value) of the adjusted linear regression coefficient for each of the nutrients. Horizontal (dotted) line represents the level of significance corresponding to FDR *x* axis shows the effect sizes (mm Hg) per 1 SD change in the nutrient variable. Filled marks represent tentatively validated nutrients in the INTERMAP testing set ($P<0.05$). Analyses are adjusted for age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease or diabetes mellitus, family history of hypertension, height, weight, and total energy intake. INTERMAP indicates International Collaborative Study on Macro-/Micronutrients and Blood Pressure; FDR, false discovery rate.

showed nonstatistically significant associations with systolic BP (−0.03 mm Hg; CI, −0.38 to 0.45; $P=0.9$).

Correlation Patterns

Evaluation of Pearson correlations showed a dense correlation pattern for many validated nutrients (Figure 4). Fiber, copper, magnesium, and folacin appear in close proximity in the correlation heatmap with correlation coefficients >0.5 in the INTERMAP population. In NHANES, similar patterns were observed. Correlation between the same nutrients in INTERMAP and NHANES population samples showed substantial agreement (correlation coefficient $\rho=0.81$).

Discussion

Using a systematic NWAS approach, we identified and validated inverse associations between BP and intake of B vitamins (folacin, riboflavin, and thiamin) previously poorly studied or unconfirmed, as well as previously established direct associations of sodium-to-potassium ratio and alcohol with BP. Nonheme iron, phosphorus, and magnesium intake also showed inverse associations with systolic BP, as previously reported.[16–18]

Our results allow interesting comparisons with recent large-scale GWAS meta-analyses on BP.[19,20] Effect sizes of individual validated nutrients in our study are considerably larger than

Table 2. Adjusted Estimated Differences in Diastolic Blood Pressure Associated With Nutrients Higher by 1SD in Training, Testing, and External Validation Sets

	INTERMAP Training Set		INTERMAP Testing Set		NHANES External Validation*	
Dietary Variable	Difference (95% CI)	*P* Value/FDR† %	Difference (95% CI)	*P* Value	Difference (95% CI)	*P* Value
Nutrients from foods						
Alcohol	0.92 (0.51, 1.34)	1×10^{-5}/0.2	0.98 (0.56, 1.41)	4×10^{-6}	0.04 (−0.26, 0.34)	0.8
Vegetable protein	−1.56 (−2.26, −0.85)	2×10^{-5}/0.2	−0.94 (−1.67, −0.21)	0.01		NA
Riboflavin	−1.06 (−1.71, −0.42)	0.001/0.01	−0.81 (−1.45, −0.17)	0.005	−0.34 (−0.64, −0.04)	0.003
Phosphorus	−1.02 (−1.71, −0.33)	0.003/2	−1.09 (−1.78, −0.41)	0.002	−0.48 (−1.22, 0.26)	0.2
Magnesium	−0.98 (−1.54, −0.41)	7×10^{-4}/1	−0.81 (−1.39, −0.24)	0.005	−0.34 (−1.18, 0.50)	0.4
Folacin	−0.62 (−1.05, −0.16)	0.008/4	−0.57 (−1.02, −0.12)	0.01	−0.52 (−0.95, −0.08)	0.02
Nutrient from foods and supplements						
Alcohol	0.92 (0.51, 1.34)	1×10^{-5}/0.2	0.98 (0.56, 1.40)	4×10^{-6}	…	…
Vegetable protein	−1.56 (−2.26, −0.85)	1×10^{-5}/0.2	−0.94 (−1.68, −0.21)	0.01	…	…
Phosphorus	−1.06 (−1.74, −0.39)	0.002/2	−1.03 (−1.71, −0.36)	0.003	−0.33 (−1.13, 0.48)	0.4
Magnesium	−0.80 (−1.29, −0.32)	0.001/1	−0.52 (−1.02, −0.01)	0.04	−0.08 (−0.89, 0.72)	0.8

Only variables that were tentatively validated in INTERMAP testing set are shown. Analyses are adjusted for age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease and diabetes mellitus, family history of hypertension, height, weight, and total energy intake (INTERMAP) and age, sex, ethnicity, diabetes mellitus, physical activity, total energy intake, supplement intake, family history of CVD, height, and weight (NHANES). INTERMAP indicates International Collaborative Study on Macro-/Micronutrients and Blood Pressure; NHANES, National Health and Nutrition Examination Survey.

*Variables that were not available in NHANES (eg, vegetable protein) were not tested. NA indicates not available.

†FDR indicates false discovery rate %.

The SDs for each variable are listed in Table I in the online-only Data Supplement.

those reported per allele increase — in, for example, largest GWAS meta-analyses effect sizes ranged between 0.31 to 1.1 mm Hg per allele copy for SBP.[20] Notably, the genetic risk score of 29 genes was associated with 1.64 mm Hg higher SBP per SD of the genetic risk score,[20] an effect size similar to that found for several individual validated nutrients in the present study. In addition, some of the nutrients validated in our study are relevant to genetic variants discovered from GWAS meta-analyses. For example, we have shown that iron intake is inversely associated with systolic BP, and GWAS studies have identified a low penetrance allele in the hemochromatosis locus for hereditary hemochromatosis, a condition characterized by

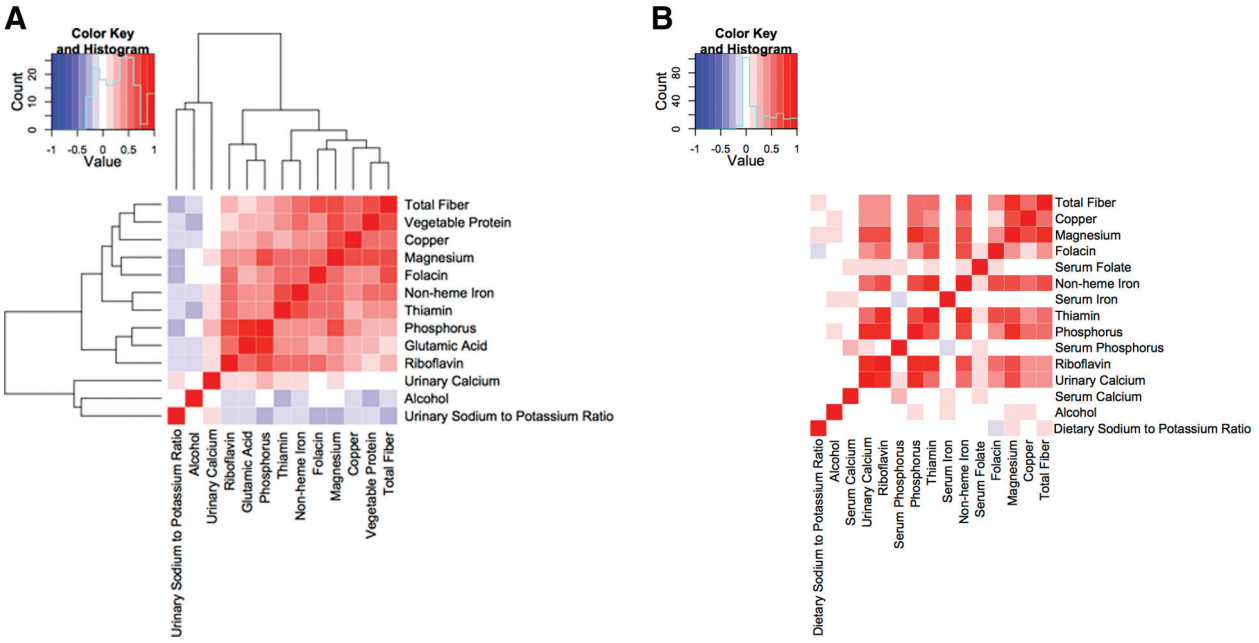

Figure 4. Pearson coefficient correlation heatmap showing all nutrients and potential confounders examined in (**A**) INTERMAP total population and (**B**) NHANES total population. Nutrients are clustered according to a hierarchical clustering algorithm in INTERMAP, grouping highly correlated factors closer to one another. For NHANES, the clustering of INTERMAP samples has been used. Correlation coefficients are adjusted for age, sex, and sample (INTERMAP)/cohort (NHANES). INTERMAP indicates International Collaborative Study on Macro-/Micronutrients and Blood Pressure; NHANES, National Health and Nutrition Examination Survey.

excessive intestinal absorption of dietary iron. Similarly, polymorphisms in the MTHFR gene, encoding an enzyme involved in homocysteine metabolism, have been reported to be associated with BP in GWAS.[20] Homocysteine levels are associated with intake of B vitamins[21]; here we validated associations between the B vitamins folate, riboflavin, and thiamin with systolic BP.

Few data have hitherto been available on relationships of B vitamins with BP. Higher total folate intake was associated with a decreased risk of incident hypertension in the large Nurses Health Study.[22] Riboflavin is a cofactor for MTHFR, and there is some evidence for interaction among riboflavin status, folacin status, and genotype in determining plasma homocysteine.[23,24] Thiamin has been little studied in relation to BP[22]; a small randomized controlled trial reported lower BP levels after thiamin supplementation,[25] and higher BP has been reported in individuals with beriberi (thiamin deficiency).[26] However, the fact that intake of the B vitamins from foods and supplements was not associated with BP in the INTERMAP data, in contrast to intake from foods only, may argue against a causal role; effects of other possibly causal nutrients may be embedded in the dense correlation pattern of these dietary factors. Moreover, the B vitamin associations did not retain nominal significance in the multivariable models for either systolic or diastolic BP in the INTERMAP test data. Nonetheless, at least for folacin and diastolic BP, results were also replicated in NHANES based on the serum biomarker, which reflects both dietary and supplemental intakes.

The NWAS approach presented has advantages. Efforts to associate single nutrients with disease risk are susceptible to selection effects and may create spurious claims of association.[27–29] Small effects such as those reported here on BP are especially susceptible to bias.[30,31] The systematic evaluation of multiple nutrients with proper adjustment for multiplicity of comparisons overcomes the limitation of selective reporting, whereas internal and external independent validation of results adds to the robustness of the associations.[31] However, many of the identified associations pertain to nutrients that are strongly correlated, and thus their independent effects are difficult to decipher. Moreover, etiologic interpretation of results requires consideration of previous evidence (observational or experimental) and further prospective validation of novel identified associations. Finally, although the focus of this study is on diet and BP, the methodology described is more generally applicable to a wide range of exposures and cardiovascular, metabolic, or other phenotypes.[4,5]

Our work has limitations. First, although we propose here a systematic approach that can give a list of BP correlates with strong statistical support, further scrutiny to assess which among them are most important requires other designs (eg, causal inference modeling and randomized trials). In addition, further studies are required to investigate the effect of other potential confounders, because associations between BP and some nutrients may require adjustment for different or additional confounders—our approach used the same set of covariates for all dietary variables. Second, some associations may have been missed as a result of limited statistical power. Third, the available confounders and nutrient measurements in INTERMAP and NHANES were not identical, though the overlap in definitions and availability of measurements was high. Standardization of datasets is a key aspect for attention for future efforts to validate nutritional and other associations across multiple studies. Fourth, the associations reflect cross-sectional analyses, limiting the ability to make causal interpretations. Fifth, the associations that we identified were substantially smaller in NHANES. This may have to do both with precision of measurements (generally much higher in INTERMAP where 4 in-depth 24-hour recall data were available rather than one or two 24-hour dietary recalls in NHANES), but may also reflect the shrinkage of effects anticipated with external validation. Some of the serum biomarkers used, such as phosphorus, are imperfect biomarkers of dietary intake and may reflect physiological differences between individuals as well as differences in dietary intake of nutrients. Finally, despite the comprehensive adjustment for confounders in our analyses, we cannot exclude the possibility of residual confounding by related dietary or other variables.

Despite these caveats, our systematic evaluation provides new knowledge on the complex array of nutritional correlates of systolic and diastolic BP. The complex pattern highlights why traditional approaches of testing 1 association at a time may be suboptimal compared with an inclusive NWAS paradigm. Some of the identified correlates may represent potentially causative associations; these need to be probed in further observational and interventional studies.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Raised blood pressure (BP) is a major risk factor for coronary heart disease and stroke. Risk increases in graded fashion across the BP range, with substantial risk of death and disability attributed to raised BP at normal and high-normal BPs, below current treatment thresholds. Thus, nonpharmacologic as well as pharmacological approaches are needed to deal with the population-wide BP problem. Dietary habits are known to be related to high BP, but the role of many nutrients is unclear despite intensive research efforts. We used a nutrient-wide association study design to systematically test and validate multiple associations between a wide range of nutrients and BP. We initially tested associations of 82 nutrients and 3 urine electrolytes/electrolyte ratios with BP in a 50% random sample of the population-based study, the International Collaborative Study on Macro-/Micronutrients and Blood Pressure (INTERMAP). Significant findings were validated in the remainder 50% INTERMAP population and among participants in the National Health and Nutrition Examination Survey (NHANES). We identified inverse associations between BP and intake of B vitamins (folacin, riboflavin, thiamin) previously poorly studied, and reidentified sodium-to-potassium ratio and alcohol with BP (direct), and non-heme iron, phosphorus, and magnesium intake with systolic BP (inverse). Our results highlight a complex array of nutritional correlates with BP and emphasize why traditional approaches of testing 1 association at a time may be suboptimal compared with our inclusive nutrient-wide association study paradigm. Findings for BP and B vitamins may represent potentially causative associations, which need to be probed in further observational and interventional studies.

SUPPLEMENTAL MATERIAL

A Nutrient-Wide Association Study on Blood Pressure

Short title: A nutrient-wide association study

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* and #: equal contribution for first and senior authors

Online Supplementary Tables 1 – 7

Online Supplementary Figure 1

Online Supplementary Tables

Supplementary Table 1. Descriptive characteristics of INTERMAP study participants by country

Variable	China (N=1145)		Japan (N=839)		UK (N=501)		US (N=2195)	
	Mean or %	SD	Mean or %	SD	Mean	SD	Mean	SD
Age (years)	49.37	5.31	48.96	5.80	49.15	5.61	49.14	5.39
Height (m)	1.61	0.09	1.59	0.08	1.69	0.09	1.68	0.10
Weight (kg)	61.22	10.15	58.93	10.01	78.22	15.25	82.25	19.56
Body mass index (kg/m2)	23.43	2.91	23.13	3.36	27.46	4.64	28.90	5.92
Males	50.0%		50.4%		46.9%		49.7%	
Previous heart disease, stroke or diabetes	11.4%		7%		10.8%		15.6%	
Family history of hypertension	46.1%		35.5%		48.3%		67.9%	
Systolic BP	117.24	13.79	121.26	17.42	120.40	14.55	118.60	13.89
Diastolic BP	73.64	10.30	73.19	10.22	77.29	9.93	73.41	9.68
Urinary excretion								
Urinary sodium to potassium ratio	4.23	1.24	6.31	2.83	2.23	0.80	3.04	1.20
Urinary calcium (mmol/24h)	4.30	1.74	4.47	2.09	4.04	1.96	4.21	2.17
Urinary magnesium (mmol/24h)	3.22	0.95	4.08	1.27	3.71	1.13	4.25	1.58
Nutrients from foods								
Estimated Dietary Total Protein	69.65	16.41	59.59	16.86	68.16	18.82	73.13	23.44
Alcohol (gm)	17.02	22.58	8.62	21.37	14.73	19.20	6.95	13.69
Animal protein (mg/day)	45.15	16.00	12.83	13.22	51.35	20.73	55.94	23.62
Beta-Carotene (mcg.day)	2978.93	2016.87	2399.88	2066.96	2207.40	1711.44	3941.94	3769.61
Caffeine (mg/day)	134.52	97.25	13.09	31.21	258.93	150.47	260.40	258.27
Calcium (mg/day)	606.12	221.24	302.50	142.45	933.04	319.15	791.30	371.61
Cholesterol (mg/day)	402.50	163.81	181.67	181.44	261.78	133.44	296.33	159.87
Copper (mg/day)	1.36	0.41	2.37	0.72	1.37	0.45	1.46	0.57
Total energy intake (kcal/day)	2038.64	449.05	2035.84	576.77	2167.78	631.80	2244.20	698.70
Folacin (mcg/day)	360.72	127.02	293.57	135.40	298.08	108.69	290.38	128.53
Iron (mg/day)	10.66	2.85	15.81	5.68	13.08	4.22	16.88	7.09
Magnesium (mg/day)	268.97	65.99	308.23	115.26	319.62	93.82	318.66	111.91
Myristoleic acid (g/day)	0.10	0.07	0.01	0.01	0.20	0.15	0.07	0.09
Palmitoleic acid (g/day)	1.01	0.40	0.542309297	0.44	1.50	0.75	1.55	0.85
Oleic acid (g/day)	18.31	6.18	15.35	8.15	24.75	9.99	29.75	12.59
Gadoleic acid (g/day)	0.61	0.31	0.32	0.30	0.48	0.32	0.19	0.14

Erucic acid (g/day)	0.35	0.29	2.27	3.28	0.32	0.27	0.05	0.10
Niacin (mg)	16.29	5.15	13.77	5.36	22.99	12.69	25.14	8.64
Pantothenic Acid (mg)	5.96	1.42	4.44	1.56	5.44	1.68	4.92	2.01
Linoleic acid (g/day)	11.26	3.86	12.16	6.64	13.30	6.30	15.82	7.31
Linolenic acid (g/day)	1.84	0.73	1.23	0.91	1.39	0.64	1.69	0.84
PFA 18:4 (gm	0.08	0.07			0.00	0.01	0.00	0.02
Arachidonic acid (g/day)	0.16	0.06	0.04	0.04	0.18	0.11	0.15	0.10
Eicosapentaenoic acid (g/day)	0.39	0.28	0.02	0.04	0.12	0.16	0.05	0.10
Docosapentaenoic acid (g/day)	0.10	0.08	0.00	0.00	0.09	0.06	0.02	0.04
Docosahexaenoic acid (g/day)	0.66	0.39	0.01	0.02	0.15	0.20	0.10	0.19
Phosphorus (mg/day)	1134.43	282.34	878.92	306.64	1392.29	410.37	1295.33	441.41
Potassium (mg/day)	2786.88	700.87	1850.46	582.62	3355.49	901.08	2909.41	1006.63
Total Protein (g/day)	80.71	19.86	63.00	19.70	83.47	25.13	84.92	28.40
Retinol (mcg/day)	373.13	706.06	98.10	171.71	468.65	451.76	467.95	527.50
Riboflavin (mg)	1.40	0.41	0.70	0.25	1.85	0.73	2.00	0.76
Selenium (mcg/day)	171.05	74.62	33.93	13.64	94.57	37.94	131.48	65.17
SFA 4:0 (gm)	0.19	0.16			0.58	0.49	0.46	0.37
Caproic acid (g/day)	0.12	0.10	0.00	0.00	0.36	0.30	0.23	0.19
Caprylic acid (g/day)	0.08	0.07	0.00	0.01	0.27	0.21	0.22	0.19
Capric acid (g/day)	0.15	0.13	0.01	0.01	0.58	0.45	0.43	0.30
Lauric acid (g/day)	0.22	0.20	0.06	0.09	1.30	0.95	1.00	1.06
Myristic acid (g/day)	1.07	0.54	0.26	0.19	3.14	1.88	2.27	1.35
Palmitic acid (g/day)	9.10	2.92	7.60	3.87	15.55	6.63	15.16	6.46
Stearic acid (g/day)	3.45	1.28	2.66	1.80	7.70	3.48	7.58	3.45
Arachidic acid (g/day)	0.20	0.08	0.26	0.16	0.25	0.14	0.03	0.06
Behenic acid (g/day)	0.08	0.06	0.56	0.47	0.22	0.20	0.04	0.08
Starch (g/day)	179.22	53.83	282.88	90.41	145.01	48.81	125.11	44.82
Sugar (g/day)	93.66	27.02	43.97	30.88	107.76	42.51	148.78	65.54
Total Fibre (gm)	15.63	4.77	28.14	9.50	25.47	9.22	19.11	7.87
Thiamin (mg)	0.92	0.25	1.05	0.33	1.93	1.51	1.89	0.67
Omega-3 polyunsaturates (g/day)	3.07	1.12	1.25	0.92	1.76	0.80	1.87	0.93
Omega-6 polyunsaturates (g/day)	11.45	3.88	12.20	6.65	13.49	6.33	15.97	7.35
Dietary Vitamin E (mg/day)	10.02	3.24	10.80	4.64	9.73	4.65	9.99	5.05
Dietary Total Carbohydrate (g/day)	272.89	63.56	326.85	99.44	252.77	76.60	273.90	91.50
Dietary Total Fat (g/day)	56.80	16.65	45.94	20.37	80.96	31.74	84.35	33.94

Dietary Total MFA (g/day)	20.60	6.73	18.53	8.65	27.26	10.98	31.88	13.46
Dietary Total PFA (g/day)	14.58	4.63	13.49	6.99	15.24	6.87	17.94	8.11
Dietary Total SFA (g/day)	14.98	5.13	11.51	5.87	29.94	13.63	28.03	12.54
Total trans-fatty acids (g/day)	0.99	0.67	0.42	0.80	3.34	1.93	5.03	2.83
Dietary Total Vitamin A (RE)	870.11	767.52	496.88	392.07	838.24	538.13	1124.94	843.74
Trans-octadecenoic acid (mg)	0.82	0.61	0.29	0.64	2.41	1.37	4.28	2.49
Trans-octadecenoic (mg)	0.15	0.07	0.09	0.16	0.50	0.45	0.64	0.35
Vegetable Protein (g/day)	35.56	8.43	50.19	15.65	32.12	10.74	28.02	10.77
Vitamin A (IU/day)	6208.38	4011.10	4326.81	3518.85	5240.96	3242.98	8141.09	6634.26
Vitamin B12 (mcg)	9.03	5.63	1.00	1.55	4.76	2.63	5.06	5.31
Vitamin B6 (mg)	1.29	0.38	1.57	0.57	2.07	0.79	1.95	0.76
Vitamin C	128.61	76.15	77.71	40.65	86.30	54.80	110.53	76.40
Sum of EPA, DPA and DHA (gr/day)	1.15	0.73	0.02	0.05	0.36	0.38	0.18	0.31
Alanine (g/day)	4.08	1.07	3.16	1.14	3.81	1.26	4.07	1.48
Arginine (g/day)	4.83	1.25	3.60	1.36	4.38	1.41	4.70	1.69
Spartic acid (g/day)	7.49	1.91	5.19	1.98	7.25	2.21	7.22	2.53
Cystine (g/day)	1.26	0.28	1.33	0.38	1.15	0.34	1.14	0.37
Glutamic acid (g/day)	14.19	3.19	14.97	5.09	16.83	4.88	16.54	5.34
Glycine (g/day)	3.46	0.94	2.74	1.02	3.43	1.15	3.63	1.37
Histidine (g/day)	2.53	0.73	1.48	0.53	2.30	0.75	2.38	0.85
Isoleucine (g/day)	3.56	0.89	2.54	0.84	3.83	1.18	3.86	1.33
Leucine (g/day)	6.21	1.52	4.86	1.53	6.38	1.95	6.57	2.24
Lysine (g/day)	5.27	1.50	2.84	1.36	5.41	1.84	5.69	2.12
Methionine (g/day)	1.89	0.50	1.09	0.41	1.84	0.60	1.93	0.69
Phenylalanine (g/day)	3.57	0.83	3.07	0.95	3.68	1.09	3.69	1.22
Proline (g/day)	4.50	1.07	3.93	1.89	5.69	1.69	5.45	1.83
Threonine (g/day)	3.16	0.82	2.28	0.82	3.20	1.01	3.28	1.15
Tryptophan (g/day)	0.95	0.23	0.92	0.30	1.01	0.30	0.99	0.34
Tyrosine (g/day)	2.74	0.68	2.14	0.71	2.90	0.88	2.96	1.02
Valine (g/day)	4.24	1.03	3.36	1.12	4.30	1.30	4.30	1.46
Nutrients from foods and supplements								
Alanine (gm)	4.09	1.08	3.16	1.14	3.82	1.28	4.07	1.48
Potassium (mg)	2790.67	702.62	1850.46	582.62	3356.33	901.11	2928.92	1011.98
Alcohol (gm)	15.96	22.47	8.96	22.07	13.42	19.54	6.83	15.35
Proline (gm)	4.50	1.08	3.93	1.89	5.69	1.70	5.45	1.83

Animal protein (gm)	45.15	16.00	12.83	13.22	51.35	20.73	55.94	23.62
Protein (gm)	80.87	20.05	63.00	19.70	83.67	25.67	84.94	28.40
Arginine (gm)	4.84	1.26	3.60	1.36	4.38	1.41	4.70	1.69
Retinol (mcg)	390.69	758.35	98.10	171.71	621.73	587.75	873.94	1068.05
Aspartic acid (gm)	7.51	1.93	5.19	1.98	7.26	2.24	7.22	2.53
Riboflavin (mg)	1.63	1.24	0.70	0.29	2.87	13.85	5.82	13.98
Beta-Carotene (mcg)	3046.47	2204.81	2399.88	2066.96	2354.19	2159.80	4543.74	4475.66
Selenium (mcg)	171.09	74.62	33.93	13.64	96.39	39.44	141.77	73.99
Caffeine (mg)	135.88	97.33	13.09	31.21	258.93	150.47	260.40	258.27
Serine (gm)	3.55	0.85	2.99	0.93	3.77	1.13	3.80	1.26
Calcium (mg)	614.62	233.73	303.22	144.01	955.81	355.94	937.71	498.05
SFA 6:0 (gm)	0.12	0.10	0.00	0.00	0.36	0.30	0.23	0.19
Cholesterol (mg)	402.50	163.81	181.67	181.44	262.62	133.77	296.42	159.85
SFA 8:0 (gm)	0.08	0.07	0.00	0.01	0.27	0.21	0.22	0.19
Copper (mg)	1.36	0.41	2.37	0.72	1.38	0.47	2.13	5.25
SFA 10:0 (gm)	0.15	0.13	0.01	0.01	0.58	0.45	0.43	0.30
Cystine (gm)	1.27	0.28	1.33	0.38	1.15	0.35	1.14	0.37
SFA 12:0 (gm)	0.22	0.20	0.06	0.09	1.30	0.95	1.00	1.06
Glutamic acid (gm)	14.23	3.24	14.97	5.09	16.84	4.90	16.55	5.34
SFA 14:0 (gm)	1.07	0.54	0.26	0.19	3.14	1.88	2.27	1.35
Glycine (gm)	3.47	0.95	2.74	1.02	3.45	1.24	3.63	1.37
SFA 16:0 (gm)	9.10	2.92	7.60	3.87	15.57	6.64	15.17	6.46
Histidine (gm)	2.54	0.73	1.48	0.53	2.30	0.76	2.38	0.85
Iron (mg)	10.82	3.57	16.53	21.33	14.31	8.28	23.21	32.59
SFA 18:0 (gm)	3.45	1.28	2.66	1.80	7.70	3.48	7.58	3.45
Isoleucine (gm)	3.57	0.90	2.54	0.84	3.84	1.20	3.86	1.33
SFA 20:0 (gm)	0.20	0.08	0.26	0.16	0.25	0.14	0.03	0.06
PFA 22:5 (gm)	0.05	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Leucine (gm)	6.23	1.54	4.86	1.53	6.39	1.97	6.57	2.24
SFA 22:0 (gm)	0.08	0.06	0.56	0.47	0.22	0.20	0.04	0.09
PFA 20:5 (gm)	0.17	0.11	0.01	0.02	0.00	0.00	0.02	0.05
Lysine (gm)	5.28	1.51	2.84	1.36	5.43	1.87	5.70	2.13
Magnesium (mg)	269.50	66.16	308.23	115.26	325.73	112.01	359.01	162.26
Starch (gm)	179.22	53.83	282.88	90.41	145.01	48.81	125.13	44.82
Methionine (gm)	1.90	0.51	1.09	0.41	1.85	0.61	1.93	0.69

Total fibre (gr)	15.63	4.77	28.14	9.50	25.47	9.22	19.17	7.91
MFA 14:1 (gm)	0.10	0.07	0.01	0.01	0.20	0.15	0.07	0.09
Threonine (mg)	3.17	0.82	2.28	0.82	3.21	1.02	3.28	1.15
MFA 16:1 (gm)	1.01	0.40	0.54	0.44	1.52	0.76	1.55	0.85
Total alpha-toc eq (mg)	12.62	16.88	11.28	9.17	12.42	14.45	70.82	143.50
MFA 18:1 (gm)	18.31	6.18	15.35	8.15	24.78	10.00	29.76	12.59
Total Carbohydrate (gm)	273.34	63.65	326.85	99.44	252.80	76.59	274.05	91.49
MFA 20:1 (gm)	0.61	0.31	0.32	0.30	0.50	0.34	0.19	0.15
Total Fat (gm)	56.80	16.65	45.94	20.37	81.24	31.81	84.39	33.94
MFA 22:1 (gm)	0.35	0.29	2.27	3.28	0.33	0.28	0.05	0.11
Total MFA (gm)	20.60	6.73	18.53	8.65	27.33	11.01	31.89	13.47
Niacin (mg)	16.41	5.28	13.82	5.43	25.19	19.43	39.20	54.74
Total PFA (gm)	14.58	4.63	13.49	6.99	15.29	6.89	17.96	8.12
Linoleic acid (gm)	11.26	3.86	12.16	6.64	13.31	6.30	15.83	7.31
Total fatty acids (gm)	14.98	5.13	11.51	5.87	29.97	13.63	28.03	12.54
Linolenic acid (gm)	1.84	0.73	1.23	0.91	1.40	0.64	1.69	0.84
Vitamin A (mg)	899.02	837.56	496.88	392.07	966.39	735.18	1631.23	1398.19
Eicosapentaenoic acid (gm)	0.16	0.06	0.04	0.04	0.18	0.11	0.15	0.10
Tryptophan (gm)	0.95	0.23	0.92	0.30	1.01	0.30	0.99	0.34
Docosapentaenoic acid (gm)	0.39	0.28	0.02	0.04			0.05	0.11
Tyrosine (gm)	2.74	0.69	2.14	0.71	2.90	0.90	2.97	1.02
Docosahexaenoic acid (gm)	0.66	0.39	0.01	0.02	0.16	0.21	0.11	0.20
Valine (gm)	4.24	1.04	3.36	1.12	4.31	1.32	4.30	1.46
Phenylalanine (gm)	3.58	0.85	3.07	0.95	3.68	1.10	3.70	1.22
Vegetable protein (gm)	35.56	8.43	50.19	15.65	32.12	10.74	28.02	10.77
Phosphorous (mg)	1136.41	283.41	878.92	306.64	1394.55	411.17	1318.64	450.61
Vitamin A (IU)	6380.37	4428.95	4326.81	3518.85	5881.70	4082.31	10672.53	8823.85
Thiamin (mg)	3.14	11.57	1.36	2.14	4.70	30.87	6.20	15.71
Vitamin B12 (mcg)	27.69	185.32	1.00	1.56	5.34	6.64	19.20	78.55
Vitamin B6 (mg)	2.01	5.85	1.75	2.66	2.66	5.70	7.15	20.19
Vitamin C (mg)	138.49	100.45	79.80	44.31	108.09	111.71	297.13	528.06
Folate (mcg)	363.02	130.07	293.57	135.40	323.08	159.68	409.35	264.08
Omega 3 (mg)	3.07	1.12	1.25	0.92	1.79	0.83	1.88	0.94
Omega 6 (mg)	11.45	3.88	12.20	6.65	13.50	6.33	15.98	7.35

Supplementary Table 2. Descriptive characteristics of NHANES cohorts

Variable	**1999-2000**		**2001-2002**		**2003-2004**		**2005-2006**	
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
Age (years)	41.76	14.9	42.44	14.86	43.54	15.52	44.3	15.88
Sex (Males)	47.90%		47.60%		48.30%		46.80%	
Ethnicity								
Non Hispanic White	70.60%		71.80%		73.20%		71.70%	
Mexican American	6.60%		7.80%		8.50%		8.90%	
Non Hispanic Blacks	9.90%		10%		10.30%		10.40%	
Other Hispanic	8.80%		5.90%		3.50%		3.70%	
Other	4.20%		4.50%		4.40%		5.40%	
Diastolic BP	71.86	11.73	71.33	12	70.61	11.46	69.46	12.03
Systolic BP	117.82	14.63	117.65	14.15	118.1	13.88	117.88	14.07
Self-reported disease								
Cardiovascular disease, %	9.4		10.4		12.2		11.5	
Diabetes	4.1		5.4		6.5		6.2	
Family history of heart disease	29.7		32		32.1		14.9	
Body Mass Index (kg/m2)	27.64	6.18	27.79	6.28	28.01	6.12	28.23	6.32
Total energy intake (kg/day)	2252.22	1044.99	2270.72	1045.95	2234.94	899.13	2155.54	862.92
Physical Activity								
Inactivity	21.6		17.2		14.8		13.7	
Low	27		27.8		31.7		29.6	
Medium	19.8		19.1		20.2		20.8	
High	31.5		35.9		33.3		36	
Calcium (mg)	860.53	607.28	890.84	611.72	913.42	520.08	952.59	511.81
Alcohol (gm)	8.27	33.12	8.81	29.29	8.03	24.41	7.73	20.21
Iron (mg)	15.21	9.55	15.36	9.62	15.81	7.91	15.97	8.1
Magnesium (mg)	272.87	151.28	267.05	141.49	266.96	120.57	281.73	126.13
MFA 16:1 (Hexadecenoic) (gm)	1.48	1.14	1.28	0.96	1.3	0.8	1.23	0.76

Phosphorus (mg)	1283.59	653.2	1315.1	685.55	1319.53	571.55	1316.3	568.73
Carbohydrate (gm)	276.81	138.72	276.94	135.29	267.74	115.31	260.34	110.73
Vitamin A, RAE (mcg)			604.51	742.87	604.32	512.65	627.39	497.49
Dietary fiber (gm)	14.76	10.32	15.06	9.61	14.92	7.94	15.16	7.94
Copper (mg)	1.23	0.86	1.26	1.18	1.21	0.8	1.3	0.82
Folic acid (mcg)			206.39	207.39	205.55	168.03	204.62	170.63
Riboflavin (Vitamin B2) (mg)	1.97	1.14	2.19	1.24	2.26	1.1	2.24	1.12
Thiamin (Vitamin B1) (mg)	1.63	0.94	1.6	0.94	1.67	0.79	1.66	0.86
Vitamin B6 (mg)	1.8	1.19	1.82	1.22	1.86	0.99	1.97	1.12
Iron (ug/dL)	89.67	37.46	88.22	38.49	81.24	36.35	78.81	35.97
Phosphorus (mg/dL)	3.52	0.58	3.82	0.6	3.88	0.59	3.91	0.62
Folate, serum (ng/mL)	16.27	10.17	14.56	8.96	14.14	13.74	14.23	9.4
Dietary Sodium/Potassium Ratio	1.43	0.7	1.4	0.75	1.37	0.53	1.39	0.55

Supplementary Table 3. Adjusted estimated differences in systolic and diastolic blood pressure associated with nutrients received from foods and supplements variables higher by 1SD in INTERMAP testing set excluding individuals on special diet. Only variables that were tentatively validated in INTERMAP testing set are shown.

	INTERMAP Testing set	
Dietary variable	Difference (95% CI)	p value
Systolic Blood Pressure		
Nutrients from foods		
Alcohol	3.5 (2.2, 4.8)	10-7
Vegetable Protein	-3.8 (-6.0, -1.6)	10-3
Riboflavin	-2.2 (-3.8, -0.55)	0.008
Non-heme iron	-0.75 (-1.72, 0.22)	0.13
Total Fibre	-0.79 (-1.69, 0.11)	0.08
Thiamin	-4.0 (-6.0, -2.0)	10-4
Glutamic acid	-2.2 (-3.8, -0.57)	0.008
Magnesium	2.1 (1.2, 2.9)	10-6
Phosphorus	-1.9 (-3.4, -0.42)	0.01
Copper	-2.1 (-3.5, -0.74)	0.003
Folacin	-1.1 (-2.3, -0.03)	0.04
Urinary excretion		
Calcium	0.90 (0.28,1.53)	0.004
Sodium to potassium ratio♯	1.75 (0.79,2.71)	10-3
Nutrient from foods and supplements		
Alcohol	1.62 (0.95,2.29)	10-6
Vegetable Protein	-1.58 (-2.81,-0.34)	0.01
Total Fibre	-0.81 (-1.71,0.09)	0.08
Phosphorus	-1.62 (-2.74,-0.50)	0.005
Magnesium	-0.92 (-1.91,0.06)	0.07
Diastolic Blood Pressure		
Nutrients from foods		
Alcohol	1.00 (0.54,1.46)	10-5
Vegetable Protein	-1.04 (-1.89,-0.19)	0.02
Riboflavin	-0.91 (-1.65,-0.17)	0.02
Phosphorus	-1.01 (-1.79,-0.23)	0.01
Magnesium	-0.84 (-1.50,-0.17)	0.01
Folacin		0.02
Nutrient from foods and supplements		
Alcohol	1.00 (0.54,1.46)	10-5
Vegetable Protein	-1.04 (-1.89,-0.19)	0.02
Phosphorus	-0.94 (-1.73,-0.16)	0.02
Magnesium	-0.64 (-1.32,0.04)	0.06

Analyses are adjusted for age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease and diabetes, family history of hypertension, height, weight and total energy intake. The SDs for each variable are listed in Tables 1 and 2.

Supplementary Table 4. Multivariable analysis in INTERMAP training and testing set. Only variables selected based on FDR<5% and AIC criterion are shown.

	INTERMAP training set		INTERMAP testing set	
	Effect size per SD	P value	Effect size per SD	P value
Systolic blood pressure				
Alcohol	1.46 (0.89,2.04)	10^{-7}	1.39 (0.74,2.04)	10^{-5}
Urinary calcium	0.78 (0.21,1.36)	0.008	1.05 (0.46,1.63)	10^{-3}
Urinary sodium to potassium ratio	0.91 (0.08,1.75)	0.031	1.53 (0.66,2.40)	0.001
Phosphorus (diet and supplement)	1.82 (0.22,3.42)	0.026	-1.41 (-3.08,0.27)	0.099
Retinol	-0.61 (-1.22,-0.01)	0.047	-0.15 (-0.75,0.46)	0.637
Magnesium (diet and supplement)	-0.71 (-1.52,0.11)	0.089	-0.21 (-1.23,0.81)	0.687
Vitamin B6 (diet and supplement)	-0.67 (-1.28,-0.06)	0.032	0.08 (-0.52,0.68)	0.795
Nonheme iron	-6.26 (-12.99,0.47)	0.068	-0.73 (-6.70,5.23)	0.810
Vitamin B12 (diet and supplement)	0.67 (0.23,1.12)	0.003	0.05 (-0.64,0.74)	0.885
Iron	5.39 (-1.58,12.35)	0.129	0.42 (-5.58,6.42)	0.891
Phenylalanine	-1.77 (-3.34,-0.19)	0.028	-0.02 (-1.63,1.58)	0.978
Diastolic blood pressure				
Alcohol	0.64 (0.25,1.03)	0.001	0.94 (0.49,1.39)	10^{-5}
Phosphoprus	0.97 (-0.12,2.06)	0.081	-1.19 (-2.31,-0.08)	0.035
Leucine	3.19 (-0.73,7.11)	0.111	2.55 (-1.96,7.06)	0.267
Nonheme iron	-5.02 (-9.95,-0.09)	0.046	2.19 (-2.07,6.46)	0.313
Glutamic acid	-1.18 (-2.58,0.22)	0.099	-0.77 (-2.29,0.75)	0.319
Iron	4.56 (-0.50,9.62)	0.077	-2.14 (-6.39,2.10)	0.322
Vitamin B6 (diet and supplement)	-0.52 (-0.91,-0.13)	0.009	0.18 (-0.22,0.59)	0.371
Retinol (diet and supplement)	-0.56 (-1.02,-0.10)	0.016	-0.17 (-0.57,0.24)	0.418
Valine	-3.58 (-7.34,0.18)	0.062	-1.44 (-5.84,2.97)	0.522
Vitamin B12 (diet and supplement)	0.52 (0.21,0.82)	0.001	-0.15 (-0.62,0.32)	0.525

Analyses are adjusted for age, sex, reported special diet, use of dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease and diabetes, family history of hypertension, height, weight, and total energy intake. The SDs for each variable are listed in Tables 1 and 2.

Supplementary Table 5. Heterogeneity estimates using random effects meta-analysis across the INTERMAP training set

	Systolic Blood Pressure			Diastolic Blood Pressure		
	Q	p value (Q)	I2	Q	p value (Q)	I2
Nutrients from foods						
Alcohol	17.68	0.34	0.00	18.28	0.31	1.51
Animal Protein	14.76	0.54	0.00	21.19	0.17	15.05
Beta-Carotene	12.12	0.74	0.00	20.80	0.19	13.46
Caffeine	17.62	0.35	0.00	13.98	0.60	0.00
Calcium	17.34	0.36	0.00	14.13	0.59	0.00
Cholesterol	28.01	0.03	35.75	28.28	0.03	36.36
Docosapentaenoic acid	13.09	0.67	0.00	10.14	0.86	0.00
Iron	15.49	0.49	0.00	6.43	0.98	0.00
Magnesium	13.77	0.62	0.00	17.39	0.36	0.00
Myristoleic acid	17.37	0.36	0.00	20.07	0.22	10.32
Palmitoleic acid	13.62	0.63	0.00	21.57	0.16	16.55
Oleic acid	14.97	0.53	0.00	12.02	0.74	0.00
Gadoleic acid	24.70	0.08	27.12	25.63	0.06	29.78
Erucic acid	20.47	0.20	12.05	16.68	0.41	0.00
Linoleic acid	23.87	0.09	24.60	30.64	0.01	41.25
Dietary PFA	4.54	0.97	0.00	4.67	0.97	0.00
Arachidonic acid	20.61	0.19	12.66	18.26	0.31	1.44
Eicosapentaenoic acid	27.30	0.04	34.07	21.35	0.17	15.68
Docosahexaenoic aci	14.87	0.53	0.00	13.95	0.60	0.00
Phosphorus	22.15	0.14	18.73	16.38	0.43	0.00
Linolenic acid	15.73	0.47	0.00	28.61	0.03	37.09
Sodium to potassium ratio	15.30	0.50	0.00	15.86	0.46	0.00
Total protein	14.62	0.55	0.00	15.70	0.47	0.00
Retinol	10.65	0.83	0.00	12.08	0.74	0.00
Selenium	13.06	0.67	0.00	16.18	0.44	0.00
Capric acid	24.22	0.08	25.68	18.04	0.32	0.24
Lauric acid	17.45	0.36	0.00	10.39	0.85	0.00
Myristic acid	23.28	0.11	22.69	18.49	0.30	2.66
Palmitic acid	18.00	0.32	0.02	14.43	0.57	0.00
Stearic acid	18.58	0.29	3.10	14.89	0.53	0.00
Arachidic acid	21.42	0.16	15.95	20.55	0.20	12.40
Behenic acid	19.23	0.26	6.39	17.86	0.33	0.00
SFA 4:0	20.62	0.08	27.26	19.02	0.12	21.15
Caproic acid	23.44	0.10	23.21	18.61	0.29	3.30
Caprylic acid	18.89	0.27	4.69	13.85	0.61	0.00
Starch	23.52	0.10	23.48	16.74	0.40	0.00
Total Fat	17.14	0.38	0.00	15.25	0.51	0.00
Total MFA	14.23	0.58	0.00	12.84	0.68	0.00
Total SFA	19.29	0.25	6.69	14.76	0.54	0.00

Total vitamin E	12.86	0.68	0.00	29.95	0.02	39.89
Total carbohydrates	17.24	0.37	0.00	21.75	0.15	17.24
Total Vitamin A	6.62	0.98	0.00	8.69	0.93	0.00
Omega-3 polyunsaturates	17.21	0.37	0.00	28.19	0.03	36.16
Omega-6 polyunsaturates	23.92	0.09	24.73	30.62	0.02	41.21
Total fibre	11.07	0.81	0.00	8.00	0.95	0.00
Trans-octadecenoic acid	25.75	0.06	30.11	19.58	0.24	8.07
Trans-octadecenoic acid	20.85	0.18	13.68	16.25	0.44	0.00
Total trans-fatty acids	23.00	0.11	21.75	16.41	0.42	0.00
Vegetable protein	11.12	0.80	0.00	9.95	0.87	0.00
Total PFA	23.27	0.11	22.66	32.12	0.01	43.96
Vitamin A	8.45	0.93	0.00	12.86	0.68	0.00
Vitamin C	18.25	0.31	1.35	18.44	0.30	2.38
Sugar	19.65	0.24	8.40	14.35	0.57	0.00
Cooper	16.50	0.42	0.00	14.57	0.56	0.00
Folacin	14.52	0.56	0.00	10.53	0.84	0.00
Niacin	17.09	0.38	0.00	29.55	0.02	39.09
Pantothenic Acid	12.71	0.69	0.00	14.54	0.56	0.00
Riboflavin	14.29	0.58	0.00	15.60	0.48	0.00
Thiamin	14.30	0.58	0.00	15.33	0.50	0.00
Vitamin B6	19.58	0.24	8.06	19.33	0.25	6.88
Vitamin B12	10.83	0.82	0.00	10.84	0.82	0.00
Heme iron	9.69	0.88	0.00	15.76	0.47	0.00
Non-heme iron	15.71	0.47	0.00	6.62	0.98	0.00
Alanine	12.76	0.69	0.00	16.05	0.45	0.00
Arginine	11.39	0.79	0.00	13.87	0.61	0.00
Aspartame	12.13	0.73	0.00	13.32	0.65	0.00
Glutamic acid	12.10	0.74	0.00	10.55	0.84	0.00
Glycine	9.72	0.88	0.00	15.55	0.48	0.00
Histidine	11.75	0.76	0.00	17.01	0.38	0.00
Isoleucine	14.11	0.59	0.00	14.76	0.54	0.00
Leucine	14.76	0.54	0.00	15.75	0.47	0.00
Lysine	12.47	0.71	0.00	16.53	0.42	0.00
Methionine	18.28	0.31	1.52	20.47	0.20	12.07
Phenylalanine	12.88	0.68	0.00	11.58	0.77	0.00
Proline	11.56	0.77	0.00	20.56	0.20	12.46
Serine	12.73	0.69	0.00	13.84	0.61	0.00
Cystine	10.50	0.84	0.00	10.82	0.82	0.00
Threonine	12.72	0.69	0.00	14.32	0.57	0.00
Tryptophan	16.96	0.39	0.00	13.30	0.65	0.00
Tyrosine	13.68	0.62	0.00	15.34	0.50	0.00
Valine	13.71	0.62	0.00	12.63	0.70	0.00
Sum of EPA, DPA and DHA	21.08	0.18	14.62	18.04	0.32	0.24
Urinary excretion						

Calcium	6.07	0.99	0.00	18.51	0.30	2.73
Magnesium	7.98	0.95	0.00	17.47	0.36	0.00
Sodium to potassium ratio	24.48	0.08	26.46	24.91	0.07	27.73
Nutrients from foods and supplements						
Alanine	13.01	0.67	0.00	16.04	0.45	0.00
Alcohol	17.69	0.34	0.00	18.27	0.31	1.48
Animal protein	14.76	0.54	0.00	21.18	0.17	15.03
Arginine	11.78	0.76	0.00	13.64	0.63	0.00
Aspartame	12.68	0.70	0.00	13.14	0.66	0.00
Beta-Carotene	8.11	0.95	0.00	16.74	0.40	0.00
Caffeine	18.04	0.32	0.20	14.42	0.57	0.00
Calcium	24.08	0.09	25.24	16.03	0.45	0.00
Cholesterol	27.77	0.03	35.18	27.96	0.03	35.63
Cooper	16.35	0.43	0.00	16.50	0.42	0.00
Cystine	10.95	0.81	0.00	10.81	0.82	0.00
Glutamic acid	12.51	0.71	0.00	10.71	0.83	0.00
Glycine	9.36	0.90	0.00	15.12	0.52	0.00
Histidine	12.20	0.73	0.00	17.27	0.37	0.00
Iron	18.78	0.28	4.14	8.73	0.92	0.00
Isoleucine	15.15	0.51	0.00	15.03	0.52	0.00
Leucine	15.82	0.47	0.00	16.03	0.45	0.00
Lysine	13.08	0.67	0.00	16.45	0.42	0.00
Magnesium	12.28	0.72	0.00	12.99	0.67	0.00
Methionine	18.83	0.28	4.41	20.30	0.21	11.34
Myristoleic acid	17.37	0.36	0.00	20.07	0.22	10.32
Palmitoleic acid	12.81	0.69	0.00	20.61	0.19	12.64
Oleic acid	14.91	0.53	0.00	12.04	0.74	0.00
Gadoleic acid	27.23	0.04	33.89	30.01	0.02	40.01
Erucic acid	22.18	0.14	18.86	19.34	0.25	6.91
Niacin	13.48	0.64	0.00	24.91	0.07	27.74
Linoleic acid	23.97	0.09	24.90	30.84	0.01	41.62
Linolenic acid	15.84	0.46	0.00	28.81	0.03	37.53
Arachidonic acid	20.00	0.22	10.00	17.70	0.34	0.00
Eicosapentaenoic acid	16.36	0.29	2.18	15.79	0.33	0.00
Gadoleic acid	16.66	0.27	3.94	10.48	0.73	0.00
Docosahexaenoic acid	2.53	0.87	0.00	2.27	0.89	0.00
Docosahexaenoic acid	14.01	0.60	0.00	13.03	0.67	0.00
Phenylalanine	14.11	0.59	0.00	12.11	0.74	0.00
Phosphorus	21.02	0.18	14.37	15.12	0.52	0.00
Sodium to potassium ratio	15.36	0.50	0.00	14.42	0.57	0.00
Proline	12.31	0.72	0.00	21.06	0.18	14.51
Total protein	15.04	0.52	0.00	15.64	0.48	0.00
Retinol	16.72	0.40	0.00	9.77	0.88	0.00
Riboflavin	36.29	0.00	50.40	22.14	0.14	18.68
Selenium	13.96	0.60	0.00	17.86	0.33	0.00

Serine	14.16	0.59	0.00	14.51	0.56	0.00
Capric acid	24.23	0.08	25.70	18.06	0.32	0.31
Lauric acid	17.45	0.36	0.00	10.39	0.85	0.00
Myristic acid	23.32	0.11	22.80	18.54	0.29	2.91
Palmitic acid	17.98	0.33	0.00	14.34	0.57	0.00
Stearic acid	18.57	0.29	3.06	14.85	0.54	0.00
Arachidic acid	21.42	0.16	15.96	20.55	0.20	12.40
Behenic acid	19.27	0.25	6.60	17.94	0.33	0.00
SFA 4:0	23.44	0.10	23.21	18.61	0.29	3.30
Caproic acid	18.86	0.28	4.56	13.91	0.61	0.00
Caprylic acid	23.52	0.10	23.45	16.74	0.40	0.00
Thiamin	13.26	0.65	0.00	5.60	0.99	0.00
Threonine	13.58	0.63	0.00	14.49	0.56	0.00
Total Fat	17.29	0.37	0.00	15.42	0.49	0.00
Total MFA	14.12	0.59	0.00	12.90	0.68	0.00
Total PFA	23.97	0.09	24.92	32.85	0.01	45.20
Total SFA	19.28	0.25	6.63	14.70	0.55	0.00
Total vitamin E	24.59	0.08	26.81	18.92	0.27	4.88
Total carbohydrates	16.83	0.40	0.00	21.69	0.15	17.03
Total Vitamin A	11.50	0.78	0.00	7.57	0.96	0.00
Tryptophan	18.39	0.30	2.10	13.77	0.62	0.00
Tyrosine	14.57	0.56	0.00	15.53	0.49	0.00
Valine	14.96	0.53	0.00	13.12	0.66	0.00
Vegetable protein	11.12	0.80	0.00	9.94	0.87	0.00
Vitamin B6	16.86	0.39	0.00	19.15	0.26	6.00
Vitamin B12	25.22	0.07	28.63	34.39	0.00	47.66
Vitamin C	20.29	0.21	11.28	23.92	0.09	24.74
Total fibre	10.15	0.86	0.00	7.38	0.97	0.00
Vitamin A	11.14	0.80	0.00	12.60	0.70	0.00
Folacin	14.83	0.54	0.00	9.19	0.91	0.00
Omega-3 polyunsaturates	17.86	0.33	0.00	30.14	0.02	40.27
Omega-6 polyunsaturates	24.04	0.09	25.13	30.84	0.01	41.64

Supplementary Table 6. Heterogeneity estimates for random effects meta-analysis across the INTERMAP testing set

	Systolic Blood Pressure			Diastolic Blood Pressure		
	Q	p value (Q)	I2	Q	p value (Q)	I2
Nutrients from foods						
Alcohol	47.76	0.00	62.31	46.93	0.00	61.64
Animal Protein	9.33	0.90	0.00	10.83	0.82	0.00
Beta-Carotene	8.23	0.94	0.00	12.62	0.70	0.00
Caffeine	17.00	0.39	0.00	12.13	0.74	0.00
Calcium	13.43	0.64	0.00	7.47	0.96	0.00
Cholesterol	18.59	0.29	3.19	23.87	0.09	24.60
Docosapentaenoic acid	11.35	0.73	0.00	12.04	0.68	0.00
Iron	18.03	0.32	0.19	29.04	0.02	38.02
Magnesium	5.94	0.99	0.00	13.15	0.66	0.00
Myristoleic acid	17.78	0.34	0.00	21.30	0.17	15.51
Palmitoleic acid	19.98	0.22	9.92	16.15	0.44	0.00
Oleic acid	13.04	0.67	0.00	12.08	0.74	0.00
Gadoleic acid	18.38	0.30	2.05	16.25	0.44	0.00
Erucic acid	23.00	0.11	21.74	19.65	0.24	8.38
Linoleic acid	9.90	0.87	0.00	16.29	0.43	0.00
Linolenic acid	19.87	0.23	9.39	23.97	0.09	24.90
Dietary PFA	8.99	0.62	0.00	11.09	0.44	0.00
Arachidonic acid	10.87	0.82	0.00	13.97	0.60	0.00
Eicosapentaenoic acid	10.97	0.81	0.00	11.17	0.80	0.00
Docosahexaenoic acid	12.30	0.72	0.00	11.42	0.78	0.00
Phosphorus	11.50	0.78	0.00	16.33	0.43	0.00
Sodium to potassium ratio	8.14	0.94	0.00	5.52	0.99	0.00
Total protein	7.51	0.96	0.00	8.43	0.93	0.00
Retinol	11.60	0.77	0.00	13.86	0.61	0.00
Selenium	7.51	0.96	0.00	12.16	0.73	0.00
Capric acid	12.71	0.69	0.00	14.57	0.56	0.00
Lauric acid	11.82	0.76	0.00	24.15	0.09	25.46
Myristic acid	11.43	0.78	0.00	19.19	0.26	6.18
Palmitic acid	16.04	0.45	0.00	17.08	0.38	0.00
Stearic acid	17.74	0.34	0.00	22.39	0.13	19.60
Arachidic acid	6.66	0.98	0.00	18.16	0.31	0.90
Behenic acid	7.63	0.96	0.00	16.31	0.43	0.00
SFA 4:0	15.91	0.25	5.73	12.61	0.48	0.00
Caproic acid	20.24	0.21	11.06	15.63	0.48	0.00
Caprylic acid	14.63	0.55	0.00	19.99	0.22	9.95
Starch	25.26	0.07	28.74	28.43	0.03	36.69
Total Fat	13.02	0.67	0.00	15.42	0.49	0.00
Total MFA	12.35	0.72	0.00	10.00	0.87	0.00
Total PFA	10.13	0.86	0.00	17.28	0.37	0.00

Total SFA	15.26	0.51	0.00	19.24	0.26	6.45
Total vitamin E	12.18	0.73	0.00	14.37	0.57	0.00
Total carbohydrates	31.72	0.01	43.26	37.88	0.00	52.49
Total Vitamin A	6.49	0.98	0.00	11.06	0.81	0.00
Omega-3 polyunsaturates	17.55	0.35	0.00	20.11	0.22	10.49
Omega-6 polyunsaturates	10.14	0.86	0.00	16.41	0.43	0.00
Total fibre	12.08	0.74	0.00	10.91	0.81	0.00
Trans-octadecenoic acid	14.80	0.54	0.00	18.83	0.28	4.41
Trans-octadecenoic acid	14.94	0.53	0.00	20.20	0.21	10.88
Total trans-fatty acids	14.33	0.57	0.00	19.50	0.24	7.69
Vegetable protein	10.26	0.85	0.00	16.96	0.39	0.00
Vitamin A	4.85	1.00	0.00	12.17	0.73	0.00
Vitamin C	19.51	0.24	7.76	15.44	0.49	0.00
Sugar	20.16	0.21	10.72	22.95	0.12	21.56
Cooper	4.21	1.00	0.00	7.50	0.96	0.00
Folacin	21.53	0.16	16.40	15.88	0.46	0.00
Niacin	22.34	0.13	19.43	21.87	0.15	17.71
Pantothenic Acid	14.25	0.58	0.00	13.16	0.66	0.00
Riboflavin	14.76	0.54	0.00	20.09	0.22	10.39
Thiamin	13.91	0.61	0.00	12.26	0.73	0.00
Vitamin B6	26.57	0.05	32.25	19.29	0.25	6.69
Vitamin B12	6.93	0.97	0.00	9.56	0.89	0.00
Heme iron	8.31	0.94	0.00	11.68	0.77	0.00
Non-heme iron	20.21	0.21	10.95	29.77	0.02	39.54
Alanine	9.70	0.88	0.00	11.00	0.81	0.00
Arginine	11.03	0.81	0.00	11.67	0.77	0.00
Aspartame	9.45	0.89	0.00	10.28	0.85	0.00
Cystine	10.25	0.85	0.00	15.22	0.51	0.00
Glutamic acid	10.27	0.85	0.00	9.98	0.87	0.00
Glycine	13.17	0.66	0.00	13.60	0.63	0.00
Histidine	8.39	0.94	0.00	9.02	0.91	0.00
Isoleucine	7.37	0.97	0.00	7.08	0.97	0.00
Leucine	7.89	0.95	0.00	7.89	0.95	0.00
Lysine	8.03	0.95	0.00	7.91	0.95	0.00
Methionine	9.45	0.89	0.00	9.31	0.90	0.00
Phenylalanine	7.39	0.96	0.00	8.04	0.95	0.00
Proline	9.98	0.87	0.00	7.50	0.96	0.00
Serine	6.99	0.97	0.00	8.84	0.92	0.00
Threonine	7.61	0.96	0.00	8.43	0.94	0.00
Tryptophan	7.96	0.95	0.00	10.12	0.86	0.00
Tyrosine	7.93	0.95	0.00	7.48	0.96	0.00
Valine	7.09	0.97	0.00	8.17	0.94	0.00
long_O7	10.66	0.83	0.00	10.22	0.86	0.00
Urinary excretion						
Calcium	20.55	0.20	12.42	18.53	0.29	2.86

Magnesium	10.56	0.84	0.00	10.12	0.86	0.00
Sodium to potassium ratio	21.09	0.17	14.67	21.11	0.17	14.74
Nutrients from foods and supplements						
Alanine	10.62	0.83	0.00	10.52	0.84	0.00
Alcohol	47.76	0.00	62.31	46.93	0.00	61.64
Animal protein	9.35	0.90	0.00	10.83	0.82	0.00
Arginine	11.27	0.79	0.00	11.91	0.75	0.00
Aspartame	9.95	0.87	0.00	10.06	0.86	0.00
Beta-Carotene	10.24	0.85	0.00	13.50	0.64	0.00
Caffeine	17.10	0.38	0.00	12.20	0.73	0.00
Calcium	10.49	0.84	0.00	11.12	0.80	0.00
Cholesterol	19.01	0.27	5.33	24.15	0.09	25.48
Cooper	10.91	0.82	0.00	11.28	0.79	0.00
Cystine	10.45	0.84	0.00	14.91	0.53	0.00
Glutamic acid	10.09	0.86	0.00	9.72	0.88	0.00
Glycine	15.79	0.47	0.00	13.49	0.64	0.00
Histidine	9.00	0.91	0.00	8.84	0.92	0.00
Iron	12.33	0.72	0.00	9.68	0.88	0.00
Isoleucine	7.70	0.96	0.00	6.78	0.98	0.00
Leucine	8.23	0.94	0.00	7.53	0.96	0.00
Lysine	8.59	0.93	0.00	7.58	0.96	0.00
Magnesium	8.74	0.92	0.00	16.52	0.42	0.00
Methionine	10.31	0.85	0.00	9.05	0.91	0.00
Myristoleic acid	17.78	0.34	0.00	21.30	0.17	15.51
Palmitoleic acid	20.83	0.19	13.58	16.87	0.39	0.00
Oleic acid	13.10	0.67	0.00	12.20	0.73	0.00
Gadoleic acid	18.65	0.29	3.48	20.85	0.18	13.67
Erucic acid	22.99	0.11	21.71	23.10	0.11	22.09
Niacin	13.69	0.62	0.00	8.11	0.95	0.00
Linoleic acid	9.90	0.87	0.00	16.34	0.43	0.00
Linolenic acid	19.85	0.23	9.32	24.18	0.09	25.55
Arachidonic acid	11.42	0.78	0.00	14.29	0.58	0.00
Eicosapentaenoic acid	12.78	0.54	0.00	13.83	0.46	0.00
Gadoleic acid	11.94	0.61	0.00	13.81	0.46	0.00
Docosahexaenoic acid	1.19	0.95	0.00	4.05	0.54	0.00
Docosahexaenoic acid	13.50	0.64	0.00	15.70	0.47	0.00
Phenylalanine	7.71	0.96	0.00	7.83	0.95	0.00
Phosphorus	11.02	0.81	0.00	16.99	0.39	0.00
Sodium to potassium ratio	7.99	0.95	0.00	5.59	0.99	0.00
Proline	9.58	0.89	0.00	7.19	0.97	0.00
Total protein	8.01	0.95	0.00	7.87	0.95	0.00
Retinol	10.36	0.85	0.00	11.38	0.79	0.00
Riboflavin	18.40	0.30	2.18	12.49	0.71	0.00
Selenium	11.99	0.74	0.00	13.40	0.64	0.00
Serine	7.10	0.97	0.00	8.34	0.94	0.00

Capric acid	12.71	0.69	0.00	14.57	0.56	0.00
Lauric acid	11.82	0.76	0.00	24.15	0.09	25.46
Myristic acid	11.50	0.78	0.00	19.36	0.25	7.04
Palmitic acid	16.13	0.44	0.00	17.25	0.37	0.00
Stearic acid	17.79	0.34	0.00	22.45	0.13	19.83
Arachidic acid	6.66	0.98	0.00	18.16	0.31	0.91
Behenic acid	10.41	0.84	0.00	22.73	0.12	20.81
SFA 4:0	20.24	0.21	11.06	15.63	0.48	0.00
Caproic acid	14.63	0.55	0.00	19.99	0.22	9.95
Caprylic acid	25.29	0.06	28.83	28.45	0.03	36.73
Thiamin	14.10	0.59	0.00	9.65	0.88	0.00
Threonine	8.29	0.94	0.00	8.03	0.95	0.00
Total Fat	13.87	0.61	0.00	15.93	0.46	0.00
Total MFA	12.53	0.71	0.00	10.33	0.85	0.00
Total PFA	10.19	0.86	0.00	17.63	0.35	0.00
Total SFA	15.33	0.50	0.00	19.42	0.25	7.30
Total vitamin E	19.22	0.26	6.35	9.03	0.91	0.00
Total carbohydrates	32.07	0.01	43.87	37.91	0.00	52.52
Total Vitamin A	9.11	0.91	0.00	13.57	0.63	0.00
Tryptophan	7.95	0.95	0.00	10.49	0.84	0.00
Tyrosine	8.30	0.94	0.00	7.17	0.97	0.00
Valine	7.33	0.97	0.00	7.79	0.95	0.00
Vegetable protein	10.26	0.85	0.00	16.95	0.39	0.00
Vitamin B6	26.00	0.05	30.78	18.12	0.32	0.65
Vitamin B12	19.37	0.25	7.05	8.83	0.92	0.00
Vitamin C	23.24	0.11	22.56	24.57	0.08	26.74
Total fibre	11.90	0.75	0.00	11.17	0.80	0.00
Vitamin A	8.18	0.94	0.00	13.78	0.61	0.00
Folacin	29.60	0.02	39.19	23.15	0.11	22.26
Omega-3 polyunsaturates	17.48	0.36	0.00	21.05	0.18	14.48
Omega-6 polyunsaturates	10.15	0.86	0.00	16.48	0.42	0.00

Supplementary Table 7. Heterogeneity estimates for random effects meta-analysis across the NHANES cohorts

	Q	p value (Q)	I^2
Systolic Blood Pressure			
Nutrients from foods			
Alcohol (gm)	2.48	0.479	0
Calcium (mg)	4.71	0.194	36
Copper (mg)	6.15	0.104	51
Folic acid (mcg)	0.76	0.684	0
Dietary fiber (gm)	13.60	0.004	78
Iron (mg)	3.83	0.281	22
Magnesium (mg)	13.41	0.004	78
Phosphorus (mg)	6.25	0.100	52
Thiamin (mg)	3.19	0.363	6
Riboflavin (mg)	5.39	0.146	44
Sodium/Potassium ratio	9.17	0.027	67
Nutrients from foods and supplements			
Total Dietary Fiber (gm)	12.93	0.005	77
Total Magnesium (mg)	11.03	0.012	73
Total Phosphorus (mg)	8.69	0.034	65
Serum biomarkers			
Folate (ng/mL)	1.22	0.748	0
Iron (ug/dL)	0.34	0.952	0
Calcium (mg/dL)	1.20	0.753	0
Phosphorus (mg/dL)	0.64	0.886	0
Diastolic Blood Pressure			
Nutrients from foods			
Alcohol (gm)	2.64	0.450	0
Folic acid (mcg)	5.89	0.053	66
Magnesium (mg)	7.98	0.046	62
Phosphorus (mg)	5.89	0.117	49
Riboflavin (Vitamin B2) (mg)	2.32	0.509	0
Nutrients from foods and supplements			
Total Magnesium (mg)	8.89	0.031	66
Total Phosphorus (mg)	6.56	0.087	54
Serum biomarkers			
Folate (ng/mL)	5.30	0.151	43
Phosphorus (mg/dL)	1.86	0.601	0

Supplementary Figure 1. Power calculations in INTERMAP study to detect different effect sizes per 1SD based on models with R^2=0.2