An evaluation by meta-analysis of the diet-wide contribution to serum urate levels

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SUPPLEMENTAL MATERIAL

An evaluation by meta-analysis of the diet-wide contribution to serum urate levels

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Supplemental Tables in multi-sheet Excel file <DWAS_BMJsupplementaltables_20Apr>

SUPPLEMENTAL TABLE LEGENDS

Table S1. Demographic, anthropomorphic, and clinical summary for the five datasets.

Values are shown as the mean ± standard deviation, or as the number of participants (percentage). For menopause status the percentage is of only the female participants.

Table S2. Food frequency questionnaire answer categories and serves per week conversion factor.

NHANES III did not specify portion size. CHS only specified relative portion size (small / medium / large). ARIC, CARDIA, and FHS did not specify the same portion sizes. Portion size was not considered in this study. Category – possible answers as designated by the study questionnaire. Conversion – number of serves per week corresponding to the average category answer.

Table S3. Summary of 63 comparable food items and their study-specific food frequency questions.

/ – indicates items were asked about together on the questionnaire. ; – indicates questions that were combined before analysis to make food items comparable between studies. * – indicates not all data-sets had a comparable question, the number of asterisks represents the number of data-sets missing data.

Table S4. Summary of the average consumption frequency for 63 food items after conversion to serves per week.

All values are presented in serves per week. * – indicates not all data-sets were included in the analysis, the number of asterisks represents the number of data-sets missing data for this food item. n – number of participants.

Table S5. Diet-wide association study results for the original and diet quality score adjusted analyses in the full cohort.

n – number of participants analysed. β – inverse-variance weighted meta-analysis beta value, reflecting the change in serum urate level (μmol/L) per one extra serve per week of the food item. 95% CI – 95% confidence intervals of the beta value. P_{β} – p-value for meta-analysis beta value, p-values in italics were nominally significant ($P_{\beta} < 0.05$; $P_{\beta} \geq 7.94\times10^{-04}$), p-values in bold were diet-wide significant ($P_{\beta} < 7.94\times10^{-04}$). R^2 – partial R^2 value (R^2_B) converted to a percentage (R^2 * 100). $P_{\mathbf{Q}}$ – p-value for the heterogeneity Q-statistic generated during the meta-analysis, if $P_Q < 0.01$ a random-effect model was used in the meta-analysis. * – indicates not all data-sets were included in the analysis, the number of asterisks represents the number of data-sets missing data.

Table S6. Diet-wide association study results for the original and diet quality score adjusted analyses in the male-only cohort.

n – number of participants analysed. β – inverse-variance weighted meta-analysis beta value, reflecting the change in serum urate level (μmol/L) per one extra serve per week of the food item. 95% CI – 95% confidence intervals of the beta value. P_{β} – p-value for meta-analysis beta value, p-values in italics were nominally significant ($P_{\beta} < 0.05$; $P_{\beta} \geq 7.94\times10^{-04}$), p-values in bold were diet-wide significant ($P_{\beta} < 7.94\times10^{-04}$). R^2 – partial R^2 value (R^2_B) converted to a percentage (R^2 * 100). $P_{\mathbf{Q}}$ – p-value for the heterogeneity Q-statistic generated during the meta-analysis, if $P_Q < 0.01$ a random-effect model was used in the meta-analysis. * – indicates not all data-sets were included in the analysis, the number of asterisks represents the number of data-sets missing data.

Table S7. Diet-wide association study results for the original and diet quality score adjusted analyses in the female-only cohort.

n – number of participants analysed. β – inverse-variance weighted meta-analysis beta value, reflecting the change in serum urate level (μmol/L) per one extra serve per week of the food item. 95% CI – 95% confidence intervals of the beta value. P_β – p-value for meta-analysis beta value, p-values in italics were nominally significant ($P_\beta < 0.05$; $P_\beta \geq 7.94\times10^{-04}$), p-values in bold were diet-wide significant ($P_\beta < 7.94\times10^{-04}$). R^2 – partial R^2 value (R^2_B) converted to a percentage (R^2 * 100). P_Q – p-value for the heterogeneity Q-statistic generated during the meta-analysis, if $P_Q < 0.01$ a random-effect model was used in the meta-analysis. * – indicates not all data-sets were included in the analysis, the number of asterisks represents the number of data-sets missing data.

Table S8. Individual association results for the 30 SNPs used in the genetic risk score.

NHANES III was unable to be included in these analyses owing to no genome-wide genotype date being available. Risk / Oth – risk / other allele. Freq – risk allele frequency. n – number of participants analysed. β – inverse-variance weighted meta-analysis beta value, reflecting the change in serum urate level (μmol/L) per risk allele. 95% CI – 95% confidence intervals of the beta value. P_β – meta analysis p-value. R^2 – partial R^2 value converted to a percentage (R^2 * 100) calculated from multivariate linear regression of all samples together (adjusted by study). R^2_{No} – R^2 for no additional diet quality score adjustment. R^2_{HES} – R^2 for additional adjustment by the healthy eating score. R^2_{DASH} – R^2 for additional adjustment by the DASH diet score. R^2_{MDT} – R^2 for additional adjustment by the Mediterranean diet score. R^2_{Factor} – R^2 for additional adjustment by the data-derived diet score. P_Q – p-value for the heterogeneity Q-statistic generated during the meta-analysis, if $P_Q < 0.01$ a random-effect model was used in the meta-analysis. P_{HWE} - Hardy-Weinberg p-value for all cohorts combined. For the two SNPs with a $P_{HWE} \leq 0.01$ (*rs653178* and *rs2079742*) all individual cohorts had a $P_{HWE} \geq 0.02$, except the ARIC cohort for *rs653178* ($P_{HWE} = 1.56\times10^{-03}$).

Table S9. Interaction between the four diet quality scores and the genetic risk score.

NHANES III was unable to be included in these analyses owing to no genome-wide genotype date being available. n – number of participants analysed. β – inverse-variance weighted meta-analysis of the interaction beta value, reflecting the change in serum urate level (μmol/L) per one unit increase in the diet score multiplied by the genetic risk score. 95% CI – 95% confidence intervals of the beta value. P_β – *P*-value for meta-analysis beta value, p-values in bold were considered significant ($P_\beta < 0.05$). R^2 – partial R^2 value (R^2_B) converted to a percentage (R^2 * 100). P_Q – *P*-value for the heterogeneity Q-statistic generated during the meta-analysis, if $P_Q < 0.01$ a random-effect model was used in the meta-analysis.

FIGURE LEGENDS

Figure S1. Exclusion criteria for each data-set.

Demographic and medical exclusion criteria are in normal font, dietary data exclusion criteria are in italics. The cohort sizes before and after exclusion are shown in bold font. Study-specific criteria were exclusion of related family members in the ARIC and NHANES III cohorts and exclusion of CHS individuals who were also part of the ARIC, Systolic Hypertension in the Elderly (SHEP), or NHANES III studies. CHS interviewers did not assess the reliability of participant's food frequency questionnaire answers nor acquire data on gout status.

Figure S2. Distribution of the 'Healthy-Eating' diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

Solid blue line – smoothed density curve of the 'Healthy-Eating' diet score distribution. Dashed red line – smoothed density curve for a random approximation of the normal distribution for data of the same length, mean, and standard deviation.

Figure S3. Distribution of the DASH diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

Solid blue line – smoothed density curve of the DASH diet score distribution. Dashed red line – smoothed density curve for a random approximation of the normal distribution for data of the same length, mean, and standard deviation.

Figure S4. Distribution of the Mediterranean diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

Solid blue line – smoothed density curve of the Mediterranean diet score distribution. Dashed red line – smoothed density curve for a random approximation of the normal distribution for data of the same length, mean, and standard deviation.

Figure S5. Parallel factor analysis scree plot of eigenvalues.

Solid blue line / triangles – eigenvalues from the actual dietary data. Dotted red line – eigenvalues from simulated data had the same mean and variance as the original data, but with no correlations among the observed variables. Dashed red line – eigenvalues from resampled data generated from the original sample. The point where the eigenvalues for the simulated / resampled data crosses the eigenvalues from the actual data is the point of inflection, indicating the number of factor analysis vectors to retain for further analysis.

Figure S6. Distribution of the data-driven diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

Solid blue line – smoothed density curve of the data-driven diet score distribution. Dashed red line – smoothed density curve for a random approximation of the normal distribution for data of the same length, mean, and standard deviation.

Figure S7. Power curves.

All sample-sets were adequately powered (≥ 80%) to detect a large, medium, or small effect size as indicated by a Cohen's f^2 of 0.35, 0.15, or 0.02, respectively (marked in grey vertical lines). The combined sample-set had power to detect an effect size of Cohen's $f^2 = 0.002$, corresponding to a linear regression partial R^2 value of approximately 0.1%. Cohen's $f^2 = \frac{R_B^2}{1 - R_{AB}^2}$, where R_B^2 is the partial R^2 corresponding to the specific food item of interest and R_{AB}^2 is the R^2 for the entire regression analysis.[PMID: 22529829]

Figure S8. Correlogram of consumption of 63 food items (serves per week).

Correlations were calculated using a Pearson's product-moment correlation test in the full cohort. Blue indicates a positive correlation, orange a negative correlation. X – non-significant correlation p-value ($P_{Cor} \geq 2.6\times10^{-5}$; Bonferroni multiple-testing correction of 0.05 divided by 1,953 correlations), no mark indicates a significant correlation ($P_{Cor} < 2.6\times10^{-5}$).

Figure S1. Exclusion criteria for each data set.

	ARIC	CARDIA	CHS	FHS	NHANES III
	15,485	**3,622**	**5,582**	**4,148**	**33,994**
< 18 Years Old	N/A	6	N/A	0	13,559
No Serum Urate Measurement	162	40	131	131	3,939
Non-European Ancestry	3,995	1,647	878	23	9,620
Not Whole-Genome Genotyped	1,707	262	1,308	205	N/A
Participant Has Gout	427	22	N/A	31	293
Participant Has Kidney Disease	137	63	141	162	174
Currently Taking Urate Lowering Therapies	11	0	68	0	18
Currently Taking Diuretics	1,229	9	625	109	669
Missing Any Covariate Data	970	78	147	63	330
Other Exclusion Criteria (Study Specific)	350	N/A	7	N/A	608
Answered < 10% of Diet Questionnaire	*5*	*1*	*14*	*325*	*2*
Average Calorie Intake ≤ 600 or ≥ 4,200 kcal/day	*135*	*134*	*309*	*82*	*546*
Answers Deemed Unreliable by Study	*99*	*25*	*N/A*	*40*	*0*
	6,258	**1,335**	**1,954**	**2,977**	**4,236**

Figure S2. Distribution of the 'Healthy-Eating' score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

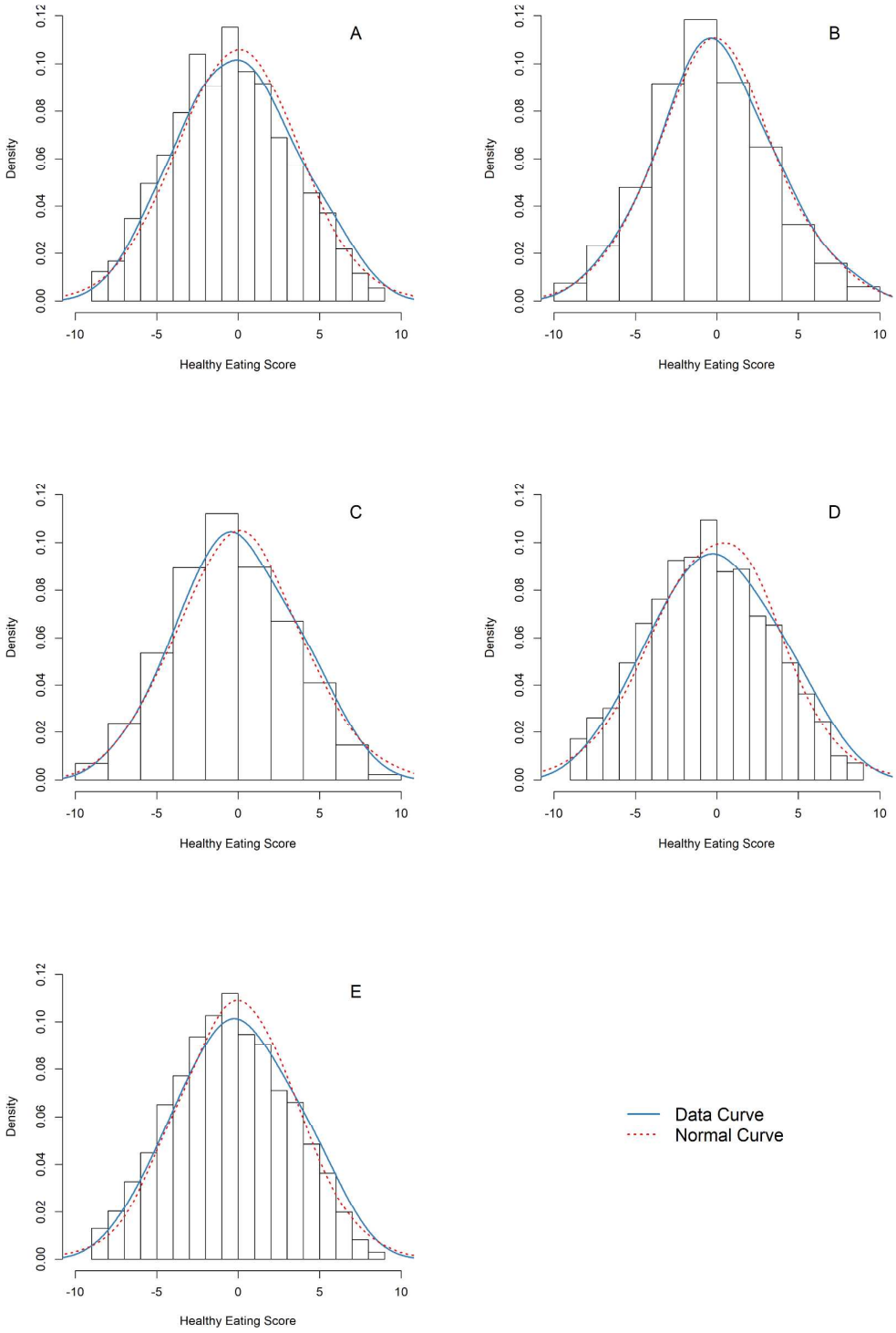


Figure S3. Distribution of the DASH diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

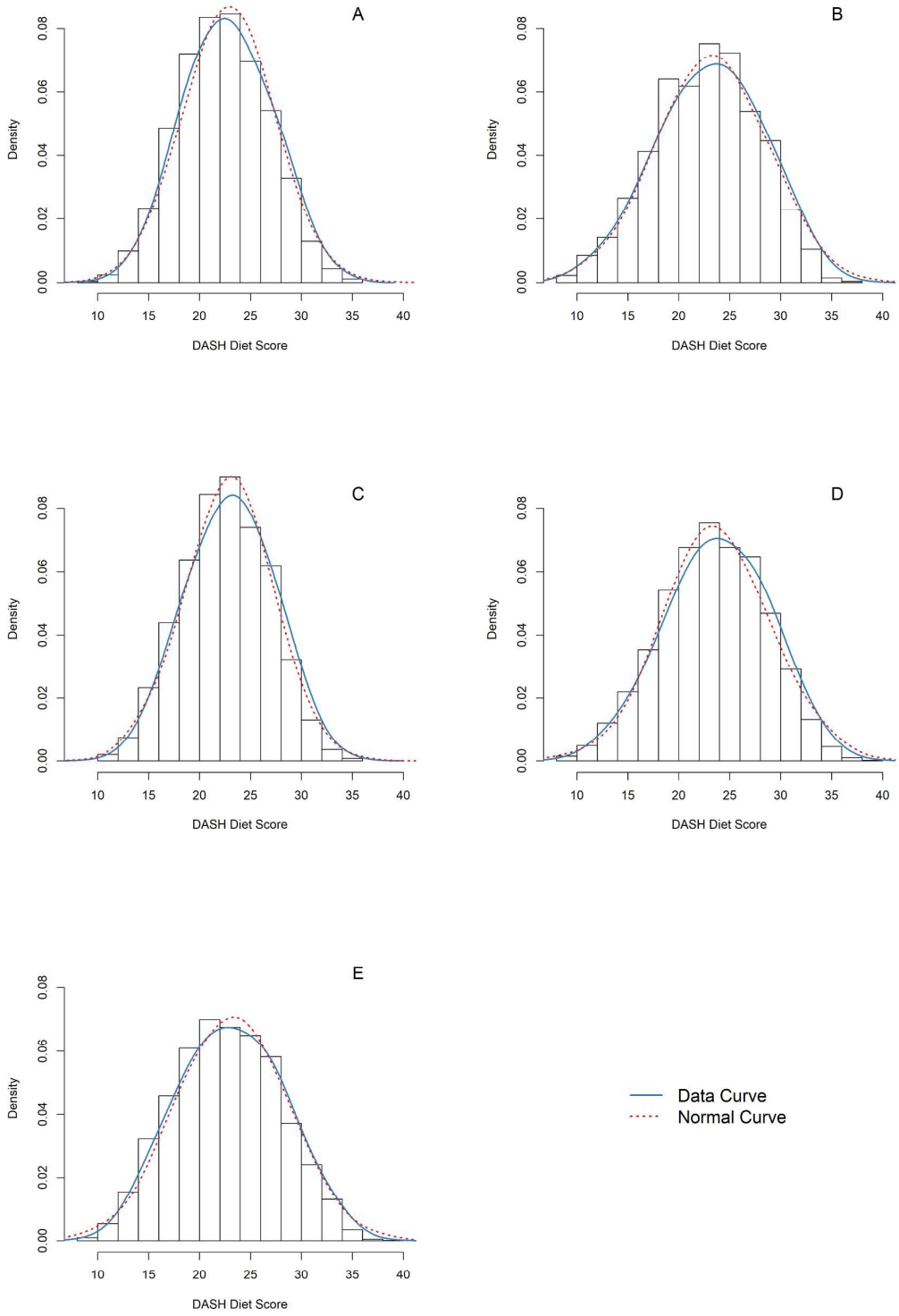


Figure S4. Distribution of the Mediterranean diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

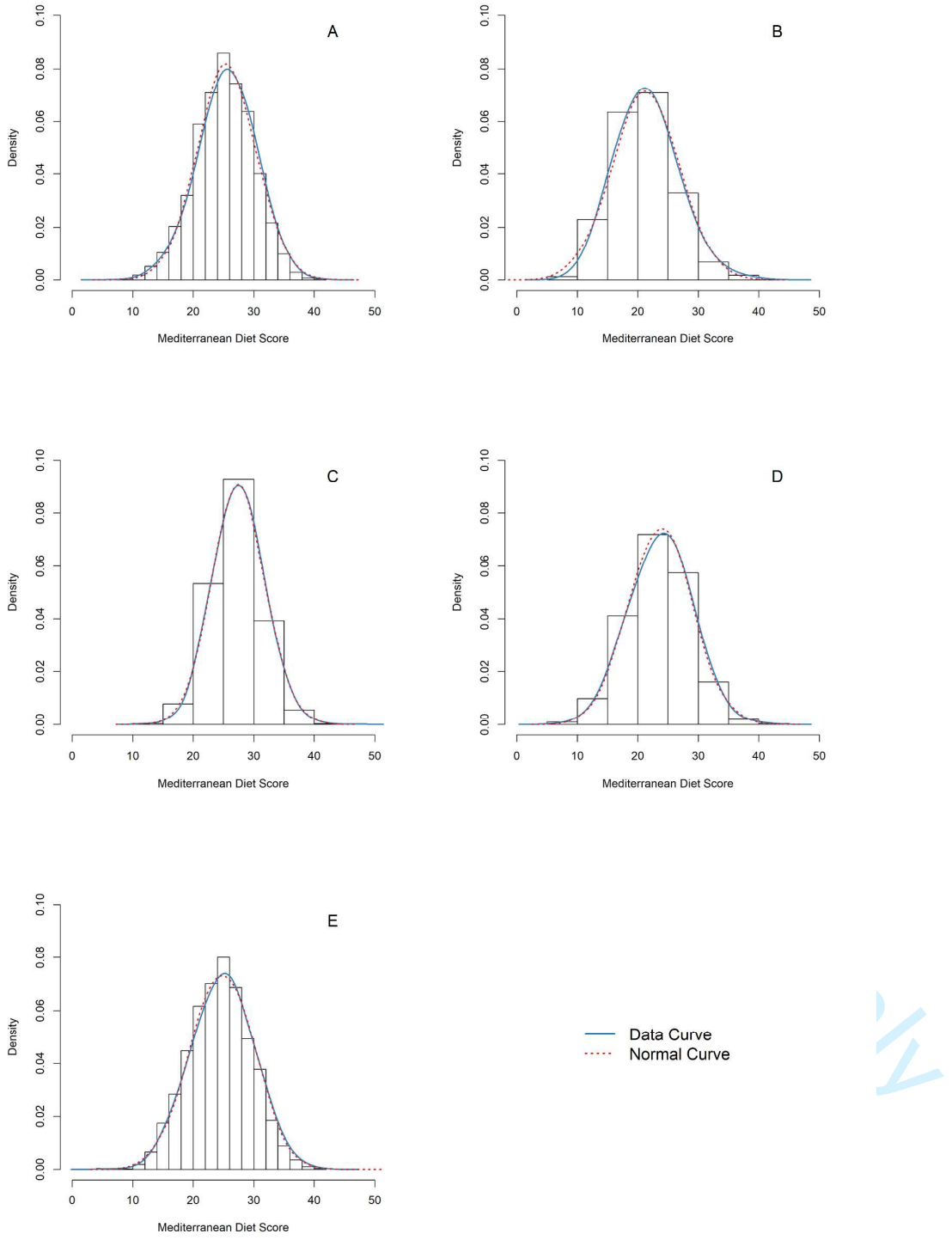


Figure S5. Parallel factor analysis scree plot of eigenvalues.

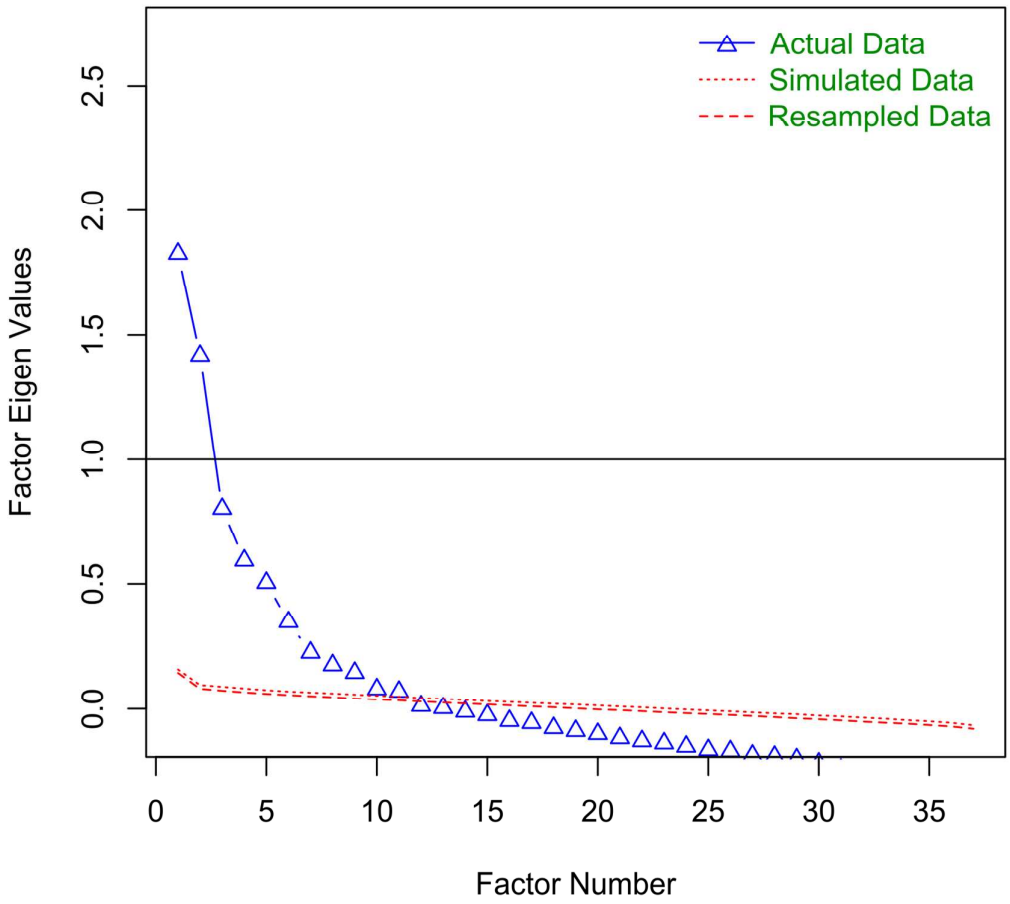


Figure S6. Distribution of the data-driven diet score in the ARIC (A), CARDIA (B), CHS (C), FHS (D), and NHANES III (E) cohorts.

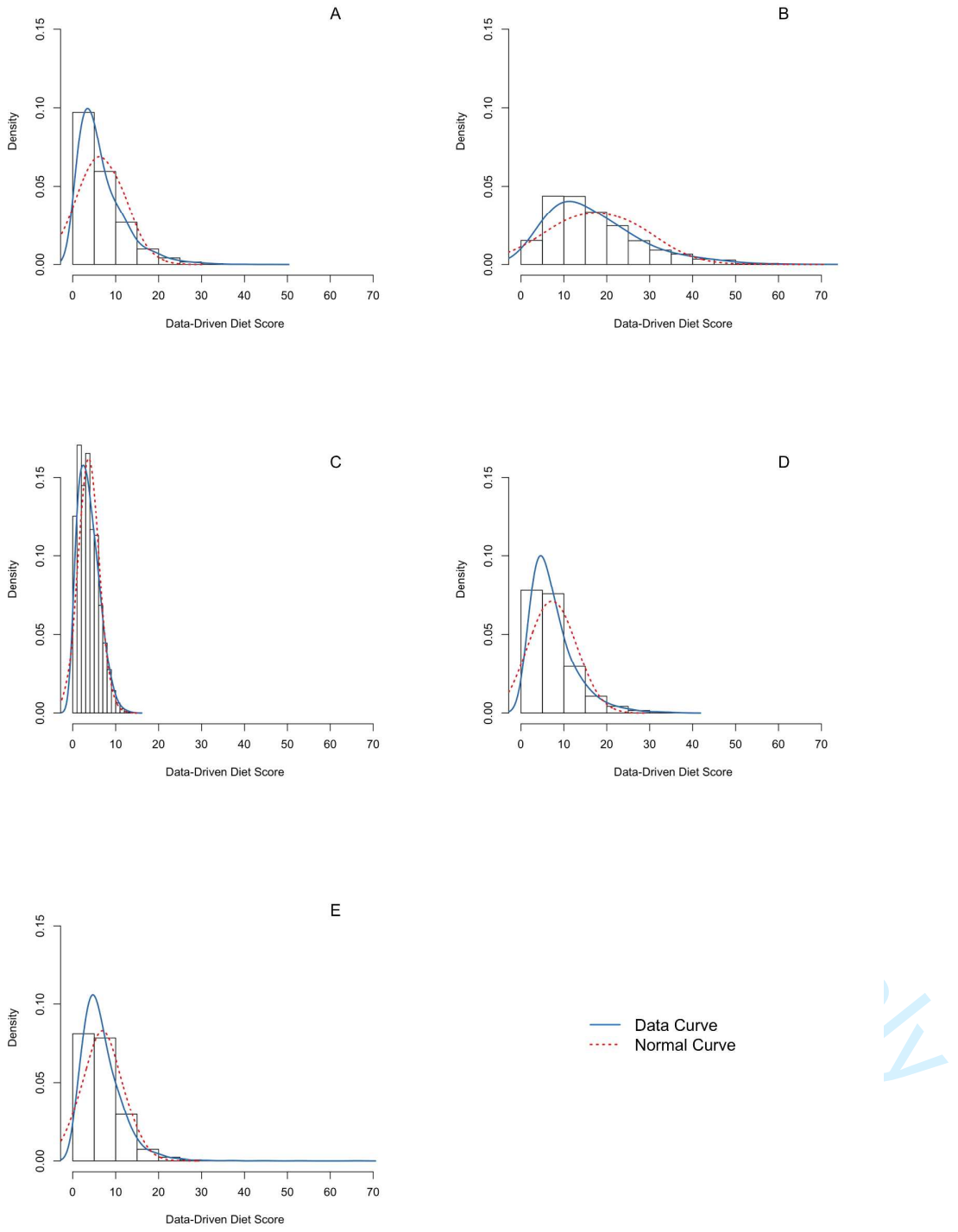
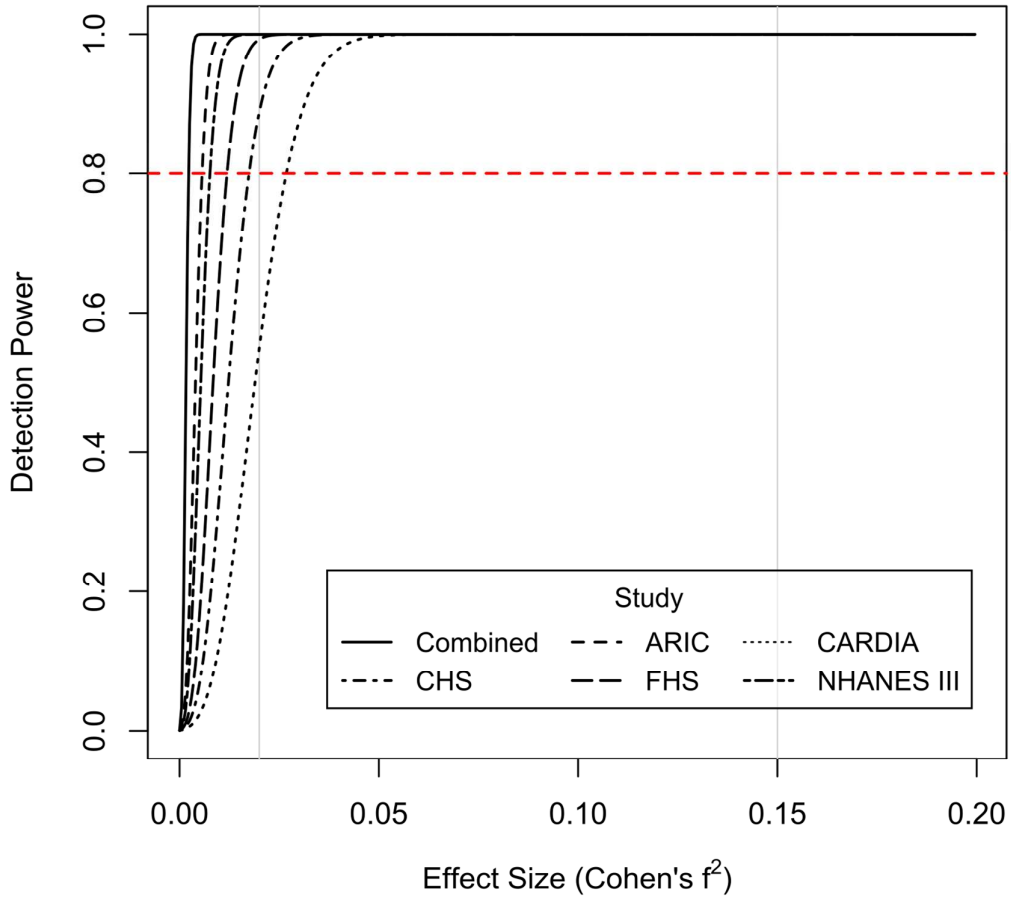


Figure S7. Power curves.



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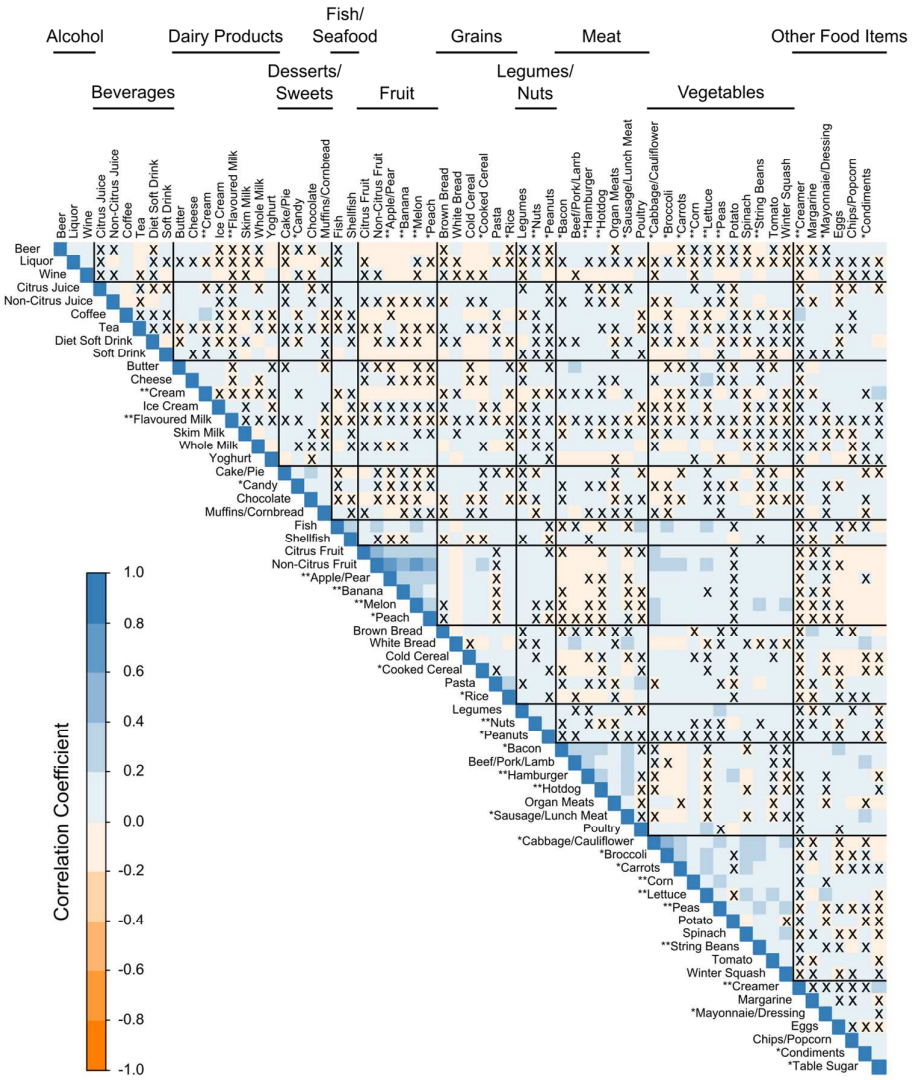

An evaluation of the diet-wide contribution to serum urate levels: meta-analysis of population based cohorts

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ABSTRACT

Objective: To systematically test dietary components for association with serum urate and to evaluate the relative contributions of percent variance in serum urate explained by estimates of diet quality and inherited genetic variants.

Design: Association testing of individual food items in a diet-wide association study (DWAS) and association of composite dietary scores with serum urate levels by meta-analysis of cross-sectional data from five cohort studies.

Setting: Atherosclerosis Risk in Communities study (1987 to 1989), Coronary Artery Risk Development in (Young) Adults study (1985), Cardiovascular Health Study (1989 to 1990), Framingham Heart Study (2002 to 2005), and Third National Health and Nutrition Examination Survey (1988 to 1991).

Participants: 16,760 North Americans of European ancestry (8,414 men and 8,346 women) over 18 years of age and without kidney disease, gout, and urate-lowering or diuretic medication use. All participants had serum urate measurements, dietary survey data, information on potential confounders (sex, age, body mass index, average daily calorie intake, years of education, exercise levels, smoking status and menopausal status), diet quality scores, and genome-wide genotypes.

Main Outcome Measures: Average serum urate levels and variance in serum urate levels. Beta-values (95% confidence intervals) and Bonferroni-corrected p-values from covariate-adjusted linear regression analyses, along with regression partial R^2 values, were used to quantitate association.

Results: Ten foods associated with raised serum urate (shellfish, beer, liquor, wine, potato, poultry, soft drinks, meat (beef / pork / lamb), table sugar, and tea) and eight foods associated with reduced serum urate (eggs, peanuts, cold cereal, skim milk, cheese, brown bread, margarine, and non-citrus fruits) in the sex-specific or combined cohorts. Three diet quality scores, constructed based on healthy diet guidelines, were inversely associated with serum urate and a fourth, data-driven diet quality score associated with rasied serum urate, but each explained $\leq$ 0.3% of variance in serum urate. In comparison, in the cohorts tested, 23.9% of variance in serum urate levels was explained by common genome-wide single nucleotide variation.

Conclusion: In contrast to genetic contributions, diet explains very little variation in serum urate levels.

PRINT ABSTRACT

Study question The primary aim was to evaluate the relative contribution of overall diet and inherited genetic variation to the population variance in serum urate levels.

Methods 16,760 people of European ancestry were participants. They were drawn from the Atherosclerosis Risk in Communities (ARIC) study, the Coronary Artery Risk Development in Adults (CARDIA) study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS) and the Third National Health and Nutrition Examination Survey. Four composite dietary scores (exposures) were constructed (Dietary Approaches to Stop Hypertension, Harvard Healthy Eating Score, Mediterranean diet, a data-driven score). Dietary scores were tested for association in multivariate-adjusted linear regression with serum urate levels (outcome) in individual cohorts and combined by meta-analysis. Individual food items were also tested for association with serum urate levels. Genome-wide genotype information (exposure) from the ARIC, CARDIA, CHS and FHS cohorts was used to estimate variance explained by common genetic variants (heritability).

Study answer and limitations All diet scores explained ≤ 0.3% of variance in serum urate whereas 23.9% of variance in serum urate levels was explained by common genome-wide single nucleotide variation. Weaknesses of the study include methodological challenges in combining differing food frequency questionnaires between studies, that food consumption data were collected at different times (1985 to 2002) and that there will be non-independence between the dietary analysis (food consumption is heritable) and the genetic analysis.

What this study adds Our data challenge widely held community perceptions that hyperuricaemia is primarily caused by diet.

Funding, competing interests, data sharing This work was supported by the Health Research Council of New Zealand and the University of Otago. All authors have completed the ICMJE uniform disclosure form, with TRM and ND declaring pharmaceutical funding and fees for work outside the submitted work. Data are available from the corresponding author.

What this paper adds / what is already known

What is already known:

- Serum urate levels are influenced by genetic and environmental exposure, including specific foods.
- No prior studies have assessed the relative contributions of genetic and dietary exposures to variance in serum urate levels.

What this study adds:

- Estimates of diet quality associate with serum urate levels in the US European population.
- Estimates of diet quality explain substantially less variation in serum urate than a heritability estimate (≤ 0.3% versus 23.9%, respectively).
- These data challenge widely held community perceptions that hyperuricaemia is primarily caused by diet.

INTRODUCTION

Hyperuricaemia (elevated serum urate concentration) is a central risk factor for gout, and is also associated with chronic kidney disease, hypertension, and metabolic syndrome.[1-4] The balance between hepatic production of urate and intestinal / renal urate excretion pathways determine an individual's serum urate levels.[5] This balance can be modified by both genetic and environmental factors. Familial and twin studies estimating the heritability of serum urate suggest genetic factors explain 25 to 60% of the variability in serum urate levels,[6-13] consistent with estimates from a genome-wide association study of unrelated individuals, which predicted that 25 to 40% of the variability in serum urate levels is controlled by common single nucleotide variants.[14] The remaining 60 to 75% of serum urate variability is therefore explained by genetic factors (common and uncommon) not tagged by common variants, and non-genetic factors such as diet or other environmental exposures.

For centuries diet has been identified as a risk factor for the development of gout.[15 16] Consumption of red meat, shellfish, alcoholic beverages, sugary drinks, and tomatoes have all been associated with increased serum urate levels, and low-fat milk and coffee consumption have been associated with reduced serum urate levels.[17-21] Certain diets (e.g. the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet) have been shown to reduce serum urate levels [22,23] and the risk of gout.[24] In addition, food consumption is heritable, for example heritability of coffee consumption is estimated to be between 36 to 58% [25], alcohol consumption to be between 43 to 53% [26] and sugar-sweetened beverage consumption to be 48% [27], and genome-wide association studies have identified genetic associations with coffee and alcohol consumption habits [28,29]. It is therefore possible that the heritable component of specific food consumption contributes to the heritability of serum urate levels (e.g. signals in the *ABCG2, GCKR,* and *MLXIPL* genes are common to coffee consumption and serum GWAS) [14,28]. To date a systematic analysis of the contribution of diet to serum urate levels has not been performed in a sufficiently large data set. Furthermore, the relative contributions of inherited genetic variants and overall diet to variance in serum urate concentrations is unknown. This study aimed to systematically test individual dietary components for association with serum urate in a 'diet-wide association study' (DWAS) and quantify the relative contributions of overall diet and common genome-wide single nucleotide variants in determining serum urate levels.

METHODS

Participants

Demographic, anthropomorphic, and clinical data are presented in Table S1. Information from the baseline visit of the Atherosclerosis Risk in Communities (ARIC; 1987 to 1989; www2.cscc.unc.edu/aric), Coronary Artery Risk Development in (Young) Adults (CARDIA; 1985; www.cardia.dopm.uab.edu), Cardiovascular Heart (CHS; 1989 to 1990; https://chs-nhlbi.org) and Framingham Heart (FHS; 2002 to 2005; www.framinghamheartstudy.org) studies was sourced through the Database of Genotypes and Phenotypes (dbGaP; www.ncbi.nlm.nih.gov/gap; project ID #834). Anonymised information from the Third National Health and Nutrition Examination Survey (NHANES III; 1988 to 1991; www.cdc.gov/nchs/nhanes/nhanes3.htm) was also used. These five studies all recruited participants from the United States of America.

Analysis sample-sets of people of European ancestry were developed using consistent exclusion criteria between study cohorts (Figure S1). People without serum urate measurements or genome-wide genotypes were excluded, along with individuals under 18 years of age, people with kidney disease and / or gout, and those taking urate-lowering drugs and / or on diuretic medication. Individuals who did not provide information for any of the covariates used in analyses were also excluded. Quality controls for the dietary data were also applied, with participants who answered less than 10% of the food frequency survey excluded, along with individuals whose estimated average daily calorie intake was less than 600 kcal / day or greater than 4,200 kcal / day (inclusive). Participants whose questionnaire answers were deemed unreliable by the study interviewer at recruitment were also excluded.

Dietary Assessment

During recruitment participants from the five cohorts completed a validated food frequency questionnaire. The ARIC, CHS, and FHS participants completed similar questionnaires in which participants were asked to answer the question “How often, on average, in the past year did you eat [this food]?” by choosing from several frequency categories (66 questions and 9 answer categories for ARIC, 99 questions and 6 answer categories for CHS, and 126 questions and 9 answer categories for FHS).[30-34] These categorical answers were converted to average serves per week for analysis (Table S2).

CARDIA participants answered a specifically designed and validated diet history which assessed their consumption frequency of 100 food items using a series of questions, "Do you eat [this food]?" if yes, "How much do you usually have?" and "How often do you usually have it?" Answers were then converted to servings per week by the study researchers using the Nutrition Coordinating Centre (NCC; www.ncc.umn.edu) dietary analysis system.[35,36] NHANES III participants were given a questionnaire (60 questions) similar to that of the ARIC, CHS, and FHS studies in which they were asked "How often, in your usual diet over the past month, have you eaten [this food item]?" Answers were given in serves per month and converted to serves per week for analysis (Table S2).[37]

As each study administered a slightly different food frequency questionnaire, with a differing number of questions (60 to 126) and a slightly different list of food items within each question, questionnaires were assessed for between-study comparability. Briefly, questions were grouped together based on food type. Where questions were identical no changes to the data were made. Where questions were not identical between studies (eg. questionnaires asked about any wine consumption vs. separate red and white wine consumption) the answers were combined (after serve per week conversion) to create identical questions. If an identical question could not be created the non-matching information was excluded, either from only the cohort with non-matching data (eg. NHANES III asked about consumption of peanuts, peanut butter, nuts, and seeds in a single question, making this non-comparable to either the nuts or peanuts questions of the other four studies), or if at least three of the five cohorts did not have identical questions the extra information was excluded from the entire analysis (eg. only CHS and FHS asked about berry consumption, so berries were not included). This resulted in a group of 63 food items with comparable questions within at least three of the five studies (Table S3). Average consumption of each of these 63 food items, per sample-set, is presented in Table S4. Average consumption was not able to be adjusted for portion size in the aggregated data, as the NHANES III study did not specify portion size, the CHS study only specified a relative portion size (small / medium / large), and the portion sizes specified by the ARIC, CARDIA, and FHS studies were inconsistent.

Serum Urate Measurement

A standard uricase oxidation assay was used to measure serum urate for the ARIC, CARDIA, and NHANES III studies.[37-40] CHS serum urate levels were measured using a Kodak Ektachem 700

analyser and reagents.[41] For FHS serum urate levels were measured with a phosphotungstic acid reagent autoanalyser.[42]

Diet-Wide Association Analysis (DWAS)

All statistical analyses were performed using R v3.2.3 (www.R-project.org). For all regression analyses individuals with partial or missing data were excluded. For each food item a multivariate linear regression adjusted for sex, age, body mass index, menopausal status, average daily calorie intake, years of education, exercise levels, and smoking status was conducted in the five cohorts separately. Analyses in ARIC, CARDIA, CHS, and FHS were additionally adjusted for whole-genome principal component vectors one to four to account for cryptic relatedness (especially within FHS) that may cause inflation of test statistics owing to possible shared diet or heritability of serum urate levels. Principal components were calculated using publicly available whole-genome genotyping data (no genotype data were available for NHANES III) and the EIGENSOFT 2.0 SmartPCA program.[43] Regression beta values from the five cohorts were combined using an inverse-variance weighted meta-analysis with a Q-statistic calculated to detect any inter-cohort heterogeneity using the 'metagen' function within the R meta package.[44] A fixed-effect model was used if there was no significant heterogeneity, with a random-effect model used in the presence of heterogeneity ($P_Q < 0.01$). The diet-wide association analysis was repeated with the inclusion of four scores estimating diet quality (detailed below) as adjusting variables. Diet-wide significance was set at $P_\beta < 7.94\times10^{-4}$ after Bonferroni correction for multiple testing (0.05 divided by 63 food items). For each food item the four basic statistical assumptions of a linear regression (linear relationship, multivariate normality, multi-colinearity, and homoscedasticity) were assessed by generating plots of the food item versus serum urate, the standardised residuals versus the normal distribution (quantile-quantile plot), and the standardised residuals versus the predicted values from the linear regression. These plots (not shown) did not indicate any substantial deviation from these basic statistical assumptions.

Diet Quality Scores

Four diet scores were evaluated. The first was a 'Healthy-Eating' diet score calculated based on the Harvard Healthy Eating Pyramid (2008) and Healthy Eating Plate (2011) guidelines and an adaptation of

the methodologies used by Nettleton *et al.*[45] Food frequency questions (in serves per week) were combined into four categories representing the different levels of the Harvard Healthy Eating Pyramid / Plate [46] – Level 1: red meat, butter, refined grains, potatoes, sugar-sweetened beverages, and desserts / sweets; Level 2: dairy products (excluding butter) and alcohol; Level 3: nuts, seeds, beans, fish, poultry, and eggs; Level 4: vegetables, fruits, and whole grains. Quartiles of these four levels were determined and labelled numerically (0, 1, 2, 3) before being multiplied by a number representing each pyramid level. Level 1 was multiplied by negative two (least favourable), level 2 was multiplied by negative one, level 3 was multiplied by one, and level 4 was multiplied by two (most favourable). These values were summed to create a 'Healthy-Eating' score with a minimum value of -9 and a maximum value of 9, with a larger number indicating 'healthier' dietary habits (Figure S2).

The second diet score was the 'Dietary Approaches to Stop Hypertension (DASH)' score calculated based on the DASH diet recommendations and a direct replication of the methodologies used previously.[47,48] Food items (in serves per week) were grouped into five food groups representing foods that are favourable in the DASH diet; fruits, vegetables, nuts / legumes, whole grains, and low-fat dairy products. Two food groups representing foods that are unfavourable in the DASH diet were also created; red / processed meats and sugar-sweetened beverages. An estimate of the total sodium intake (calculated as part of the food to macro-nutrient conversion protocols performed by each study[30,31,33,35,37]) was included as a third food group that is unfavourable in the DASH diet. Each food group was classified into quintiles. Those foods that are favourable in the DASH diet were labelled numerically in ascending order (1, 2, 3, 4, 5) and those foods that are unfavourable in the DASH diet were labelled in descending order (5, 4, 3, 2, 1). These component scores were summed together to create the final DASH diet score with a minimum value of 8 and a maximum value of 40, with a larger number indicating 'healthier' dietary habits (Figure S3).

The third diet score was the Mediterranean diet score, constructed as previously described.[49] The index ascertains consumption of nine major food groups (non-refined cereals, potatoes, fruit, vegetables, legumes, fish, red meat, poultry, and full-fat dairy products), along with olive oil and alcohol intake. Olive oil was unable to be included as these data were not collected by all five of the study cohorts. Food items were grouped into the nine food groups, before each food group was split into six categories

of consumption (0; > 0, ≤ 1; > 1, ≤ 2; > 2, ≤ 3; > 3, ≤ 4; and > 4 serves per week). These categories were labelled from 0 to 5 in ascending order (0, 1, 2, 3, 4, 5) for the food groups favoured in the Mediterranean diet (non-refined cereals, potatoes, fruit, vegetables, legumes, and fish) and in descending order (5, 4, 3, 2, 1, 0) for the food groups not favoured in the Mediterranean diet (red meat, poultry, and full-fat dairy). Alcohol consumption was split into similar consumption categories, however those who reported consuming no alcohol were grouped with those who reported consuming > 4 serves per week of alcohol (> 0, ≤ 1; > 1, ≤ 2; > 2, ≤ 3; > 3, ≤ 4; and > 4 or 0 serves per week) as the Mediterranean diet considers moderate alcohol intake to be favourable. The alcohol categories were labelled from 0 to 4 in descending order (4, 3, 2, 1, 0). The labelled food groups (and alcohol) were summed together to create the Mediterranean diet score, with a minimum value of 0 and a maximum value of 49, with a larger number number indicating 'healthier' dietary habits (Figure S4).

The final diet quality score was a data-driven measure of the true dietary patterns. To create this score the five cohorts were combined and the 37 food items with complete information in all cohorts were extracted (beer, liquor, wine, citrus juice, non-citrus juice, coffee, tea, diet soft drink, soft drink, butter, cheese, ice cream, skim milk, whole milk, yoghurt, cake / pie, chocolate, biscuits / muffins, fish, shellfish, citrus fruit, non-citrus fruit, brown bread, white bread, cold cereal, pasta, legumes, beef / pork / lamb, liver, poultry, potato, spinach, tomato, winter squash, margarine, eggs, chips / popcorn). A parallel factor analysis was conducted using these 37 food items to visualise the point of inflection and determine the number of factors to use (n = 11) by comparing the scree plot from the actual data to simulated and resampled versions of the same data (Figure S5).[50] The 11 retained factors were rotated by an orthogonal transformation (varimax) - factors that had a sum of square loadings > 1 were identified (n = 1) and factor loadings (for each food item) > 0.2 were extracted based on the methodologies of [50-53]. This resulted in the construction of a single data-driven diet score based on factor loadings for seven food items (non-citrus juice = 0.22, soft drink = 0.40, butter = 0.34, white bread = 0.47, pasta = 0.21, beef / pork / lamb = 0.50, and chips / popcorn = 0.30). Consumption of each food item (in serves per week) was multiplied by the corresponding factor loading and these values were summed together resulting in a data-driven diet score with minimum 0 and maximum 71 (Figure S6).

The correlation between diet quality scores was assessed using a Pearson's product-moment correlation test. The diet quality scores were included in separate multivariate linear regression of serum urate levels adjusted for sex, age, body mass index, menopausal status, average daily calorie intake, years of education, exercise levels, smoking status, whole-genome principal component vectors one to four for ARIC, CARDIA, CHS, and FHS, and alcohol for the DASH diet score analysis (the DASH diet score does not include a separate component for alcohol). Regression beta values from each cohort were combined using an inverse-variance weighted meta-analysis with a fixed-effect model if there was no significant heterogeneity, and a random-effect model if there was heterogeneity present ($P_Q < 0.01$). A p-value less than 0.05 was considered statistically significant for the diet quality score analyses.

Genetic Analysis

The percentage of variance in serum urate explained by common genetic variants was assessed in two ways. Firstly, the 30 genome-wide significant variants identified in the largest European genome-wide association study[14] were obtained from the whole-genome genotyping data of the ARIC, CARDIA, CHS, and FHS cohorts. All variants were in Hardy-Weinberg equilibrium ($P > 0.01$) within the combined analysis group, except for *rs653178* ($P_{HWE} < 0.001$) and *rs2079742* ($P_{HWE} = 0.005$). For these two SNPs the individual cohorts were in Hardy-Weinberg equilibrium, except *rs653178* for ARIC ($P_{HWE} = 0.002$). A weighted genetic risk score was constructed from these genotypes and assessed for its contribution to serum urate variability. To create the genetic risk score genotypes were coded (0, 1, 2) to represent the number of risk alleles present, as defined by the effect directions previously reported and were multiplied by the effect size (converted to μmol/L) [14] These weighted variables were summed together, resulting in a genetic risk score with a minimum value of 0 and a maximum value of 236.15. The genetic risk score was tested for association with serum urate levels using a multivariate linear regression, adjusted for sex, age, body mass index, menopausal status, average daily calorie intake, years of education, exercise levels, smoking status, and whole-genome principal component vectors one to four. The resultant regression beta values from each cohort were combined using an inverse-variance weighted meta-analysis.

The second method to assess the contribution of common genetic variants to the variability of serum urate was the generation of heritability estimates under an additive model in the combined cohort

(excluding NHANES III). Briefly, non-imputed whole-genome genotypes for the ARIC, CARDIA, CHS, and FHS cohorts were merged, then filtered to exclude variants deviating from Hardy-Weinberg equilibrium ($P < 0.001$), with a variant call rate (< 70%), or a minor allele frequency < 0.01 using PLINK v1.90,[54,55] before a genetic relationship matrix was created using GCTA v1.26.0.[56] The genetic heritability of serum urate was then calculated using the restricted maximum likelihood (REML) analysis procedure within GCTA v1.26.0. This heritability estimate was adjusted for sex, age, body mass index, menopausal status, average daily calorie intake, years of education, exercise levels, smoking status, and whole-genome principal component vectors one to four.

RESULTS

Study power

After applying the standardised exclusion criteria to each study cohort a total of 16,760 participants (8,414 men and 8,346 women) were available for analysis. Based on these numbers power to detect an association at the diet-wide significance level ($P_\beta = 7.94\times10^{-4}$) was calculated, as described (Figure S7).[56] All sample-sets were adequately powered (≥ 80%) to detect an effect size corresponding to an R^2 of approximately 1%.

Diet-Wide Association Analysis (DWAS)

Eighteen food items were significantly associated with serum urate levels in the full or sex-specific cohorts ($P_\beta < 7.94\times10^{-4}$; Figure 1, Table 1). Ten associated with raised serum urate levels (shellfish, beer, liquor, wine, potato, poultry, soft drink, beef / pork / lamb, table sugar, and tea), and eight associated with lower serum urate levels (eggs, peanuts, cold cereal, skim milk, cheese, brown bread, margarine, and non-citrus fruit). The food with the strongest urate-raising effect (shellfish) associated with a 2.49 µmol/L increase in serum urate per serving per week, equating to a 17.43 µmol/L (0.28 mg/dL) increase per daily serving. In the full cohort table sugar was only nominally significant ($P_\beta < 0.05$, $P_\beta \geq 7.94\times10^{-4}$). It was significantly associated with serum urate in the male-only analysis, along with ten other food items (beer, liquor, wine, soft drink, skim milk, peanuts, eggs, cold cereal, brown bread, and non-citrus fruit). In the female-only subset eight food items (beer, liquor, wine, soft drink, cold cereal, cheese, brown bread and margarine) significantly associated with serum urate (Table 1). The effect sizes for shellfish, skim milk, and non-citrus fruit were similar to those reported in previous studies, while the effect sizes for soft drink, beer, liquor, and beef / pork / lamb were within the range of previously reported values.

Diet Quality Scores: Association with Serum Urate Levels

Increases in the 'Healthy-Eating', DASH, and Mediterranean diet scores (indicating a healthier diet) significantly associated with lowered serum urate levels in the full cohort (Table 2; β = -0.72 µmol/L, $P_\beta < 0.001$; β = -0.73 µmol/L, $P_\beta < 0.001$; β = -0.38 µmol/L, $P_\beta < 0.001$, respectively) and the male-only cohort (Table 2; β = -0.97 µmol/L, $P_\beta < 0.001$; β = -0.86 µmol/L, $P_\beta = < 0.001$; β = -0.53 µmol/L, $P_\beta < 0.001$ respectively), but only the DASH diet score was significantly associated with serum urate in the

female-only cohort (Table 2; β = -0.64 μmol/L, P_{β} = 0.03). The data-driven diet score, which represented a diet high in 'unhealthy' foods, associated with increased serum urate levels in the combined, and male-only, and female-only cohorts (Table 2; β = 0.59 μmol/L, $P_{\beta} < 0.001$; β = 0.62 μmol/L, $P_{\beta} < 0.001$; β = 0.53 μmol/L, $P_{\beta} < 0.001$, respectively). These diet quality scores were significantly correlated with each other (all ≥ 0.29 (absolute values), $P_{Cor} < 0.001$) and the results of the regression analyses for the 'Healthy-Eating', DASH, and Mediterranean diet scores were not significantly different in the sex-stratified cohorts ($P_{Diff} \geq 0.10$ and $P_{Diff} \geq 0.17$ for the male-only, and female-only cohorts respectively). In the full cohort the 'Healthy-Eating' and DASH diet scores and the 'Healthy-Eating' and Mediterranean diet scores did not have significantly different results ($P_{Diff} = 0.95$ and $P_{Diff} = 0.06$, respectively), whilst the DASH and Mediterranean diet score results were mildly different ($P_{Diff} = 0.03$). The results of the data-driven diet score were significantly different to the other three diet scores in the full, male-only, and female-only cohorts ($P_{Diff} < 0.001$, $P_{Diff} < 0.001$, and $P_{Diff} \leq 0.03$, respectively).

Given that foods are rarely consumed in isolation, and significant correlations ($P_{Cor} < 0.001$) were observed between every food item and at least one other food item (Figure S8), the diet-wide analysis was repeated with adjustment for the diet quality scores to account for confounding due to usual dietary habits. Twelve of the eighteen food items in the full cohort remained significantly associated (Table S5). Non-citrus fruit was non-significant after adjustment for all four of the diet quality scores, while peanuts, meat (beef / pork / lamb), potatoes, and poultry all had an attenuated association after adjustment for one (or more) of the diet quality scores. In addition, the nominally significant association between serum urate levels and table sugar consumption in the full cohort was significant after adjustment for all four of the diet quality scores. Similarly, adjustment for the 'Healthy-Eating,' DASH, and Mediterranean diet scores resulted in significant associations between serum urate and fish or legume consumption. In the male-only analysis seven of the eleven previously associated foods maintained their significance after adjustment for four of the diet quality scores (Table S6). Peanuts, cold cereal, and table sugar did not maintain their significance after adjustment for one of the diet quality scores, but did maintain significance when adjusted for the other three diet quality scores (Table S6). In the female-only analysis only beer, liquor, wine, cheese, and skim milk were consistently significant after the diet quality score adjustments, while soft drink, brown bread, cold cereal, and

margarine maintained significance when adjusted for three of the four diet quality scores, but not the other one (Table S7).

Table 1. Diet-wide significant associations with serum urate levels (μmol/L) in the full or sex-specific cohorts.

Food Items	Full Cohort						Male-Only						Female-Only					
	n	β	[95% CI]	P_β	R^2	β^	n	β	[95% CI]	P_β	R^2		n	β	[95% CI]	P_β	R^2	
Associated with higher urate levels																		
Shellfish	16,731	**2.49**	[1.36 to 3.61]	< 0.001	0.10%	2.12	8,401	**2.64**	[1.07 to 4.21]	< 0.001	0.13%		8,330	**2.31**	[0.64 to 3.98]	0.007	0.09%	
Beer	16,724	**1.34**	[1.13 to 1.56]	< 0.001	0.99%	3.91	8,392	**1.28**	[1.04 to 1.52]	< 0.001	1.31%		8,332	**1.78**	[1.22 to 2.34]	< 0.001	0.49%	
Liquor	16,743	**1.33**	[1.01 to 1.66]	< 0.001	0.40%	2.46	8,403	**1.16**	[0.77 to 1.56]	< 0.001	0.41%		8,340	**1.84**	[1.21 to 2.48]	< 0.001	0.44%	
Wine	16,743	**1.29**	[0.87 to 1.71]	< 0.001	0.17%	-	8,402	**1.30**	[0.64 to 1.96]	< 0.001	0.16%		8,341	**1.31**	[0.78 to 1.85]	< 0.001	0.20%	
Potato	16,754	**0.87**	[0.42 to 1.32]	< 0.001	0.11%	-	8,411	**0.90**	[0.25 to 1.56]	0.007	0.09%		8,343	**0.77**	[0.15 to 1.40]	0.02	0.09%	
Poultry	16,740	**0.70**	[0.29 to 1.10]	< 0.001	0.08%	-	8,403	**0.94**	[0.33 to 1.56]	0.003	0.10%		8,337	**0.50**	[-0.02 to 1.02]	0.06	0.05%	
Soft Drink	16,745	**0.68**	[0.50 to 0.86]#	< 0.001	0.30%	1.29; 0.71; 0.56	8,404	**0.79**	[0.53 to 1.04]	< 0.001	0.39%		8,341	**0.53**	[0.27 to 0.79]	< 0.001	0.16%	
Beef / Pork / Lamb	16,757	**0.63**	[0.32 to 0.95]	< 0.001	0.08%	1.95; 0.43	8,412	**0.72**	[0.28 to 1.16]	0.001	0.12%		8,345	**0.47**	[0.02 to 0.92]	0.04	0.04%	
*Table Sugar	12,488	**0.47**	[0.08; 0.85]#	0.02	0.11%		6,274	**0.40**	[0.20 to 0.61]	< 0.001	0.20%		6,214	**0.57**	[-0.08 to 1.22]#	0.08	0.04%	
Tea	16,702	**0.24**	[0.11 to 0.38]	< 0.001	0.07%		8,385	**0.22**	[0.02 to 0.42]	0.04	0.06%		8,317	**0.24**	[0.07 to 0.42]	0.006	0.09%	
Associated with lower urate levels																		
Eggs	16,736	**-1.10**	[-1.54 to -0.66]	< 0.001	0.13%	-	8,403	**-1.45**	[-2.03 to -0.86]	< 0.001	0.27%		8,333	**-0.23**	[-0.90 to 0.45]	0.51	0.01%	
*Peanuts	12,504	**-0.88**	[-1.25 to -0.51]	< 0.001	0.18%	-	6,277	**-1.01**	[-1.51 to -0.52]	< 0.001	0.24%		6,227	**-0.65**	[-1.23 to -0.07]	0.03	0.07%	
Cold Cereal	16,751	**-0.72**	[-0.97 to -0.47]	< 0.001	0.14%	-	8,409	**-0.73**	[-1.07 to -0.38]	< 0.001	0.19%		8,342	**-0.67**	[-1.04 to -0.30]	< 0.001	0.08%	
Skim Milk	16,714	**-0.63**	[-0.78 to -0.48]	< 0.001	0.40%	-0.63	8,390	**-0.78**	[-1.00 to -0.56]	< 0.001	0.55%		8,324	**-0.48**	[-0.68 to -0.28]	< 0.001	0.24%	
Cheese	16,755	**-0.62**	[-0.89 to -0.35]	< 0.001	0.09%	-	8,410	**-0.64**	[-1.05 to -0.23]	0.002	0.10%		8,345	**-0.64**	[-0.99 to -0.29]	< 0.001	0.09%	
Brown Bread	16,710	**-0.60**	[-0.77 to -0.42]	< 0.001	0.22%	-	8,382	**-0.68**	[-0.93 to-0.44]#	< 0.001	0.34%		8,328	**-0.45**	[-0.71 to -0.20]	< 0.001	0.11%	
Margarine	16,716	**-0.29**	[-0.44 to -0.15]	< 0.001	0.10%	-	8,383	**-0.29**	[-0.50 to -0.08]#	0.007	0.10%		8,333	**-0.34**	[-0.53 to -0.14]	< 0.001	0.11%	
Non-Citrus Fruit	16,760	**-0.28**	[-0.43 to -0.13]	< 0.001	0.06%	--	8,414	**-0.43**	[-0.66 to -0.19]	< 0.001	0.14%		8,346	**-0.14**	[-0.33 to 0.04]	0.13	0.01%	

Food items are presented in order of those with the largest effect (absolute β-value) to those with the smallest effect. n – number of participants analysed. β – inverse-variance weighted meta-analysis beta value, reflecting the change in serum urate level (μmol/L) per one extra serve per week of the food item. 95% CI – 95% confidence intervals of the beta value. P_β – p-value for meta-analysis beta value. R^2 – partial R^2 value (R^2_B) converted to a percentage (R^2 * 100). For each regression analysis the partial R^2 (R^2_B) attributable to the food item was calculated by comparing the regression R^2 (R^2_{AB}) to the R^2 (R^2_A) of a corresponding regression using all the adjusting variables, but not the food item using the 'partial.R2' function within the R 'asbio' package.[57] * – indicates not all data-sets were included in the analysis, the number of asterisks represents the number of data-sets missing data. # – a random-effect model was used in the meta-analysis ($P_Q < 0.05$). β^ – β-values (μmol/L change per serve per week) from significantly associated analyses from published data in combined men and women: shellfish was compared to seafood data from [19]; beer and liquor to data from [21]; soft drink to sugar-sweetened soft drink data from [58-60]; beef / pork / lamb to meat data from [19,60]; skim milk to data from [60]. Refs [19,21,58] analysed NHANES III therefore are not independent of our study.

Variance in Serum Urate Explained by Dietary Scores and Inherited Genetic Variants

Individually, the eighteen food items associating with serum urate in the full-cohort explained 0.06% to 0.99% of the variation in serum urate levels, and combined they explained 3.64% of the variation (Table 1). All 63 food items, collectively, explained 4.29% of variation in serum urate levels (Table S5). Food groups (fruit, vegetables, meat, and dairy) explained between 0.16% and 0.52% of variation in serum urate levels (Table S5). The DASH diet score explained more of the variation in serum urate levels in the full cohort (Table 2; 0.28%) than the 'Healthy-Eating' (0.15%), Mediterranean (0.06%), or data-driven (0.16%) diet scores, but each diet quality score explained less variation in serum urate than the most strongly associated individual food items (Table 1).

In contrast, 30 genetic variants previously associated with serum urate levels at a genome-wide level of significance in Europeans[14] additively explained 8.7% of the variance in serum urate levels in the full cohort (excluding NHANES III; Table S8) and a weighted serum urate genetic risk score constructed from these 30 variants[14] explained 7.9% of the variance (Table 2). When included in models with the dietary scores the percentage variance explained did not substantially change in the full, male-only, and female-only cohorts (maximum difference of -0.04%; Table 2), whilst the percentage variance explained by the dietary scores after adjustment for the genetic risk score fluctuated from a -0.09% difference for the data-driven diet quality score in the male-only cohort to a +0.13% difference in the Mediterranean diet score in the male-only cohort (Table 2). Genome-wide estimations of serum urate heritability explained 23.9% (95% CI [20.2 to 27.5], $P < 0.001$) of variance in serum urate levels in the full cohort (excluding NHANES III); the sex-specific heritability estimates were 23.8% (95% CI [16.6 to 30.0], $P < 0.001$) in the male-only cohort and 40.3% (95% CI [33.5 to 47.1], $P < 0.001$) in the female-only cohort. There was evidence for interaction between any of the four diet scores and the weighted genetic risk score only for the DASH diet in the female-only cohort (P=0.04), for all others P was $P \geq 0.21$ (Table S9)..

Table 2. Percent variance in serum urate levels (µmol/L) explained by dietary and genetic factors.

Diet / Genetic Score	Additional Adjustor	Full Cohort					Male-Only					Female-Only				
		n	β	[95% CI]	P_β	R^2	n	β	[95% CI]	P_β	R^2	n	β	[95% CI]	P_β	R^2
Dietary Effect																
'Healthy-Eating'	-	16,759	-0.72	[-1.01 to -0.43]	< 0.001	0.15%	8,413	-0.97	[-1.41 to -0.54]	< 0.001	0.21%	8,346	-0.43	[-1.25 to 0.38]#	0.30	0.07%
	Genetic Risk Score	12,162	-0.61	[-0.93 to -0.29]	< 0.001	0.12%	6,109	-0.82	[-1.31 to -0.33]	< 0.001	0.16%	6,053	-0.35	[-1.31 to 0.61]#	0.48	0.05%
DASH	-	16,731	-0.73	[-0.96 to -0.50]	< 0.001	0.28%	8,402	-0.86	[-1.20 to -0.52]	< 0.001	0.31%	8,329	-0.64	[-1.23 to -0.05]#	0.03	0.17%
	Genetic Risk Score	12,139	-0.75	[-1.01 to -0.50]	< 0.001	0.37%	6,100	-0.89	[-1.28 to -0.51]	< 0.001	0.43%	6,039	-0.71	[-1.45 to 0.03]#	0.06	0.25%
Mediterranean	-	16,719	-0.38	[-0.59 to -0.18]	< 0.001	0.06%	8,392	-0.53	[-0.83 to -0.22]	< 0.001	0.10%	8,327	-0.18	[-0.46 to 0.09]	0.19	0.01%
	Genetic Risk Score	12,131	-0.47	[-0.70 to -0.23]	< 0.001	0.12%	6,092	-0.71	[-1.06 to -0.36]	< 0.001	0.23%	6,039	-0.15	[-0.46 to 0.16]	0.35	0.02%
Data-Driven	-	16,652	0.59	[0.39 to 0.80]	< 0.001	0.16%	8,354	0.62	[0.33 to 0.91]	< 0.001	0.17%	8,298	0.53	[0.24 to 0.83]	< 0.001	0.14%
	Genetic Risk Score	12,078	0.48	[0.25 to 0.71]	< 0.001[5]	0.08%	6,063	0.43	[0.10 to 0.76]	0.01	0.08%	6,015	0.54	[-0.18 to 1.27]#	0.14	0.10%
Genetic Effect																
Genetic Risk Score	-	12,162	0.99	[0.93 to 1.05]	< 0.001	7.85%	6,109	0.93	[0.84 to 1.03]	< 0.001	5.89%	6,053	1.04	[0.97 to 1.12]	< 0.001	10.55%
	'Healthy Eating'	12,162	0.99	[0.93 to 1.05]	< 0.001	7.82%	6,109	0.93	[0.84 to 1.03]	< 0.001	5.87%	6,053	1.04	[0.96 to 1.12]	< 0.001	10.51%
	DASH	12,147	0.99	[0.93 to 1.05]	< 0.001	7.85%	6,106	0.94	[0.84 to 1.03]	< 0.001	5.91%	6,041	1.04	[0.96 to 1.12]	< 0.001	10.55%
	Mediterranean	12,131	0.99	[0.93 to 1.05]	< 0.001	7.86%	6,092	0.94	[0.84 to 1.03]	< 0.001	5.93%	6,039	1.04	[0.97 to 1.12]	< 0.001	10.53%
	Data-Driven	12,078	0.99	[0.93 to 1.05]	< 0.001	7.84%	6,063	0.94	[0.84 to 1.03]	< 0.001	5.89%	6,015	1.04	[0.97 to 1.12]	< 0.001	10.53%

NHANES III was unable to be included in the genetic risk score or heritability analyses. n – number of participants analysed. β – inverse-variance weighted meta-analysis beta value, reflecting the change in serum urate level (µmol/L) per one number increase in diet score or genetic risk score. 95% CI – 95% confidence intervals of the beta value. P_β – p-value for meta-analysis beta value. R^2 – partial R^2 value (R^2_B) converted to a percentage (R^2 * 100). # – indicates a random-effect model was used in the meta-analysis due to a heterogeneity P_Q < 0.05. Where a particular variant in the genetic risk score was not directly genotyped, it was imputed using the IMPUTE2 imputation method and the 1000 Genomes phase 3 reference panel [61]. Imputation quality was high for all SNPs analysed (quality score ≥ 0.71).

DISCUSSION

Principal findings

Eighteen different food items were significantly associated with serum urate levels. These foods included seven established urate-modifying foods; shellfish, beer, liquor, wine, soft drink, skim milk, and meat (beef / pork / lamb). The eleven other foods included three less established urate-modifying foods (tea, cheese, and non-citrus fruit) and eight food items with novel associations – poultry, potatoes, brown bread, peanuts, margarine, cold cereal, table sugar, and eggs. The associations observed in this diet-wide study with known, confirmed serum urate-influencing food items were consistent in direction of effect and magnitude with previously reported associations (urate-raising: beer, liquor, wine, soft drinks, meat (beef / pork / lamb), and shellfish; urate-lowering: skim milk) (Table 1). However, each of these established foods explained < 1% of variation in serum urate levels within the full cohort. Similarly, the dietary risk scores explained very little variance in serum urate levels (0.28% by DASH; 0.15% by the 'Healthy-Eating' score; 0.06% by the Mediterranean score and 0.16% by the data-driven score) (Table 2). In comparison, the heritability explained by common genetic variants, was estimated to be 23.9%, with a weighted GWAS-identified genetic risk score explaining 7.9% of the variability in serum urate levels (Table 2). Thus, in the datasets analysed here, overall diet explains much less variance in serum urate levels when compared to inherited genetic variants.

Strengths and limitations of study

There are limitations to our study. The primary limitation is the use of differing food frequency questionnaires between studies, which led to methodological challenges when combining the study-specific effects and may have led to the study participants giving information of variable accuracy between studies. To circumvent these issues the food frequency data were carefully inspected for between-study comparability and several quality-controls were applied to the data before use. Adjustment for estimated average daily calorie intake was also consistently performed during analysis to further minimise any bias or inaccuracies caused by these differing questionnaires. Given that data were collected at different times (1985 to 2002) food compositions may also have changed, resulting in unintentional combining of non-comparable food items in this analysis. This situation may be particularly important when processed foods are being assessed (such as cereals, bread, mayonnaise / dressing).[68] This is also an important consideration in generalisation of results to the present-day or to other countries. This study population was individuals of European ancestry living in the United States of America, and the dietary and genetic analysis may not be generalisable to other populations. Additionally, as with any large-scale set of analyses the likelihood of finding a

falsely significant result increases with every extra test added. With the application of a Bonferroni correction to account for this multiple-testing effect this likelihood is reduced. However, it is possible that some of the food items that were nominally significant ($P < 0.05$) may have a real effect undetected in this study (type II error). Furthermore, measurement error of dietary intake[63] will contribute to suppressed R^2 estimates of the contribution of diet to variance in serum urate levels relative to that of the genetic R^2 estimates, which will have minimal measurement error. Finally, there is a heritable component to food preferences including food consumption and alcohol [26,27], implying non-independence between dietary scores and the genetic risk score. To mitigate this the additionally adjusted analyses presented in Table 2 included both dietary and genetic risk scores in the same model.

Comparison with other studies

Due to the diet-wide approach to our analysis, associations with novel and less established foods were identified. Of the eleven novel / less established associations we found some evidence within the literature to support the tea, cheese, non-citrus fruit, egg, brown bread and cold cereal associations. Egg consumption has previously been associated with reduced urate levels in a Croatian study[64] and protection from hyperuricaemia in a Taiwanese Nutrition and Health Survey.[65] In a third study there was no significant association with the risk of hyperuricaemia in elderly Taiwanese men, although a trend towards protection was evident.[66] Finally, association between egg consumption and increased serum urate levels has been reported in two cohorts of European ancestry.[67] Certainly the current cumulative evidence is ambiguous regarding a possible role for egg consumption in urate control. Similarly, tea consumption was associated with increased serum urate levels in our study, contradictory to a recent meta-analysis that found no evidence for association of tea consumption with serum urate,[68] although the meta-analysis did provide weak evidence for association of green tea consumption with increased serum urate levels. Our study did not distinguish between black and green tea. We also observed an association between non-citrus fruit and reduced serum urate levels, which is supported by association of fruit consumption with reduced urate levels in an Australian cohort.[67] The loss of significance (in the full cohort) when the association of non-citrus fruit with serum urate was adjusted for the diet quality scores may indicate that greater consumption of fruit is reflective of differing general dietary habits (also inferred from the correlation matrix; Figure S8) and may reflect confounding due to healthier dietary habits. That coarse bread and cheese associate with reduced urate levels in two cohorts of European ancestry [67] and cereal in one of two cohorts of European ancestry [67] provides support for our data associating brown bread, cold cereal and cheese with reduced serum urate levels (Table 1). We

are not aware of other studies specifically testing for association of potato, table sugar, peanut and margarine consumption with serum urate levels. Thus these findings require replication before being claimed as genuine urate-raising or urate-lowering foods.

Several studies have used food frequency data to estimate the effect of dietary habits on serum urate levels (similar to the various diet score analyses presented here) with varying results. Heidemann *et al.*[53] used a factor analysis to create two indicators of dietary habits in a group of German individuals. This study showed that individuals whose diet was characterised by high intake of refined grains, processed meats, eggs, and sugar-sweetened beverages (processed food dietary pattern) had significantly higher urate levels than people who did not commonly eat these foods. We also used factor analysis, identifying a single dietary habit, comprising non-citrus juice, soft drinks, butter, white bread, pasta, meat (beef / pork / lamb), and chips / popcorn, within the five combined cohorts. Given that this pattern includes similar foods to those in Heidemann *et al.*'s processed food pattern and several established urate-raising foods it was not unexpected that it was associated with raised serum urate levels (Table 2; $\beta = 0.59$ μmol/L per unit change). Interestingly, when Heidemann *et al.* reversed their analysis, using a diet score that represented a health conscious dietary pattern (characterised by a high intake of fruit, vegetables, and whole grains), no association with serum urate was seen.[53] This is contradictory to the results we have presented here for both the individual effects of non-citrus fruit and brown bread, and the urate-lowering influence of the three dietary scores constructed based on conventional healthy diet advice. Another study which assessed the association between estimates of three dietary patterns and serum urate levels in Taiwanese individuals, found no significant association between estimates of a urate-raising dietary pattern (consuming high levels of seafood, meat, sugar-sweetened beverages, and organ meats), a fish and fried food dietary pattern, or a vegetable and fruit dietary pattern. They posited that other clinical factors such as obesity and concomitant medications are more important than diet in determining serum urate levels,[52] a suggestion supported by the greater effect of genetics versus diet observed here.

Our results using the DASH diet score compare well to the Juraschek *et al.* randomised control trial that demonstrated an average reduction of serum urate of 21 μmol/L (0.35 mg/dL) when comparing the DASH diet to an 'average American diet' in individuals with pre- or Stage 1-hypertension.[23] There was a greater reduction of 77 μmol/L (1.29 mg/dL) in participants with hyperuricaemia (although there were very few hyperuricaemic subjects (n = 8)). In our analysis the DASH dietary

scores could vary from 8 to 40, with each unit increase in score associated with a 0.73 μmol/L decrease in serum urate. This corresponds with a decrease of 23.4 μmol/L between the least DASH-like diet and the most DASH-like diet, comparable to the decrease of 21 μmol/L reported by Juraschek *et al*.[23] Certainly, if a DASH diet is able to be maintained outside the research setting our and Juraschek *et al.*'s data[23] indicate that, relative to a non-DASH diet, a clinically-relevant decrease in serum urate levels can be achieved. However, implementation of the DASH diet may not be straightforward; although this diet was reported two decades ago,[47] the barriers to implementing this diet both at the population level and primary care setting are yet to be overcome.[69]

Conclusions and policy implications

This study has identified an association between estimates of healthier dietary habits and reduced urate in people of European ancestry. Aside from the CHS cohort for which gout ascertainment information was not available, the study population excluded people with a diagnosis of gout or those on urate-lowering therapy, and therefore these results cannot be generalised to people with gout. Nor can results be generalised to people of non-European ancestry. Our data are important in demonstrating the relative contributions of overall diet and inherited genetic factors to the population variance of serum urate levels. Our data challenge widely held community perceptions that hyperuricaemia is primarily caused by diet,[70-73] showing for the first time that genetic variants have a much greater contribution to hyperuricaemia than dietary exposure.

FIGURE LEGEND

Figure 1. Manhattan plot of –log10(p-values) for 63 food items associated with serum urate levels.

Green dots indicate a serum urate-raising effect; orange dots indicate a serum urate-lowering effect. Red line – Bonferroni corrected multiple-testing significance threshold ($P_\beta < 7.94\times10^{-4}$). Blue dashed line – nominal significance level ($P_\beta < 0.05$). * – indicates not all data-sets were included in the analysis, the number of asterisks represents the number of data-sets missing data.

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ETHICAL APPROVAL AND INFORMED CONSENT

The ARIC, FHS, CHS and CARDIA datasets were accessed through the Database of Genotype and Phenotype (www.ncbi.nlm.nih.gov/gap) via approval #834 and access was approved by the relevant

Data Access Committees. All participants, including those in the NHANES III study, gave their written informed consent.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; ND has received consulting fees, speaker fees, or grants from the following companies who have developed or marketed urate-lowering therapies for management of gout: Takeda, Ardea Biosciences / AstraZeneca, Cymabay / Kowa, Crealta / Horizon. TRM has received grants from Ardea Biosciences / AstraZeneca and Ironwood Pharmaceuticals. TJM and RKT have had no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and; no other relationships or activities that could appear to have influenced the submitted work.

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CONTRIBUTORSHIP STATEMENT

TJM, ND and TRM conceived the study. TJM and RKT managed and analysed data. TJM and TRM wrote the manuscript. ND and RKT commented on drafts. All authors approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

TRANSPARENCY DECLARATION

TRM (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA SHARING

Code available from the corresponding author at tony.merriman@otago.ac.nz. Dataset also available provided that requestor has appropriate Database of Genotype and Phenotype approval.

PATIENT INVOLVEMENT STATEMENT

No patients were asked for input in creation of this article. ND and TRM are founding members of the Auckland-based Counties Manukau District Health Board Maaori Gout Action Group [74] that has identified that "to achieve modern management of gout, those with gout need to be supported by primary care practitioners who are aware of the need for early intervention with allopurinol, as well as whaanau/families and communities who understand the impact and causes of gout" [74]. This group includes patient advocacy from Arthritis New Zealand. The views of the Maaori Gout Action Group inform our research into the causes and management of gout and have influenced our design and conclusions of this study. In qualitative research with gout patients during her PhD research at the University of Otago (awarded 2016) TJM was informed by the lived experiences of gout patients that led to publication of the role of tomato consumption as a trigger of gout [20]. This work was a key genesis for the work presented here.

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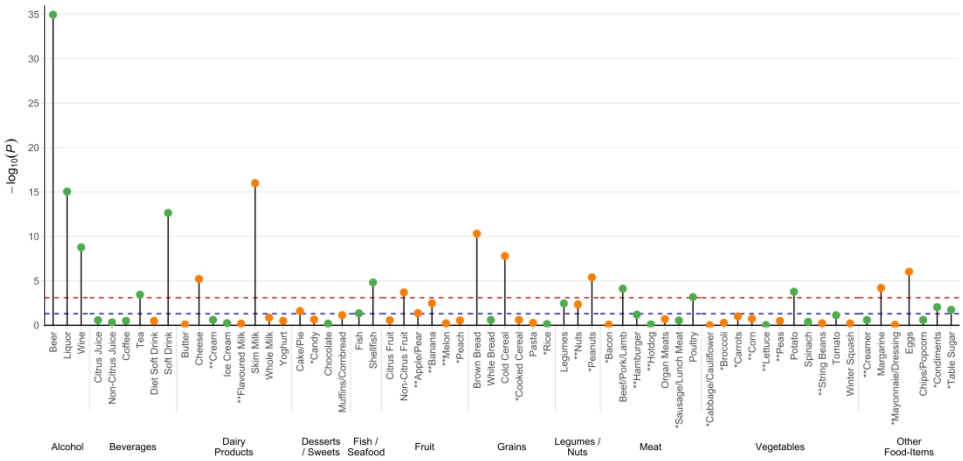
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Ice Cream
**Flavoured Milk
Skim Milk
Whole Milk
Yoghurt
Cake/Pie
*Candy
Chocolate
Muffins/Cornbread
Fish
Shellfish
Citrus Fruit
Non-Citrus Fruit
**Apple/Pear
**Banana
**Melon
*Peach
Brown Bread
White Bread
Cold Cereal
*Cooked Cereal
*Pasta
*Rice
Legumes
**Nuts
*Peanuts
*Bacon
Beef/Pork/Lamb
**Hamburger
**Hotdog
Organ Meats
*Sausage/Lunch Meat
Poultry
*Cabbage/Cauliflower
*Broccoli
*Carrots
**Corn
**Lettuce
**Peas
Potato
Spinach
**String Beans
Tomato
Winter Squash
**Creamer
Margarine
*Mayonnaie/Dressing
Eggs
Chips/Popcorn
*Condiments
*Table Sugar
Alcohol
Beverages
Dairy Products
Desserts / Sweets
Fish / Seafood
Fruit
Grains
Legumes / Nuts
Meat
Vegetables
Other Food-Items