British Journal of Nutrition (2017), **117**, 686–697
doi:10.1017/S0007114517000411

Genetic risk scores, sex and dietary factors interact to alter serum uric acid trajectory among African-American urban adults

May A. Beydoun[1]*, Jose-Atilio Canas[2], Marie T. Fanelli-Kuczmarski[3], Salman M. Tajuddin[1], Michele K. Evans[1]† and Alan B. Zonderman[1]†

[1]*Laboratory of Epidemiology and Population Sciences, National Institute on Aging (NIA), National Institutes of Health, Intramural Research Program (NIH/IRP), Baltimore, MD 21224, USA*
[2]*Pediatric Endocrinology, Diabetes and Metabolism, Nemour's Children's Clinic, Jacksonville, FL 32207, USA*
[3]*Department of Behavioral Health and Nutrition, University of Delaware, Newark, DE 19716, USA*

(Submitted 26 July 2016 – Final revision received 5 December 2016 – Accepted 3 February 2017 – First published online 27 March 2017)

Abstract

Serum uric acid (SUA), a causative agent for gout among others, is affected by both genetic and dietary factors, perhaps differentially by sex. We evaluated cross-sectional (SUA_{base}) and longitudinal (SUA_{rate}) associations of SUA with a genetic risk score (GRS), diet and sex. We then tested the interactive effect of GRS, diet and sex on SUA. Longitudinal data on 766 African-American urban adults participating in the Healthy Aging in Neighborhood of Diversity across the Lifespan study were used. In all, three GRS for SUA were created from known SUA-associated SNP (GRS_{base} (*n* 12 SNP), GRS_{rate} (*n* 3 SNP) and GRS_{total} (*n* 15 SNP)). Dietary factors included added sugar, total alcohol, red meat, total fish, legumes, dairy products, caffeine and vitamin C. Mixed-effects linear regression models were conducted. SUA_{base} was higher among men compared with that among women, and increased with GRS_{total} tertiles. SUA_{rate} was positively associated with legume intake in women ($\gamma = +0{\cdot}14$; 95 % CI +0·06, +0·22, $P = 0{\cdot}001$) and inversely related to dairy product intake in both sexes combined ($\gamma = -0{\cdot}042$; 95 % CI −0·075, −0·009), $P = 0{\cdot}010$). SUA_{base} was directly linked to alcohol consumption among women ($\gamma = +0{\cdot}154$; 95 % CI +0·046, +0·262, $P = 0{\cdot}005$). GRS_{rate} was linearly related to SUA_{rate} only among men. Legume consumption was also positively associated with SUA_{rate} within the GRS_{total}'s lowest tertile. Among women, a synergistic interaction was observed between GRS_{rate} and red meat intake in association with SUA_{rate}. Among men, a synergistic interaction between low vitamin C and genetic risk was found. In sum, sex–diet, sex–gene and gene–diet interactions were detected in determining SUA. Further similar studies are needed to replicate our findings.

Key words: Serum uric acid: Diets: Genetic risk scores: African-Americans: Urban adults

Uric acid (UA), the final catabolic product of purine oxidation, is the causative agent of gout, characterised by urate crystal deposition in joints and elevated serum uric acid (SUA) or hyperuricaemia[1]. Gout affects 6–8 % of the elderly (>80 years) and approximately 3·9 % of the entire US population[2]. Moreover, hyperuricaemia independently predicts myocardial infarction and premature death[3]. Two key physiological mechanisms determining hyperuricaemia are increased liver production of urate from dietary and endogenous substrates that raise purine levels, and reduced renal and gut excretion of UA[4]. Thus, uncovering a genetic basis for both mechanisms might elucidate the aetiological factors behind gout. Recent genome-wide association studies (GWAS) have identified various genetic loci with the strongest influences on SUA such as ATP binding cassette subfamily G member 2 (*ABCG2*), sodium/phosphate cotransporter 4 (NPT4) (solute carrier family 17 (organic anion transporter), member 3), NPT1 (solute carrier family 17 (organic anion transporter), member 1 (*SLC17A1*)), solute carrier family 22 (organic anion/urate transporter), member 12 (URAT1) (solute carrier family 22 (organic anion/urate transporter), member 12 (*SLC22A12*)), organic anion uptake transporter 4 (OAT4) (solute carrier family 22 (organic anion/urate transporter), member 11) and GLUT9 (solute carrier family 2 (facilitated GLUT), member 9 (*SLC2A9*))[2] However, no study thus far has compiled all recently identified SNP into a genetic risk score (GRS) for SUA in a longitudinal study of African-American (AA) adults. Moreover, the sex-specific effect of this GRS is yet to be uncovered.

Although genetics has a strong influence on SUA, dietary factors including the Mediterranean Diet Score[5,6] and specific components may have equally important effects[2]. On the basis of recent data[1,7–12], it is hypothesised that red meat and seafood consumption are linked to an increased risk for gout and/or hyperuricaemia[1,9], with similar adverse effects found

Abbreviations: AA, African-American; GRS, genetic risk score; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Lifespan; SLC2A9, solute carrier family 2 (facilitated GLUT), member 9; SUA, serum uric acid; UA, uric acid.

* **Corresponding author:** M. A. Beydoun, fax +1 410 558 8236, email baydounm@mail.nih.gov

† Co-senior authors.

for alcohol, particularly from beer and liquor[1,7,9,10,13,14], and fructose-containing foods including soft drinks[1,9,11,12] as well as intake of legumes in animal studies[15]. In contrast, dairy products, particularly low-fat milk and yogurt[1,9,10,14]intake, caffeine intake[1,9,14] and vitamin C[1,9,14] intake are all hypothesised to be inversely related to gout and/or hyperuricaemia risk. This study evaluated the cross-sectional (SUA_{base}) and longitudinal (SUA_{rate}) associations of SUA with GRS, diet and sex. We then tested interactive effect of GRS, diet and sex on SUA.

Thus, using genetic data available on the AA urban adults participating in the Healthy Aging in Neighborhoods of Diversity Across the LifeSpan (HANDLS), this study had several key aims: first, the study generates and evaluates the effects of GRS for elevated SUA by relating it to both baseline SUA and over-time change in SUA among AA urban adults. Second, the study examines sex-specific association between this GRS and SUA, an association previously observed in individual SNP[16–18]. Finally, the study evaluates the relationship between the eight previously described dietary factors and SUA at baseline and change over time, while examining sex–diet interactions and gene–diet interactions within sex groups.

Methods

Database

HANDLS is a prospective cohort study of a representative sample of AA and White men and women aged 30–64 years at baseline. Details of the study design have been described previously[23] (http://handls.nih.gov/). In brief, data were collected in two separate phases at baseline (2004–2009; visit 1), with Phase 1 assessing socio-demographic information (age, sex, education, poverty status, etc.), physiological and psychological chronic exposure, and including the first 24-h dietary recall, whereas Phase 2 consisting of in-depth examinations in Mobile Research Vehicles and including a second 24-h dietary recall, psychometric, anthropometric, body composition and laboratory parameter measurements[19]. Visit 2 of HANDLS, initiated in 2009, followed a similar protocol, from which laboratory measurements, specifically SUA, were utilised in this study.

Procedures followed the ethical standards of the institution and approval was obtained from The MedStar Institutional Review Board, and written informed consent was obtained from all HANDLS participants.

Study sample

Data were derived from baseline visit 1 (2004–2009) and the first follow-up examination (visit 2; 2009–2013), and were appended in the long format to facilitate mixed-effects regression modelling analyses (N is the number of persons, N' the number of observations and k the number of observations/person). Follow-up time (range: <1–approximately 8 years) had a mean of 4·64 (SD 0·93) years, with time = 0 for the baseline visit and time = elapsed years to the nearest day for follow-up visit. HANDLS initially recruited N_1 3720 participants (sample 1, n_1 2198 AA), with total observations at both visits being N_1' 6025 (n_1' 3616 AA). Among all HANDLS participants, SUA was available at either visits 1 or 2 for N_2 3021 (N_2' 5315), of whom n_2 1,792 were AA with n_2' 3199 observations (sample 2). Of AA in sample 2, participants with missing data on any of the two baseline 24-h dietary recalls were excluded, yielding a sample size of n_3 1235 (n_3' 2206) (sample 3). Out of these participants, only those with complete genetic data (original sample, n 1024 AA) were selected (n_4 766; n_4' 1375; visits/person, k 1·8) (sample 4). Thus, our final sample consisted of AA with complete genetic data, complete baseline dietary data with two 24-h recalls and SUA measured at either of the two visits. Sample 4 differed from the unselected participants of sample 1 AA, by having a lower proportion above poverty (49·5 *v.* 54·3 %, $P = 0·032$), with no notable differences by sex or age (online Supplementary Fig. S1). The same pattern was noted when comparing AA with complete genetic data who were selected (n_4 766, 49·5 % above poverty) to those who were not (n 258/1024, 62·8 % above poverty).

Serum uric acid

Using 1 ml of fasting blood serum, SUA was measured using a standard spectrophotometry method at both visits (Quest Diagnostics) (http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=905). SUA was measured at both visits in HANDLS, and expressed in mg/dl, whereby 1 mg/dl of SUA is equivalent to 0·01681237 μmol/l.

Dietary assessment

Dietary factors included in our analyses were measured at the baseline visit. Both baseline 24-h dietary recalls were obtained using the US Department of Agriculture Automated Multiple Pass Method, a computerised structured interview[20]. Measurement aids were used and included measuring cups, spoons, a ruler and an illustrated *Food Model Booklet*. Both recalls were administered in-person by trained interviewers, 4–10 d apart. Trained nutrition professionals used Survey Net, matching foods consumed with eight-digit codes from the Food and Nutrient Database for Dietary Studies version 3.0[21], and MyPyramid Equivalents Database (MPED) for food groups (MPED 2: http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/mped/mped2_doc.pdf). Eight dietary factors were chosen as proxy or direct measures for dietary components previously linked SUA: (1) added sugars (teaspoon/d), (2) alcoholic beverages (drinks/d, with one drink defined as twelve fluid ounces of beer, five fluid ounces of wine, or one-and-a-half fluid ounces of 80-proof distilled spirits), (3) ounce equivalents/d of red meats, (4) ounce equivalents/d of fish (sum of fish high and low in n-3 fatty acids), and (5) cup equivalents/d of legumes, (6) cup equivalents/d of dairy products (milk, cheese and yogurt), (7) dietary vitamin C from foods (mg/d), and (8) caffeine (g/d); the later three were associated with reduced SUA[1,9].

Serum uric acid–genetic risk score construction

Genotyping was performed in 1024 HANDLS AA participants using Illumina 1M SNP genotyping array (online Supplementary Appendix S1). A high-quality review paper of GWAS studies examining SNP at various gene loci in relation to phenotypes

of SUA, gout or hyperuricaemia was used as a starting point for listing the SNP in the online Supplementary Table S1[22]. This list was updated with four more recent GWAS studies[22–26]. Despite the paucity of studies in AA adults, all SNP were included in the pool of potentially influential polymorphisms prospectively affecting SUA in our AA urban sample. Genotypes were imputed using the 1000 Genomes Project phase 1 multiethnic reference panel, with SNP extracted only from high-quality imputed genotypes. Of sixty-eight SNP, four were unavailable and rs72552713 was excluded because of poor imputation quality (imputation quality R^2 0·0073). After performing linkage disequilibrium (LD)-based SNP pruning, using an LD threshold R^2 of 0·8 in a 500 kb sliding window, forty-three independent markers were selected for further analysis. Using mixed-effects regression models adjusted for socio-demographic and lifestyle variables, dietary factors, ten principal components (PC) and the inverse Mills ratio, the forty-three SNP were screened for significant effects on SUA at baseline and rate of change in SUA at a type I error rate of 0·10 (online Supplementary Appendix S2 and Table S2). Only fifteen of the forty-three showed a significant association with baseline SUA (*n* 12) or rate of change in SUA (*n* 3). Those fifteen SNP were used to construct three GRS, one for total (GRS_{total}, *n* 15), one for baseline (GRS_{base}, *n* 12), and one for rate of change (GRS_{rate}, *n* 3). Given the marked difference in interpretation of effects (base *v.* rate), only unweighted GRS were constructed and could range from 0 to 30 for GRS_{total}, 0 to 24 for GRS_{base} and 0 to 6 for GRS_{rate}. The online Supplementary Table S1 describes those SNP, along with the selection process leading to the three GRS. The online Supplementary Table S2 shows the results of the mixed-effects regression models of the fifteen selected SNP. Notably, seven of the fifteen selected SNP were located on or near the *SLC2A9* gene. The remaining eight SNP were located on *ABCG2* (*n* 1), *SLC22A12* (*n* 1), *SLC17A1* (*n* 1), glucokinase (hexokinase 4) regulator (*n* 1), leucine rich repeat containing 16 A (*n* 1), neurexin 2 (*n* 1), nuclear factor of activated T-cells 5, tonicity-responsive (*n* 1) and hepatic leukaemia factor (*n* 1).

Covariates

Covariates included sex, age, education (<high school (HS) (grades 1–8), HS (grades 9–12), >HS (grade 13+)), poverty status (household incomes below or above 125 % of the 2004 Federal poverty guidelines), smoking status (current smoker *v.* no use of cigarettes), illicit drug use (current *v.* no use of either marijuana, cocaine or opiates), BMI measured as weight/squared measured height (kg/m^2) ten PC to control for population stratification (online Supplementary Table S1) and selected food groups determined using the MPED2 (http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/mped/mped2_doc.pdf), namely total fruits, total vegetables (cup equivalents/d), total grains (ounce equivalents/d), other meats (ounce equivalents/d) and discretionary solid fats and oils (g/d).

Statistical methods

Using Stata 13.0., sampling weights were included only in descriptive analyses, whereby means and proportions were compared across sex and GRS tertiles, using design-based *F* test. Moreover, $P_{for\ trend}$ values were estimated by entering GRS as an ordinal predictor in a bivariate regression model. Baseline and follow-up SUA were also plotted (box plots) and compared across GRS tertiles and sex[27]. In the main part of the analysis, four sets of time-interval mixed-effects regression models with the outcome SUA measured at either visits 1 or 2 were conducted, which assumes missingness at random[28]. (online Supplementary Appendix S2)

In a first model set, eight dietary components predicted baseline SUA (SUA_{base}) and annual rate of change in SUA (SUA_{rate}), overall and stratifying by sex. Type I error in analyses examining dietary factors was corrected for multiple testing using Bonferroni correction, assuming an initial type I error rate of 0·05 for main effects and 0·10 for interaction terms, yielding a corrected error rates of 0·05/8 = 0·006 and 0·10/8 = 0·013, respectively[29,30].

In a second model set, the GRS uppermost two tertiles were contrasted with the lowest in their association with SUA_{base} (cross-sectional, exposure main effect, GRS_{base}) and SUA_{rate} (longitudinal, exposure × Time, GRS_{rate}); (model A). Cross-sectional and longitudinal effects were compared between sexes and tested for effect modification by including two-way and three-way interactions with sex in unstratified models. In model B, GRS_{total} tertiles substituted GRS_{base} and GRS_{rate}.

In a third model set, eight dietary factors were also of primary interest, while effect modification was tested for GRS_{total} tertiles, by adding two-way and three-way interaction terms in the unstratified model.

Finally, stratifying the analysis by sex, gene–diet interactions were tested in a fourth model set, whereby each of eight dietary factors were separately interacted with continuous GRS_{base} to test their interactive effects on SUA_{base}. Similarly, three-way interactions between each dietary component, Time and continuous GRS_{rate} were also examined in separate models. Predictive margins were estimated and plotted across Time, stratifying by exposure group, from selected mixed-effects regression models.

Selection bias due to the non-random selection of participants with complete data was corrected for, using a two-stage Heckman selection process, as was done in other previous studies[31,32].

Results

Table 1 describes baseline characteristics of the study sample by sex and by GRS tertile. While 55·2 % of the sample consisted of women, mean age overall was estimated at 47·4 years. Being below poverty was more likely in women, whereas being a current illicit drug user was more likely in men. Women also had a higher mean BMI than men. Men consumed higher amounts of all selected dietary factors than women, except for fish, caffeine and total vegetables (Table 1). Men had higher SUA at both baseline and follow-up compared with women, and there was a consistent positive association between GRS_{total} tertiles and SUA (baseline and follow-up). (online Supplementary Fig. S2 and S3)

Several key findings emerged from the mixed-effects regression models (Tables 2–5). After correction for multiple testing, overall, (Table 2; online Supplementary Fig. S4), higher

Table 1. Baseline study characteristics by sex and genetic risk score (GRS) tertile (T), Healthy Aging in Neighborhoods of Diversity Across the Lifespan (Mean values with their standard errors)

			Sex					GRS_{total} tertile						
	Total (*n* 766)		Men (*n* 343)		Women (*n* 423)			T1		T2		T3		
	Mean	SEM	Mean	SEM	Mean	SEM	*P**	Mean	SEM	Mean	SEM	Mean	SEM	$P_{for\ trend}$†
Age (years)	47·4	0·6	48·4	0·8	46·6	0·8	0·14	45·7	1·1	48·2	0·7	48·8	1·2	0·043
Marital status (%)							0·23							0·81
Married	27·5		30·2		25·1			23·9		29·7		29·1		
Missing	3·6		4·8		2·5			3·7		3·7		3·0		
Education (%)							0·53							0·25
<High school	3·4		2·6		4·0			3·0		3·0		4·7		
High school	59·6		57·3		61·7			69·0		54·0		55·0		
> High school	37·0		40·1		34·3			28·0		43·0		40·3		
Poverty:income ratio <125 %, (%)	23·5		18·6		27·9		0·015	24·8		23·6		21·6		0·83
Current smoking status (%)							0·08							0·07
Yes	48·0		56·2		40·9			55·2		39·0		52·6		
Missing	6·4		4·1		8·4			4·9		10·3		1·9		
Current illicit drug use (%)							0·009							0·09
Yes	23·6		31·8		16·3			29·5		18·6		23·0		
Missing	4·9		2·2		7·4			1·8		8·8		3·1		
BMI (kg/m^2)	29·4	0·5	27·3	0·5	31·2	0·8	<0·001	28·5	0·8	30·0	0·8	29·6	1·1	0·36
Key dietary intake factors														
Added sugars (teaspoon/d)	22·6	1·2	25·3	1·7	20·2	1·6	0·031	25·9	2·2	21·2	1·8	20·0	1·6	0·029
Alcoholic beverages (drinks/d)	0·70	0·1	1·13	0·2	0·32	0·06	<0·001	0·4	0·1	0·9	0·2	0·8	0·2	0·08
Red meat (oz equiv/d)	1·70	0·15	2·25	0·25	1·22	0·17	0·001	2·1	0·3	1·5	0·2	1·5	0·2	0·09
Fish (oz equiv/d)	1·12	0·15	1·13	0·17	1·10	0·23	0·92	1·2	0·2	1·2	0·3	0·9	0·2	0·42
Legumes (cup equiv/d)	0·04	0·01	0·06	0·02	0·02	0·06	0·034	0·02	0·01	0·06	0·02	0·04	0·01	0·13
Dairy products (cups equiv/d)	0·96	0·07	1·15	0·10	0·79	0·08	0·008	1·03	0·13	0·95	0·09	0·85	0·13	0·33
Vitamin C (mg/d)	83·7	5·2	99·9	8·6	69·4	5·2	0·003	79·1	7·6	89·0	8·6	81·9	11·5	0·75
Caffeine (mg/d)	76·4	5·0	80·8	7·3	72·5	6·9	0·40	84·2	9·5	63·0	7·2	87·3	8·2	0·96
Other dietary intake factors														
Total grains (oz equiv/d)	5·90	0·21	6·82	0·33	5·09	0·23	<0·001	6·0	0·3	5·7	0·3	6·2	0·5	0·79
Total fruits (cup equiv/d)	0·77	0·05	0·93	0·08	0·62	0·06	0·003	0·7	0·1	0·8	0·1	0·9	0·1	0·40
Total vegetables (cup equiv/d)	1·39	0·10	1·54	0·19	1·25	0·07	0·15	1·3	0·1	1·5	0·2	1·3	0·1	0·62
Other meats (oz equiv/d)	4·76	0·22	5·92	0·37	3·73	0·21	<0·001	5·0	0·4	4·3	0·3	5·0	0·4	0·83
Discretionary oil (g/d)	18·04	1·56	22·04	3·03	14·49	0·95	0·017	14·9	1·5	20·1	2·5	19·2	4·3	0·26
Discretionary solid fat (g/d)	47·45	1·96	58·26	2·84	37·87	2·37	<0·001	51·7	3·6	45·6	2·9	44·3	3·5	0·13

* *P* value for null hypothesis of no sex difference based on a design-based *F* test.
† $P_{for\ trend}$ value was based on design-based *F* test for trend in exposures across tertiles of GRS.

rate of change in SUA was associated with lower dairy product intake (γ_{16} −0·042; 95 % CI −0·075, −0·009, $P=0·010$) When examining sex-specific associations, the association of legume intake with SUA_{rate} was stronger among women (γ +0·14; 95 % CI +0·06, +0·22, $P=0·001$), while alcohol intake was positively associated with SUA_{base} also among women (γ +0·154; 95 % CI +0·046, +0·262, $P=0·005$).

Table 3 tests associations between GRS_{base} tertiles and baseline SUA and between GRS_{rate} tertiles and rate of change in SUA, overall and stratified by sex (model A). Both the middle and uppermost tertiles of GRS_{base} were associated with higher SUA compared with the lowest tertile, with a significantly stronger association of the highest tertile *v.* lowest among women and the middle tertile *v.* lowest among men. Only the uppermost tertile of GRS_{rate} was linked to faster rate of increase in SUA_{rate} compared with the lowest tertile. This effect was significantly stronger among men and non-significant in women. The predictive margins of SUA across time by tertiles of GRS_{base} and GRS_{rate} are presented in Fig. 1(a) and (b). Mixed-effects regression models with GRS_{total} tertiles (model B) indicated that higher GRS_{total} was associated with higher SUA_{base} overall though no association was detected with SUA_{rate}.

In Table 4, after correction for multiple testing, the association between legume consumption and SUA_{rate} was restricted to the lowest tertile of $GRS_{total;}$ (γ_{15} +0·491; 95 % CI +0·246, +0·736, $P<0·001$), indicating an antagonistic $GRS_{total}\times$legume interaction.

In Table 5, among women, we detected a synergistic interaction between GRS_{rate} and red meat consumption in relation to SUA_{rate} (γ_{139} +0·025 (standard error of the estimate (SEE) 0·010), $P=0·012$). Specifically, GRS_{rate} among women was associated with non-significant increase in SUA over time among non-consumers of red meat, which was accelerated with red meat consumption. Among men, lower vitamin C intake was associated with higher SUA_{base}, particularly at higher GRS_{base} (γ_{079} +0·001 (SEE 0·000), $P=0·006$) indicating also a synergistic effect between having high genetic and high dietary risk in terms of lower vitamin C intake.

Discussion

To our knowledge, this is the first study to evaluate SUA_{base} and SUA_{rate} associations with GRS in a large sample of AA urban adults, while examining sex-specific genetic and dietary

Table 2. Mixed-effects regression models of serum uric acid (SUA) by dietary components, stratified by sex*
(Regression coefficients (γ) with their standard errors of the estimate (SEE))

	Total: model 1†			Men: model 2†			Women: model 3†		
	n 766		*n′* 1341	*n* 343		*n′* 583	*n* 423		*n′* 758
SUA	γ	SEE	*P*	γ	SEE	*P*	γ	SEE	*P*
Fixed effects									
Added sugar (γ_{01} for π_{0i})	+0·002	0·004	0·69	+0·003	0·005	0·55	−0·003	0·006	0·65
Added sugar × Time (γ_{11} for π_{1i})	+0·0005	0·0009	0·63	−0·0002	0·001	0·90	+0·002‡	0·001	0·083‡
Alcohol (γ_{02} for π_{0i})	+0·082§	0·032	0·010§	+0·05	0·04	0·22	+0·154§‖	0·055	0·005§‖
Alcohol × Time (γ_{12} for π_{1i})	−0·008	0·008	0·30	−0·002	0·011	0·83	−0·018	0·012	0·12
Red meat (γ_{03} for π_{0i})	+0·046§	0·021	0·031§	+0·035	0·025	0·15	+0·090§	0·045	0·044§
Red meat × Time (γ_{13} for π_{1i})	−0·002	0·005	0·70	−0·003	0·006	0·55	−0·001	0·010	0·94
Fish (γ_{04} for π_{0i})	+0·025	0·025	0·31	+0·011	0·040	0·78	+0·028	0·032	0·39
Fish × Time (γ_{14} for π_{1i})	−0·004	0·006	0·44	−0·002	0·010	0·87	−0·006	0·007	0·39
Legumes (γ_{05} for π_{0i})	−0·28	0·18	0·12	−0·33	0·37	0·38	−0·29	0·21	0·17
Legumes × Time (γ_{15} for π_{1i})	+0·09§	0·04	0·018§	−0·073	0·087	0·40¶	+0·14§‖	0·04	0·001§‖
Dairy products (γ_{06} for π_{0i})	+0·09	0·07	0·24	+0·07	0·11	0·50	+0·15	0·11	0·17
Dairy products × Time (γ_{16} for π_{1i})	−0·042§‖	0·017	0·010§‖	−0·037	0·025	0·14	−0·057§	0·024	0·015§
Vitamin C (γ_{07} for π_{0i})	−0·001	0·001	0·12	−0·003§	0·001	0·044§	−0·001	0·001	0·71
Vitamin C × Time (γ_{17} for π_{1i})	+0·0003	0·0002	0·16	+0·0003	0·0003	0·34	+0·0002	0·0003	0·49
Caffeine (γ_{08} for π_{0i})	−0·0001	0·001	0·88	−0·0002	0·0008	0·83	−0·0002	0·0008	0·84
Caffeine × Time (γ_{18} for π_{1i})	−0·0000	0·0001	0·92	+0·0001	0·0002	0·70	−0·0002	0·0002	0·40

n, number of participants in the analysis; *n′*, total number of visits included in the analysis; Age_{base}, baseline age at visit 1.

* Random effects are not shown for simplicity.

† Models were further adjusted for marital status, poverty status, education (years), baseline current smoking status, current illicit drug use and baseline BMI centred at 30 kg/m^2, the ten principal components for population structure, other dietary factors namely total grains, total fruit, total vegetables, other meats, discretionary solid fat and discretionary oils, and the inverse Mills ratio. Age_{base} was centred at 50 years, sex was coded as 0 = women, 1 = men. All dietary factors were centred at their weighted means (see Table 1, total).

‡ $P < 0{\cdot}10$.

§ $P < 0{\cdot}05$

‖ Passed correction for multiple testing.

¶ $P < 0{\cdot}05$ for interaction with sex to test effect modification by sex for each of the eight dietary factors on SUA at baseline and SUA change over time.

Table 3. Mixed-effects regression models of serum uric acid (SUA) by genetic risk score (GRS) tertiles (GRS_{base} and GRS_{rate}: model A; GRS_{total}: model B), stratified by sex*
(Regression coefficients (γ) with their standard errors of the estimate (SEE))

	Total†			Men†			Women†		
	n 766		*n′* 1341	*n* 343		*n′* 583	*n* 423		*n′* 758
SUA	γ	SEE	*P*	γ	SEE	*P*	γ	SEE	*P*
Model A: GRS base and rate									
Fixed effects									
GRS_{21base} (γ_{021} for π_{0i})	+0·32	0·11	0·004	+0·36	0·18	0·043‡	+0·30	0·14	0·029
$GRS_{21rate} \times$ Time (γ_{121} for π_{1i})	+0·02	0·020	0·47	+0·03	0·041	0·42	+0·02	0·03	0·56
GRS_{31base} (γ_{031} for π_{0i})	+0·54	0·12	<0·001	+0·44	0·18	0·013‡	+0·60	0·15	<0·001
$GRS_{31rate} \times$ Time (γ_{131} for π_{1i})	+0·06	0·03	0·037	+0·11	0·05	0·021‡	+0·004	0·039	0·90
Model B: GRS total									
Fixed effects									
$GRS_{21total}$ (γ_{021} for π_{0i})	+0·31	0·11	0·007	+0·40	0·18	0·022	+0·23	0·15	0·12
$GRS_{21total} \times$ Time (γ_{121} for π_{1i})	+0·01	0·03	0·73	+0·02	0·05	0·61	+0·02	0·03	0·56
$GRS_{31total}$ (γ_{031} for π_{0i})	+0·50	0·12	<0·001	0·44	0·19	0·020	+0·56	0·16	0·001
$GRS_{31total} \times$ Time (γ_{131} for π_{1i})	+0·04	0·03	0·20	0·01	0·05	0·81	+0·03	0·04	0·36

n, number of participants in the analysis; *n′*, total number of visits included in the analysis; Age_{base}, baseline age at visit 1; GRS_{21}, High Serum Uric Acid Risk Score dummy for tertile 2 *v.* tertile 1; GRS_{31}, High Serum Uric Acid Risk Score dummy for tertile 3 *v.* tertile 1.

* Random effects are not shown for simplicity.

† Models were further adjusted for marital status, poverty status, education (years), baseline current smoking status, current illicit drug use and baseline BMI centred at 30 kg/m^2, the ten principal components for population structure, other dietary factors namely total grains, total fruit, total vegetables, other meats, discretionary solid fat and discretionary oils, and the inverse Mills ratio. Age_{base} was centred at 50 years, sex was coded as 0 = women, 1 = men. All dietary factors were centred at their weighted means (see Table 1, total). Tertiles of GRS_{base} had the following distribution: T1 (*N* 258, mean 7·80, SD 1·95, range 2–10); T2 (*N* 279, mean 11·76, SD 0·94, range 10–13); T3 (*N* 229, mean 15·18, SD 1·28, range 13–19). Tertiles of GRS_{rate} had the following distribution: T1 (*N* 325, mean 0·68, SD 0·46, range 0–1); T2 (*N* 291, mean 1·85, SD 0·34, range 1–2); T3 (*N* 150, mean 2·88, SD 0·61, range 2–5). See Table 4 for ranges and mean values and standard deviations of GRS_{total} within its tertiles.

‡ $P < 0·05$ for interaction with sex to test effect modification by sex for each of the two dummy variables (i.e. GRS_{21} and GRS_{31}) on SUA at baseline and SUA change over time.

Table 4. Mixed-effects regression models of serum uric acid (SUA) by dietary components, stratified by genetic risk score(GRS) tertile (GRS_{total})*
(Mean values and standard deviations; regression coefficients (γ) with their standard errors of the estimate (SEE))

	GRS_{total} (T1)			GRS_{total} (T2)			GRS_{total} (T3)		
GRS_{total} score									
Mean	9·19			13·51			16·88		
SD	2·05			1·09			1·37		
Range	3–12			12–15			15–22		
	Model 1†			Model 2†			Model 3†		
	n 256		*n′* 453	*n* 297		*n′* 514	*n* 213		*n′* 374
SUA	γ	SEE	*P*	γ	SEE	*P*	γ	SEE	*P*
Fixed effects									
Added sugar (γ_{01} for π_{0i})	+0·005	0·063	0·94	+0·004	0·006	0·55	+0·004	0·008	0·65
Added sugar × Time (γ_{11} for π_{1i})	+0·002	0·001	0·15	+0·001	0·002	0·59	−0·002	0·002	0·21
Alcohol (γ_{02} for π_{0i})	+0·005	0·063	0·94	+0·161‡	0·061	0·009‡	+0·091§	0·047	0·05§
Alcohol × Time (γ_{12} for π_{1i})	−0·005	0·013	0·71	−0·012	0·02	0·48	−0·015	0·012	0·19
Red meat (γ_{03} for π_{0i})	+0·078‡	0·031	0·011‡	+0·01	0·05	0·84	−0·055	0·042	0·19‖
Red meat × Time (γ_{13} for π_{1i})	−0·005	0·006	0·37	+0·02	0·01	0·22‖	+0·005	0·010	0·58
Fish (γ_{04} for π_{0i})	+0·001	0·04	0·98	+0·11‡	0·05	0·021‡	−0·010	0·045	0·82
Fish × Time (γ_{14} for π_{1i})	−0·000	0·008	0·99	−0·005	0·012	0·66	−0·012	0·010	0·25
Legumes (γ_{05} for π_{0i})	−0·759	0·660	0·25	−0·211	0·409	0·61	−0·49‡	0·23	0·034‡
Legumes × Time (γ_{15} for π_{1i})	+0·491‡¶	0·125	<0·001‡¶	−0·038	0·102	0·71‖	+0·083	0·050	0·10‖
Dairy products (γ_{06} for π_{0i})	−0·049	0·13	0·70	+0·160	0·124	0·20	+0·102	0·139	0·46
Dairy products × Time (γ_{16} for π_{1i})	−0·013	0·024	0·61	−0·057§	0·030	0·053§	−0·036	0·033	0·26
Vitamin C (γ_{07} for π_{0i})	+0·000	0·002	0·91	−0·001	0·001	0·66	−0·005‡	0·002	0·008‡
Vitamin C × Time (γ_{17} for π_{1i})	+0·000	0·000	0·50	+0·000	0·000	0·30	+0·000	0·000	0·31
Caffeine (γ_{08} for π_{0i})	+0·001	0·001	0·17	−0·002§	0·001	0·065§	−0·001	0·001	0·34
Caffeine × Time (γ_{18} for π_{1i})	−0·000	0·000	0·47	+0·000	0·000	0·97	+0·000	0·000	0·30

T1, lowest tertile; T2, middle tertile; T3, highest tertile; *n*, number of participants in the analysis; *n′*, total number of visits included in the analysis; Age_{base}, baseline age at visit 1; GRS_{total}, High Serum Uric Acid Risk Score, total.
* Random effects are not shown for simplicity.
† Each of the model's intercepts and slopes were further adjusted for marital status, poverty status, education (years), baseline current smoking status, current illicit drug use and baseline BMI centred at 30 kg/m^2, the ten principal components for population structure, other dietary factors namely total grains, total fruit, total vegetables, other meats, discretionary solid fat and discretionary oils, and the inverse Mills ratio. Age_{base} was centred at 50 years, sex was coded as 0 = women, 1 = men, and all dietary factors were centred at their weighted means (see Table 1, total).
‡ $P < 0·05$.
§ $P < 0·10$.
‖ $P < 0·05$ for interaction with GRS_{total} tertiles to test effect modification by GRS_{total} tertiles for each of the eight dietary factors on SUA at baseline and SUA change over time.
¶ Passed correction for multiple testing.

Table 5. Sex-specific interactions between genetic risk score (GRS) tertiles (GRS_{base} and GRS_{risk}) and dietary factors in their association with serum uric acid (SUA): mixed-effect regression models*
(Regression coefficients (γ) with their standard errors of the estimate (SEE))

	Men†			Women†		
	n 343		*n*′ 583	*n*′ 423		*n*′ 758
SUA	γ	SEE	*P*	γ	SEE	*P*
Added sugar						
Model 1.A						
Added sugar (γ_{01} for π_{0i})	+0·013	0·016	0·41	+0·023	0·016	0·14
GRS_{base} (γ_{09} for π_{0i})	+0·093‡	0·039	0·018‡	+0·126‡	0·032	<0·001‡
Added sugar × GRS_{base} (γ_{019} for π_{0i})	−0·001	0·01	0·57	−0·002§	0·001	0·098§
Model 1.B						
Added sugar × Time (γ_{11} for π_{1i})	−0·000	0·001	0·91	−0·0026§	0·0014	0·07§
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·044‡	0·019	0·018‡	−0·019	0·016	0·24
Added sugar × GRS_{rate} × Time (γ_{119} for π_{1i})	+0·001	0·001	0·31	+0·002	0·001	0·16
Alcohol						
Model 2.A						
Alcohol (γ_{02} for π_{0i})	−0·004	0·011	0·73	−0·07	0·26	0·79
GRS_{base} (γ_{09} for π_{0i})	+0·073‡	0·024	0·003‡	+0·077‡	0·019	<0·001‡
Alcohol × GRS_{base} (γ_{029} for π_{0i})	+0·001	0·009	0·90	+0·016	0·019	0·41
Model 2.B						
Alcohol × Time (γ_{12} for π_{1i})	+0·004	0·011	0·73	−0·018	0·014	0·13
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·048‡	0·019	0·010‡	+0·016	0·016	0·30
Alcohol × GRS_{rate} × Time (γ_{129} for π_{1i})	−0·012	0·011	0·31	+0·001	0·011	0·90
Red meat						
Model 3.A						
Red meat (γ_{03} for π_{0i})	+0·13‡	0·06	0·026‡	+0·38‡	0·13	0·003‡
GRS_{base} (γ_{09} for π_{0i})	+0·095‡	0·025	<0·001‡	+0·118‡	0·023	<0·001‡
Red meat × GRS_{base} (γ_{039} for π_{0i})	−0·010§	0·06	0·09§	−0·026‡	0·010	0·014‡
Model 3.B						
Red meat × Time (γ_{13} for π_{1i})	−0·001	0·008	0·86	−0·003	0·010	0·80
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·044‡	0·018	0·014‡	+0·023	0·016	0·15
Red meat × GRS_{rate} × Time (γ_{139} for π_{1i})	+0·001	0·007	0·93	+0·025‡‖	0·010	0·012‡‖
Fish						
Model 4.A						
Fish (γ_{04} for π_{0i})	−0·018	0·154	0·91	−0·002	0·087	0·98
GRS_{base} (γ_{09} for π_{0i})	+0·072‡	0·024	0·003‡	+0·077‡	0·020	<0·001‡
Fish × GRS_{base} (γ_{049} for π_{0i})	+0·003	0·014	0·82	+0·004	0·007	0·57
Model 4.B						
Fish × Time (γ_{14} for π_{1i})	−0·003	0·010	0·76	−0·006	0·007	0·39
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·048‡	0·019	0·010‡	+0·017	0·016	0·29
Fish × GRS_{rate} × Time (γ_{149} for π_{1i})	−0·006	0·008	0·46	+0·001	0·008	0·90
Legumes						
Model 5.A						
Legumes (γ_{05} for π_{0i})	+2·146	2·315	0·35	+1·222	1·311	0·35
GRS_{base} (γ_{09} for π_{0i})	+0·082‡	0·023	<0·001‡	+0·088‡	0·019	<0·001‡
Legumes × GRS_{base} (γ_{059} for π_{0i})	−0·219	0·202	0·28	−0·102	0·083	0·22
Model 5.B						
Legumes × Time (γ_{15} for π_{1i})	−0·056	0·091	0·54	+0·258‡	0·077	0·001‡
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·048‡	0·019	0·013‡	+0·007	0·016	0·66
Legumes × GRS_{rate} × Time (γ_{159} for π_{1i})	−0·073	0·153	0·63	+0·219§	0·121§	0·072§
Dairy products						
Model 6.A						
Dairy products (γ_{06} for π_{0i})	−0·42	0·32	0·20	+0·314	0·290	0·28
GRS_{base} (γ_{09} for π_{0i})	+0·035	0·033	0·29	+0·093‡	0·025	<0·001‡
Dairy products × GRS_{base} (γ_{069} for π_{0i})	+0·041	0·026	0·12	−0·015	0·026	0·55
Model 6.B						
Dairy products × Time (γ_{16} for π_{1i})	−0·054‡	0·027	0·043‡	−0·053‡	0·024	0·027‡
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·043‡	0·018	0·018‡	+0·019	0·016	0·23
Dairy products × GRS_{rate} × Time (γ_{169} for π_{1i})	+0·005	0·018	0·77	+0·014	0·019	0·45
Vitamin C						
Model 7.A						
Vitamin C (γ_{07} for π_{0i})	−0·0121‡	0·004	0·001‡	+0·002	0·003	0·51
GRS_{base} (γ_{09} for π_{0i})	+0·0134	0·031	0·66	+0·097‡	0·0263	<0·001‡
Vitamin C × GRS_{base} (γ_{079} for π_{0i})	+0·001‡‖	0·000	0·006‡‖	−0·0001	0·0002	0·47
Model 7.B						
Vitamin C × Time (γ_{17} for π_{1i})	+0·0002	0·0003	0·79	−0·0002	0·0003	0·58
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·043‡	0·018	0·018‡	+0·017	0·016	0·26
Vitamin C × GRS_{rate} × Time (γ_{179} for π_{1i})	−0·0005‡	0·0002	0·026‡	+0·0003	0·0002	0·19

Table 5. *Continued*

	Men†			Women†		
	n 343		*n′* 583	*n′* 423		*n′* 758
SUA	γ	SEE	*P*	γ	SEE	*P*
Caffeine						
Model 8.A						
Caffeine (γ_{08} for π_{0i})	+0·002	0·002	0·51	+0·0048§	0·028	0·083§
GRS_{base} (γ_{09} for π_{0i})	+0·089‡	0·029	0·002‡	+0·111‡	0·023	<0·001‡
Caffeine × GRS_{base} (γ_{089} for π_{0i})	−0·0001	0·0002	0·46	−0·0004§	0·0002	0·055§
Model 8.B						
Caffeine × Time (γ_{18} for π_{1i})	+0·0001	0·0002	0·71	−0·0001	0·0002	0·48
GRS_{rate} × Time (γ_{19} for π_{1i})	+0·046‡	0·019	0·013‡	+0·020	0·016	0·21
Caffeine × GRS_{rate} × Time (γ_{189} for π_{1i})	−0·0001	0·0002	0·79	+0·0003§	0·0002	0·055§

n, number of participants in the analysis; *n′*, total number of visits included in the analysis; Age_{base}, baseline age at visit 1.
* Random effects are not shown for simplicity.
† Each of the models' intercepts and slopes were further adjusted for Age_{base}, marital status, poverty status, education (years), baseline current smoking status, current illicit drug use and baseline BMI centred at 30 kg/m^2, the ten principal components for population structure, and all the remaining dietary factors, that is, seven of the eight key dietary factors in addition to total grains, total fruit, total vegetables, other meats, discretionary solid fat and discretionary oils, and the inverse Mills ratio. Age_{base} was centred at 50 years, and all dietary factors were centred at their weighted means (see Table 1, total). GRS_{base} was centred at 11·5 and GRS_{rate} was centred at 1·6.
‡ $P<0·05$.
§ $P<0·10$.
‖ Passed correction for multiple testing.

associations with SUA and gene–diet interactions. Among key findings, SUA_{base} was higher among men and increased with GRS_{total} tertiles. SUA_{rate} was positively associated with legume intake among women (γ +0·14; 95 % CI +0·06, +0·22, $P=0·001$) and inversely related to dairy product intake in both sexes combined ($\gamma=-0·042$; 95 % CI −0·075, −0·009, $P=0·010$). SUA_{base} was directly linked to alcohol consumption among women (γ +0·154; 95 % CI +0·046, +0·262, $P=0·005$). GRS_{rate} was linearly related to SUA_{rate} only among men. Legume consumption's positive association with SUA_{rate} was restricted to GRS_{total}'s lowest tertile. Among women, a synergistic interaction was observed between GRS_{rate} and red meat intake in association with SUA_{rate}. Among men, a synergistic interaction between low vitamin C and genetic risk was also found.

Doring *et al.* indicated that the most significant SNP's associated with SUA were within the *SLC2A9* gene, introns 4 and 6 ($P<1·2\times10^{-8}$). This gene encodes two GLUT9 isoforms of the class II facilitative glucose transport family[16]. The long isoform GLUT9a (SLC2A9_L, GLUT9, 540 amino acids) is strongly expressed among humans in the basolateral side of the proximal renal tubular cells, and is responsible for the transport of UA back into the bloodstream[33], whereas the shorter isoform GLUT9b (SLC2A9_S, GLUT9ΔN, 511 amino acids) is expressed only in the apical membrane of polarised renal tubular cells, and gain of function mutations would be expected to increase the reuptake of excreted UA causing hyperuricaemia[34]. Although RNA expression analysis has confirmed that the short isoform of *SLC2A9* was significantly and positively associated with SUA, to our knowledge SNP associated with *SLC2A9b* have yet to predict amino acid changes in GLUT9b which would predict a gain of function. Conversely, loss of function mutations in *SLC2A9b* have been reported to be causative of renal hypouricaemia in human subjects[16,35,36]. However, none of the *SLC2A9* SNP are predicted to be deleterious in *in silico* functional annotation. Experimental studies are required to assess the biological consequences of these variants. Fructose is also a substrate for liver GLUT9a (the longer isoform), as well as GLUT5 and GLUT11[16]. Following its transport into hepatocytes, fructose is phosphorylated by fructokinase, generating ADP that is rapidly transformed into UA[16]. Therefore, the net effect of increasing fructose intake would be facilitative of liver purine breakdown into UA, thus increasing SUA[24].

In a large GWAS by Kolz *et al.*, the rs734553 minor allele in *SLC2A9* had a stronger effect on reducing SUA in women, while the effect was stronger in men for the minor allele of rs2231142 in ABCG2 which elevates SUA[17]. The percentage variance explained by *SLC2A9* variants in SUA differs between sexes with genotypes explaining 1·2 % in men and 6 % in women and expression levels explaining 3·5 % in men and 15 % in women[16]. Another confirmatory study genotyped four previously identified SNP in the *SLC2A9* gene (rs6855911, rs7442295, rs6449213 and rs12510549) and found significant associations with SUA in the expected direction. However, this association was significantly stronger among women and among individuals with higher BMI[18]. Our study indicated that the uppermost tertile of GRS_{base} was more strongly associated with SUA_{base} in women compared with men, though the reverse was true for the middle tertile. However, GRS_{rate} was positively linked to SUA_{rate} only in men, while comparing the uppermost tertile to the lowest. As most other studies were cross-sectional and considering the uppermost tertile *v.* lowest contrast as the most important finding, our results replicated those prior studies, particularly that GRS_{base} consisted mostly of SLC2A9 gene SNP[16–18].

The association between diet and SUA were also explored in previous studies, though failing to test sex-related differences. Given the consistently higher levels of SUA in men compared with that in women, it is important to include sex as an effect modifier when examining other risk factors for SUA levels. Large prospective cohort studies showed that higher meat and seafood intakes were associated with higher gout risk and higher SUA concentrations[1,8]. However, no association was detected for other purine-rich foods including peas, lentils,

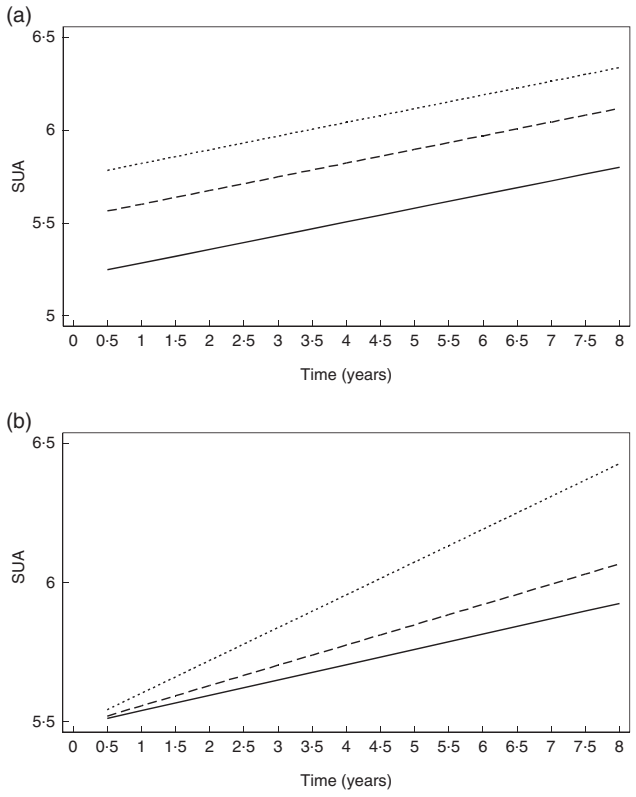


Fig. 1. Predictive margins of serum uric acid (SUA) by time and tertiles (T) of genetic risk scores (GRS), (a) GRS_{base} and (b) GRS_{rate}, from mixed-effects regression model, total population. Predictive margins obtained from mixed-effects regression model with SUA as the outcome, random effects added to slope and intercept, and both slopes and intercept adjusted for multiple factors including age, sex, poverty status, marital status, education, smoking and drug use, several dietary factors, BMI, ten principal components for population structure and an inverse Mills ratio. The figure simulates the trajectory of a population with comparable characteristics (covariates set at their observed values in the sample) when exposed alternatively to T1, T2 and T3 of GRS_{base} and GRS_{rate}, respectively (see Table 3, model 1). (a): ———, GRS_{base}, T1; - - - - -, GRS_{base}, T2; ·····, GRS_{base}, T3; (b): ———, GRS_{rate}, T1; - - - - -, GRS_{rate}, T2; ·····, GRS_{rate}, T3. Tertiles of GRS_{base} had the following distribution: T1 (*n* 258, mean 7·80, SD 1·95, range 2–10); T2 (*n* 279, mean 11·76, SD 0·94, range 10–13); T3 (*n* 229, mean 15·18, SD 1·28, range 13–19). Tertiles of GRS_{rate} had the following distribution: T1 (*n* 325, mean 0·68, SD 0·46, range 0–1); T2 (*n* 291, mean 1·85, SD 0·34, range 1–2); T3 (*n* 150, mean 2·88, SD 0·61, range 2–5).

beans, spinach, mushrooms and cauliflower[1], highlighting the importance of amount, bioavailability and types of purines in foods[1]. We found that among women, there was a synergistic interaction between GRS_{rate} and red meat intake in association with faster increase in SUA_{rate}. Thus, even though GRS_{rate} by itself was not associated with SUA_{rate} among AA women (unlike among AA men), red meat consumption in this group may accelerate the genetic risk's effect on SUA's rate of increase. In other words, there is a super-additive effect of increasing meat consumption and increasing genetic risk on the rate of change in SUA among women. The biological mechanism behind this finding is worth further exploration. Furthermore, randomised controlled trials of red meat consumption in relation SUA_{rate} should be conducted among AA women while stratifying by genetic risk, to replicate those findings.

The positive association between legume consumption with SUA_{rate} was restricted to the lowest tertile of GRS_{total}, indicating an antagonistic interaction, and was significantly stronger in women. Thus, legume consumption may affect the rate at which SUA increases over time in women and among individuals with lower genetic risk for elevated SUA. This finding is novel and worth further exploration in larger AA adult samples, particularly that the positive association between legume intake and SUA was only found in animal studies[15].

Fructose intake, as discussed earlier, exerts a direct effect on SUA, through liver ATP utilisation for phosphorylation and production of ADP. In addition, SLC2A9 transports both fructose and UA with maximal transport of fructose occurring in the absence of UA. In fact, oral fructose administration in hyperuricaemic patients further increased SUA[1,37]. Using national data (National Health and Nutrition Examination Survey III (NHANES III)) on 14 761 adults, soft drink consumption was shown to increase SUA in a dose–response way from +0·08 mg/dl higher SUA (for <0·5 servings *v.* no intake), to 0·42 mg/dl higher SUA (for ≥4 servings/d *v.* no intake), $P_{for\ trend} = 0{\cdot}003$. Findings were similar for sugar-sweetened soft drinks in relation to the odds of hyperuricaemia[11], and were replicated only in men in another analysis using NHANES 2001–2002[12]. At least one study found a non-additive interaction between SLC2A9 genotype and sugar-sweetened beverage consumption in determining the risk for gout, when analysing genotype-specific groups[38]. Our study did not detect an association between added sugars and $SUA_{base/rate}$, possibly due to differences between our study and previous ones in terms of racial/ethnic composition. However, larger studies of AA adult populations are needed to replicate those findings.

Based on a recent meta-analysis of 42 924 adults, alcohol consumption had a linear dose–response relationship with gout. Compared with no/little alcohol drinking, light (≤1 drink/d), moderate (>1– <3 drinks/d) and heavy drinking (≥3 drinks/d) had a risk ratio of 1·16 (95 % CI 1·07, 1·25), 1·58 (95 % CI 1·50, 1·66) and 2·64 (95 % CI 2·26, 3·09), respectively[39]. Studies also indicated that the association between alcohol and SUA pertained mostly to beer and liquor/spirits[7]. Similar to fructose, alcohol increases liver UA production through ATP degradation, leading to accumulation of ADP and AMP. Alcohol intake additionally leads to dehydration and metabolic acidosis, resulting in a decreased urate excretion[1]. A study among Japanese adults confirmed an association between SUA and an LDL-receptor-related protein (*LRP2*) polymorphism rs2544390 (C/T). The study found this association to be stronger among males drinking five times or more per week, with a significant gene–diet interaction, indicating synergism[40]. In contrast, an antagonistic interaction on gout outcomes was found in another study that combined Maori and Pacific Islanders, in which alcohol consumption was associated with higher risk for gout only in the rs2544390 CC genotype group[41]. Another study showed alcohol consumption and *ABCG2* Q141K was independently and jointly associated with the risk for chronic tophaceous gout[42]. Our findings indicated sex-specific associations between alcohol and SUA (stronger cross-sectional positive effect in women), without detecting any gene–diet interactions. This suggests that among women, reducing alcohol consumption may potentially reduce SUA, irrespective of genetic risk for elevated SUA.

Vitamin C may also reduce SUA based on a cross-sectional study[43] and a meta-analysis of randomised controlled trials that administered a median dose of 500 mg/d[44]. Biological mechanisms involved include a uricosuric effect of vitamin C at the URAT1 and a sodium-dependent anion co-transporter solute carrier family 5, member 8 (SLCA5A8)/A12; an enhanced fractional kidney clearance of UA; and a reduced oxidative damage of body cells which reduces SUA[14]. In our study, among men, low vitamin C was shown to increase SUA_{base} only at higher GRS_{base} levels, indicating a synergistic interaction. This suggests that among AA men, increasing intake of vitamin C may potentially reduce SUA_{base}, particularly when genetic risk is elevated. However, randomised controlled trials among AA men and stratified by genetic risk are needed to confirm this observation.

Several studies have shown a relationship between dairy product consumption and SUA/gout[10,14]. The evidence thus far points to a protective effect of milk and low-fat yogurt against gout occurrence and hyperuricaemia[8]. There is also evidence that a vegan diet lacking dairy products is more hyperuricaemic than a vegetarian or fish eating type of diet, with the differences most pronounced among men[45]. Several mechanisms were suggested including the effects of orotic acid in milk which promotes renal urate excretion, the uricosuric effect of milk casein and lactalbumin, and a putative biological effect of vitamin D on SUA which has yet to be confirmed[14]. Besides specific dietary components, a higher Mediterranean diet score was linked to lower SUA[5,6], particularly among women[5]. We found that SUA_{rate} was inversely related to dairy product intake in the overall AA sample (Dairy product × Time effect: γ −0·042 (SEE 0·017), $P = 0{\cdot}010$). However, there were no gene–diet or sex–diet interactions for this dietary component.

Among its strengths, this study systematically examined SNP previously shown to be associated with higher SUA and evaluated SUA's sex-specific association with a composite GRS, while testing gene–diet interactions. Our study is among the few to include AA. Despite its strengths, some limitations include a statistical power-limiting small sample size, which precluded further adjustment for incomplete potential confounders such as lipid profiles, ferritin, C-reactive protein and depressive symptoms. In fact, further analyses suggested that the power to detect the effect that was detected in our models was more adequate for the total population than for sex-stratified models. Another limitation is the lack of adequately measured baseline covariates that could potentially act as confounders, including baseline physical activity. Moreover, most of our selected SNP came from studies conducted among subjects of European ancestry as well as other ethnic groups because of the paucity of studies among AA. Availability of genetic data in our HANDLS study among Whites would have strengthened our findings if replicated. Moreover, although GRS weighting by effect size was possible, we opted not to weight our gene scores due to the multiplicity of racial and ethnic groups in previous studies and for ease of interpretation. Finally, because of the low level of correlation between dietary factors that were related to SUA ($r < 0{\cdot}20$), a valid index for elevated SUA or faster increase in SUA could not be computed.

In sum, sex-diet, sex–gene and gene–diet interactions were detected in determining SUA. Dietary factors which interacted with genetic risk to alter $SUA_{base/rate}$ included legumes (overall), red meat (among women) and vitamin C (among men). Legumes and alcohol intakes were shown to potentially alter SUA's trajectory only in women. Finally, the GRS_{rate} altered the rate of change in SUA only among men. Further studies on similar AA adult populations and incorporating larger samples of men and women are needed to replicate our findings.

Acknowledgements

The authors would like to thank Gregory A. Dore and Ola S. Rostant for their internal review of the manuscript.

This work was fully supported by the Intramural Research Program of the NIH, National Institute on Aging.

M. A. B.: had full access to the data used in this paper, performed data management and all statistical analyses and had primary responsibility for the final content; J.-A. C. and M. T. F.-K.: participated in the literature review; M. A. B., J.-A. C., M. T. F.-K., S. M. T., M. K. E. and A. B. Z.: wrote and revised the manuscript; M. A. B., J.-A. C., M. T. F.-K. and A. B. Z.: participated in the plan of analysis; M. T. F.-K., M. K. E. and A. B. Z.: participated in data acquisition; S. M. T.: participated in data management and statistical analysis. All authors read and approved the final version of the manuscript.

None of the authors has any conflicts of interest to declare.

Supplementary material

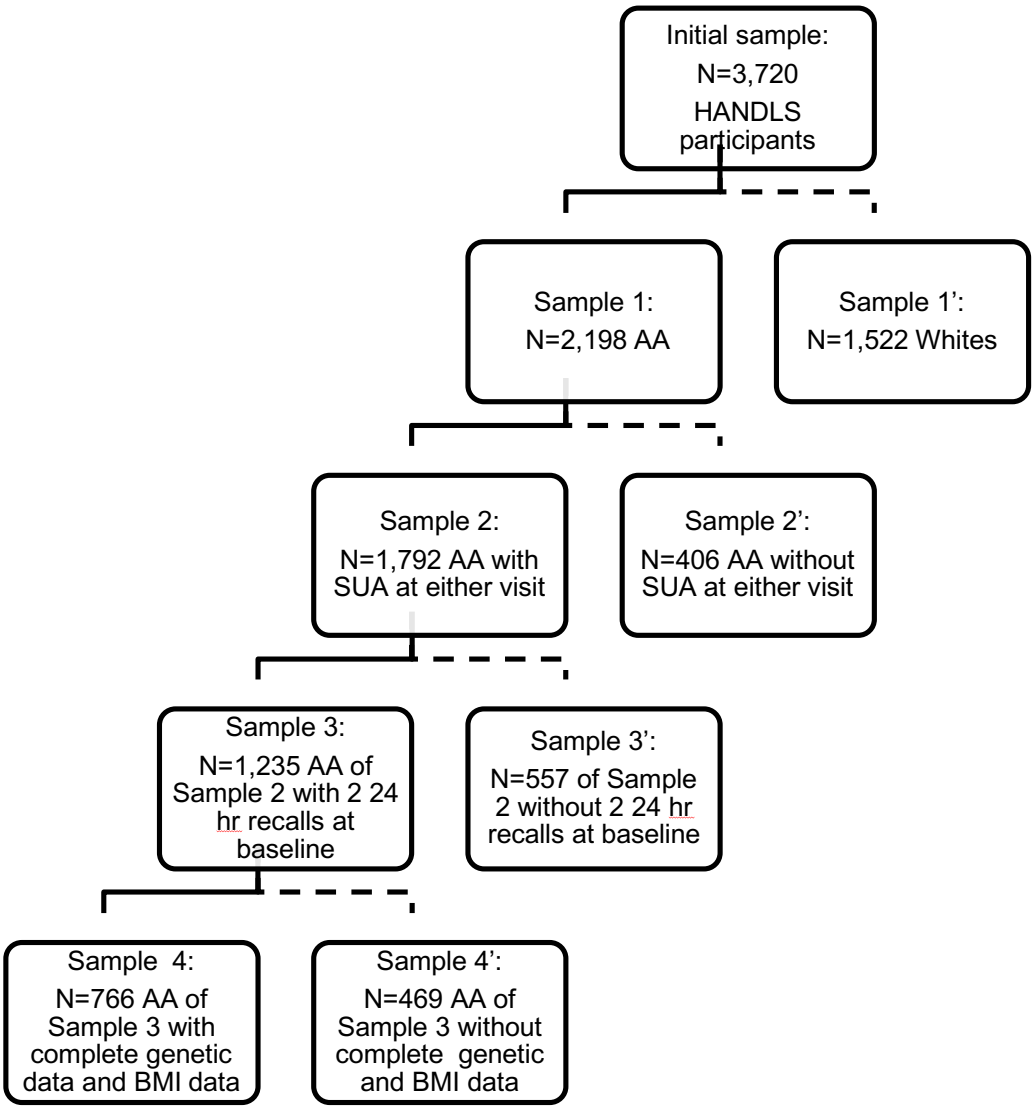
For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517000411

References

1. Choi H, Mount D & Reginato A (2005) Pathogenesis of gout. *Ann Intern Med* **143**, 499–516.
2. George RL & Keenan RT (2013) Genetics of hyperuricemia and gout: implications for the present and future. *Curr Rheumatol Rep* **15**, 309.
3. Fang J & Alderman M (2000) Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. *JAMA* **283**, 2404–2410.
4. Merriman TR (2015) An update on the genetic architecture of hyperuricemia and gout. *Arthritis Res Ther* **17**, 98.
5. Kontogianni MD, Chrysohoou C, Panagiotakos DB, *et al.* (2012) Adherence to the Mediterranean diet and serum uric acid: the ATTICA study. *Scand J Rheumatol* **41**, 442–449.
6. Chrysohoou C, Skoumas J, Pitsavos C, *et al.* (2011) Long-term adherence to the Mediterranean diet reduces the prevalence of hyperuricaemia in elderly individuals, without known cardiovascular disease: the Ikaria study. *Maturitas* **70**, 58–64.
7. Choi HK, Atkinson K, Karlson EW, *et al.* (2004) Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* **363**, 1277–1281.
8. Choi HK, Atkinson K, Karlson EW, *et al.* (2004) Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* **350**, 1093–1103.

9. Torralba KD, De Jesus E & Rachabattula S (2012) The interplay between diet, urate transporters and the risk for gout and hyperuricemia: current and future directions. *Int J Rheum Dis* **15**, 499–506.
10. Poletto J, Harima HA, Ferreira SR, *et al.* (2011) Hyperuricemia and associated factors: a cross-sectional study of Japanese-Brazilians. *Cad Saude Publica* **27**, 369–378.
11. Choi JW, Ford ES, Gao X, *et al.* (2008) Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum* **59**, 109–116.
12. Gao X, Qi L, Qiao N, *et al.* (2007) Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. *Hypertension* **50**, 306–312.
13. Gaffo AL, Roseman JM, Jacobs DR, *et al.* (2010) Serum urate and its relationship with alcoholic beverage intake in men and women: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. *Ann Rheum Dis* **69**, 1965–1970.
14. Towiwat P & Li ZG (2015) The association of vitamin C, alcohol, coffee, tea, milk and yogurt with uric acid and gout. *Int J Rheum Dis* **18**, 495–501.
15. Rotimi SO, Olayiwola I, Ademuyiwa O, *et al.* (2010) Inability of legumes to reverse diabetic-induced nephropathy in rats despite improvement in blood glucose and antioxidant status. *J Med Food* **13**, 163–169.
16. Doring A (2008) SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nat Genet* **40**, 430–436.
17. Kolz M (2009) Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet* **5**, e1000504.
18. Brandstatter A (2008) Sex-specific association of the putative fructose transporter SLC2A9 variants with uric acid levels is modified by BMI. *Diabetes Care* **31**, 1662–1667.
19. Evans MK, Lepkowski JM, Powe NR, *et al.* (2010) Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. *Ethn Dis* **20**, 267–275.
20. Moshfegh AJ, Rhodes DG, Baer DJ, *et al.* (2008) The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. *Am J Clin Nutr* **88**, 324–332.
21. US Department of Agriculture Agricultural Research Service & Food Surveys Research Group (2016) USDA Food and Nutrient Database for Dietary Studies, 3.0. http://www.ars.usda.gov/Services/docs.htm?docid=12089 (accessed February 2017).
22. Reginato AM, Mount DB, Yang I, *et al.* (2012) The genetics of hyperuricaemia and gout. *Nat Rev Rheumatol* **8**, 610–621.
23. Voruganti VS, Laston S, Haack K, *et al.* (2015) Serum uric acid concentrations and SLC2A9 genetic variation in Hispanic children: the Viva La Familia Study. *Am J Clin Nutr* **101**, 725–732.
24. Yang B, Mo Z, Wu C, *et al.* (2014) A genome-wide association study identifies common variants influencing serum uric acid concentrations in a Chinese population. *BMC Med Genomics* **7**, 10.
25. Li C, Yu Q, Han L, *et al.* (2014) The hURAT1 rs559946 polymorphism and the incidence of gout in Han Chinese men. *Scand J Rheumatol* **43**, 35–42.
26. Kottgen A (2013) Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet* **45**, 145–154.
27. Lohr SL (1999) *Sampling: Design and Analysis*. Boston, MA: Duxbury-Press.
28. Ibrahim JG & Molenberghs G (2009) Missing data methods in longitudinal studies: a review. *Test (Madr)* **18**, 1–43.
29. Selvin S (2004) *Statistical Analysis of Epidemiologic Data*, 3rd ed. New York: Oxford University Press.
30. Hochberg Y & Tamhane AC (1987) *Multiple Comparison Procedures*. New York: Wiley.
31. Beydoun MA, Beydoun HA, Kitner-Triolo MH, *et al.* (2013) Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. *J Clin Endocrinol Metab* **98**, 3470–3481.
32. Beydoun MA, Beydoun HA, Rostant OS, *et al.* (2015) Thyroid hormones are associated with longitudinal cognitive change in an urban adult population. *Neurobiol Aging* **36**, 3056–3066.
33. Witkowska K, Smith KM, Yao SY, *et al.* (2012) Human SLC2A9a and SLC2A9b isoforms mediate electrogenic transport of urate with different characteristics in the presence of hexoses. *Am J Physiol Renal Physiol* **303**, F527–F539.
34. Augustin R, Carayannopoulos MO, Dowd LO, *et al.* (2004) Identification and characterization of human glucose transporter-like protein-9 (GLUT9): alternative splicing alters trafficking. *J Biol Chem* **279**, 16229–16236.
35. Anzai N, Kanai Y & Endou H (2007) New insights into renal transport of urate. *Curr Opin Rheumatol* **19**, 151–157.
36. Matsuo H, Chiba T, Nagamori S, *et al.* (2008) Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. *Am J Hum Genet* **83**, 744–751.
37. Emmerson BT (1974) Effect of oral fructose on urate production. *Ann Rheum Dis* **33**, 276–280.
38. Batt C, Phipps-Green AJ, Black MA, *et al.* (2014) Sugar-sweetened beverage consumption: a risk factor for prevalent gout with SLC2A9 genotype-specific effects on serum urate and risk of gout. *Ann Rheum Dis* **73**, 2101–2106.
39. Wang M, Jiang X, Wu W, *et al.* (2013) A meta-analysis of alcohol consumption and the risk of gout. *Clin Rheumatol* **32**, 1641–1648.
40. Hamajima N, Naito M, Okada R, *et al.* (2012) Significant interaction between LRP2 rs2544390 in intron 1 and alcohol drinking for serum uric acid levels among a Japanese population. *Gene* **503**, 131–136.
41. Rasheed H, Phipps-Green A, Topless R, *et al.* (2013) Association of the lipoprotein receptor-related protein 2 gene with gout and non-additive interaction with alcohol consumption. *Arthritis Res Ther* **15**, R177.
42. Tu HP, Ko AM, Chiang SL, *et al.* (2014) Joint effects of alcohol consumption and ABCG2 Q141K on chronic tophaceous gout risk. *J Rheumatol* **41**, 749–758.
43. Ryu KA, Kang HH, Kim SY, *et al.* (2014) Comparison of nutrient intake and diet quality between hyperuricemia subjects and controls in Korea. *Clin Nutr Res* **3**, 56–63.
44. Juraschek SP, Miller ER 3rd & Gelber AC (2011) Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken)* **63**, 1295–1306.
45. Schmidt JA, Crowe FL, Appleby PN, *et al.* (2013) Serum uric acid concentrations in meat eaters, fish eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *PLOS ONE* **8**, e56339.

Supplemental Figure 1. Participant flow chart



AA=African-American; BMI=Body Mass Index; HANDLS=Healthy Aging in Neighborhoods of Diversityacross the Life Span; SUA=Serum Uric Acid.

Appendix 1. Genotyping and quality control

HANDLS participants were genotyped using the Illumina 1M genotyping array. A total of 1,024 individuals were successfully genotyped. Sample quality control inclusion criteria were: **(1)** concordance between self-reported sex and X-chromosome based sex; **(2)** >95% call rate per participant (across all equivalent arrays), **(3)** concordance between self-reported African ancestry and genotyped SNPs confirmed ancestry, and **(4)** proportional sharing of genotypes < 15% between samples, excluding close relatives from the final sample. Moreover, SNPs in HANDLS were selected when the following criteria were met: **(1)** Hardy-Weinberg equilibrium (HWE) p-value>10^{-7}; **(2)** Missing by haplotype p-values > 10^{-7}; **(3)** Minor allele frequency>0.01, and **(4)** Call rate > 95%. Basic quality control and data management for each genotype was conducted using PLINKv1.06.(1) Cryptic relatedness was estimated via pairwise identity by descent analyses in PLINK and confirmed using RELPAIR.(2) STRUCTUREv2.3(3-5) and the multidimensional scaling (MDS) function in PLINKv1.06 were used to determine ancestry among HANDLS participants. HANDLS participants with component vector estimates consistent with the HapMap African ancestry samples for the first 4 component vectors were included. Moreover, in our main analyses, we adjusted for all 10 principal components to control for any residual effects of population structure.(6). SNPs that passed the above quality control criteria were used for genotype imputation using MACH and minimac softwares (http://www.sph.umich.edu/csg/abecasis/mach/). The 1000 Genomes Project phase 1 alpha freeze multiethnic panel were used as a reference population to impute SNPs. Imputed SNP with imputation quality measure of R^2<0.3 or minor allele frequency of <1% were excluded from the analysis. Serum uric acid (SUA) associated SNPs identified by genome-wide association and candidate gene studies were selected from those SNPs that passed the imputation quality control criteria.

References:

1. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81(3):559-75. doi: S0002-9297(07)61352-4 [pii]

10.1086/519795.
2. Epstein MP, Duren WL, Boehnke M. Improved inference of relationship for pairs of individuals. Am J Hum Genet 2000;67(5):1219-31. doi: S0002-9297(07)62952-8 [pii]

10.1016/S0002-9297(07)62952-8.
3. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics 2000;155(2):945-59.
4. Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics 2003;164(4):1567-87.
5. Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: dominant markers and null alleles. Mol Ecol Notes 2007;7(4):574-8. doi: 10.1111/j.1471-8286.2007.01758.x.
6. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nature genetics 2006;38(8):904-9. doi: ng1847 [pii]

10.1038/ng1847.

Supplemental Table 1. List of SNP selected from various GWAS and confirmatory studies [1; 2; 3; 4; 5] shown to be associated with high serum uric acid (SNPhsua)

Variant	Location	Risk allele (Higher SUA)	Other allele (Lower SUA)	Population, references	Minor Allele Frequency	Status
SLC2A9 (chromosome 4)						
rs1014290	**Intron 3**	**T**	**C**	**European ancestry[6]**	**G=0.33**	**A**
rs6449213	**Intron 4**	**T**	**C**	**White [6; 7; 8; 9; 10], AA[11; 12], Hispanic[2]**	**C=0.14**	**A**
rs734553	Intron 6	T	G	White,[13; 14; 15] Icelandic,[16] AA[12]	G=0.30	D
rs7442295	**Intron 6**	**A**	**G**	**White[7; 14; 15; 17]**	**G=0.26**	**A**
rs737269	Intron 7	T	C	European ancestry[6; 15]	T=0.41	C
rs6855911	Intron 7	A	G	White, [7; 14; 15; 17] AA[12]	G=0.30	D
rs13129697	**Intron 7**	**T**	**G**	**White,[15; 18] AA[12], Hispanic[2]**	**G=0.48**	**A**
rs2241480	**Intron 8**	**T**	**A/C**	**European ancestry[12]**	**T=0.33**	**B**
rs7663032	Intron 9	T	G/C	AA,[12] Croatian[15]	C=0.37	D
rs3775948	Intron 9	C	G	Croatian,[15] AA[11]	G=0.34	D
rs16890979	Intergenic	C	T	White,[15; 19; 20] AA[12], Amish,[21] Croatian, [15] Pacific Islander,[20] New Zealander[20]	T=0.26	D
rs717615	Intergenic	A	G	Croatian[15]	G=0.43	C
rs6856396	Intergenic	T	A	AA[11]	A=0.14	C
rs11942223	Intergenic	T	C	European[22]	C=0.27	D
rs11723388	Intergenic	G	A	Hispanic[2]	A=0.12	C
rs11721501	Intergenic	G	A	Hispanic[2]	A=0.13	D
rs6843466	Intergenic	G	A	Hispanic[2]	T=0.49	E
rs17251963	Intergenic	A	G	Hispanic[2]	C=0.13	D
rs13113918	Exon 3	G	A	Hispanic[2]	A=0.18	D
rs7683856	Intron	G	A	Hispanic[2]	A=0.18	D
rs9991278	**Intron**	**G**	**A**	**Hispanic[2]**	**T=0.17**	**A**
rs11723439	Intron	G	A	Hispanic[2]	T=0.12	C
rs4697745	Intergenic	G	A	Hispanic[2]	A=0.19	C
rs7675964	Intron	G	A	Hispanic[2]	T=0.47	D
rs938552	Intron	G	A	Hispanic[2]	T=0.26	D
rs12510549	Intergenic	A	G	Hispanic[2]	C=0.17	C
rs11722228	Intron	T	C	Chinese[3]	T=0.31	C
rs12498742	**Intron**	**A**	**G**	**European[5]**	**G=0.30**	**A**
ABCG2 (chromosome 4)						
rs2231137	Exon 2	A	G	Japanese[23]	A= 0.16	D
rs72552713 (Q126X)	Exon 4	T	C	Japanese[23]	A=0.001	F
rs2231142(Q141K)	**Exon 5**	**T**	**G**	**White,[13; 14; 15; 19; 24], European,[5] African, [12; 19]Chinese,[3; 25] Icelandic,[16] Japanese, [23; 26]**	**T=0.12**	**A**

				Pacific Islander,[27] New Zealander[27; 28]		
rs2199936	Intergenic	A	G	White[13; 15; 18]	N/A	E
rs4148152	Intron	T	C	Chinese[3]	C=0.16	C
rs3114018	Intron	G	T	Chinese[3]	C=0.50	C
SLC22A12 (chromosome 11)						
rs11231825	Exon 1	C	T	Chinese,[29] White,[13; 30] AA[12]	C=0.39	D
rs12800450	Exon 2	G	T	AA[12]	**T=0.01**[12]	E
rs559946	Intron 3	C	T	Chinese[31]	T=0.43	C
rs893006	Intron 4	G	T	Japanese,[32] Chinese[33]	G/T=0.50	C
rs1529909	Intron 4	T	C	Korean[34]	C=0.39	E
rs17300741	Intron 4	A	G	European[13; 35]	G=0.33	C
rs7932775	**Exon 8**	**C**	**T**	**German,[30] Chinese,[29; 31] Solomon Islander[29]**	**C=0.40**	**A**
rs505802	Intergenic	C	T	European,[13; 15] AA[12]	T=0.43	D
rs11602903	Intergenic	A	T	German,[30] Chinese[31]	T=0.39	D
rs3825018	Intergenic	G	A	European[22]	A=0.39	D
SLC16A9 (chromosome 10)						
rs12356193	Intron 1	A	G	European,[13] Icelandic[16]	G=0.09	C
SLC17A1 (chromosome 6)						
rs1165196	Exon 7	A	G	White,[18] Icelandic,[16] Japanese[19; 36]	G=0.28	D
rs1183201	Intron 10	T	A	European[13]	A=0.29	D
rs11751616	Intergenic	A	G	AA[12]	G=0.02	C
rs2051541	Intergenic	G	A	European ancestry[12]	A=0.50	C
rs3799344	**Intergenic**	**C**	**T**	**European[37]**	**T=0.37**	**A**
SLC17A3 (chromosome 6)						
rs1165205	Intron 1	C	T	White[19]	T=0.31	C
SLC22A11 (chromosome 11)						
rs10792443	Intron 4	G	C	European ancestry[12]	C=0.39	C
rs2078267	Intron 6	C	T	European[5], White,[18] Icelandic[16]	T=0.23	C
GCKR (chromosome 2)						
rs780094	Intron 16	T	C	European[13; 35]	T=0.30	C
rs780093	Intron 17	T	C	White,[18] Icelandic[16]	T=0.29	D
rs814295	Intron 17	G	A	AA[12]	G=0.23	C
rs1260326	**Exon 15**	**T**	**C**	**European[5]**	**T=0.29**	**A**
LRRC16A (chromosome 6)						
rs9321453	Intron 12	T	C	AA[12]	T=0.24	C
rs742132	**Intron 30**	**A**	**G**	**European[13; 35]**	**G=0.29**	**A**

		(G increases SUA in our sample)				
PDZK1 (chromosome 1)						
rs882211	Intron 1	C	G	AA[12]	G=0.06	C
rs1967017	Intergenic	T	C	White[18], European[22]	C=0.30	C
R3HDM2-INHBC region (chromosome 12)						
rs1106766	Intergenic	C	T	White, [18] Icelandic[16]	T=0.14	C
RREB1 (chromosome 6)						
rs675209	Intergenic	T	C	White, [18] Icelandic,[16] Croatian[15], European[5; 22]	C=0.45	C
NRXN2 (chromosome 11)						
rs478607	**Intron**	**G**	**A**	**European[5]**	**G=0.28**	**B**
UBE2Q2 (chromosome 15)						
rs1394125	Intron	A	G	European[5]	G=0.26	C
IGF1R (chromosome15)						
rs6598541	Intron	A	G	European[5]	A=0.45	C
NFAT5 (chromosome16)						
rs71931165778	**Intergenic**	**C**	**T**	**European[5]**	**C=0.08**	**B**
HLF (chromosome 17)						
rs7224610	**Intron**	**C**	**A**	**European[5]**	**C=0.22**	**A**

Excluded SNPs of n=68	
Reason #1: Missing from database	
4 SNPs were not available in the HANDLS genotype imputed database: Status E.	
AA	rs12800450
Korean	rs1529909
Whites	rs2199936
Hispanic	rs6843466
Reason #2: Poor imputation quality	
SNP rs72552713 has poor imputation quality (imputation quality measure of $R^2 = 0.0073$: Status F	
Reason #3: High linkage disequilibrium with another SNP	
At LD R^2 of 0.8, in 500 kb window, LD pruning was done, regardless of MAF; 20/63 were excluded, resulting in 43 tag SNPs. 12 found to be associated with baseline SUA (Status A)	

3 found to be associated with SUA rate of change (Status B) 28 non-significant (Status C) 20 remaining SNPs (Status D)
Initially selected SNPs: n=43
Finally selected SNPs: N=15 (12 for baseline and 3 for rate of change in SUA)

Note: Minor allele frequency is obtained from: http://www.ncbi.nlm.nih.gov/snp, except when bolded (the MAF is obtained from a study). The risk allele is determined from the largest study. Both risk allele and other allele indicate the direction of reported association with serum uric acid (SUA) in previous studies regardless of their allele frequency in the population. Minor Allele Frequency indicates which allele (risk or other) is the less frequent one.

References

1. Reginato AM, Mount DB, Yang I *et al.* (2012) The genetics of hyperuricaemia and gout. *Nature reviews Rheumatology* **8**, 610-621.
2. Voruganti VS, Laston S, Haack K *et al.* (2015) Serum uric acid concentrations and SLC2A9 genetic variation in Hispanic children: the Viva La Familia Study. *The American Journal of Clinical Nutrition* **101**, 725-732.
3. Yang B, Mo Z, Wu C *et al.* (2014) A genome-wide association study identifies common variants influencing serum uric acid concentrations in a Chinese population. *BMC Medical Genomics* **7**, 10.
4. Li C, Yu Q, Han L *et al.* (2014) The hURAT1 rs559946 polymorphism and the incidence of gout in Han Chinese men. *Scandinavian journal of rheumatology* **43**, 35-42.
5. Kottgen A (2013) Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet* **45**, 145 - 154.
6. Vitart V (2008) SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* **40**, 437 - 442.
7. Doring A (2008) SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nat Genet* **40**, 430 - 436.
8. Wallace C (2008) Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. *Am J Hum Genet* **82**, 139 - 149.
9. Dehghan A (2008) High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care* **31**, 361 - 362.
10. Brandstatter A (2008) Sex-specific association of the putative fructose transporter SLC2A9 variants with uric acid levels is modified by BMI. *Diabetes Care* **31**, 1662 - 1667.
11. Charles BA, Shriner D, Doumatey A *et al.* (2011) A genome-wide association study of serum uric acid in African Americans. *BMC Med Genomics* **4**, 17.
12. Tin A, Woodward OM, Kao WH *et al.* (2011) Genome-wide association study for serum urate concentrations and gout among African Americans identifies genomic risk loci and a novel URAT1 loss-of-function allele. *Hum Mol Genet* **20**, 4056-4068.
13. Kolz M (2009) Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet* **5**, e1000504.
14. Stark K, Reinhard W, Neureuther K *et al.* (2008) Association of common polymorphisms in GLUT9 gene with gout but not with coronary artery disease in a large case-control study. *PloS one* **3**, e1948.

15. Karns R, Zhang G, Sun G *et al.* (2012) Genome-wide association of serum uric acid concentration: replication of sequence variants in an island population of the Adriatic coast of Croatia. *Ann Hum Genet* **76**, 121-127.
16. Sulem P, Gudbjartsson DF, Walters GB *et al.* (2011) Identification of low-frequency variants associated with gout and serum uric acid levels. *Nat Genet* **43**, 1127-1130.
17. Li S (2007) The GLUT9 gene is associated with serum uric acid levels in Sardinia and Chianti cohorts. *PLoS Genet* **3**, e194.
18. Yang Q, Kottgen A, Dehghan A *et al.* (2010) Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circulation Cardiovascular genetics* **3**, 523-530.
19. Dehghan A (2008) Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet* **372**, 1953 - 1961.
20. Hollis-Moffatt JE, Xu X, Dalbeth N *et al.* (2009) Role of the urate transporter SLC2A9 gene in susceptibility to gout in New Zealand Maori, Pacific Island, and Caucasian case-control sample sets. *Arthritis and rheumatism* **60**, 3485-3492.
21. McArdle PF, Parsa A, Chang YP *et al.* (2008) Association of a common nonsynonymous variant in GLUT9 with serum uric acid levels in old order amish. *Arthritis and rheumatism* **58**, 2874-2881.
22. Phipps-Green AJ, Merriman ME, Topless R *et al.* (2014) Twenty-eight loci that influence serum urate levels: analysis of association with gout. *Ann Rheum Dis*.
23. Matsuo H (2011) Identification of ABCG2 dysfunction as a major factor contributing to gout. *Nucleosides Nucleotides Nucleic Acids* **30**, 1098 - 1104.
24. Woodward O (2009) Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci U S A* **106**, 10338 - 10342.
25. Wang B, Miao Z, Liu S *et al.* (2010) Genetic analysis of ABCG2 gene C421A polymorphism with gout disease in Chinese Han male population. *Human genetics* **127**, 245-246.
26. Yamagishi K (2010) The rs2231142 variant of the ABCG2 gene is associated with uric acid levels and gout among Japanese people. *Rheumatology* **49**, 1461 - 1465.
27. Phipps-Green AJ, Hollis-Moffatt JE, Dalbeth N *et al.* (2010) A strong role for the ABCG2 gene in susceptibility to gout in New Zealand Pacific Island and Caucasian, but not Maori, case and control sample sets. *Hum Mol Genet* **19**, 4813-4819.
28. Caulfield M (2008) SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* **5**, e197.
29. Tu HP, Chen CJ, Lee CH *et al.* (2010) The SLC22A12 gene is associated with gout in Han Chinese and Solomon Islanders. *Ann Rheum Dis* **69**, 1252-1254.
30. Graessler J, Graessler A, Unger S *et al.* (2006) Association of the human urate transporter 1 with reduced renal uric acid excretion and hyperuricemia in a German Caucasian population. *Arthritis and rheumatism* **54**, 292-300.
31. Li C, Han L, Levin AM *et al.* (2010) Multiple single nucleotide polymorphisms in the human urate transporter 1 (hURAT1) gene are associated with hyperuricaemia in Han Chinese. *Journal of medical genetics* **47**, 204-210.
32. Shima Y, Teruya K, Ohta H (2006) Association between intronic SNP in urate-anion exchanger gene, SLC22A12, and serum uric acid levels in Japanese. *Life sciences* **79**, 2234-2237.
33. Guan M (2011) Association of an intronic SNP of SLC2A9 gene with serum uric acid levels in the Chinese male Han population by high-resolution melting method. *Clin Rheumatol* **30**, 29 - 35.
34. Jang WC, Nam YH, Park SM *et al.* (2008) T6092C polymorphism of SLC22A12 gene is associated with serum uric acid concentrations in Korean male subjects. *Clinica chimica acta; international journal of clinical chemistry* **398**, 140-144.
35. van der Harst P, Bakker SJ, de Boer RA *et al.* (2010) Replication of the five novel loci for uric acid concentrations and potential mediating mechanisms. *Hum Mol Genet* **19**, 387-395.

36. Urano W, Taniguchi A, Anzai N *et al.* (2010) Sodium-dependent phosphate cotransporter type 1 sequence polymorphisms in male patients with gout. *Ann Rheum Dis* **69**, 1232-1234.
37. Hollis-Moffatt JE, Phipps-Green AJ, Chapman B *et al.* (2012) The renal urate transporter SLC17A1 locus: confirmation of association with gout. *Arthritis research & therapy* **14**, R92.

Appendix 2. Mixed-effects regression models

The main multiple mixed-effects regression models can be summarized as follows:

	Multi-level models vs. **Composite models**	
Eq.		
1.1-1.4	$Y_{ij} = \pi_{0i} + \pi_{1i} Time_{ij} + \varepsilon_{ij}$	$\pi_{0i} = \gamma_{00} + \gamma_{0a} X_{aij} + \sum_{k=1}^{l} \gamma_{0k} Z_{ik} + \zeta_{0i}$ $\pi_{1i} = \gamma_{10} + \gamma_{1a} X_{aij} + \sum_{m=1}^{n} \gamma_{1m} Z_{im} + \zeta_{1i}$
		$Y_{ij} = \gamma_{00} + \gamma_{0a} X_{aij} + \sum_{k=1}^{l} \gamma_{0k} Z_{ik} + \gamma_{10} Time_{ij} + \gamma_{1a} X_{aij} Time_{ij} + \sum_{m=1}^{n} \gamma_{1m} Z_{im} Time_{ij} + (\zeta_{0i} + \zeta_{1i} Time_{ij} + \varepsilon_{ij})$

Where Y_{ij} is the outcome (SUA) for each individual "i" and visit "j"; π_{0i} is the level-1 intercept for individual i; π_{1i} is the level-1 slope for individual i; γ_{00} is the level-2 intercept of the random intercept π_{0i}; γ_{10} is the level-2 intercept of the slope π_{1i}; Z_{ik} is a vector of fixed covariates for each individual *i* that are used to predict level-1 intercepts and slopes and included baseline age (Age_{base}) among other covariates. $X_{ija,}$ represents the main predictor variables (8 dietary components or the two dummy variables for GRS tertiles); ζ_{0i} and ζ_{1i} are level-2 disturbances; ε_{ij} is the within-person level-1 disturbance. Of primary interest are the main effects of each exposure X_a (γ_{0a}) and their interaction with *TIME* (γ_{1a}), as described in a previous methodological paper.(1)

Reference

1. Blackwell E, de Leon CF, Miller GE. Applying mixed regression models to the analysis of repeated-measures data in psychosomatic medicine. Psychosom Med 2006;68(6):870-8. doi: 01.psy.0000239144.91689.ca [pii]

10.1097/01.psy.0000239144.91689.ca.

Supplemental Table 2. Mixed-effects regression models of SUA by each of the 15 selected SNP[1,2]

	Gene locus	Risk allele Dosage	γ±SEE	p-value
Serum Uric Acid			**n=766[3]**	**n'=1,341[3]**
Model 1: rs1260326	*GCKR*	T(0,1,2)		
rs1260326 (γ_{01} for π_{0i})			**+0.204±0.099**	**0.041**
rs1260326×Time (γ_{11} for π_{1i})			+0.027±0.024	0.26
Model 2: rs1312969	*SLC2A9*	T(0,1,2)		
rs1312969 (γ_{01} for π_{0i})			**+0.195±0.069**	**0.005**
rs1312969×Time (γ_{11} for π_{1i})			+0.003±0.016	0.86
Model 3: rs1249874	*SLC2A9*	A(0,1,2)		
rs1249874 (γ_{01} for π_{0i})			**+0.211±0.068**	**0.002**
rs1249874×Time (γ_{11} for π_{1i})			+0.012±0.016	0.47
Model 4: rs7442295	*SLC2A9*	A(0,1,2)		
rs7442295 (γ_{01} for π_{0i})			**+0.142±0.069**	**0.038**
rs7442295×Time (γ_{11} for π_{1i})			+0.014±0.016	0.38
Model 5: rs6449213	*SLC2A9*	T(0,1,2)		
rs6449213 (γ_{01} for π_{0i})			**+0.256±0.095**	**0.007**
rs6449213×Time (γ_{11} for π_{1i})			+0.025±0.023	0.27
Model 6: rs1014290	*SLC2A9*	T(0,1,2)		
rs1014290 (γ_{01} for π_{0i})			**+0.199±0.073**	**0.007**
rs1014290×Time (γ_{11} for π_{1i})			+0.000±0.017	0.98
Model 7: rs9991278	*SLC2A9*	G(0,1,2)		
rs9991278 (γ_{01} for π_{0i})			**+0.213±0.084**	**0.011**
rs9991278×Time (γ_{11} for π_{1i})			+0.014±0.020	0.46

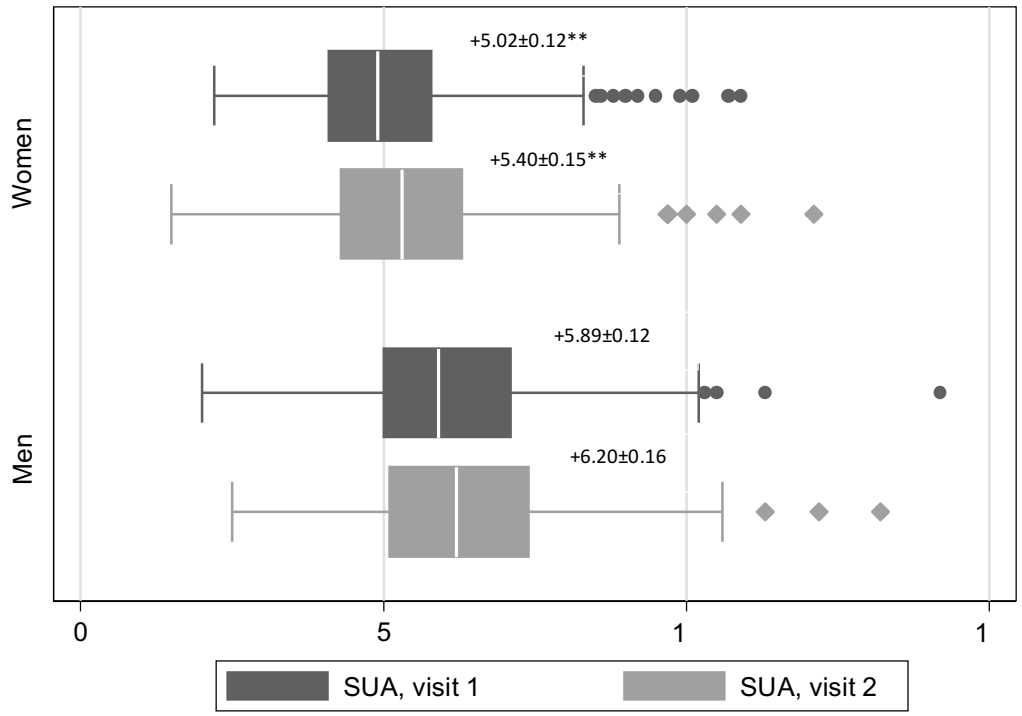
Model 8: rs2231142	*ABCG2*	T(0,1,2)		
rs2231142 (γ_{01} for π_{0i})			**+0.581±0.229**	**0.011**[3]
rs2231142×Time (γ_{11} for π_{1i})			+0.039±0.055	0.47[3]
Model 9: rs742132	*LRRC16A*	G(0,1,2)		
rs742132 (γ_{01} for π_{0i})			*+0.132±0.074*	*0.076*
rs742132×Time (γ_{11} for π_{1i})			-0.002±0.018	0.89[4]
Model 10: rs3799344	*SLC17A1*	C(0,1,2)		
rs3799344 (γ_{01} for π_{0i})			**+0.185±0.072**	**0.010**
rs3799344×Time (γ_{11} for π_{1i})			-0.008±0.017	0.63
Model 11: rs7932775	*SLC22A12*	C(0,1,2)		
rs7932775 (γ_{01} for π_{0i})			**+0.145±0.072**	**0.045**[3]
rs7932775×Time (γ_{11} for π_{1i})			+0.013±0.017	0.444
Model 12: rs7224610	*HLF*	C(0,1,2)		
rs7224610 (γ_{01} for π_{0i})			**+0.237±0.117**	**0.042**
rs7224610×Time (γ_{11} for π_{1i})			-0.043±0.028	0.13
Model 13: rs2241480	*SLC2A9*	T(0,1,2)		
rs2241480 (γ_{01} for π_{0i})			-0.085±0.081	0.30
rs2241480×Time (γ_{11} for π_{1i})			*+0.032±0.018*	*0.096*
Model 14: rs478607	*NRXN2*	G(0,1,2)		
rs478607 (γ_{01} for π_{0i})			-0.030±0.069	0.66
rs478607×Time (γ_{11} for π_{1i})			*+0.027±0.016*	*0.094*
Model 15: rs71931165778	*NFAT5*	C(0,1,2)		
rs71931165778 (γ_{01} for π_{0i})			+0.270±0.213	0.21
rs71931165778×Time (γ_{11} for π_{1i})			*+0.080±0.047*	*0.090*

Abbreviations: Age_{base}=Baseline age at visit 1, SUA=Serum Uric Acid.

[1] Each of the models' intercepts and slopes were further adjusted for Age_{base}, for marital status, poverty status, education (years), baseline current smoking status, current illicit drug use and baseline body mass index, BMI centered at 30 $kg.m^{-2}$, the

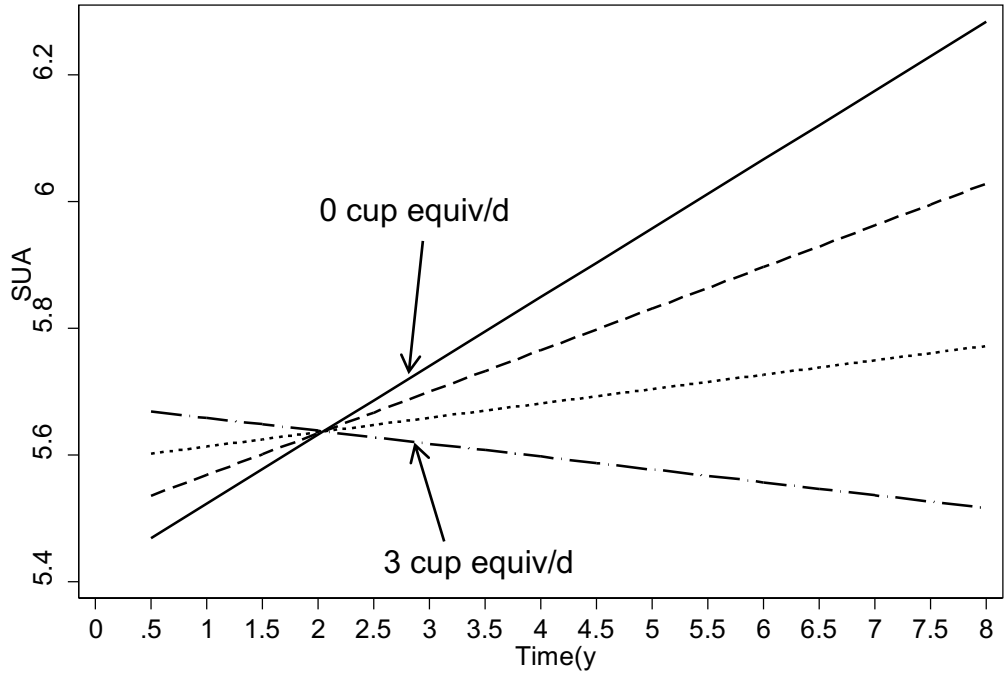
10 principal components for population structure, and 8 key dietary factors factors in addition to total grains, total fruits, total vegetables, other meats, discretionary solid fat and discretionary oils, and the inverse mills ratio. Age_{base} was centered at 50y, and all dietary factors were centered at their weighted means (See Table 1, Total). [2]Values are regression coefficients $\gamma \pm$ standard error of the estimate (SEE). n=number of participants in the analysis; n'=total number of visits included in the analysis. [3] $P<0.05$ for interaction with sex, suggestive of a stronger positive effect among men. [4] $P<0.05$ for interaction with sex, suggestive of a stronger positive effect among women.

Supplemental Figure 2. Boxplot of serum uric acid (SUA) at baseline and follow-up, by sex



**P<0.001 based on design-based F-test from linear regression models accounting for sampling weight, with SUA (visits 1 and 2) as outcome and sex as the only predictor. Values are means±standard error.

Supplemental Figure 4. Predictive margins of SUA by Time and dairy intake, from mixed-effects regression model, total population[1]



[1] Predictive margins obtained from mixed-effects regression model with SUA as the outcome, random effects added to slope and intercept, and both slopes and intercept adjusted for multiple factors including age, sex, poverty status, marital status, education, smoking and drug use, several dietary factors, BMI, 10 principal components for population structure and an inverse mills ratio. The Figure simulates the trajectory of a population with comparable characteristics (covariates set at their observed values in the sample) when exposed alternatively to 4 levels of dairy intakes (0,1,2,3 cups equiv./d, bottom to top) (See Table 2, Model 1).

Supplementary Table 3. Genotype call rate and imputation quality score of serum uric acid linked genetic variants in the HANDLS study.

Variant	Imputed or Genotyped	Genotype call rate	R-squared*
rs1014290	Genotyped	0.99	-
rs10792443	Imputed	-	0.99
rs1106766	Imputed	-	0.99
rs11231825	Genotyped	0.99	-
rs11602903	Imputed	-	0.99
rs1165196	Genotyped	0.99	-
rs1165205	Imputed	-	0.97
rs11721501	Imputed	-	0.91
rs11722228	Imputed	-	0.99
rs11723388	Imputed	-	0.91
rs11723439	Genotyped	0.99	-
rs11751616	Genotyped	0.99	-
rs1183201	Imputed	-	0.99
rs11942223	Imputed	-	0.99
rs12356193	Genotyped	0.99	-
rs12498742	Imputed	-	0.99
rs12510549	Imputed	-	0.95
rs1260326	Genotyped	0.99	-
rs12800450	NA	NA	NA
rs13113918	Genotyped	1	-
rs13129697	Genotyped	0.99	-
rs1394125	Genotyped	0.98	-
rs1529909	NA	NA	NA
rs16890979	Genotyped	0.99	-
rs17251963	Imputed	-	0.97
rs17300741	Genotyped	0.99	-
rs1967017	Genotyped	0.99	-
rs2051541	Genotyped	0.99	-
rs2078267	Genotyped	0.99	-
rs2199936	NA	NA	NA
rs2231137	Imputed	-	0.99
rs2231142	Genotyped	0.99	-
rs2241480	Genotyped	0.98	-
rs3114018	Genotyped	0.99	-
rs3775948	Imputed	-	0.99
rs3799344	Genotyped	1	-
rs3825018	Imputed	-	0.99

rs4148152	Genotyped	1	-
rs4697745	Imputed	-	0.97
rs478607	Imputed	-	0.99
rs505802	Genotyped	0.99	-
rs559946	Imputed	-	0.98
rs6449213	Genotyped	0.99	-
rs6598541	Imputed	-	0.93
rs675209	Genotyped	0.99	-
rs6843466	NA	NA	NA
rs6855911	Imputed	-	0.99
rs6856396	Imputed	-	0.71
rs717615	Genotyped	0.99	-
rs7193778	Imputed	-	0.97
rs7224610	Genotyped	1	-
rs72552713	Imputed	-	0.0073
rs734553	Genotyped	0.99	-
rs737269	Imputed	-	0.98
rs742132	Imputed	-	0.99
rs7442295	Imputed	-	0.99
rs7663032	Genotyped	0.99	-
rs7675964	Imputed	-	0.98
rs7683856	Imputed	-	0.98
rs780093	Genotyped	0.99	-
rs780094	Genotyped	0.99	-
rs7932775	Genotyped	0.99	-
rs814295	Imputed	-	0.99
rs882211	Imputed	-	0.82
rs893006	Genotyped	0.96	-
rs9321453	Imputed	-	0.99
rs938552	Imputed	-	0.99
rs9991278	Imputed	-	0.98

NA, SNP not available in the HANDLS study participants.

* Variant imputation quality score, R square, was from MACH/minimac.