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Multiple Genetic Loci Influence Serum Urate and Their Relationship with Gout and Cardiovascular Disease Risk Factors

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Abstract

Background—Elevated serum urate levels can lead to gout and are associated with cardiovascular risk factors. We performed genome-wide association to search for genetic susceptibility loci for serum urate and gout, and investigated the causal nature of the associations of serum urate with gout and selected cardiovascular risk factors and coronary heart disease (CHD).

Methods and Results—Meta-analyses of genome-wide association studies (GWAS) were performed in 5 population-based cohorts of the CHARGE consortium for serum urate and gout in 28,283 white individuals. The effect of the most significant SNP at all genome-wide significant loci on serum urate was added to create a genetic urate score. Findings were replicated in the Women's Genome Health Study (WGHS; n=22,054). SNPs at 8 genetic loci achieved genome-wide significance with serum urate levels (p-values 4×10^{-8} to 2×10^{-242}; *SLC22A11, GCKR, R3HDM2-INHBC* region, *RREB1, PDZK1*, *SLC2A9, ABCG2, SLC17A1*). Only two loci [*SLC2A9, ABCG2*] showed genome-wide significant association with gout. The genetic urate score was strongly associated with serum urate and gout (odds ratio 12.4 per 100 umol/L; p-value=3×10^{-39}), but not with blood pressure, glucose, eGFR, chronic kidney disease, or CHD. The lack of association between the genetic score and the latter phenotypes was also observed in WGHS.

Conclusions—The genetic urate score analysis suggested a causal relationship between serum urate and gout but did not provide evidence for one between serum urate and cardiovascular risk factors and CHD.

Keywords

urate; gout; cardiovascular disease risk factors; genome-wide association study; Mendelian randomization

Introduction

Hyperuricemia is a key risk factor for gout, a common inflammatory arthritis caused by deposition of mono-sodium urate crystals in the joints and surrounding tissues.[1] Multiple renal transporters contribute to the maintenance of normal serum urate levels, but the identity and regulators of these transporters are incompletely understood.

While the role of serum urate in the causal pathway for gout has been well-characterized, substantial controversy exists regarding whether elevated serum urate may also be a cause of cardiovascular disease (CVD) risk factors or CVD, or if the association with urate observed in observational studies merely is a consequence of these conditions or an artifact of uncontrolled confounding factors.[2] A recent randomized clinical trial of allopurinol in adolescents with newly diagnosed hypertension suggested that drugs that affect serum urate levels may also reduce blood pressure, further highlighting the potential role of serum urate in the pathogenesis of hypertension.[3]

We now expand on work by our consortium[4] and others[5-8] with GWAS and meta-analysis to identify genetic loci associated with urate and gout in a large sample of 28,283 individuals

from five population-based cohorts, the CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) consortium.[9] Capitalizing on Mendelian randomization, we then create a new genetic urate score of susceptibility to hyperuricemia, and examine its association with gout, blood pressure, glucose, chronic kidney disease (CKD), and coronary heart disease (CHD) to improve causal inference from observational studies. Finally, genetic score association findings are replicated in a second, large cohort, the Women's Genome Health Study (WGHS).

Methods

Five large population- or community-based cohorts from the CHARGE consortium including the Atherosclerosis Risk in Communities Study (ARIC), Cardiovascular Health Study (CHS), and Framingham Heart Study (FHS), the Rotterdam Study (including RS-I and RS-II), and Age Gene/Environment Susceptibility Reykjavik Study (AGES) constituted the discovery cohorts to identify genetic variants associated with urate levels and gout and for the genetic urate score analyses. An additional cohort, Women's Health Genome Study (WHGS), was used as a replication cohort to confirm the genetic urate score findings.

Each participant of the CHARGE cohorts provided written informed consent, and study protocols were approved by the Institutional Review Boards of their respective institutions. All members of the WGHS cohort were participants in the Women's Health Study who provided an adequate baseline blood sample for plasma and DNA analysis and who gave consent for blood-based analyses and long-term follow-up; the study has been approved by the Institutional Review Board of the Brigham and Women's Hospital.

Additional details pertaining to the study samples, including participant recruitment, phenotype definition, genotyping, imputation and data quality control are provided in the Supplementary Methods and Supplementary Table 1s.

CHD, CVD Risk Factors and Covariates in CHARGE Cohorts

CHD and CVD Risk Factors—Systolic and diastolic blood pressure (SBP, DBP) were measured using a sphygmomanometer in the seated position following a standard protocol in each study. For subjects treated with antihypertensive medications, 10 mm Hg were added to their SBP values and 5 mm Hg to DBP values to impute the untreated blood pressure.[10]Hypertension was defined as SBP >=140 or DBP >=90 mm Hg or on antihypertensive treatment. Glucose was obtained after an overnight fast. Diabetes was defined by fasting plasma glucose of at least 126 mg/dl, non-fasting plasma glucose of at least 200 mg/dl, diabetes medication, or self report. Fasting insulin was measured as described in the supplement. Serum creatinine was determined using a modified kinetic Jaffe reaction in all studies but AGES, who used an enzymatic method. Creatinine values were calibrated statistically, and estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) Study equation.[11] CKD was defined as eGFR <60 ml/min/1.73 m^2.[12] CHD was defined as incident myocardial infarction (AGES, ARIC, CHS, FHS, RS), fatal CHD (ARIC, CHS, FHS, RS), silent MI from EKG (ARIC), sudden cardiac arrest (CHS), percutaneous coronary interventions (AGES), coronary artery bypass grafting (AGES, RS), coronary revascularization procedure (ARIC) or percutaneous transluminal coronary angioplasty (RS).

Covariate Measurements—Body mass index was calculated as weight in kilograms divided by squared height in meters; alcohol consumption was recorded as drinks per week and converted to grams/week, and antihypertensive treatment was defined as self-reported intake of any antihypertensive medication.

Statistical Analyses in CHARGE Cohorts

GWAS and meta analyses—Separate GWAS analyses of ~ 2.5 million SNPs were first performed within each CHARGE cohort for urate levels adjusting for age, sex, BMI, alcohol, antihypertensive treatment and study-site or cohort and potential population admixture (Supplementary Methods and Table 1s). Fixed-effects meta-analyses were then used to combine the results from all CHARGE cohorts using the software METAL (http://www.sph.umich.edu/csg/abecasis/metal/index.html). The overall effect size of a SNP from the meta-analyses was defined as the inverse variance weighted average of the beta coefficients for the same allele in each cohort. A threshold of 5×10^{-8} defined genome-wide significance, corresponding to a Bonferroni adjusted alpha = 0.05 for 1 million independent tests, the estimated multiple testing burden for a GWAS of individuals of European ancestry.[13] For gout meta-analyses, SNPs with minor allele frequency (MAF) <0.02 were excluded from the analyses to minimize the risk of false positive results.

Genetic urate score analysis—To model the cumulative effects of the loci identified from the urate meta-analysis, we multiplied, for each locus, the number of minor alleles of the most significant SNP each person carried (0-2) by the beta coefficient from the meta-analysis, and added the results to calculate a genetic urate score. Specifically, the genetic urate score equals rs1967017(T)x3.3+rs780093(T)x5.2-rs13129697(G)x22.2+rs2199936(A)x18.1+rs675209(T)x4.4-rs1165196(G)x6.2+rs2078267(C)x6.8-rs1106766(T)x5.2, where each SNP ID followed by the allele in parenthesis denotes the number of copies of that allele carried by an individual and the number multiplied to is the effect size per copy of the allele in μmol/l estimated in our meta analyses. This genetic score calculation is the first step of a two-step least squares instrumental variables analysis to estimate the effect of a genetic score on the intermediary variable (serum urate) in a Mendelian randomization design.[14] The score assigns zero to individuals who carry all major alleles and has the unit of umol/L. Thus, the genetic urate score is the difference in mean serum urate levels of individuals with a specific combination of genotypes compared to individuals who carry two copies of the major alleles at all the susceptibility loci. The genetic urate risk score was then tested for association with CHD and CVD risk factors, with limited adjustment (for age, sex and center) and more extensive adjustment for major confounders.[2] Meta-analyzed associations are presented per 100 umol/L (1.68 mg/dl) increase in the genetic urate score, since it is similar to the range of the genetic urate score. Since power is a concern for using this approach, we calculated 80% power for each trait for a one sided test at alpha 0.05. Details of the power calculation are presented in the Supplementary Methods.

Replication of Genetic Urate Score Findings in WGHS

An independent cohort of 22,054 from the Women's Genome Health Study (WGHS) was used to validate the genetic urate score findings from the CHARGE cohorts. Details pertaining to the WGHS are included in the Supplementary Materials and Supplemental Table 1.

Results

Characteristics of individual CHARGE cohorts are presented in Table 1 for the 28,283 participants with serum urate levels.

Urate and Gout GWAS Meta-analysis in CHARGE Cohorts

Eight loci (*SLC22A11, GCKR, R3HDM2-INHBC* region, *RREB1, PDZK1*, *SLC2A9, ABCG2, SLC17A1*) showed genome-wide significant association in the meta-analysis for urate (meta analysis p-value range 3.5×10^{-8} to 1.5×10^{-242}; Table 2). A genome-wide

overview of the p-values from the meta-analyses is presented in Supplementary Figure 1s. Supplementary Figure 2s presents regional association plots for each of the eight loci. Details of study specific GWAS results for the eight loci are presented in Supplementary Table 2s and in a forest plot in Supplementary Figure 3s that demonstrates consistent results across studies. Imputation scores for all loci are shown in Supplemental Table 3s, indicating generally good imputation quality across cohorts. All the SNPs with meta-analysis p-value $<4\times10^{-7}$ are presented in Supplementary Table 6s and 7s for serum urate and gout, respectively.

Of the loci identified, 6 were also nominally associated with gout (Table 2). Besides *SLC2A9* and *ABCG2,* a separate GWAS of gout did not identify additional loci reaching genome-wide significance.

Genetic Urate Score Association with Serum Urate and Gout in CHARGE Cohorts

The genetic urate risk score was strongly and linearly associated with serum urate (Figure 1; multivariable adjusted p-value $<4.5\times10^{-308}$). The score ranged from −67 to +76 umol/L and explained an average of 6.0% of serum urate variance, compared to an average of 0.8% for the individual SNPs and 3.7% for the strongest SNP (*SLC2A9*). The gout prevalence varied 10-fold across genetic urate score categories (Figure 1; multivariable adjusted p-value 5.5×10^{-34}). Across genes, the odds ratio for gout was highly correlated with the effect size for serum urate for each additional minor allele (Figure 2; r=0.97). Overall, for a 100 umol/L higher genetic urate score, average serum urate was 99.3 umol/L higher and gout odds ratios were 12.4 (95% CI 8.5-18.0) times higher (Table 3).

Comparison of Serum Urate and Genetic Urate Score Associations with CVD Risk Factors and CHD in CHARGE Cohorts

Serum urate adjusted for age, sex and center was strongly associated with all of the cardiovascular disease risk factors examined (Table 3, $p<0.001$). Further covariate adjustment reduced the magnitude of the associations but all associations remained highly significant ($p<0.001$) except for fasting glucose. In contrast, the genetic urate risk score was not associated ($p\geq0.05$) with SBP, DBP, fasting glucose levels, fasting insulin, eGFR, CKD (n=3092 cases) or incident CHD (n=3050 cases). Excluding individuals on hypertension treatment from the SBP and DBP analyses or individuals with diabetes from the glucose analysis made little difference. We evaluated the detectable genetic urate score effect size per 100 umol/L with 80% power (Table 3, last column) in the context of observed effect sizes of serum urate per 100 umol/L on each phenotype (Table 3, column 3 and 5). For gout, fasting glucose, SBP, DBP, and eGFR, our study had good power as the observed serum urate effect sizes are generally higher than the detectable genetic urate effect sizes. For CKD, although the observed effect size is higher than detectable effect size, the detectable effect size (OR=1.38) is considered high for a genetic association. For CHD, observed serum urate effect size is smaller than detectable genetic score effect size with 80% power. Therefore a modest association with CKD and CHD cannot be ruled out due to insufficient power.

Replication in the Women's Genome Health Study (WGHS)

Analyses of the association of the urate risk score with CHD and CVD risk factors in the Women's Genome Health Study demonstrated similar null results (Supplementary Table 4s). Per 100 umol/L higher genetic urate score, the age and sex adjusted odds ratio of hypertension incidence was 0.93 (95% CI 0.78-1.11, p=0.43); coefficients for self reported blood pressure, diabetes, eGFR, and CKD were non-significant. The age and sex-adjusted hazard ratio for incidence of CHD was 0.83 (95% CI 0.53-1.30; p=0.42). Similar results were obtained for multivariable adjusted analyses.

Secondary Analyses Results

We additionally evaluated the association of individual SNPs with cardiovascular risk factors and CHD to examine possible pleiotropy effects, examined a possible threshold effect of the genetic urate score, and conducted sensitivity analyses for the genetic urate score. Description of these analyses and results is included in the Supplementary Materials and Table 5s.

Discussion

We have identified genetic variants in 8 genetic loci associated with serum urate. Our genetic urate score was strongly associated with a 10-fold variation in gout prevalence. In marked contrast, we did not observe an association between the genetic urate score and blood pressure, fasting glucose, CKD or CHD. This lack of association was also observed in another independent large cohort.

Our GWAS results are similar to another recent GWAS with more than 28,000 European individuals.[8] Six (*PDZK1*, *GCKR*, *SLC2A9*, *ABCG2*, *SLC17A1*, *SLC22A11*) of the nine loci identified by Kolz et al[8] were also identified by the present study. Among the remaining three loci identified by Kolz et al[8], *SLC16A9* and *LRRC16* were borderline genome-wide significant ($p=1.7\times10^{-7}$ and 1.3×10^{-7}) in the present study; *SLC22A12* reached significance in our study but was not considered as an independent locus because of its close proximity with *SLC22A11* and the uncertainty that the signals represent independent variants. We additionally identified *R3HDM2-INHBC* and *RREB1.*

We confirmed urate transporters *ABCG2, SLC2A9* and *SLC17A1* identified in our previous GWAS that included a subset of current study cohorts and a subsequent functional study.[4;15] Among our additional findings, *SLC22A11* encodes a known renal urate transporter, OAT4,[16] but it is also in close proximity to *SCL22A12,* which encodes another well known urate transporter, URAT1[17] *PDZK1* has been shown in experimental settings to directly interact with protein products of *SLC22A11* and *SLC17A1*, and has been proposed as a regulator of urate transport activities.[18] The biologic mechanisms underlying the association of SNPs in *RREB1*, the *R3HDM2-INHBC* region, and *GCKR* with serum urate are unknown. RREB1 is a zinc finger transcription factor reported to regulate the androgen receptor and the calcitonin gene.[17;19] INHBC is a member of the TGF-beta superfamily;[20] the top associated SNP rs4760254 maps to the intergenic region between *INHBC* and *R3HDM2* genes. SNPs in *GCKR* were previously reported in association with higher CRP, higher triglyceride levels, and lower glucose levels, suggesting pleiotropic mechanisms.[21]

Multiple lines of evidence link serum urate levels to hypertension, diabetes, CKD and CHD.[2;3] However, epidemiologic studies of metabolic traits are limited in determining causation, and serum urate can be elevated secondary to disease or confounders. Because the association between genes and disease is not generally subject to confounding by environmental factors or reverse causality, causal inferences between exposure and disease can be examined more specifically using Mendelian randomization. [14;22]

The percentage of variation explained by the genetic score is moderate. However, power calculation taking into account the variation explained by the genetic score indicated that this study had enough power to detect genetic score effect sizes similar to observed epidemiology effects of urate for all phenotypes but CHD. For the initial analyses only involving CHARGE cohorts, the genetic score has been constructed and tested for association with cardiovascular risk factors in the same individuals. As a result, the genetic score effects may be overestimated and should be interpreted with caution. However, the potential of overestimating effect sizes of the genetic score is contrary to its lack of

association with cardiovascular risk factors except gout in CHARGE. Similar lack-of-association findings have been reported by other studies that examined the association between individual genetic variants for serum urate and cardiovascular risk factors including blood pressure, hypertension, glucose, lipids, and coronary artery diseases.[6;23;24] Taken together, these findings raise questions about whether the observed epidemiologic associations between serum urate and CVD risk factors present in our cohorts and previous studies are due to causal associations.

Limitations of our study pertaining to the generalizability of our findings are: our study focused on CVD risk factors and incident CHD in middle-aged and older individuals, and therefore could not investigate the association of serum urate levels with blood pressure and new onset cardiovascular disease and its risk factors in adolescents and young adults. Participants of this study are white; findings may not be generalizable to other ethnicities. Gout ascertainment was based on self-report or medication records which may have resulted in inaccurate disease classification for some individuals and reduced power to detect an association. However the two loci identified associated with gout showed consistent effects across cohorts and were also the ones identified by other independent studies[5-8;25], demonstrating the robustness of our results to the gout ascertainment. We only tested the association of genetic urate score with CKD defined as eGFR < 60 ml/min/1.73 m^2. We were not able to examine more extreme definitions of CKD due to lack of power. We were also not able to adjust for the effects of antihyperuricemic treatment (e.g. allopurinol) in our analyses since information on such treatment was not available in all cohorts. However ignoring antihyperuricemic treatment is unlikely to have had a substantial impact on our results since only a small percentage of the study sample is expected to have been treated. Finally, we modeled a linear association of the genetic score with outcomes. We observed no association when the data were stratified by serum urate at the median. However, we cannot rule out the possibility of a threshold effect where low serum urate levels are protective but higher levels do not show progressively more deleterious cardiovascular effects. Despite these limitations, our study was large and well powered. The findings were consistent across all participating studies, and an independent replication sample.

In conclusion, we identified eight genetic loci associated with serum urate in genome-wide association and meta-analyses. Consistent with the association of serum urate and gout, the combined effect of all the genes summarized in a urate genetic risk score is associated with a ten-fold increase of gout risk. Conversely, the urate genetic risk score was not significantly associated with cardiovascular risk factors or CHD, which stands in contrast to the association between serum urate and vascular risk factors observed in epidemiologic studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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While the role of serum urate in the causal pathway for gout has been well-characterized, substantial controversy exists regarding whether elevated serum urate may also be a cause of high blood pressure (BP), hyperglycemia, and chronic kidney disease (CKD), or if the association with serum urate observed in observational studies merely is a consequence of these conditions or if it is an artifact of uncontrolled confounding factors. Because the association between genes and disease is not generally subject to confounding by environmental factors or reverse causality, causal inferences between exposure and disease can be examined more specifically using Mendelian randomization. In the present investigation, we tested the association of a genetic score constructed using 8 loci associated with serum urate with coronary heart disease (CHD) and its risk factors including gout, glucose, systolic BP, diastolic BP, estimated glomerular filtration rate and CKD. Except for gout, none of the associations was statistically significant, and the lack of associations was replicated in another equally large independent sample. Although further confirmation is warranted, our study helps elucidate the association of serum urate with CHD and its risk factors, which may contribute to a better understanding of the usefulness of controlling serum urate for preventing and designing treatments for CHD and its risk factors.

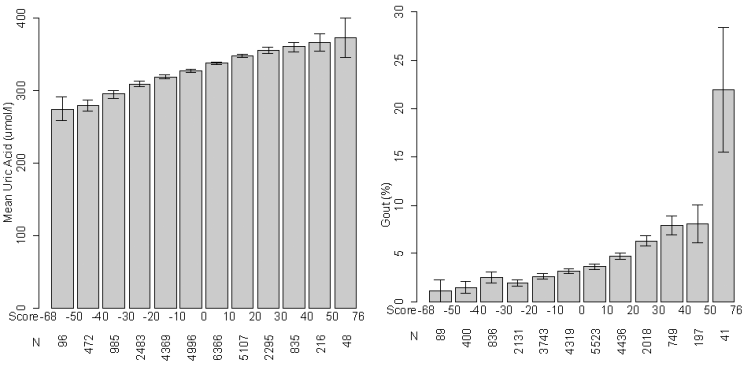

Figure 1. Mean urate levels and prevalence of gout across genetic urate score

Panel A: crude mean urate levels and its 95% confidence intervals for each interval of 10 μmol/l genetic urate score based on estimates from meta analysis. Panel B: crude prevalence of gout and its 95% confidence intervals for each interval of 10 μmol/l genetic urate score by pooling the counts from five studies.

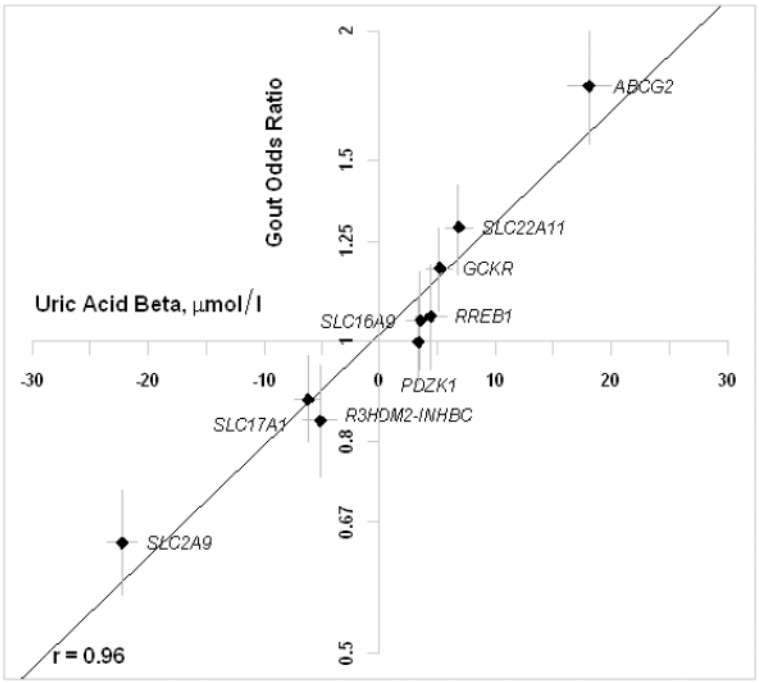

Figure 2. Relationship between urate beta coefficients and gout odds ratios across all 8 loci

Gout odds ratio per minor allele (y-axis) is plotted in natural logarithmic scale against corresponding urate beta coefficient per minor allele (x-axis) for each of the 8 urate loci (each point represents a SNP, with SNP name plotted nearby). A regression line is fitted using the 8 data points. The confidence intervals for each gout odds ratio estimate and beta coeffeicent were plotted as a vertical grey bar and as a horizontal bar respectively both centered at the point.

Table 1

Characteristics of study participants in CHARGE cohorts, mean (SD) or % (n).

Study sample	AGES	ARIC	CHS	FHS	RS-I	RS-II
Urate, gout and covariates	**2002-2006**	**visit 1 (1987-89)**	**baseline (1989-90)**	**1948, 1971, 2001**	**visit 1 (1990-1993)**	**2000-2001**
Sample size, n	3202	8092	3252	7699	4148	1890
Serum Urate (μmol/l)*	354.8 (96.3)	353.9 (89.4)	327.4(85.7)	315.2 (89.22)	321.2 (80.9)	324.3 (117.2)
Female (%)	58	53	61	53	61	55
Body Mass Index (kg/m^2)	27.1 (4.4)	27.0 (4.9)	26.3(4.4)	25.9 (4.9)	26.3 (3.7)	27.3 (4.2)
Age (y)	76 (6)	54 (6)	72(5)	38 (9)	70 (9)	65 (8)
Alcohol drinking (g/week)†	6 (2, 20)	66 (30, 138)	15 (3, 87)	48 (12, 120)	43 (3, 85)	-
Current Drinker (%)	65	66	54	81	79	-
Hypertension treatment (%)	64	26	35	5	33	29
Gout (%,n)‡	4.3 (137)	5.3 (349)	5.1(164)	2.7 (197)	3.3 (190)	3.3 (63)
Cardiovascular Risk Factors						
SBP (mm Hg)	143 (20)	119 (17)	139 (23)	119 (15)	139 (22)	143 (21)
DBP (mm Hg)	74 (10)	72 (10)	74 (13)	77 (10)	73 (12)	79 (11)
Antihypertensive treatment (%)	64	26	35	5	33	29
Fasting Glucose (mmol/l)§	5.5 (0.5)	5.5 (0.5)	5.5 (0.6)	5.4 (0.5)	5.7 (1.0)	5.6 (0.6)
eGFR creatinine (ml/min/1.73m^2)	73 (20)	90 (18)	80 (23)	85 (21)	77 (17)	81 (17)
CKD (%, n)	24 (780)	9 (731)	19 (603)	8 (231)	14 (577)	9 (169)
CHD (%, n)	15 (447)	17 (1365)	21 (660)	5 (197)	16 (928)	3 (65)

*Serum urate 100 umol/L = 1.68 mg/dl; glucose 1 mmol/l =18.18 mg/dl;

†median (1st and 3rd quartile), among current drinkers

‡Gout: AGES during2002-2006; ARIC obtained at visit 4, 1996-98; FHS at offspring exam 4-7(1987-1999) and third generation exam 1 (2001); RS-1 during 1990-2006; RSII 1999-2006

§individuals with diabetes were excluded from the analyses.

Table 2

Most significant SNPs in 8 loci associated with serum urate or gout based on meta analysis of GWAS within individual CHARGE cohorts.

SNP	Location*	Gene	MAF†	Minor† (Major) Allele	Urate			Gout		
					Beta‡(se)	R^2§	p-value	OR‖	95% CI	p-value
rs13129697	Chr 4: 9536065	SLC2A9	0.27	G(T)	−22.21(0.67)	3.70%	1.50E-242	0.66	0.59-0.74	3.70E-13
rs2199936	Chr 4:89264355	ABCG2	0.11	A(G)	18.08(0.98)	1.20%	1.20E-75	1.86	1.64-2.10	2.60E-23
rs2078267	Chr 11: 64090690	SLC22A11	0.46	C(T)	6.8(0.64)	0.38%	2.40E-26	1.26	1.14-1.38	1.30E-06
rs1165196	Chr 6:25921129	SLC17A1#	0.46	G(A)	−6.21(0.60)	0.37%	4.95E-25	0.89	0.82-0.98	0.013
rs780093	Chr 2: 27596107	GCKR	0.4	T(C)	5.15(0.61)	0.23%	3.80E-17	1.17	1.07-1.28	4.70E-04
rs1106766	Chr 12: 56095723	INHBC	0.23	T(C)	−5.16(0.77)	0.16%	1.90E-11	0.82	0.73-0.92	7.70E-04
rs675209	Chr 6: 7047083	RREB1	0.26	T(C)	4.39(0.72)	0.12%	1.00E-09	1.08	0.97-1.20	0.16
rs1967017	Chr 1: 144435002	PDZK1	0.47	T(C)	3.33(0.60)	0.10%	3.50E-08	1.00	0.92-1.10	0.96

Each GWAS was adjusted for age, sex, BMI, alcohol consumption (except RS-II), hypertension treatment, study center/cohort where applicable.

*SNP location, gene annotation were based on human genome reference sequence of NCBI build 36.2; alleles were called on forward strand.

†Minor allele frequency (MAF) was sample size weighted average of the frequency of less common allele (minor allele) over all cohorts.

‡beta is the increase of UA (umol/l) per copy of the minor allele under an additive model and se is its standard error, obtained from inverse variance weighted meta analysis.

§Sample size weighted average of the R^2 from individual studies, where R^2 denotes the R-square coefficient, i.e. total phenotypic variance explained by the additive effect of SNP genotype.

‖OR is the odds ratio for gout per copy increment of the minor allele, obtained from inverse variance weighted meta analysis.

#SLC17A1 refers to the entire SLC17A4/ SLC17A1/ SLC17A3/SLC17A2 gene cluster

Table 3

Comparison of the association of serum urate and genetic urate score (per 100 umol/L) with serum urate, gout and cardiovascular risk factors in CHARGE cohorts.

		Serum Urate, per 100 umol/L				Genetic Urate Score, per 100 umol/L			
		Age-Sex Adjusted[//]		Multivariable Adjusted[#]		Multivariable Adjusted[#]			Detectable at 80% power[**]
Phenotype[†]	N/n Events	Beta[*] (Odds Ratio)	P-value	Beta[*] (Odds Ratio)	P-value	Beta[*] (Odds Ratio)	995% CI	P-value	Beta[*] (Odds Ratio)
Serum Urate and Gout									
Serum Urate (umol/L)	28220	100	--	100	--	99.3	95.0 , 103.7	<5E-308	6.3
Gout (odds ratio)	25982/1033	(2.35)	<0.001	(2.1)	<0.001	(12.4)	8.5 , 18.0	3E-39	(1.7)
CVD Risk Factors									
SBP (mm Hg)[‡]	28199	3.44	<0.001	1.89	<0.001	−1.01	−2.10 , 0.09	0.07	1.57
SBP (not treated; mmHg)[§]	20673	2.82	<0.001	1.26	<0.001	−0.83	−1.96 , 0.30	0.15	1.61
DBP (mmHg)[‡]	28194	1.84	<0.001	1.03	<0.001	−0.15	−0.80 , 0.49	0.64	0.92
DBP (not treated; mmHg)[§]	20669	1.67	<0.001	0.78	<0.001	−0.34	−1.04 , 0.35	0.33	0.99
Fasting Glucose (mmol/l)	25877	0.12	<0.001	−0.002	0.80	−0.058	−0.13 , 0.02	0.13	0.11
Fasting Glucose (diabetes excluded, mmol/l)	23726	0.14	<0.001	0.09	<0.001	−0.0001	−0.036 , 0.036	1.00	0.05
Fasting Insulin (no DM) [††]	19899	35.84	<0.001	20.22	<0.001	−0.015	-	0.99	-
log eGFR (ml/min/1.73m^2)	23884	−0.08	<0.001	−0.08	<0.001	0.001	−0.01 , 0.02	0.91	−0.02
CKD	23387/3092	(2.31)	<0.001	(2.18)	<0.001	(1.20)	0.96 , 1.50	0.12	(1.38)
Incident CHD	23362/3050	(1.23)	<0.001	(1.09)	<0.001	(1.03)	0.85 , 1.25	0.76	(1.32)

To convert to mg/dl: Urate 100 umol/L = 1.68 mg/dl; glucose 1 mmol/l =18.18 mg/dl;

[*] Beta coefficients and their standard errors were obtained from inverse variance weighted meta-analyses of individual study results.

[†] For each phenotype, the analysis was restricted to those who had serum urate levels, all multivariable covariates and gene score available.

[‡] 10 mm Hg was added to SBP if treated with antihypertensive medication, and 5 mm Hg to DBP if treated.

[§] Individuals taking anti-hypertensive treatment were excluded from the analyses.

[//] Adjusted for age, sex and study center/cohort where applicable

[#]Covariates adjusted include: age, sex, BMI, alcohol consumption, antihypertensive medication for serum urate and gout; age, sex, BMI, SBP, antihypertensive medication, diabetes for eGFR and CKD; age,sex, BMI for blood pressure and glucose; and study center/site where applicable.

[**]Effect Size detectable with 80% power in the current study with one-sided p-value ≤ 0.05.

[††]Due to the lack of a standard to covert insulin in different studies to the same scale, sample size weighted meta analyses was performed instead. Z-statistics was reported in place for beta coefficient.