

# Serum urate gene associations with incident gout, measured in the Framingham Heart Study, are modified by renal disease and not by body mass index

Richard J. Reynolds<sup>1</sup> · Ana I. Vazquez<sup>2</sup> · Vinodh Srinivasasainagendra<sup>2</sup> ·  
Yann C. Klimentidis<sup>3</sup> · S. Louis Bridges Jr.<sup>1</sup> · David B. Allison<sup>4</sup> · Jasvinder A. Singh<sup>1</sup>

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**Abstract** We hypothesized that serum urate-associated SNPs, individually or collectively, interact with BMI and renal disease to contribute to risk of incident gout. We measured the incidence of gout and associated comorbidities using the original and offspring cohorts of the Framingham Heart Study. We used direct and imputed genotypes for eight validated serum urate loci. We fit binomial regression models of gout incidence as a function of the covariates, age, type 2 diabetes, sex, and all main and interaction effects of the eight serum urate SNPs with BMI and renal disease. Models were also fit with a genetic risk score for serum urate levels which corresponds to the sum of risk alleles at the eight SNPs. Model covariates, age ( $P = 5.95E-06$ ), sex ( $P = 2.46E-39$ ), diabetes ( $P = 2.34E-07$ ), BMI ( $P = 1.14E-11$ ) and the SNPs, rs1967017 ( $P = 9.54E-03$ ), rs13129697 ( $P = 4.34E-07$ ), rs2199936 ( $P = 7.28E-03$ ) and rs675209 ( $P = 4.84E-02$ )

were all associated with incident gout. No BMI by SNP or BMI by serum urate genetic risk score interactions were statistically significant, but renal disease by rs1106766 was statistically significant ( $P = 6.12E-03$ ). We demonstrated that minor alleles of rs1106766 (intergenic, *INHBC*) were negatively associated with the risk of incident gout in subjects without renal disease, but not for individuals with renal disease. These analyses demonstrate that a significant component of the risk of gout may involve complex interplay between genes and environment.

**Keywords** Obesity · Gout comorbidities · Metabolic syndrome · Genetic urate score

## Introduction

The prevalence of gout and hyperuricemia in the USA is increasing due partly to changing population age structure and increasing obesity rates [1–3]. Many large-effect genetic risk factors for gout and hyperuricemia are known from GWAS studies, including *SLC2A9* and *ABCG2*, which encode proteins important for urate reabsorption and excretion in the kidney [4, 5]. Hypertension and diuretic use are also risk factors for gout [6, 7]. These observations have stimulated the analysis of interactions between environmental risk factors involving renal function and serum urate genes and their association with gout [8]. Diuretic use has been associated with increased gout risk of individuals homozygous for validated hyperuricemia risk alleles *SLC2A9* (rs13129697) and *SLC22A11* (rs2078267) [8]. However, the same interaction was not found using a sample from the Nurses Health Study [9]. It is well known that gene–environment interactions are dynamic and with allele frequencies and exposures may vary among populations

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✉ Jasvinder A. Singh  
Jasvinder.md@gmail.com

<sup>1</sup> Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Faculty Office Tower 805B, 510 20th Street S, Birmingham, AL 35294, USA

<sup>2</sup> Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA

<sup>3</sup> Division of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

<sup>4</sup> Nutrition Obesity Research Center, University of Alabama at Birmingham, Birmingham, AL, USA

[10]. Therefore, the interpretation of gene–environment interactions can be difficult. Nevertheless, studies of gene–environment interactions can provide more complete knowledge of associations of environmental exposures and disease and add to our understanding of disease mechanisms [11].

A number of environmental risk factors, most interrelated, associated with gout and hyperuricemia are increasing in prevalence. Diet [12, 13] and traits associated with the metabolic syndrome, including hypertension, high body mass index (BMI) and type 2 diabetes, are also associated with increased serum urate and gout risk [14]. Reduced renal function is associated with gout. Results from the Atherosclerosis Risk in Communities Study (ARIC) showed that low glomerular filtration rate (GFR) was highly associated with incident gout. This result was abrogated when serum urate was included in the multivariable model reflecting the known link between reduced kidney function (whether due to hypertension, or other causes), urate excretion, hyperuricemia and gout risk [6].

In this study, we tested the hypothesis that particular genotype–environment interactions are important risk factors for gout. We report novel findings from analysis of the Framingham Heart Study (FHS) cohorts documenting BMI and renal disease interactions with each of eight validated serum urate loci. We also present results of the interactions of BMI and renal disease with a genetic risk score (GRS) representing the cumulative genetic risk with gout across the eight validated serum urate loci [4].

## Methods

### Clinical variables

The current study was performed using the original and offspring cohorts of the FHS [15]. These cohorts represent the age distribution for reasonable estimates of incident gout, whereas the third generation cohort is much younger, with gout prevalence much lower than observed in the normal population. Incident gout was defined as the presence of a clinical diagnosis of gout where none was present in any prior examination. Gout has been similarly defined and used in numerous published studies from the FHS, e.g., [16–19]. Sex of the subject was noted. Last age known (years) is the age at last follow-up and controls for exposure, or variable observation times to each subject. Type 2 diabetes was defined as present for each subject by searching examinations for patient history of diabetes. Hypertension in gout patients was defined as present for those with systolic or diastolic measurement higher or equal to 140 and 90 mmHg, respectively, at any examination up to gout diagnosis, and for non-gout subjects across all

examinations. BMI in gout patients was taken from examination at gout diagnosis and for non-gout subjects, the BMI at the last record. Renal disease at gout was defined as present for individuals with gout if clinical impression of renal disease was recorded at any examination up to gout diagnosis and for non-gout subjects, across all examinations. In addition, the last creatinine measurement was recorded before gout diagnosis or, for non-gout subjects, the last recorded creatinine measurement. These values were used to compute another objective measure of chronic kidney disease (CKD), eGFR. Individuals with eGFR <90 were defined as stage 2 CKD or greater. All variables are defined in detail including the dbGaP accession number in the supplemental materials.

### Genetic data

Genetic data for the two cohorts were initially obtained from the Affymetrix 6.0 gene array. Only two SNPs, rs1165196 and rs1106766, were directly genotyped. The other six SNPs, rs1967017, rs780093, rs13129697, rs2199936, rs675209 and rs2078267 were imputed with IMPUTE2, using the 1000 genomes as reference data [20]. Prior to imputation, standard quality control measured was used to eliminate poorly genotyped SNPs and individuals. All eight SNPs had “info” (imputation quality) scores >0.8, indicating a high level of statistical confidence in these imputed genotypes [21]. There were 5109 genotyped individuals with non-missing clinical variables in the sample.

### Data analysis

The general modeling strategy was to fit binomial regression models of gout incidence conditional on genetic and environmental covariates and their interactions. A major strength of our approach is the longitudinal nature of the FHS data, as we measured comorbidities as they occurred prior to gout diagnosis. By contrast, in a cross-sectional analysis the chronology of the outcome of interest and its comorbidities is unknown. For example, to estimate a BMI–urate SNP interaction effect, we observed BMI at gout and tested whether the allele frequency difference varied between gout and non-gout cases as a function of BMI. For non-gout cases, the comorbidities and environmental exposures were assessed across all examinations. We evaluated the comorbidities at the last examination time and at the time of maximum BMI of the non-gout cases. Results were similar and we only present results of the last examination time. To test hypotheses related to interaction effects of urate SNPs with BMI and renal disease, we fit six models of gout incidence with relevant covariates and additive genetic effects of the urate SNPs as described below. The analysis approach is depicted in Fig. 1.

**Fig. 1** Six generalized linear models to test the association of genetic and environmental covariates with gout incidence. Asterisk indicates excluding intercept. Double asterisk indicates GRS calculated as the sum of reference (gout increasing) alleles across the eight serum urate-associated loci

**Outline of modeling approach for testing urate gene and environmental effects on gout risk:**

**I. Model fitting**

A. Generalized linear models of gout incidence

The probability of gout case as the logit of 
$$p(y_i = 1) = \frac{\exp(\eta_i)}{1 + \exp(\eta_i)}$$

The linear predictor for the genetic, environmental effects and their interactions\* 
$$\eta_i = f(x_i) = \beta_0 + \sum_p \beta_j X_{ij}$$

B. Variables extracted from the Framingham Heart Study

Explanatory Variables,  $X_j$ , Age, Sex, Diabetes, Renal disease, Hypertension; BMI; rs1967017; rs780093; rs13129697; rs2199936; rs675209; rs1165196; rs2078267; rs1106766.

C. Six specific fitted models

SNP models	GRS** models
<p><b>Model 1:</b> Main effects only 14 model parameters**</p> <p><b>Model 2:</b> Model 1 plus BMI-SNP Interaction effects. 22 model parameters</p> <p><b>Model 3:</b> Model 1 plus renal disease--SNP Interaction effects. 22 model parameters</p>	<p><b>Model 4:</b> main effects only 7 model parameters</p> <p><b>Model 5:</b> Model 4 plus BMI-GRS interaction effect. 8 model parameters</p> <p><b>Model 6:</b> Model 4 plus Renal disease-GRS interaction effect. 8 model parameters</p>

**II. Hypothesis Testing**

A. Primary Hypothesis:

*BMI and renal disease x urate genotype interaction effects are important explanatory variables for gout incidence.*

B. Log likelihood ratio tests

Test statistic: change in model deviance between models 2, 1, and 3, 1, is  $\sim \chi^2$  DF = 8  
change in model deviance between models 5, 4, and 6 & 4 is  $\sim \chi^2$  DF = 1

*Additive model (1)*

We modeled the probability of incident gout, using the logit link, as a function of clinical and demographic variables and the eight urate SNPs:

$$p(y_i = 1) = \frac{\exp(\eta_i)}{1 + \exp(\eta_i)}$$

where  $\eta_i$  is a linear predictor for subject  $i$  of the form,

$$\eta_i = f(x_i) = \beta_0 + \sum_p \beta_j X_{ij},$$

$\beta_0$  is an intercept common to all subjects and  $p$  is the number of covariates. The  $p$  covariates are as follows: age at last examination, sex, diabetes (Y/N), renal disease (Y/N), hypertension (Y/N), BMI, and the count of copies of reference alleles associated with increased serum urate

rs1967017, rs780093, rs13129697, rs2199936, rs675209, rs1165196, rs2078267, rs1106766 accordingly to Yang et al. [4]. In the case of the SNP covariates, the count will yield  $\{x_{ij} = 0, 1, 2\}$  for the  $i$ th individual  $j$ th covariate. If the SNP was imputed, then the posterior probability weighted by expected number of alleles was used as the allele count.

*BMI–SNP interaction model (2)*

The additive model (1) was extended by adding eight interaction effects of BMI with each SNP.

*RD–SNP interaction model (3)*

The additive model (1) was extended by incorporating interaction effects of renal disease and the eight SNPs.

### Fitting models with genetic risk score

For every person, we counted number of risk alleles present (the eight urate SNPs) creating a new variable, GRS. For the GRS calculation, reference alleles for all SNPs were used such that increasing dosages of the alleles increased risk of incident gout. In addition, a weighted genetic urate score (GUSw) was calculated in which each SNP was multiplied by its effect on serum urate. The eight SNPs, risk alleles and effect sizes were obtained from Yang et al. [4] a meta-analysis of the CHARGE cohorts.

#### GRS model (4)

We refit our additive model (1), but replacing the eight SNPs with the GRS variable.

#### BMI–GRS model (5)

The GRS model was extended by adding an interaction term BMI by GRS.

#### RD–GRS model (6)

The GRS model was extended by adding the interaction term of renal disease by GRS.

Tests of individual effects from models 1 to 4 were one degree of freedom (1 *df*) tests whose *P* values were

obtained by the change in deviance ( $-2 \times \log$  likelihood) between the full model and a reduced model without the focal parameter. The test statistics for BMI and renal disease by genetic interactions were calculated as the change in model deviance between models 2 and 1, and models 3 and 1 and are distributed as  $\chi^2$  with *df* = 8. The corresponding test statistics for the GUS models 4 and 5 and models 4 and 6 have 1 *df*. For the eight *df* interaction effect tests, we considered the *P* value significant at the  $\alpha = 0.05$  level. For the 1 *df* tests of specific gene by environment interactions, *P* values less than the Bonferroni corrected  $\alpha$  level of  $6.25E-03$  were considered highly significant. All models were fit using the “glm” function in R with logit link function [22]. All tests of significance were performed with log-likelihood ratio tests (LRT) implemented using the “anova” function in R.

### Results

The total number of individuals analyzed in the study was 5097. We identified 423 incident gout cases from the original and offspring cohorts with available genetic data (Table 1). Gout patients had a mean age of 77.4 years and mean BMI of 29 kg/m<sup>2</sup>; 74 % were men, 26 % had diabetes, 61 % had hypertension, and 42 % had renal disease. The total number of individuals for which eGFR was computed was 3687. An eGFR <90 was only available for five incident

**Table 1** Clinical and demographic variables and frequencies of serum urate markers in the sample of the Framingham Heart Study

	Gout	Non-gout	Univariate <i>P</i> value
Clinical variables			
Age	77.4 (10.7)	73.9 (11.8)	5.31E–11
Sex (female)	0.26	0.57	3.15E–35
Type 2 diabetes	0.26	0.18	4.83E–06
Hypertension	0.61	0.50	6.69E–06
Renal disease	0.42	0.38	0.07
BMI	29.0 (5.2)	27.5 (5.3)	1.09E–08
eGFR	126 (38)	108 (38)	1.4E–04
SNP	Chr	Gene	Reference allele frequency (controls) (Cases)
Urate markers			
rs1967017	1	<i>PDZK1</i>	0.49 0.53
rs780093	2	<i>GCKR</i>	0.44 0.47
rs13129697	4	<i>SLC2A9</i>	0.70 0.79
rs2199936	4	<i>ABCG2</i>	0.10 0.13
rs675209	6	<i>RREB1</i>	0.27 0.30
rs1165196	6	<i>SLC17A1</i>	0.55 0.57
rs2078267	11	<i>SLC22A11</i>	0.51 0.49
rs1106766	12	<i>INHBC</i>	0.21 0.17

Mean (SD) or proportion reported. There were 423 gout cases and 4674 non-gout individuals in the study

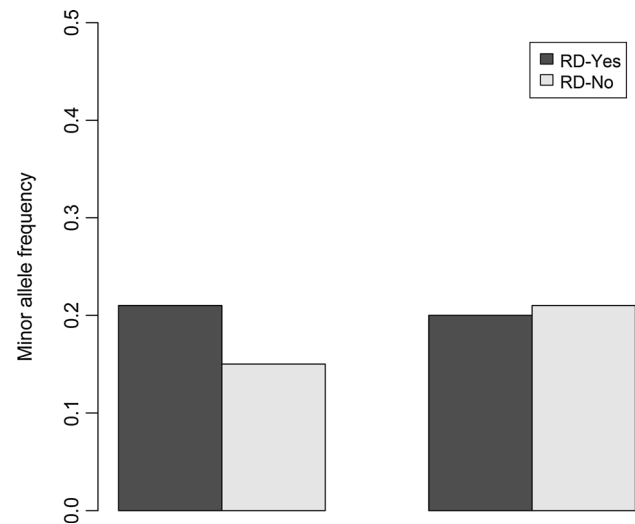
**Table 2** Parameter estimates (odds ratio  $\pm$  95 % confidence limits) and *P* values from indicated models

Source	Odds ratio	<i>P</i> value
Model 1		
Age	1.03 (1.02, 1.04)	5.95E–06
Sex (female)	0.17 (0.13, 0.23)	2.46E–39
Type 2 diabetes	2.50 (1.77, 3.52)	2.34E–07
Hypertension	1.19 (0.91, 1.54)	0.19
Renal disease	0.82 (0.62, 1.09)	0.17
BMI	1.08 (1.06, 1.10)	1.14E–11
rs1967017	1.23 (1.05, 1.45)	9.54E–03
rs780093	1.11 (0.94, 1.31)	0.19
rs13129697	1.62 (1.33, 1.98)	4.34E–07
rs2199936	1.63 (1.18, 1.98)	7.28E–03
rs675209	1.20 (1.00, 1.43)	4.84E–02
rs1165196	1.05 (0.90, 1.24)	0.52
rs2078267	0.92 (0.78, 1.09)	0.33
rs1106766	0.86 (0.70, 1.07)	0.16
Model 2 (model 1 + BMI by SNP interactions)		
BMI by rs1967017	1.00 (0.97, 1.03)	0.90
BMI by rs780093	0.99 (0.96, 1.02)	0.56
BMI by rs13129697	1.01 (0.97, 1.05)	0.56
BMI by rs2199936	1.05 (1.00, 1.10)	0.06
BMI by rs675209	0.98 (0.95, 1.01)	0.21
BMI by rs1165196	0.99 (0.96, 1.02)	0.39
BMI by rs2078267	0.98 (0.95, 1.01)	0.26
BMI by rs1106766	0.98 (0.94, 1.02)	0.28
Model 3 (model 1 + renal disease by SNP interactions)		
Renal disease by rs1967017	1.04 (0.75, 1.45)	0.85
Renal disease by rs780093	0.85 (0.62, 1.18)	0.34
Renal disease by rs13129697	0.85 (0.57, 1.27)	0.49
Renal disease by rs2199936	0.76 (0.44, 1.32)	0.32
Renal disease by rs675209	0.73 (0.51, 1.06)	0.14
Renal disease by rs1165196	0.89 (0.64, 1.23)	0.47
Renal disease by rs2078267	1.28 (0.91, 1.81)	0.15
Renal disease by rs1106766	1.79 (1.17, 2.73)	6.12E–03

*P* values are 1 *df* likelihood ratio tests of the full model and the full model without the indicated variable

gout cases with genetic data, and thus, we did not fit genetic models to these data. Non-gout patients differed from gout patients in all but one of these measures (Table 1). In univariate models, age, sex, BMI, type 2 diabetes, eGFR and hypertension were all significantly associated with gout, but a clinical diagnosis of renal disease was not (Table 1).

Hypothesis tests of model 1 demonstrated that the covariates, age ( $P = 5.95E-06$ ), sex ( $P = 2.46E-39$ ), BMI ( $P = 1.14E-11$ ) and diagnosis of diabetes ( $P = 2.34E-07$ ), were all significantly associated with the risk of gout (Table 2). Hypertension and renal disease were not statistically significantly associated with gout



**Fig. 2** Renal disease and the serum urate-associated loci, *INHBC* has a non-additive association with incident gout. The interaction plot shows the minor allele frequency of the *INHBC* SNP (rs1106766) by category of renal disease and incident gout

in the multivariable model. Four out of the eight serum urate-associated SNPs were significantly ( $\alpha$  level = 0.05) associated with incident gout in the multivariate model: rs1967017 ( $P$  value =  $6.79E-03$ ), rs13129697 ( $P$  value =  $4.13E-07$ ), rs2199936 ( $P$  value =  $1.76E-03$ ) and rs675209 ( $P$  value =  $2.34E-02$ ) (Table 2).

LRT (model 1 vs model 2) demonstrated that interaction effects of these eight SNPs and BMI do not appear to be important explanatory variables for gout incidence ( $\chi^2 = 8.3$ ,  $df = 8$ ,  $P$  value = 0.40). In addition, model 2 was refit with BMI as a dichotomous variable (BMI  $<30 = 0$ , BMI  $\geq 30 = 1$ ), and in this case, the deviance of the model exceeded that of model 1 (data analysis not shown). The RD-SNP interaction model (model 3) was significantly different than model 1 ( $\chi^2 = 15.86$ ,  $df = 8$ ,  $P$  value =  $4.44E-02$ ) indicating at least one statistically significant interaction effect. A 1 *df* LRT demonstrated that a single interaction effect, renal disease by rs1106766, was statistically significant ( $P$  value =  $6.12E-03$ ) (Table 2).

The interaction of renal disease and the *INHBC* SNP, rs1106766 (OR 1.8, 95 % CI 1.2, 2.7), was visualized by plotting its minor allele frequency in cases and controls by categories of renal disease. As seen in Fig. 2, there is no genetic risk of gout at this locus among individuals with renal disease; however, there is a negative genetic risk of gout (“protective” effect of the *INHBC* locus), among individuals without renal disease. Based on the frequencies of this SNP observed among those without gout, we would have expected a much lower frequency among incident gout cases with renal disease than that which was observed (0.21).

**Table 3** Parameter estimates (odds ratio  $\pm$  95 % confidence limits) and *P* values from indicated models

Source	Odds ratio	<i>P</i> value
Model 4		
Age	1.03 (1.02, 1.04)	6.65E–06
Sex (female)	0.18 (0.13, 0.24)	4.68E–39
Type 2 diabetes	2.51 (1.78, 3.54)	1.87E–07
Hypertension	1.19 (0.92, 1.55)	0.17
Renal disease	0.81 (0.61, 1.08)	0.15
BMI	1.08 (1.06, 1.10)	9.54E–12
GUS	1.20 (1.12, 1.28)	1.54E–08
Model 5		
BMI by GUS	1.00 (0.99, 1.01)	0.72
Model 6		
Renal disease by GUS	0.82 (0.72, 0.94)	3.20E–03

*P* values are 1 *df* log-likelihood ratio tests of the full model and the full model without the indicated variable

Hypothesis tests of the GRS model, in which an unweighted GRS replaced the individual SNP markers, demonstrated that the GRS alone was significantly associated with gout incidence ( $P = 1.54E-08$ ) (Table 3). The BMI-GRS interaction was not a significant explanatory variable for gout risk (model 5 vs model 4), but the renal disease-GRS interaction was statistically significant (model 6 vs model 4;  $P = 3.2E-03$ ). These results generally mirror the results from models 1 to 3. Models 4–6 were also fit using GUSw, and hypothesis tests of the weighted GUS effect, the BMI by GUS and the renal disease by GUS interaction resulted in *P* values that were highly similar to models fit with the unweighted GUS (Table 3).

## Discussion

In this study, we tested the hypothesis that environmental factors affecting serum urate and genetic loci for serum urate concentration may exhibit context-dependent associations with the risk of developing gout. Genes encoding urate transporters have been consistently associated with serum urate concentration and gout in population-based studies [4, 5]. Two loci alone, SLC2A9 and ABCG2, which are the only loci genome-wide significant for gout, account for 50 % of the variance in serum urate explained by the 26 replicated loci identified from GWAS (total variance explained by all loci is 7 %) [5]. The directions of the effect sizes of SNPs for serum urate concentration are consistent with the magnitudes of OR's observed for gout [5]. We hypothesized that BMI and renal disease, both associated with hyperuricemia, may mask or accentuate the associations of the SNPs with gout. For example, high

BMI, perhaps a result of lifestyle or diet, and associated increased serum urate concentration, may increase risk of developing gout, but only when combined with genotypes associated with high serum urate. Therefore, our approach seeks to further our understanding of the environmental sources of variation for gout, mediated by serum urate loci, with implications for gout's pathogenesis.

We found support for the hypothesis that renal disease and urate-associated SNPs were also non-additive sources of variation for gout risk. BMI and urate SNPs were both highly associated with gout risk, but BMI by urate SNP interaction effects were not. Results from the main effects model demonstrated that neither rs1106776 (*INHBC*) nor renal disease were statistically significant risk factors for incident gout. However, the *INHBC* risk with gout appears contextual given the presence of renal disease. Among individuals without renal disease, the *INHBC* SNP was protective, but there was no protective association evident at this locus for individuals with renal disease. The *INHBC* SNP has not been validated in GWAS meta-analyses as a genetic risk factor for gout at genome-wide  $\alpha$  levels [5]. Interestingly, in New Zealanders of European and Polynesian ancestry, the effect for gout, in rigorously phenotyped cohorts, appears reversed [23]. It is conceivable that renal disease, which reverses rs1106776's lowered gout risk observed among those with normal renal function, is masking *INHBC*'s effects on gout from the GWAS meta-analyses. For complex diseases such as gout, more modest genetic effects may frequently be overlooked especially if pervasive genetic and environmental correlation for gout comorbidities exist and obscure findings from simple models of trait-SNP associations.

The role of the renal disease exposure appears to be mediating the direction and magnitude of the SNP's effect on gout away from that expected based on the SNP's association with serum urate. We demonstrated that renal disease and urate risk SNPs as a whole contribute to gout risk. Indeed, the interaction of renal disease and the GRS was a significant source of gout risk. However, these context-dependent genetic effects were not observed at all the urate-associated loci. LRT demonstrated that only 1 out of 8 of the individual effects was statistically significant (rs1106766). The renal disease by SNP interaction effects just described involve genetic loci of much more modest effect together explaining <0.3 % of the variance in urate concentration [4, 5]. These results suggest that gout comorbidities related to kidney function can mediate the distribution of genetic effects on gout.

It is possible that the same loci associated with gout are also associated with its comorbidities, i.e., the variables considered environmental mediators are themselves genetically correlated with the outcome of interest. For example, the *INHBC* locus has been found to be associated

with eGFR [24]. The SLC2A9 and ABCG2 loci together explain 3.4 % of the variance in serum urate concentration and are the only validated gout risk loci at genome-wide  $\alpha$  level [5]. *SLC2A9* and *ABCG2* have known functional roles in serum urate concentration and gout risk and also have indirect negative effects on GFR and serum creatinine and thus renal function [25]. It appears then that there is positive genetic correlation due to pleiotropy between renal disease and gout at these loci. However, we were not able to find statistically significant main effects of rs13129697 (*SLC2A9*) or rs2199936 (*ABCG2*) on renal disease (data not shown) nor did we find interaction effects for gout involving the SLC2A9 and ABCG2 SNPs with BMI or renal disease. In addition, no SNP tested in this study was known to have an association with BMI [26]. Nevertheless, the multivariable models we used to test for significant interactions between the SNPs and genetically correlated exposures could be limited if the genetic effect of the exposure on gout nullifies the SNP's effect and its interaction. These observations suggest that it would be interesting to study the pairwise genetic correlations of gout comorbidities especially if the results improve the estimates of genetic risk of the disease.

We acknowledge several limitations of the study. First, our measure of renal disease, a clinical diagnostic impression, does not include objective measures of renal function. In this study, we were not able to make a strong link between our eGFR variable and renal disease, which could be due to a mismatch between the time points of creatinine measurement and clinical diagnostic impression of renal disease. However, the results are hypothesis generating and call for future studies of genetic associations with gout and renal function in well-phenotyped prospective studies.

We used measures of incident gout, thus allowing an accurate assessment of risk associated with gout comorbidities. We were not able to establish that BMI, a known risk factor for gout and hyperuricemia, and urate loci interact in their association with gout risk. We were able to conclude that some genetic risk of gout seems to be context dependent on normal kidney function. Finally, we conclude that future studies of gout risk prediction should include multivariate models of genetic and environmental correlations to better understand the connections between gout comorbidities and their joint effects on gout risk.

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#### Compliance with ethical standards

**Conflict of interest** J.A.S. has received research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron and Allergan. J.A.S. is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the American College of Rheumatology's Guidelines Subcommittee of the Quality of Care Committee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee. Dr. Allison has received grants, donations, or consulting fees from Pfizer, Arena and Eisai pharmaceuticals.

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