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Do Serum Urate–associated Genetic Variants Influence Gout Risk in People Taking Diuretics? Analysis of the UK Biobank

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ABSTRACT. ***Objective.*** The aim of this study was to determine whether serum urate (SU)–associated genetic variants differ in their influence on gout risk in people taking a diuretic compared to those not taking a diuretic.

Methods. This research was conducted using the UK Biobank Resource (n = 359,876). Ten SU-associated single-nucleotide polymorphisms (SNP) were tested for their association with gout according to diuretic use. Gene-diuretic interactions for gout association were tested using a genetic risk score (GRS) and individual SNP by logistic regression adjusting for relevant confounders.

Results. After adjustment, use of a loop diuretic was positively associated with prevalent gout (OR 2.34, 95% CI 2.08–2.63), but thiazide diuretics were inversely associated with prevalent gout (OR 0.60, 95% CI 0.55–0.66). Compared with a lower GRS (< mean), a higher GRS (≥ mean) was positively associated with gout in those not taking diuretics (OR 2.63, 2.49–2.79), in those taking loop diuretics (OR 2.04, 95% CI 1.65–2.53), in those taking thiazide diuretics (OR 2.70, 2.26–3.23), and in those taking thiazide-like diuretics (OR 2.11, 95% CI 1.37–3.25). No nonadditive gene-diuretic interactions were observed.

Conclusion. In people taking diuretics, SU-associated genetic variants contribute strongly to gout risk, with a similar effect to that observed in those not taking a diuretic. These findings suggest that the contribution of genetic variants is not restricted to people with "primary" gout, and that genetic variants can play an important role in gout susceptibility in the presence of other risk factors.

Key Indexing Terms: diuretics, genetics, gout, hyperuricemia

Many factors are associated with the development of gout, including genetic variability, comorbid conditions, and medications. Cross-sectional studies have identified different phenotypic clusters for gout based on the presence or absence of various comorbidities and medications[1,2]. Identification of different disease clusters may reflect different pathophysiological processes involved in the development of gout[1,3]. One cluster includes patients with "isolated gout" in whom few comorbidities exist. This cluster is often termed *primary gout* and is presumed to have a strong genetic basis. Genome-wide association studies have identified many single-nucleotide polymorphisms (SNP) associated with serum urate (SU) and gout[4,5,6,7].

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Another phenotypic cluster includes patients with cardiovascular disease and kidney disease, many of whom are receiving diuretic therapy[1,2]. This cluster is often referred to as *secondary gout* and is thought to have less of a basis in inherited genetic risk factors. Diuretic agents are widely prescribed, and their main site of action is the kidneys. Loop diuretics inhibit the sodium-potassium-chloride cotransporter at the loop of Henle and are used in fluid overload states[8]. Thiazide and thiazide-like diuretics inhibit the sodium-chloride cotransporter at the distal convoluted tubule and their main indication is hypertension (HTN)[9,10]. An association between diuretic use and gout has been reported by many investigators with most, but not all, early studies reporting an increased risk of gout with diuretic use[11,12,13,14]. More recently, larger studies have tested for an association between diuretic use and incident gout while attempting to adjust for confounders. All have confirmed a positive association and reported a higher risk of gout with loop diuretics compared to thiazide diuretics[15,16]. Diuretics are thought to increase gout risk by inducing hyperuricemia through their action on renal urate transporters. A possible mechanism involves competitive inhibition of urate transporters on renal tubular cells normally involved in urate secretion, such as OAT1 and OAT3 on the basolateral membrane[17], and MRP4 and NPT4 on the apical membrane[17,18]. There is also evidence for diuretic-induced uptake of urate through OAT4 on the basolateral membrane of renal tubular cells[19]. Further, diuretics also affect renal urate excretion through indirect mechanisms

related to intravascular volume contraction and salt loss, which stimulates renal solute (including urate) reabsorption[20].

The aim of our study was to determine whether the genetic risk for gout attributed by SU-associated genetic variants differs in people taking a diuretic compared to those not taking a diuretic.

MATERIALS AND METHODS

Study population and diuretic classification. This research was conducted using the UK Biobank Resource (approval number 12611). UK Biobank obtained approval from the North West Multi-Centre Research Ethics Committee (11/NW/0382). Full written informed consent was obtained from all participants prior to the study. Participants of European ancestry aged 40–69 years and with genome-wide genotypes were included in our study. Exclusion criteria included mismatch between self-reported sex and genetic sex, genotyping quality control failure, and related individuals. Gout was defined using the following validated definition criteria: self-report of gout or urate-lowering therapy (includes allopurinol, febuxostat, sulphinpyrazone) use, and without a hospital diagnosis of leukemia or lymphoma based on the International Classification of Diseases, 10th Revision, codes C81–C96[21]. For participants who did not meet the gout definition, further exclusion criteria included prescriptions for corticosteroids, nonsteroidal antiinflammatories, or probenecid. This definition has been previously tested in an analysis of the first tranche of the UK Biobank and was found to detect the highest number of gout cases and had the best precision for genetic association analyses compared to other methods for defining gout status[21]. In addition, when compared to gold standard synovial fluid microscopy results, this definition was found to have the best test performance characteristics out of 10 different definitions used in epidemiological studies that contributed to the Global Urate Genetics Consortium[22]. Variables collected through self-report were medication use, comorbidities (including renal failure, heart failure, and HTN), alcohol intake, and smoking status data. Diuretic agents were classified into 4 groups: loop diuretics, thiazide diuretics, thiazide-like diuretics, and potassium-sparing diuretics. Participants taking 2 or more diuretics were assigned to the particular diuretic class based on a hierarchy grading: loop diuretic to thiazide diuretic to thiazide-like diuretic to potassium-sparing diuretics.

Genotyping analysis. UK Biobank samples were genotyped using an Axiom array (820,967 markers; Affymetrix) and imputed to about 73.3 million SNP using SHAPEIT3 and IMPUTE2 with a combined UK10K and 1000 Genomes reference panel[23]. For quality control, SNP with a minor allele frequency (< 0.001), and Hardy-Weinberg equilibrium ($< 1 \times 10^{-6}$) were excluded. Thirty SU-associated SNP have been previously reported[4]. However, not all of these SNP associated with gout in a previous analysis of the UK Biobank[21]. Therefore, we analyzed the 10 SU-associated SNP with the strongest association for gout (that included renal urate transporters) as reported by Cadzow, *et al*[21] in the analysis from the first tranche (n = 105,421) of the UK Biobank genotyping dataset. These included 2 loci encoding urate transporters for which a gene-diuretic interaction for gout has previously been reported [*SLC2A9* (encoding GLUT9) and *SLC22A11* (encoding OAT4)][24], and 4 loci encoding for other urate transporters and ancillary genes [*ABCG2* (encoding ABCG2), *SLC17A3* (encoding NPT4), *SLC22A12* (encoding URAT1), and *PDZK1* (encoding PDZK1)]. The SNP and effect allele for each locus tested in this analysis were the lead SNP at the respective locus as identified by Köttgen, *et al*[4].

Genetic risk score. A weighted genetic risk score (GRS) for gout was calculated from the UK Biobank dataset to model the cumulative effects of an individual's risk for gout for the 10 variants. For each of the 10 SU-associated SNP, allelic OR were calculated to determine the risk of gout adjusting for age, sex, and BMI. The OR were converted into a logarithmic value and for each individual, these logarithmic values were multiplied by the number of urate-raising alleles and summed into a weighted GRS. Higher scores indicate a greater genetic predisposition for gout.

Study power. Details on study power are provided in the Supplementary Methods and Supplementary Table 1 (available with the online version of this article).

Statistical analysis. Data were analyzed using IBM SPSS Statistics 25 software (IBM Corp.). Baseline characteristics according to diuretic use were summarized using standard descriptive statistics including means, SD, number, and percent, and were compared using unpaired *t* tests or Pearson chi-square tests where appropriate. Logistic regression of diuretic use with gout as the dependent variable was performed in an unadjusted model; a model adjusted for age, sex, and BMI; and a model adjusted for age, sex, BMI, HTN, renal failure, and heart failure. GRS-diuretic interactions for gout association were assessed using logistic regression models that included a GRS by diuretic interaction term. Interaction models were calculated with GRS as a categorized variable [lower (< mean) or higher (≥ mean)], and as a continuous variable. Association of the SNP with gout according to diuretic use was determined based on the presence or absence of the allele that increased the risk of gout. SNP-diuretic interactions for gout association were analyzed using logistic regression models that included an SNP by diuretic interaction term. The following were included as variables in all interaction analyses: age, sex, BMI, HTN, renal failure, and heart failure. A sensitivity analysis was also performed in which the GRS was modeled using effect sizes for gout from Köttgen, *et al*[4]. Data were reported at experiment-wide significance ($P < 0.005$) to account for multiple testing in the individual SNP analysis.

RESULTS

Clinical features of participants. Data including genome-wide genotypes were available for 359,517 participants. Baseline characteristics according to diuretic use are shown in Table 1. There were 29,352 (8.2%) diuretic users, of whom 3728 (12.7%) were taking a loop diuretic, 23,623 (80.5%) were taking a thiazide diuretic, and 2001 (6.8%) were taking a thiazide-like diuretic.

Overall, there were 7324 (2.0%) participants with gout. In participants with gout, those taking any diuretic were older, had a higher BMI, and had a higher prevalence of comorbidities including HTN compared to participants who were not taking a diuretic. For participants with gout taking a loop diuretic, those with gout had a higher prevalence of renal failure and heart failure compared to participants with gout who were not taking a diuretic (Table 1).

Association of diuretic use and gout. Gout was present in 6145 (1.9%) nondiuretic users, 462 (12.4%) loop diuretic users, 615 (2.6%) thiazide diuretic users, and 102 (5.1%) thiazide-like diuretic users. Supplementary Table 2 (available with the online version of this article) shows unadjusted and adjusted OR for prevalent gout according to diuretic use. Participants taking a loop diuretic had the highest OR for gout in the unadjusted model (OR 7.46, 95% CI 6.74–8.25) and this association persisted in the fully adjusted model (OR 2.34, 95% CI 2.08–2.63). For participants taking a thiazide diuretic, there was a positive association with gout in the unadjusted model (OR 1.41, 95% CI 1.30–1.53); however, in the fully adjusted model there was an inverse association with gout (OR 0.60, 95% CI 0.55–0.66). For participants taking a thiazide-like diuretic, an increased OR for

Table 1. Baseline characteristics of participants according to diuretic use.

	No Diuretic, n = 330,165		Loop Diuretic*, n = 3728		Thiazide Diuretic*, n = 23,623		Thiazide-like Diuretic* n = 2001	
	Control, n = 324,020	Gout, n = 6145	Control, n = 3266	Gout, n = 462	Control, n = 23,008	Gout, n = 615	Control, n = 1899	Gout, n = 102
Age, yrs (SD)	56.5 (8.0)	59.5 (7.0)	62.2 (5.8)	62.8 (5.6)	61.7 (5.8)	62.2 (5.9)	61.5 (5.7)	62.7 (5.0)
BMI, kg/m^2 (SD)	26.9 (4.5)	30.3 (4.7)	32.1 (6.6)	33.2 (6.1)	29.6 (5.1)	32.5 (5.2)	29.9 (5.2)	32.8 (6.4)
Sex								
Male	152,311 (47.0)	5771 (93.9)	1520 (46.5)	368 (79.7)	9927 (43.1)	529 (86.0)	957 (50.4)	86 (84.3)
Female	171,709 (53.0)	374 (6.1)	1746 (53.5)	94 (20.3)	13,081 (56.9)	86 (14.0)	942 (49.6)	16 (15.7)
Smoker *	33,351 (10.3)	554 (9.1)	293 (9.0)	30 (6.5)	1430 (6.2)	41 (6.7)	96 (5.1)	3 (2.9)
Alcohol frequency *								
Daily or almost daily	68,557 (21.2)	2,135 (34.8)	484 (14.8)	113 (24.5)	4759 (20.7)	197 (32.1)	441 (23.2)	25 (24.5)
3–4 times/week	79,423 (24.5)	1755 (28.6)	482 (14.8)	87 (18.9)	4886 (21.3)	155 (25.2)	387 (20.4)	28 (27.5)
1–2 times/week	86,186 (26.6)	1375 (22.4)	725 (22.2)	121 (26.2)	5702 (24.8)	141 (23.0)	467 (24.6)	26 (25.5)
Infrequent #	68,961 (21.3)	644 (10.5)	1010 (30.9)	92 (20.0)	568 (24.7)	83 (13.5)	437 (23.0)	14 (13.7)
Never	20,685 (6.4)	230 (3.7)	563 (17.2)	48 (10.4)	1962 (8.5)	38 (6.2)	167 (8.8)	9 (8.8)
Comorbidities *								
Hypercholesterolemia	34,034 (14.9)	1563 (25.6)	1083 (33.4)	192 (41.6)	7067 (30.8)	249 (40.5)	664 (35.0)	44 (43.1)
Hypertension	63,644 (27.8)	3113 (51.0)	2199 (67.9)	360 (77.9)	21,707 (94.6)	578 (94.0)	1806 (95.3)	96 (94.1)
Angina	9033 (4.0)	451 (7.4)	839 (25.9)	136 (29.4)	1210 (5.3)	65 (10.6)	141 (7.4)	7 (6.9)
Myocardial infarction	6687 (2.9)	343 (5.6)	757 (23.4)	130 (28.1)	675 (2.9)	42 (6.8)	82 (4.3)	4 (3.9)
Heart failure	75 (< 0.1)	10 (0.2)	90 (2.8)	32 (6.9)	17 (0.1)	2 (0.3)	2 (0.1)	0 (0.0)
Stroke	1707 (0.7)	42 (0.7)	214 (6.6)	43 (9.3)	849 (3.7)	42 (6.8)	126 (6.6)	11 (10.8)
Transient ischemic attack	3527 (1.5)	156 (2.6)	43 (1.3)	8 (1.7)	225 (1.0)	6 (1.0)	16 (0.8)	2 (2.0)
Renal failure	336 (0.1)	69 (1.1)	58 (1.8)	28 (6.1)	41 (0.2)	9 (1.5)	4 (0.2)	1 (1.0)
Diabetes mellitus	10,374 (4.5)	570 (9.3)	775 (23.9)	143 (31.0)	2136 (9.3)	116 (18.9)	296 (15.6)	32 (31.4)

Data are n (%) unless otherwise indicated. * Smoking status, alcohol frequency, diuretic use, and comorbidity data collected by self-report. # Infrequent alcohol use defined as 1–3 times a month, or special occasions only.

gout was also present in the unadjusted model (OR 2.83, 95% CI 2.32–3.46). However, following adjustment for all confounders, no association with gout was observed (OR 1.05, 95% CI 0.85–1.29; Supplementary Table 2).

Association of GRS and gout. The mean (SD) GRS for all participants, including those with gout, was 1.15 (0.26). In the entire study population, 174,115 participants (48.9%) had a higher (≥ mean) GRS. Participants with gout had a significantly higher GRS compared to those without gout [mean (SD) 1.30 (0.26) vs 1.15 (0.26); $P < 1 \times 10^{-300}$; Table 2].

Compared to participants with a lower (< mean) GRS, the unadjusted OR (95% CI) for gout was 2.48 (2.36–2.61) in participants with a higher GRS (Supplementary Table 3, available with the online version of this article). After adjusting for age, sex, BMI, HTN, renal failure, and heart failure, a significant association for gout persisted (OR 2.60, 95% CI 2.46–2.74).

Table 2. Mean genetic risk scores according to diuretic use.

	Genetic Risk Score, mean (SD)		
	Control	Gout	Control vs gout, *P*
No diuretic	1.15 (0.26)	1.30 (0.26)	$< 1 \times 10^{-300}$
Loop diuretic	1.14 (0.26)	1.25 (0.26)	1.26×10^{-16}
Thiazide diuretic	1.14 (0.26)	1.28 (0.25)	1.34×10^{-41}
Thiazide-like diuretic	1.14 (0.25)	1.29 (0.28)	2.10×10^{-8}

In this analysis, the genetic risk score was modeled using effect sizes for gout from the UK Biobank dataset.

Association between GRS and gout, according to diuretic use. The mean GRS was higher in participants with gout compared to participants without gout for nondiuretic users, loop diuretic users, thiazide diuretic users, and thiazide-like diuretic users. Data for the prevalence of gout according to GRS category and diuretic use are shown in Figure 1. Compared to participants with a lower GRS, the prevalence of gout was higher in those with a higher GRS in nondiuretic users (1.12%, 95% CI 1.07–1.17 vs 2.79%, 95% CI 2.71–2.87), loop diuretic users (8.98%, 95% CI 7.67–10.28 vs 15.88%, 95% CI 14.21–17.55), thiazide diuretic users (1.54%, 95% CI 1.32–1.76 vs 3.76%, 95% CI 3.41–4.11), and thiazide-like diuretic users (3.52%, 95% CI 2.39–4.65 vs 6.88%, 95% CI 5.27–8.48; Figure 1).

For nondiuretic users, a higher GRS was positively associated with gout compared to those with a lower GRS (OR 2.63, 95% CI 2.49–2.79; $P = 8.74 \times 10^{-240}$). A higher GRS was also positively associated with gout compared to those with a lower GRS in loop diuretic users (OR 2.04, 95% CI 1.65–2.53; $P = 4.09 \times 10^{-11}$), thiazide diuretic users (OR 2.70, 95% CI 2.26–3.23; $P = 1.17 \times 10^{-27}$), and thiazide-like diuretic users (OR 2.11, 95% CI 1.37–3.25; $P = 6.48 \times 10^{-4}$) with similar OR and overlapping CI compared to participants not taking diuretics (Table 3).

When the GRS was analyzed as a categorical variable, no nonadditive GRS-diuretic interactions were observed (Table 3).

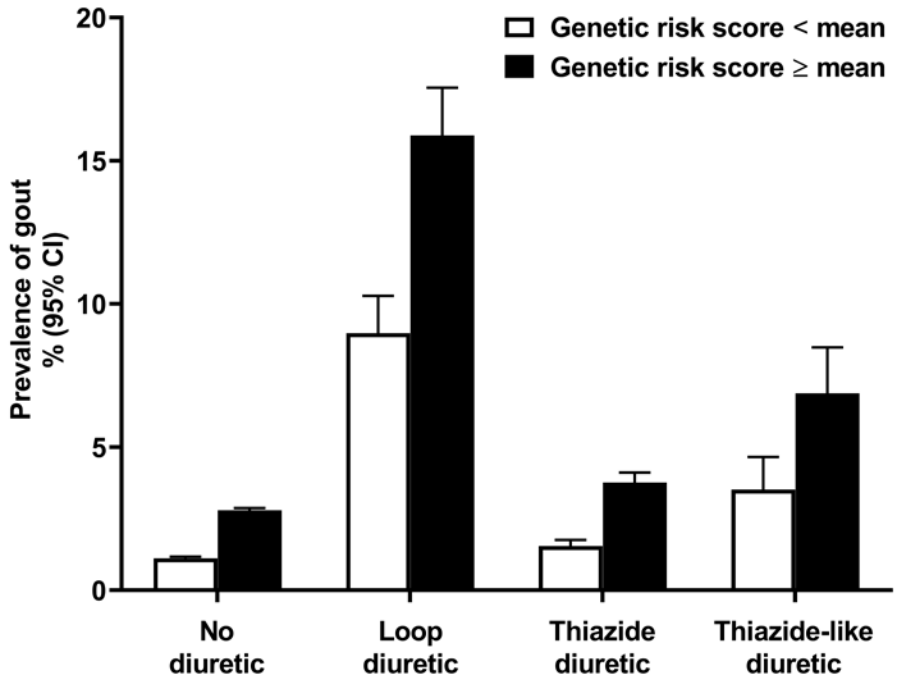

Figure 1. Prevalence of gout according to genetic risk score category and diuretic use.

Table 3. Association and interaction between genetic risk score (GRS) and diuretic use for gout.

	OR (95% CI) for Gout if GRS ≥ Mean*#	*P*	Interaction *P*^
No diuretic	2.63 (2.49–2.79)	8.74×10^{-240}	–
Loop diuretic	2.04 (1.65–2.53)	4.09×10^{-11}	0.32
Thiazide diuretic	2.70 (2.26–3.23)	1.17×10^{-27}	0.71
Thiazide-like diuretic	2.11 (1.37–3.25)	6.48×10^{-4}	0.39

In this analysis, the genetic risk score was modeled using effect sizes for gout from the UK Biobank dataset. * GRS categorized according to the mean GRS for the entire study population; mean GRS = 1.15. # Data are adjusted by age, sex, BMI, hypertension, renal failure, and heart failure, and the association analysis was performed using GRS < mean as the referent group. ^ Interaction *P* determined using a GRS by diuretic interaction term in comparison to no diuretic use.

Similarly, when GRS was analyzed as a continuous variable, no nonadditive GRS-diuretic interactions were observed for loop diuretic use ($P = 0.16$), thiazide diuretic use ($P = 0.76$), and thiazide-like diuretic use ($P = 0.89$). Probability and interaction data for GRS (analyzed as a continuous variable) and loop diuretic use are shown in Figure 2.

Association of SU-associated SNP and gout, according to diuretic use. Genotype distribution of the SU-associated SNP according to diuretic use is shown in Supplementary Table 4 (available with the online version of this article). For nondiuretic users, association with gout at experiment-wide significance was observed for all 10 SU-associated SNP (Table 4). For loop diuretic users, experiment-wide association for gout was observed for 2 SNP: *ABCG2* (rs2231142) and *SLC2A9* (rs12498742). For thiazide diuretic users, the same 2 SNP were associated with gout, as well as *GCKR* (rs1260326), *SLC17A3* (rs1165151), and *SLC22A11* (rs2078267). For thiazide-like diuretic users, *ABCG2* (rs2231142) was associated with gout. For some of the other SNP tested in the diuretic groups, similar OR for gout association were found compared to nondiuretic users; however, these did not reach experiment-wide significance. The *ABCG2* and *SLC2A9* effect alleles exerted the highest OR for gout in nondiuretic users and users of each diuretic class, with similar OR, and overlapping CI for each group. For all SNP tested, no nonadditive SNP-diuretic interactions were observed (Table 4).

Because of the low power to detect an association between some SU-associated SNP and gout in participants taking a thiazide-like diuretic (Supplementary Table 5, available with the online version of this article), a permutation test for logistic regression was performed for the SU-associated SNP for which the power to detect an association with gout was < 10%. The results of the permutation test were identical to those in the main analysis (Supplementary Table 5). This is in keeping with evidence suggesting that the permutation test is equivalent to that of asymptotic tests in datasets with > 1000 observations[25].

Sensitivity analysis. In the sensitivity analysis, the GRS was modeled using effect sizes for gout from Köttgen, *et al*[4]. In this

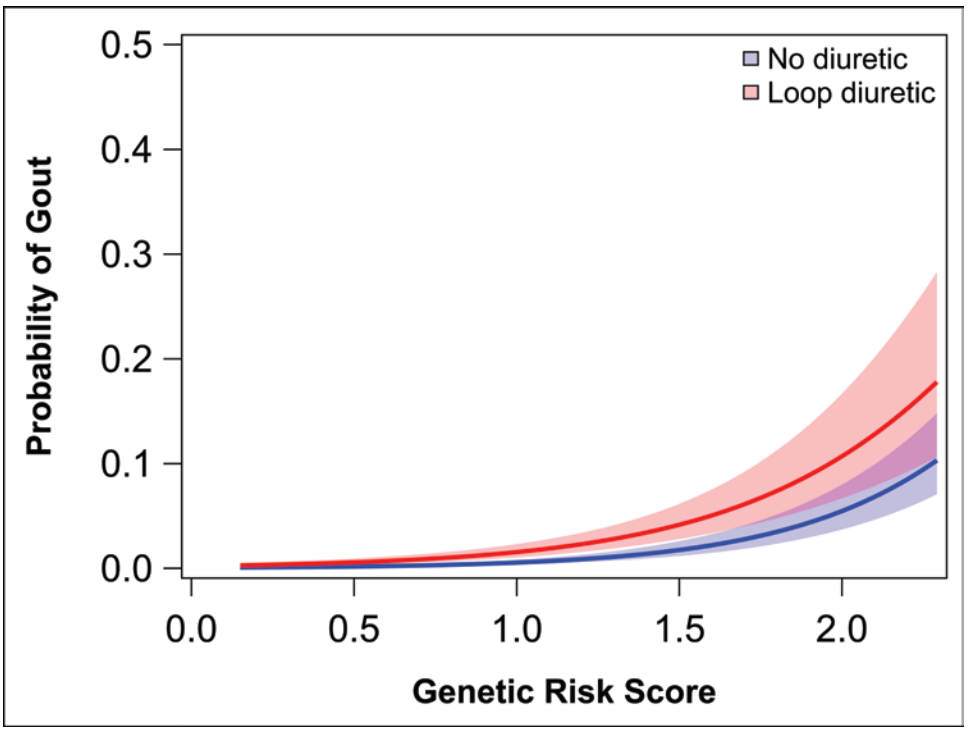

Figure 2. Probability of gout according to genetic risk score and no diuretic use or loop diuretic use. Genetic risk score is shown as a continuous variable in this analysis. Solid lines represent probability of gout and shaded areas represent 95% CI. Data are adjusted by age, sex, BMI, hypertension, renal failure, and heart failure. Genetic risk score-loop diuretic interaction $P = 0.16$.

analysis, the mean (SD) GRS for all participants, including those with gout, was 0.78 (0.18). Participants with gout had a significantly higher GRS compared to those without gout [0.88 (0.19) vs 0.78 (0.18); $P < 1 \times 10^{-300}$). The mean GRS was higher in participants with gout compared to participants without gout for nondiuretic users, loop diuretic users, thiazide diuretic users, and thiazide-like diuretic users (Supplementary Table 6, available with the online version of this article). Similar to the main analysis, a higher GRS was positively associated with gout compared to those with a lower GRS in nondiuretic users, loop diuretic users, thiazide diuretic users, and thiazide-like diuretic users (Supplementary Table 7, available with the online version of this article). No nonadditive GRS-diuretic interactions were observed.

DISCUSSION

In this large cohort of European ancestry, we have shown that genetic susceptibility contributes significantly to gout risk in people taking diuretics, with associations of similar magnitude observed between those not taking a diuretic and those taking a diuretic. Our data demonstrate that the effects of SU-associated genetic variants also contribute to gout susceptibility in diuretic users. Our data also suggest that the influence of SU-associated genetic variants is not restricted to people with primary gout, and that genetic variability is an important contributor to gout risk in people who may also have secondary risk factors for gout.

Although a nonadditive gene-loop diuretic interaction was not observed, our analysis demonstrated a high prevalence of gout (> 15%) in the presence of both a higher GRS and loop diuretic use. This high prevalence is likely due to the independent and additive effects of both risk factors for gout association and represents a clinically important increase in the prevalence of gout in this group.

The individual SU-associated SNP analysis demonstrated an association with gout for all 10 SNP in participants not taking a diuretic. Associations with gout were also observed for some individual SNP in those taking a loop, thiazide, or thiazide-like diuretic. This included *ABCG2* (rs2231142) and *SLC2A9* (rs12498742), which, consistent with previous reports[4,7,26], exerted the highest association for gout of all SNP tested and suggests that the effects of a higher GRS for gout risk are primarily driven by these 2 SNP. For other SNP tested, similar OR for gout association were found compared to the nondiuretic group, and experiment-wide significance may not have been reached because of low power to detect association, most likely explained by a relatively lower number of participants in the diuretic groups and lower effect size.

Previous studies testing for nonadditive interactions between SU-associated genetic variants and diuretics for incident gout risk have reported conflicting results. McAdams-DeMarco, *et al*[24] reported differential effects of diuretic use (loop or thiazide) on incident gout risk according to genetic urate score (GUS). An increased risk of gout was observed with loop or thiazide diuretic use in those with a GUS above the median, but no change in

Table 4. Association and interaction of serum urate–associated single-nucleotide polymorphisms with gout according to diuretic use.

Gene, SNP	Effect Allele	No Diuretic, n = 330,165 OR (95% CI), *P*		Loop Diuretic, n = 3,728 OR (95% CI), *P*	Interaction *P*^	Thiazide Diuretic, n = 23,623 OR (95% CI), *P*	Interaction *P*^	Thiazide-like Diuretic, n = 2,001 OR (95% CI), *P*	Interaction *P*^
ABCG2, rs2231142	T	2.37 (2.24–2.50), 3.10×10^{-209}		1.93 (1.54–2.43), 1.50×10^{-8}	0.59	2.17 (1.82–2.59), 5.60×10^{-18}	0.40	1.98 (1.26–3.10), 3.04×10^{-3}	0.43
SLC2A9, rs12498742	A	3.06 (2.54–3.69), 7.73×10^{-32}		4.19 (2.02–8.71), 1.23×10^{-4}	0.15	2.59 (1.51–4.44), 5.41×10^{-4}	0.61	3.92 (0.92–16.81), 0.07	0.67
GCKR, rs1260326	T	1.38 (1.30–1.46), 9.94×10^{-29}		1.13 (0.91–1.40), 0.26	0.14	1.51 (1.26–1.81), 7.23×10^{-6}	0.31	1.61 (1.01–2.57), 0.04	0.46
SLC22A12, rs478607	A	0.72 (0.62–0.85), 4.74×10^{-5}		1.55 (0.70–3.43), 0.28	0.08	0.77 (0.46–1.28), 0.31	0.85	1.35 (0.31–5.77), 0.69	0.36
MLXIPL, rs1178977	A	1.31 (1.13–1.53), 4.03×10^{-4}		1.31 (0.71–2.44), 0.39	0.99	1.02 (0.65–1.60), 0.91	0.26	1.29 (0.39–4.26), 0.67	0.98
PDZK1, rs1471633	A	1.24 (1.16–1.31), 8.02×10^{-12}		1.26 (1.00–1.59), 0.05	0.49	1.29 (1.07–1.57), 0.01	0.63	1.80 (1.07–3.03), 0.03	0.13
SLC16A9, rs1171614	T	0.81 (0.77–0.86), 1.50×10^{-13}		0.87 (0.70–1.07), 0.18	0.61	0.98 (0.83–1.16), 0.81	0.04	0.69 (0.45–1.07), 0.09	0.37
SLC17A3, rs1165151	T	0.80 (0.76–0.85), 3.99×10^{-15}		0.91 (0.73–1.13), 0.38	0.52	0.75 (0.63–0.89), 1.02×10^{-3}	0.44	1.21 (0.77–1.90), 0.42	0.08
INHBE, rs3741414	T	0.83 (0.79–0.87), 8.24×10^{-12}		0.81 (0.65–0.99), 0.04	0.51	0.80 (0.67–0.94), 0.01	0.66	0.75 (0.49–1.14), 0.18	0.46
SLC22A11, rs2078267	T	0.77 (0.72–0.82), 3.12×10^{-17}		0.92 (0.72–1.18), 0.51	0.15	0.75 (0.62–0.90), 2.74×10^{-3}	0.73	0.86 (0.52–1.41), 0.54	0.85

Data are adjusted by age, sex, body mass index, hypertension, renal failure, and heart failure. ^ Interaction *P* determined using an SNP by diuretic interaction term with comparison to no diuretic use. Experiment-wide significance was defined as $P < 0.005$. SNP: single-nucleotide polymorphism.

risk was observed in those with a GUS below the median. Further analysis demonstrated this interaction was driven by 2 specific genetic variants [*SLC22A11* (encoding OAT4) and *SLC2A9* (encoding GLUT9)]. Nine-year cumulative incidence of gout was higher in participants taking a diuretic who had 2 *SLC22A11* risk alleles compared to those with 1 or no risk allele, with a significant nonadditive interaction. Similar findings were also seen for the *SLC2A9* risk allele[24]. However, these interaction findings were not replicated in a subsequent analysis of the Health Professionals Follow-up Study and Nurses' Health Study, which tested for nonadditive gene-diuretic interactions for incident gout using 29 SU-associated SNP[27] that included the 10 (or their surrogates) studied here. The lack of nonadditive gene-diuretic interactions in this larger analysis suggests that the risk of gout associated with loop or thiazide diuretics does not vary according to the genetic risk for hyperuricemia[27]. Our study of prevalent gout also did not demonstrate nonadditive gene-diuretic interactions for gout, consistent with the findings of the Health Professionals Follow-up Study and Nurses' Health Study.

Our data show that genetic susceptibility to gout is important in people taking diuretics. However, our study did not address the causal relationship between exposure to diuretics and incident gout. Causality of diuretic exposure for gout has yet to be shown and the strong association reported from previous studies might have resulted from indication bias. This has been demonstrated in a case-control study based in a Dutch primary healthcare center in which diuretic use was associated with gout in an unadjusted logistic regression model, but after adjustment for HTN, heart failure, and myocardial infarction, there was a lack of association between diuretic use and incident gout[13].

In contrast to prior studies of incident gout that reported that loop, thiazide, and thiazide-like diuretics were associated with an increased risk of developing gout[15,16,28], we have identified variable associations for prevalent gout according to diuretic class. Following adjustment for relevant confounders, use of a loop diuretic was positively associated with gout. However, use of a thiazide diuretic was associated with a lower OR for gout, and no association was found with thiazide-like diuretics. These contrasting findings may be due to differences in study design, because our cross-sectional study reports prevalent gout compared to longitudinal studies that reported incident gout. The inverse association found in our study for thiazide diuretic use and the lack of association for thiazide-like diuretic use may therefore reflect physicians' prescribing behavior, with avoidance of these diuretic agents in people with gout, consistent with the current guidance for HTN management[9,10,29,30]. It is also important to note that the inverse association for thiazide diuretic use was observed after adjustment for relevant confounders, including HTN, which also suggests that physicians' prescribing behavior may explain the inverse association.

We acknowledge the limitations of our study. First, our analysis was restricted to participants of European ancestry and our results may not be generalizable to populations of non-European ancestry. The age range for recruitment into UK Biobank means

that younger people with early-onset gout and participants over the age of 70 years were not included in the analysis. Despite the large size of the UK Biobank, the power to detect association between some SU-associated SNP was low. This is likely due to a relatively lower number of participants in the diuretic groups, and a high or low effect allele frequency for some SNP. Comorbidity and medication use data collected by the UK Biobank resource was through self-report. This method of data collection may not accurately represent the true prevalence of comorbidities and medication use. However, this imprecision is likely to have applied systemically to all groups in the analysis. A GRS modeled using effect sizes from the same dataset used for analysis may introduce bias. However, in our sensitivity analysis we modeled a GRS using effect sizes from an external dataset and demonstrated similar findings to the main analysis. Strengths of this study include the large sample size with consistent methods of data collection, and comprehensive assessment including patient interviews, hospitalization records, and medical information.

In people taking diuretics, SU-associated genetic variants contribute strongly to gout risk, with a similar effect to that observed in those not taking a diuretic. This suggests that the contribution of genetic variants is not restricted to people with primary gout and that it can play an important role in gout susceptibility in the presence of other risk factors.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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