

ONLINE SUPPLEMENTARY MATERIAL

Supplementary Methods

Study Power

Power calculations were performed using Quanto (version 1.2.4, May 2009, University of Southern California, USA) and PASS 16 Power Analysis and Sample Size Software (2018, NCSS, LLC. Kaysville, Utah, USA). Power to detect an association for diuretic use with gout at $P < 0.05$ significance was calculated based on previously reported association data between diuretic use and gout (1). Power to detect an association with gout was $> 99\%$ for loop diuretic use, thiazide diuretic use, and thiazide-like diuretic use. For potassium-sparing diuretic use, power to detect an association with gout was 5%. Therefore, data for potassium-sparing diuretic use are not presented in the analysis. Power to detect an association for genetic risk score with gout according to diuretic use was calculated at $P < 0.05$ significance. Power was $> 90\%$ for participants not on a diuretic, and for those on a loop, thiazide and thiazide-like diuretic.

Power to detect association for serum urate-associated SNPs with gout were calculated at a $P < 0.005$ significance level based on previously reported association data between serum urate-associated SNPs and gout (Supplementary Table 1) (2). For non-diuretic users, the power to detect association with gout was $> 80\%$ for all SNPs. For loop diuretic users, power was $> 80\%$ for *ABCG2* (rs2231142), *SLC2A9* (rs12498742), and *GCKR* (rs1260326). For thiazide diuretic users, the same SNPs had $> 80\%$ power to detect an association with gout as well as *PDZK1* (rs1471633), and *SLC22A11* (rs2078267). For thiazide-like diuretic users, power was $< 80\%$ for all SNPs, except for *ABCG2* (rs2231142) and *SLC2A9* (rs12498742), (Supplementary Table 1).

Power to detect genetic risk score-diuretic interactions for gout association were calculated at a $P < 0.05$ significance level for a range of presumed interaction effects (ORs 2.00-10.00). These were calculated *post hoc*, using association data generated from this analysis. Power was $> 80\%$ for all ranges of

interaction effects for loop diuretic and thiazide diuretic use. For thiazide-like diuretic use, power was > 80% for interaction effects > 4.00.

Power to detect SNP-diuretic interactions (for *ABCG2*, *SLC2A9* and *SLC22A11*) for gout association were calculated for a range of presumed interaction effects (ORs 2.00–10.00). These were calculated *post hoc*, using association data generated from this analysis. Power was > 80% to detect SNP-loop diuretic, SNP-thiazide diuretic, and SNP-thiazide-like diuretic interactions for all presumed interaction effects.

References

1. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of Diuretics and Risk of Incident Gout A Population-Based Case-Control Study. *Arthritis Rheumatol* 2014;66:185-96.
2. Narang RK, Topless R, Cadzow M, Gamble G, Stamp LK, Merriman TR, et al. Interactions between serum urate-associated genetic variants and sex on gout risk: analysis of the UK Biobank. *Arthritis Res Ther* 2019;21.

Supplementary Table 1: Power to detect association between serum urate-associated single nucleotide polymorphisms and gout according to diuretic use.

Participants not on a diuretic							
Gout prevalence (%)	Gout cases	Controls	Gene	SNP	Effect allele frequency	Presumed genetic effect (OR) for gout*	Power to detect association with gout at type 1 error of 0.005 (%)
1.9	6145	324020	<i>ABCG2</i>	rs2231142	0.114	2.26	> 99.9
			<i>SLC2A9</i>	rs12498742	0.767	3.07	> 99.9
			<i>GCKR</i>	rs1260326	0.396	1.37	> 99.9
			<i>SLC22A12</i>	rs478607	0.849	0.78	> 99.9
			<i>MLXIPL</i>	rs1178977	0.804	1.32	> 99.9
			<i>PDZK1</i>	rs1471633	0.465	1.25	> 99.9
			<i>SLC16A9</i>	rs1171614	0.230	0.83	> 99.9
			<i>SLC17A3</i>	rs1165151	0.452	0.81	> 99.9
			<i>INHBE</i>	rs3741414	0.241	0.82	> 99.9
			<i>SLC22A11</i>	rs2078267	0.547	0.78	> 99.9
Participants on a loop diuretic							
Gout prevalence (%)	Gout cases	Controls	Gene	SNP	Effect allele frequency	Presumed genetic effect (OR) for gout*	Power to detect association with gout at type 1 error of 0.005 (%)
12.4	462	3266	<i>ABCG2</i>	rs2231142	0.114	2.26	> 99.9
			<i>SLC2A9</i>	rs12498742	0.774	3.07	> 99.9
			<i>GCKR</i>	rs1260326	0.394	1.37	94.7
			<i>SLC22A12</i>	rs478607	0.852	0.78	34.0
			<i>MLXIPL</i>	rs1178977	0.808	1.32	56.5
			<i>PDZK1</i>	rs1471633	0.460	1.25	64.4
			<i>SLC16A9</i>	rs1171614	0.236	0.83	30.7
			<i>SLC17A3</i>	rs1165151	0.453	0.81	57.2
			<i>INHBE</i>	rs3741414	0.239	0.82	36.6
			<i>SLC22A11</i>	rs2078267	0.546	0.78	75.1
Participants on a thiazide diuretic							

Gout prevalence (%)	Gout cases	Controls	Gene	SNP	Effect allele frequency	Presumed genetic effect (OR) for gout*	Power to detect association with gout at type 1 error of 0.005 (%)
2.6	615	23008	<i>ABCG2</i>	rs2231142	0.109	2.26	> 99.9
			<i>SLC2A9</i>	rs12498742	0.766	3.07	> 99.9
			<i>GCKR</i>	rs1260326	0.395	1.37	99.5
			<i>SLC22A12</i>	rs478607	0.847	0.78	54.8
			<i>MLXIPL</i>	rs1178977	0.805	1.32	78.6
			<i>PDZK1</i>	rs1471633	0.465	1.25	85.4
			<i>SLC16A9</i>	rs1171614	0.228	0.83	49.3
			<i>SLC17A3</i>	rs1165151	0.454	0.81	79.8
			<i>INHBE</i>	rs3741414	0.245	0.82	59.4
			<i>SLC22A11</i>	rs2078267	0.550	0.78	92.2
Participants on a thiazide-like diuretic							
Gout prevalence (%)	Gout cases	Controls	Gene	SNP	Effect allele freq	Presumed genetic effect (OR) for gout*	Power to detect association with gout at type 1 error of 0.005 (%)
5.1	102	1899	<i>ABCG2</i>	rs2231142	0.112	2.26	92.2
			<i>SLC2A9</i>	rs12498742	0.760	3.07	99.5
			<i>GCKR</i>	rs1260326	0.406	1.37	26.5
			<i>SLC22A12</i>	rs478607	0.842	0.78	5.4
			<i>MLXIPL</i>	rs1178977	0.808	1.32	8.6
			<i>PDZK1</i>	rs1471633	0.477	1.25	10.5
			<i>SLC16A9</i>	rs1171614	0.232	0.83	4.7
			<i>SLC17A3</i>	rs1165151	0.441	0.81	9.0
			<i>INHBE</i>	rs3741414	0.257	0.82	5.9
			<i>SLC22A11</i>	rs2078267	0.541	0.78	13.6

*Odds ratios for association between serum urate-associated single nucleotide polymorphism and gout from previously reported data (21). OR, odds ratio;

SNP, single nucleotide polymorphism.

Supplementary Table 2: Odds ratios of prevalent gout according to diuretic use.

Model	Loop diuretic OR (95% CI), p	Thiazide diuretic OR (95% CI), p	Thiazide-like diuretic OR (95% CI), p
Unadjusted	7.46 (6.74-8.25), <1.00x10 ⁻³⁰⁰	1.41 (1.30-1.53), 1.14x10 ⁻¹⁵	2.83 (2.32-3.46), 2.95x10 ⁻²⁴
Model 1	3.32 (2.96-3.72), 5.16x10 ⁻⁹³	0.89 (0.82-0.98), 0.01	1.54 (1.24-1.90), 6.85x10 ⁻⁵
Model 2	2.34 (2.08-2.63), 9.39x10 ⁻⁴⁶	0.60 (0.55-0.66), 8.07x10 ⁻²⁸	1.05 (0.85-1.29), 0.66

Model 1: adjusted for age, sex and body mass index. Model 2: adjusted for age, sex, body mass index, hypertension, renal failure and heart failure. For diuretic class analyses, comparator groups excluded all participants on diuretic agents of other classes. CI, confidence interval; OR, odds ratio.

Supplementary Table 3. Odds ratios of prevalent gout according to genetic risk score category.

Model	Lower GRS (< mean) Referent OR	Higher GRS (≥ mean) OR (95% CI)	P
Unadjusted	1	2.48 (2.36-2.61)	1.20x10 ⁻²⁷¹
Model 1	1	2.60 (2.47-2.74)	2.34x10 ⁻²⁸⁶
Model 2	1	2.60 (2.46-2.74)	5.22x10 ⁻²⁸⁰

In this analysis, the genetic risk score was modelled using effect sizes for gout from the UK Biobank dataset. Model 1: adjusted for age, sex and body mass index. Model 2: adjusted for age, sex, body mass index, hypertension, renal failure and heart failure. CI, confidence interval; GRS, genetic risk score; OR, odds ratio.

Supplementary Table 4: Genotype distribution of 10 serum urate-associated single nucleotide polymorphisms according to diuretic class.

Gene SNP	Effect allele (frequency)	Genotype	No diuretic n=330165		Loop diuretic n=3728		Thiazide diuretic n=23623		Thiazide-like diuretic n=2001	
			Control n (%)	Gout n (%)	Control n (%)	Gout n (%)	Control n (%)	Gout n (%)	Control n (%)	Gout n (%)
ABCG2 rs2231142	T (0.114)	GG	255609 (78.9%)	3836 (62.4%)	2604 (79.7%)	320 (69.3%)	18365 (79.8%)	407 (66.2%)	1513 (79.7%)	69 (67.6%)
		TG	64233 (19.8%)	2047 (33.3%)	629 (19.3%)	129 (27.9%)	4375 (19.0%)	186 (30.2%)	361 (19.0%)	29 (28.4%)
		TT	4178 (1.3%)	262 (4.3%)	33 (1.0%)	13 (2.8%)	268 (1.2%)	22 (3.6%)	25 (1.3%)	4 (3.9%)
SLC2A9 rs12498742	G (0.767)	AA	189616 (58.5%)	4422 (72.0%)	1918 (58.7%)	331 (71.6%)	13412 (58.3%)	444 (72.2%)	1079 (56.8%)	75 (73.5%)
		GA	116227 (35.9%)	1604 (26.1%)	1146 (35.1%)	123 (26.6%)	8268 (35.9%)	157 (25.5%)	707 (37.2%)	25 (24.5%)
		GG	17831 (5.5%)	116 (1.9%)	199 (6.1%)	8 (1.7%)	1306 (5.7%)	14 (2.3%)	112 (5.9%)	2 (2.0%)
GCKR rs1260326	T (0.396)	CC	118861 (36.7%)	1837 (29.9%)	1204 (36.9%)	160 (34.6%)	8497 (36.9%)	179 (29.1%)	680 (35.8%)	26 (25.5%)
		TC	154603 (47.7%)	3091 (50.3%)	1561 (47.8%)	228 (49.4%)	10926 (47.5%)	308 (50.1%)	906 (47.7%)	58 (56.9%)
		TT	50556 (15.6%)	1217 (19.8%)	501 (15.3%)	74 (16.0%)	3585 (15.6%)	128 (20.8%)	313 (16.5%)	18 (17.6%)
SLC22A12 rs478607	A (0.849)	AA	233120 (71.9%)	4220 (68.7%)	2363 (72.4%)	335 (72.5%)	16448 (71.5%)	423 (68.8%)	1343 (70.7%)	76 (74.5%)
		GA	82483 (25.5%)	1727 (28.1%)	809 (24.8%)	120 (26.0%)	5983 (26.0%)	175 (28.5%)	496 (26.1%)	24 (23.5%)
		GG	7419 (2.3%)	184 (3.0%)	78 (2.4%)	7 (1.5%)	513 (2.2%)	16 (2.6%)	54 (2.8%)	2 (2.0%)
MLXIPL rs1178977	A (0.803)	AA	209059 (64.5%)	4229 (68.8%)	2123 (65.0%)	310 (67.1%)	14866 (64.6%)	422 (68.6%)	1236 (65.1%)	69 (67.6%)
		GA	102277 (31.6%)	1728 (28.1%)	1020 (31.2%)	139 (30.1%)	7277 (31.6%)	172 (28.0%)	595 (31.3%)	30 (29.4%)
		GG	12636 (3.9%)	186 (3.0%)	123 (3.8%)	13 (2.8%)	860 (3.7%)	21 (3.4%)	68 (3.6%)	3 (2.9%)
PDZK1	A (0.465)	AA	69720 (21.5%)	1523 (24.8%)	672 (20.6%)	104 (22.5%)	4974 (21.6%)	156 (25.4%)	454 (23.9%)	32 (31.4%)

rs1471633		AC	160902 (49.7%)	3115 (50.7%)	1630 (49.9%)	240 (51.9%)	11379 (49.5%)	308 (50.1%)	884 (46.6%)	51 (50.0%)
		CC	93095 (28.7%)	1501 (24.4%)	960 (29.4%)	118 (25.5%)	6639 (28.9%)	151 (24.6%)	558 (29.4%)	19 (18.6%)
SLC16A9 rs1171614	T (0.230)	CC	190935 (58.9%)	3918 (63.8%)	1889 (57.8%)	280 (60.6%)	13646 (59.3%)	370 (60.2%)	1115 (58.7%)	68 (66.7%)
		TC	114560 (35.4%)	1979 (32.2%)	1176 (36.0%)	167 (36.1%)	8082 (35.1%)	213 (34.6%)	668 (35.2%)	30 (29.4%)
		TT	17149 (5.3%)	228 (3.7%)	191 (5.8%)	13 (2.8%)	1194 (5.2%)	31 (5.0%)	110 (5.8%)	4 (3.9%)
SLC17A3 rs1165151	T (0.452)	GG	96931 (29.9%)	2131 (34.7%)	971 (29.7%)	145 (31.4%)	6757 (29.4%)	215 (35.0%)	614 (32.3%)	29 (28.4%)
		TG	160299 (49.5%)	2991 (48.7%)	1621 (49.6%)	218 (47.2%)	11521 (50.1%)	302 (49.1%)	892 (47.0%)	56 (54.9%)
		TT	66332 (20.5%)	1013 (16.5%)	667 (20.4%)	97 (21.0%)	4702 (20.4%)	97 (15.8%)	392 (20.6%)	17 (16.7%)
INHBE rs3741414	T (0.242)	CC	186386 (57.5%)	3808 (62.0%)	1900 (58.2%)	286 (61.9%)	13068 (56.8%)	381 (62.0%)	1036 (54.6%)	62 (60.8%)
		TC	118317 (36.5%)	2082 (33.9%)	1143 (35.0%)	156 (33.8%)	8537 (37.1%)	209 (34.0%)	739 (38.9%)	38 (37.3%)
		TT	19120 (5.9%)	252 (4.1%)	222 (6.8%)	20 (4.3%)	1391 (6.0%)	24 (3.9%)	123 (6.5%)	2 (2.0%)
SLC22A1 rs2078267	T (0.547)	CC	66242 (20.4%)	1523 (24.8%)	661 (20.2%)	102 (22.1%)	4650 (20.2%)	152 (24.7%)	407 (21.4%)	23 (22.5%)
		CT	160664 (49.6%)	3075 (50.0%)	1633 (50.0%)	229 (49.6%)	11359 (49.4%)	305 (49.6%)	927 (48.8%)	51 (50.0%)
		TT	97114 (30.0%)	1547 (25.2%)	972 (29.8%)	131 (28.4%)	6999 (30.4%)	158 (25.7%)	565 (29.8%)	28 (27.5%)

SNP, single nucleotide polymorphism.

Supplementary Table 5: Permutation test to detect association between serum urate-associated SNPs and gout in participants on a thiazide-like diuretic.

Gene SNP	Effect allele	Thiazide-like diuretic n=2001
		OR (95% CI), P
<i>SLC22A12</i> rs478607	A	1.35 (0.31-5.77), 0.69
<i>MLXIPL</i> rs1178977	A	1.29 (0.39-4.26), 0.68
<i>SLC16A9</i> rs1171614	T	0.69 (0.45-1.07), 0.09
<i>SLC17A3</i> rs1165151	T	1.21 (0.77-1.90), 0.42
<i>INHBE</i> rs3741414	T	0.75 (0.49-1.14), 0.18

The SNPs included in the permutation test were those for which the power to detect an association with gout in participants on a thiazide-like diuretic was < 10%. CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism. Experiment-wide significance was defined as $P < 0.005$.

Supplementary Table 6: Sensitivity analysis showing the mean genetic risk scores according to diuretic use. In this analysis, the genetic risk score was modelled using effect sizes for gout from Köttgen et al (4).

	Genetic risk score, mean (SD)		
	Control	Gout	Control vs gout P
No diuretic	0.78 (0.18)	0.89 (0.19)	<1x10 ⁻³⁰⁰
Loop diuretic	0.77 (0.18)	0.85 (0.18)	1.16x10 ⁻¹⁶
Thiazide diuretic	0.77 (0.18)	0.87 (0.18)	5.16x10 ⁻⁴⁰
Thiazide-like diuretic	0.77 (0.18)	0.87 (0.19)	8.22x10 ⁻⁸

SD, standard deviation.

Supplementary Table 7: Sensitivity analysis showing the association and interaction between genetic risk score and diuretic use for gout. In this analysis, the genetic risk score was modelled using effect sizes for gout from Köttgen et al (4).

	OR (95% CI) for gout if genetic risk score \geq mean*#	P	Interaction P [^]
No diuretic	2.60 (2.46-2.76)	2.15x10 ⁻²²⁸	-
Loop diuretic	2.10 (1.69-2.60)	1.49x10 ⁻¹¹	0.42
Thiazide diuretic	2.54 (2.12-3.04)	3.92x10 ⁻²⁴	0.87
Thiazide-like diuretic	2.33 (1.50-3.61)	1.58x10 ⁻⁴	0.70

*Genetic risk score categorised according to the mean genetic risk score for the entire study population; mean genetic risk score = 0.78. #Data are adjusted by age, sex, body mass index, hypertension, renal failure and heart failure, and the association analysis was performed using genetic risk score < mean as the referent group. ^Interaction P determined using a genetic risk score by diuretic interaction term with comparison to no diuretic use. CI, confidence interval; OR, odds ratio.