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Lack of Gene-Diuretic Interactions on the Risk of Incident Gout: the Nurses' Health Study and Health Professionals Follow-Up Study

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Abstract

Background—Diuretic-induced gout might occur only among those with a genetic predisposition to hyperuricemia, as suggested by a recent study with 108 self-reported gout cases.

Methods—We examined the role of urate genes on the risk of diuretic-induced incident gout in 6850 women from the Nurses' Health Study (NHS) and in 4,223 men from the Health Professionals Follow-up Study (HPFS). Two published genetic risk scores (GRS) were calculated using urate-associated SNPs for eight genes (GRS8) and for 29 genes (GRS29).

Results—Our analyses included 727 and 354 confirmed incident gout cases in the HPFS and NHS, respectively. The multivariate RR for diuretic use was 2.20 and 1.69 among those with a GRS8 < and the median (p for interaction=0.27). The corresponding RRs using GRS29 were 2.19 and 1.88 (p for interaction=0.40). The lack of interaction persisted in the NHS (all p values >0.20) and in our analyses limited to those with hypertension in both cohorts. SLC22A11 (OAT4) showed a significant interaction only among women but in the opposite direction to the recent study.

Conclusion—In these large prospective studies, individuals with a genetic predisposition for hyperuricemia are not at a higher risk of developing diuretic-induced gout than those without.

Keywords

Gout; genetic; diuretic; prospective

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INTRODUCTION

Gout is a common and excruciatingly painful inflammatory arthritis caused by hyperuricemia. In addition to various environmental risk factors for gout, substantial genetic predisposition has also been recognized.[1] The majority of the eight genes discovered by the initial genome-wide association studies (GWAS) are involved in the renal urate-transport system.[1–3] In 2013, the Global Urate Genetics Consortium identified and replicated 20 additional genome-wide significant loci in association with serum urate concentrations.[4]

Diuretics, particularly thiazide and loop diuretics, increase the risk of incident gout,[5,6] likely through urate transporters (e.g., OAT4)[3] and volume depletion promoting urate reabsorption.[7] If diuretic use differentially affects the risk of gout according to a certain genetic predisposition for hyperuricemia, such genes could be used to predict gout risk in relation to diuretic use. Indeed, a recent analysis based on the Atherosclerosis Risk in Communities (ARIC) Study (with 108 self-reported incident cases of gout) reported that diuretic-induced gout occurs only among those with a genetic predisposition to hyperuricemia.[3] To our knowledge, no study has replicated or refuted these findings. To examine these issues with a large number of confirmed cases of incident gout (N=1081), we analyzed GWAS data obtained from participants in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

PARTICIPANTS AND METHODS

Study Population

As previously described in detail,[8,9] the NHS and HPFS are prospective cohorts of women and men, respectively, who have been administered the validated food frequency questionnaire (FFQ) every 4 years, as well as biennial questionnaires for new disease diagnoses and drug use (including diuretics). The current analysis included 6,850 and 4,223 initially healthy women and men, respectively, of European ancestry for whom genotype data based on GWAS were available[10] and who were gout-free at baseline.

This study was approved by the Partners HealthCare System institutional review board.

Assessment of Incident Gout Cases, Diuretic Use, and Covariates

We ascertained incident gout cases using the American College of Rheumatology (ACR) gout survey criteria, as previously described.[8,9] In the NHS, diuretic use (i.e., thiazides and loop diuretics) was determined in 1980, 1982, 1988, 1994, and every 2 years thereafter. In the HPFS, diuretic use was determined in 1986 and every 2 years thereafter. Baseline and biennial follow-up questionnaires inquired about physician-diagnosed hypertension. A participant was considered to have hypertension from the time first reported on the questionnaire. Dietary covariates were obtained via validated FFQs. Information on non-dietary factors (e.g., medication or supplement use, medical conditions, menopausal status, and postmenopausal hormone use) was assessed every 2 to 4 years [6,8,9,11–15].

Genotyping and genetic risk score

We selected single-nucleotide polymorphisms (SNPs) known to be associated with serum urate levels. Two sets of genetic risk scores (GRSs) were calculated as published previously; one based on 8 SNPs[2] (GRS8, used by the ARIC study above[3]) and the other based on 29 SNPs (GRS29, a new score incorporating additional novel genes[4]) (Table S1). Higher scores indicate a greater genetic predisposition to higher serum uric acid levels. Of note, the aforementioned ARIC study analysis used GRS8,[3] which mostly consisted of urate transporters.[1–3] SNP genotyping and imputation have been described in detail elsewhere. [4,16–20] Most of the SNPs were genotyped or had a high imputation quality score (MACH $r^2 \geq 0.8$).[10]

Statistical Analysis

We examined the association between diuretic use and the risk of gout, according to the median of GRS, using Cox proportional hazards models adjusting for previously identified risk factors [6,8,9,11–15]. Information on use on diuretic use was updated according to the biennial questionnaires as a time-varying exposure. Tests for interaction by GRS were performed by the Wald test of a cross-product term of GRS ($\geq$ median versus $<$ median) and diuretic use (yes or no). We then repeated the analyses among participants with hypertension. All statistical analyses were performed with SAS 9.1. All P values are two sided.

RESULTS

At baseline, the distribution of gout risk factors was similar between the group with GRS $<$ median and the group with GRS $\geq$ median (Table 1). Further, at baseline, those using diuretics were older and more likely to have a higher BMI and hypertension; other characteristics were similar (Table S2). The GRS8[3] ranged from -3.67 to 4.24 and the GRS29[4] ranged from 12.2 to 44.5 . In both cohorts, participants with a higher GRS had a higher risk of incident gout (Table S3).

In the HPFS, compared with no use, the multivariate RR of gout for thiazide or loop diuretic use was 2.20 (95% CI, $1.42, 3.42$) among those with a GRS8 $<$ median and 1.69 (95% CI, $1.21, 2.37$) among those with a GRS8 $\geq$ median (p for interaction $=0.27$) (Table 2). The corresponding multivariate RRs according to GRS29 median value categories were 2.19 (95% CI, $1.40, 3.43$) among those with a GRS29 $<$ median and 1.88 (95% CI, $1.34, 2.63$) among those with a GRS29 $\geq$ median (p for interaction $= 0.40$). Similar results were found in the NHS (Table 2).

We additionally evaluated two individual urate genes previously shown to have a significant interaction with diuretic use (SLC2A9 and SLC22A11).[3] A significant interaction was observed only for SLC22A11 among women but in the opposite direction to the ARIC study finding [3] (Table 3).

Further analyses restricted to participants with hypertension yielded similar results to the main analyses in both cohorts (Tables S4–8).

DISCUSSION

In these two large prospective studies of white adults, the risk of gout induced by thiazide or loop diuretics did not vary according to the genetic risk for elevated serum urate. This lack of significant interaction was evident using the previously employed genetic score based on eight SNPs[3] as well as the score that included the most updated list of SNPs.[4] Similarly, no significant interaction existed with the individual genes previously shown to have significant interactions, except for *SLC22A11* among women, which showed an interaction opposite to the ARIC study finding.[3] These findings persisted in the subgroups of those with hypertension. Collectively, our findings reject the hypothesis that individuals with a genetic predisposition for hyperuricemia are at a higher risk of developing diuretic-induced gout as compared to those without such a predisposition.

Our findings do not replicate the aforementioned report based on the ARIC study cohort.[3] Several aspects of that study notably differ from the current study. The ARIC analysis analyzed a relatively small number of cases for a subgroup/interaction analysis (i.e., 108 patients with gout and hypertension),[3] whereas our cohorts had substantially more gout cases (1081 cases, including 506 with hypertension). The ARIC study had only one gout case in the group of thiazide use and four cases in the group of thiazide or loop diuretic use among those with a *GRS8* < median. These small sample sizes likely contributed to the main conclusion of the paper: a null or inverse impact of thiazide or loop diuretic use among those with a *GRS* < median. In our study, each group used for comparison had substantially more cases than the ARIC study, including the subgroup analyses limited to those with hypertension. Furthermore, our gout cases were confirmed based on the ACR survey criteria, [8,9] whereas the ARIC study was based on self-reported diagnosis.[3]

Not being able to replicate the findings by our two larger cohorts underscores the need for an appropriate sample size in this type of interaction analysis, as well as the value of replication data (preferably in the same paper, as is now commonly required in papers reporting on genetics). This appears particularly relevant, as many published subgroup/interaction genetic analyses have not been replicated in follow-up studies. Indeed, we found that the significant interaction with *SLC22A11* among women was in the opposite direction to the ARIC study finding, which is an extreme example of this issue. This inconsistency may reflect a difference in the sample sizes, multiple testing, or random chance, and would not justify biological speculations.

Several strengths and potential limitations of our study deserve comment. The strengths include the use of large cohort studies with long-term follow-up, multiple measures of diuretic use and BMI, comprehensive measures of diet and lifestyle factors, and a *GRS* combining genetic information from the most updated list of variants associated with serum urate levels.[4] Furthermore, the overall consistent findings of the lack of interaction using *GRSs* in our two cohorts indicate the robustness of our results. Certain measurement errors in dietary factors (our covariates) are inevitable, but the FFQs have been well validated in our cohorts and have been successfully used for many dietary risk factor studies of gout. Furthermore, the participants in our study were middle-aged and older adults of European

ancestry recruited in the US, and it is unknown whether our findings could be generalized to other demographic or ethnic groups.

In conclusion, these prospective studies based on a large number of incident cases of confirmed gout suggest that individuals with a genetic predisposition for hyperuricemia are not at a greater risk of developing diuretic-induced gout than those without such a predisposition. These findings do not appear to support the potential utility of these genes to assess gout risk in relation to diuretic use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline gout risk factors by genetic scores in NHS and HPFS participants

	HPFS				NHS			
	Genetic score of 8 SNPs		Genetic score of 29 SNPs		Genetic score of 8 SNPs		Genetic score of 29 SNPs	
	< median (n = 2053)	median (n = 2170)	< median (n = 2042)	median (n = 2181)	< median (n = 3394)	median (n = 3456)	< median (n = 3404)	median (n = 3446)
Age, years, mean (SD)	54.5(8.6)	54.2(8.6)	54.4(8.6)	54.3(8.5)	48.1(6.6)	47.9(6.7)	48.1(6.6)	47.9(6.7)
Systolic blood pressure, mm Hg, mean (SD)	128.2(12.5)	128.6(12.5)	128.1(12.6)	128.6(12.4)	123.4(14.1)	123.8(14.5)	123.5(14.1)	123.7(14.6)
Diastolic blood pressure, mm Hg, mean (SD)	81.0(7.1)	81.0(7.1)	81.0(7.2)	81.1(7.0)	78.4(7.3)	78.9(7.7)	78.4(7.4)	78.9(7.7)
Reported hypertension, %	19.4	21.5	20.0	20.9	14.1	16.7	14.5	16.4
BMI, kg/m ² , mean (SD)	25.4(3.0)	25.5(3.0)	25.3(3.0)	25.5(3.0)	24.3(4.3)	24.2(4.0)	24.3(4.3)	24.1(4.1)
Physical activity, MET-hours/week, mean (SD)	19.3(26.1)	18.8(22.3)	19.0(25.7)	19.1(22.6)	15.2(21.7)	13.5(15.9)	15.2(21.5)	13.5(15.9)
Alcohol, g/d, mean (SD)	13.0(16.5)	13.1(16.4)	13.0(16.1)	13.1(16.8)	6.8(10.8)	6.6(10.0)	6.8(10.5)	6.7(10.3)
Sweetened soft drink intake, servings/d, mean (SD)	0.2(0.5)	0.2(0.5)	0.2(0.5)	0.2(0.5)	0.2(0.6)	0.2(0.5)	0.3(0.6)	0.2(0.5)
Meat intake, servings/d, mean (SD)	1.6(0.9)	1.5(0.8)	1.5(0.9)	1.5(0.9)	1.1(0.8)	1.1(0.8)	1.1(0.7)	1.1(0.8)
Seafood intake, servings/d, mean (SD)	0.3(0.3)	0.3(0.3)	0.3(0.3)	0.3(0.3)	0.2(0.2)	0.2(0.2)	0.2(0.2)	0.2(0.2)
Low-fat dairy foods intake, servings/d, mean (SD)	1.0(1.0)	1.0(1.1)	1.0(1.0)	1.0(1.1)	0.9(1.0)	0.9(1.0)	1.0(1.0)	0.9(1.0)
High-fat dairy foods intake, servings/d, mean (SD)	1.3(1.4)	1.3(1.3)	1.3(1.3)	1.3(1.3)	1.4(1.3)	1.4(1.4)	1.4(1.3)	1.4(1.3)
Diuretic use, %	9.0	10.4	9.8	9.7	9.7	9.6	9.6	9.7

Values are age-adjusted (except for age).

Table 2

RR of gout by diuretic use, stratified by median genetic scores

	HPFS				NHS			
	< median	median	P for interaction		< median	median	P for interaction	
Genetic score of 8 SNPs								
Any diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	229	38	404	56	73	53	120	108
Person-Years	37835	1673	37533	1836	78216	13386	79389	12936
Age-adjusted	1.00	4.57 (3.08, 6.76)	1.00	3.10 (2.29, 4.20)	1.00	3.89 (2.69, 5.62)	1.00	4.81 (3.67, 6.31)
MV-adjusted	1.00	2.20 (1.42, 3.42)	1.00	1.69 (1.21, 2.37)	1.00	1.97 (1.32, 2.93)	1.00	2.33 (1.73, 3.13)
Thiazide diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	237	30	414	46	88	38	146	82
Person-Years	38060	1448	37725	1644	79787	11815	80731	11594
Age-adjusted	1.00	3.91 (2.55, 5.99)	1.00	2.86 (2.06, 3.98)	1.00	2.77 (1.88, 4.10)	1.00	3.53 (2.67, 4.67)
MV-adjusted	1.00	1.81 (1.13, 2.90)	1.00	1.49 (1.03, 2.13)	1.00	1.44 (0.95, 2.17)	1.00	1.73 (1.28, 2.33)
Genetic score of 29 SNPs								
Any diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	218	35	415	59	73	57	120	104
Person-Years	37698	1704	37670	1805	78292	13585	79313	12737
Age-adjusted	1.00	4.19 (2.81, 6.23)	1.00	3.46 (2.56, 4.68)	1.00	4.04 (2.82, 5.79)	1.00	4.79 (3.65, 6.30)
MV-adjusted	1.00	2.19 (1.40, 3.43)	1.00	1.88 (1.34, 2.64)	1.00	1.97 (1.34, 2.90)	1.00	2.39 (1.77, 3.24)
Thiazide diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	226	27	425	49	89	41	145	79
Person-Years	37914	1489	37871	1604	79905	11972	80613	11437
Age-adjusted	1.00	3.60 (2.33, 5.57)	1.00	3.21 (2.32, 4.44)	1.00	2.89 (1.98, 4.22)	1.00	3.52 (2.65, 4.67)
MV-adjusted	1.00	1.78 (1.10, 2.88)	1.00	1.67 (1.17, 2.40)	1.00	1.43 (0.96, 2.13)	1.00	1.77 (1.30, 2.40)

MV models were adjusted for age (continuous), BMI (continuous), menopause (yes or no), use of hormone therapy (never, past, or current), history of hypertension (yes or no), systolic and diastolic blood pressure (continuous), alcohol (continuous), total energy intake (continuous), and intake of sugar-sweetened soft drinks, meat, seafood, and dairy foods (continuous).

Table 3
RR of gout by diuretic use, stratified by SLC2A9 (rs13129697) and SLC22A11 (rs2078267)

	HPFS				NHS			
	GG or GT	TT	P for interaction		GG or GT	TT	P for interaction	
SLC2A9								
Any diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	257	38	376	56	65	50	128	111
Person-Years	36795	1643	38556	1866	74268	12653	83337	13669
Age-adjusted	1.00	3.85 (2.63, 5.64)	1.00	3.28 (2.42, 4.46)	1.00	4.17 (2.84, 6.11)	1.00	4.69 (3.60, 6.11)
MV-adjusted	1.00	2.02 (1.32, 3.09)	1.00	1.75 (1.24, 2.47)	1.00	2.18 (1.44, 3.29)	1.00	2.23 (1.67, 2.98)
Thiazide diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	263	32	388	44	79	36	155	84
Person-Years	36999	1439	38770	1652	75701	11220	84817	12189
Age-adjusted	1.00	3.75 (2.50, 5.62)	1.00	2.89 (2.06, 4.05)	1.00	2.95 (1.97, 4.42)	1.00	3.50 (2.66, 4.61)
MV-adjusted	1.00	1.88 (1.20, 2.94)	1.00	1.47 (1.01, 2.14)	1.00	1.52 (0.99, 2.34)	1.00	1.71 (1.27, 2.30)
SLC22A11								
Any diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	492	72	141	22	137	129	56	32
Person-Years	58316	2709	17052	801	123229	20490	34377	5832
Age-adjusted	1.00	3.54 (2.70, 4.64)	1.00	3.49 (2.09, 5.83)	1.00	5.34 (4.17, 6.85)	1.00	2.53 (1.60, 4.00)
MV-adjusted	1.00	1.81 (1.34, 2.44)	1.00	2.07 (1.14, 3.74)	1.00	2.62 (2.00, 3.44)	1.00	1.32 (0.81, 2.15)
Thiazide diuretic use	No	Yes	No	Yes	No	Yes	No	Yes
No. of Cases	507	57	144	19	170	96	64	24
Person-Years	58647	2377	17138	715	125597	18122	34922	5287
Age-adjusted	1.00	3.14 (2.33, 4.22)	1.00	3.29 (1.92, 5.62)	1.00	3.84 (2.98, 4.97)	1.00	1.90 (1.17, 3.10)
MV-adjusted	1.00	1.53 (1.11, 2.11)	1.00	1.90 (1.03, 3.51)	1.00	1.89 (1.44, 2.49)	1.00	1.01 (0.60, 1.69)

MV models were adjusted for age (continuous), BMI (continuous), menopause (yes or no), use of hormone therapy (never, past, or current), history of hypertension (yes or no), systolic and diastolic blood pressure (continuous), alcohol (continuous), total energy intake (continuous), and intake of sugar-sweetened soft drinks, meat, seafood, and dairy foods (continuous).