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Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study

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Abstract

Objective—Evidence on the potential independent impact of gout on the risk of diabetes is limited to a single study of men with a high cardiovascular risk profile. Our objective was to examine this relation in the general population, particularly among women.

Methods—We conducted a sex-stratified matched cohort study using data from The Health Improvement Network (THIN), an electronic medical records database representative of the UK general population. Up to five non-gout individuals were matched to each case of incident gout by year of birth, year of enrolment and body mass index (BMI). Multivariate HRs for incident diabetes were calculated after additionally adjusting for smoking, alcohol consumption, physician visits, comorbidities and medication use.

Results—Among 35 339 gout patients (72.4% men, mean age of 62.7 years), the incidence rates of diabetes in women and men were 10.1 and 9.5 cases per 1000 person-years, respectively, whereas the corresponding rates were 5.6 and 7.2 cases per 1000 person-years among 137 056 non-gout subjects. The BMI-matched univariate and multivariate HRs of diabetes were higher among women compared with those among men (1.71; 95% CI 1.51 to 1.93 vs 1.22; 95% CI 1.13 to 1.31) and (1.48; 95% CI 1.29 to 1.68 vs 1.15; 95% CI 1.06 to 1.24), respectively (p values for interaction <0.001). This sex difference persisted across age-specific subgroups.

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Conclusions—This general population-based study suggests that gout may be independently associated with an increased risk of diabetes and that the magnitude of association is significantly larger in women than in men.

INTRODUCTION

Gout is the most common inflammatory arthritis in most western countries, and its disease burden and cardiovascular (CV) complications are substantial. Although gout's cardinal feature is excruciatingly painful inflammatory arthritis, it is a metabolic condition associated with an elevated uric acid burden.¹² Thus, gout is associated with obesity, hypertension, the metabolic syndrome³ and an increased future risk of major CV events and premature mortality (independent of known risk factors).^{4–7}

Furthermore, gout has been linked to the risk of incident diabetes (multivariate relative risk, 1.26)⁸; however, this report was based only on men with a high CV risk profile. Thus, it is unknown whether this relation is generalisable among women or among individuals unselected by this CV risk profile, such as the general population. Of particular relevance, serum uric acid (SUA) levels, the causal precursor of gout, have been associated with the risk of diabetes,⁹ with some reports indicating a higher risk in women.^{10–13} For example, a Taiwanese study of hyperuricemic subjects found that SUA levels were associated with the risk of diabetes in women (OR, 1.44), but not in men (OR, 0.76).¹¹

Since diabetes leads to significant morbidity, vascular sequelae and premature mortality,¹⁴ clarifying its risk in gout, particularly independent of the influence of obesity (a key risk factor for diabetes¹⁵), is essential. To address this, we examined the risk of diabetes stratified by sex in the general population.

METHODS

Data source

We used data from The Health Improvement Network (THIN),¹⁶ an electronic dataset of 477 general practices within the UK from 1986 to 2010. Data on approximately 7.3 million patients are systematically recorded and sent anonymously to THIN. Because the National Health Service (NHS) in the UK requires every individual to be registered with a general practitioner (GP) regardless of health status, THIN is a population-based cohort representative of the UK general population. The computerised information includes demographics, details from GP visits, diagnoses from specialists' referrals and hospital admissions, results of laboratory tests and additional systematically recorded health information including height, weight, blood pressure, smoking status and vaccinations. The Read classification is used to code specific diagnoses,¹⁷ and a drug dictionary based on data from the Multilex classification is used to code drugs.¹⁸ Health information is recorded on site at each practice using a computerised system with quality control procedures to maintain high data completion rates and accuracy. We included subjects from THIN who were at least 20 years of age and had at least 1 year of active enrolment during 1 January 1995 to 31 May 2010 (N=4.7 million). The study research protocol was approved by the Boston University Institutional Review Board and the Multicenter Research Ethics Committee.

Study design and cohort definition

We conducted a sex-stratified cohort analysis of incident diabetes among adults with incident gout compared with up to five non-gout individuals matched by age, date of study entry, enrolment year and body mass index (BMI) (within a calliper of $\pm 0.5 \text{ kg/m}^2$) (comparison cohort) using data from THIN. We matched on BMI, as obesity is a very strong risk factor for both gout¹⁹ and type 2 diabetes (a 39-fold increased risk compared with normal weight¹⁵). Participants were required to be continuously enrolled in the database for 12 months prior to inclusion in the cohort, and those diagnosed with gout or diabetes prior to study entry were excluded. Our study period spanned the period from 1 January 1995 through 31 May 2010. Participants entered the cohort when all inclusion criteria were met or on the matched date for subjects in the comparison cohort (index dates) and were followed until they developed diabetes, died or the follow-up ended, whichever came first.

Ascertainment of gout

Gout was defined by the diagnostic code using the Read classification.²⁰ Through a computer search using Read codes we identified all patients with a first-ever diagnosis of gout recorded by a GP. The date of gout onset (index date) was defined as the date of the first diagnosis of gout. We considered incident cases as those who had an index date (gout onset) occurring after the date of entry to the study cohort (n=35 339).

To evaluate the robustness of gout case ascertainment, we performed a sensitivity analysis where we restricted gout cases to those receiving gout treatment (total N=117 041; gout N=23 997) as previously described.^{20,21} For this, we used the following operational definition: we identified within 90 days after the first-ever diagnosis of gout any antigout treatment (colchicine or urate-lowering drugs such as allopurinol, febuxostat, rasburicase, probenecid or sulfinpyrazone) and/or a prescription for a non-steroidal anti-inflammatory drug on the same day. A similar case definition of gout has been shown to have a validity of 90% in the General Practice Research Database.^{22,23}

Diabetes mellitus outcome assessment

Our outcome of interest was incident diabetes requiring at least one prescription for a medication used for the treatment of diabetes, including all insulin preparations and oral agents, as done previously.^{24,25} A similar classification was reported to have a specificity of >90%.^{26,27}

Assessment of covariates

From the THIN database, we collected data on personal characteristics and lifestyle factors such as alcohol use, smoking, and BMI, as well as healthcare use (ie, GP visits), comorbidities (ie, ischaemic heart disease, hypertension, hyperlipidaemia (diagnosis or antihyperlipidaemia medication)), medication use (ie, glucocorticosteroids (oral agents or injections), diuretics (loop or thiazide)) and the Charlson Comorbidity Index (CCI)²⁸ prior to the index date. BMI, smoking status and alcohol consumption status were recorded to the nearest possible measurement prior to the index date. Drug use, the CCI and the number of visits to a GP were ascertained within 1 year prior to the index date.

Statistical analysis

We compared the baseline characteristics between sex-stratified gout and comparison cohorts (table 1). We identified incident cases of diabetes during the follow-up and calculated incidence rates for diabetes. Further, we estimated the cumulative incidence of diabetes in each cohort, accounting for the competing risk of death.²⁹ Cox proportional hazard regression models were used to calculate HRs after accounting for matched clusters (age, entry date and BMI). Our intermediate multivariate model adjusted for lifestyle factors (smoking and alcohol consumption) and GP visits, whereas our full multivariate model adjusted additionally for comorbidities and medication use. Further, in all multivariate models, we adjusted for BMI as a continuous variable in order to help eliminate residual confounding. Examination of log-log survival curves in our model demonstrated that the assumptions of proportional hazards were met. We conducted further subgroup analyses by age groups (<55 years, 55–69 years and ≥70 years) to examine their influence.

As previously described,²⁴³⁰ our primary analysis used imputed missing values for covariates (ie, smoking and alcohol use), employing a sequential regression method based on a set of covariates as predictors (IVEware for SAS, V.9.2; SAS Institute, Cary, North Carolina, USA). To minimise random error, we imputed five datasets and then combined estimates from these datasets.²⁴³⁰ Our secondary analysis used a complete dataset without missing values (total N=153 613; gout N=31 650). We calculated 95% CIs for all HRs. All p values were two-sided.

RESULTS

The cohort included 35 339 gout subjects (9693 women and 25 646 men) and 137 056 matched non-gout subjects (37 881 women and 99 175 men). The baseline characteristics of the cohorts are shown in table 1. Female gout patients were older than male gout patients (67.9±14.3 vs 60.7±15 years). Gout patients tended to consume more alcohol, visit the GP more often, have more comorbidities and use glucocorticoids and diuretics more often.

The cumulative incidence of diabetes stratified by sex is depicted in figure 1, and the incidence rate and HRs for incident diabetes according to study cohorts are shown in table 2. Overall, new diagnoses of diabetes occurred among 5856 individuals during 793 967 person-years, and the mean follow-up time was 4.6 years. The incidence rate for diabetes in the total gout population was 9.6 cases per 1000 person-years (95% CI 9.4 to 9.8), higher than that in the total non-gout population (6.7 cases per 1000 person-years, 95% CI 6.6 to 6.8). Female gout patients had higher incidence rates than male gout patients (10.1 cases per 1000 person-years vs 9.5 cases per 1000 person-years; table 2), although the background risks were higher in men than in women. These trends persisted across age subgroups. The resulting absolute risk difference for incident diabetes was 4.5 cases per 1000 person-years among women and 2.3 cases per 1000 person-years among men (p for interaction=0.001).

The sex difference was also apparent in relative risks as the univariate HR for diabetes in women was higher than that of men (HR, 1.71; 95% CI 1.51 to 1.93 among women vs HR, 1.22; 95% CI 1.13 to 1.31 among men), indicating sex-specific effect modification. This trend was consistent across the intermediate and multivariate models (multivariate HR, 1.48;

95% CI 1.29 to 1.68 among women vs HR, 1.15; 95%CI 1.06 to 1.24 among men) (p for trend <0.001, table 2). Such effect modification of gout by sex persisted across all age categories (table 2). Our complete analysis using a dataset without missing values showed similar results (see online supplementary table S1).

In our sensitivity analysis, restricting gout cases to those receiving antigout treatment (n=23 997) showed that both main and sex-specific results (as well as the significant interaction) persisted (see online supplementary table S2).

DISCUSSION

In this large general practice cohort representative of the UK population, we found that the risk of diabetes is higher among gout patients compared with non-gout subjects. These findings were independent of BMI, lifestyle factors and other known risk factors. The magnitude of excess diabetes risk in gout was significantly larger among women than men, both in risk difference and relative risk, and these findings persisted across all age categories. The current study provides the first general population evidence for an independent association between gout and the risk for type 2 diabetes, and it fills the knowledge gap about the relation among women. Further, these findings support aggressive management of risk factors of diabetes in patients with gout, particularly among women.

A potential mechanism behind this excess risk is that ongoing low-grade inflammation among patients with gout may promote the diabetogenic process.⁸³¹ Alternatively, the link may stem from the shared metabolic factors of the two conditions, such as the correlates of the metabolic syndrome or shared genes.³² Furthermore, the link between hyperuricaemia and the risk of type 2 diabetes may originate at the renal level⁸¹² as insulin resistance and higher insulin levels are known to reduce renal excretion of urate.^{833–36} Nevertheless, hyperuricaemia was an independent risk factor for the development of hyperinsulinaemia and thereby preceded hyperinsulinaemia among non-diabetic individuals over an 11-year follow-up.³⁷

We found significant effect modification by sex, with a larger association among women than men. These findings agreed with previous findings that the impact of SUA levels on insulin resistance or diabetes was higher among women.^{10–13} For example, the Finnish Diabetes Prevention study showed that baseline SUA and its changes were associated with a twofold increased risk of type 2 diabetes, and the association tended to be stronger among women.¹² Another study from the Pacific Island of Nauru found that SUA is independently associated with the risk of glucose intolerance only among women. Similarly, a Taiwanese study of hyperuricemic subjects found that SUA levels were associated with the risk of diabetes in women (OR, 1.44), but not in men during a 7-year follow-up.¹¹ Collectively, these data suggest that hyperuricaemia and gout have a larger diabetogenic association among women. Interestingly, a remarkably similar gender difference was found in a previous general population study for the risk of myocardial infarction (multivariate HR of 1.39 among women vs 1.11 among men), which is a well-established sequelae of diabetes.³⁸

Although the exact mechanism behind this effect modification remains unclear, baseline SUA level differences between men and women,^{39,40} and perhaps a difference in uric acid metabolism,³⁹ may explain the stronger risk of diabetes associated with female gout patients than that among men.³⁸ SUA levels in men are about 1 mg/dl higher than in women during adulthood, although levels in women increase around natural menopause. Thus, the physiological impact of uric acid levels, which are high enough to cause gout, could be stronger among women than men. Furthermore, female gout patients may have higher SUA levels on average than male gout patients,^{39,40} which could also contribute to a larger association with the risk of diabetes among women.

Our study has several strengths and limitations. First, our study can be viewed as a confirmation of the previous MRFIT study,⁸ which was limited to a population of men with a high CV risk profile. Nevertheless, our study population is much larger (~172 395) and consists of both men and women from the general population. Thus, our findings are likely to be more generalisable. For example, the incidence of diabetes in our non-gout cohorts (6.7 cases per 1000 person-years) is comparable to a previous estimate (5.8 cases per 1000 person-years) from another general population database.²⁵ However, unlike the MRFIT study, our analyses were not adjusted for dietary factors (eg, sugary drinks), physical activity and family history of diabetes as these variables have not been consistently collected in THIN. Future general population-based studies adjusting for these variables would be valuable. Because the definition of gout was based on doctors' diagnoses, a certain level of misclassification is inevitable. A diagnosis of gout could often have been recorded based on the suggestive clinical presentation of gout without documentation of monosodium urate crystals. However, any non-differential misclassification of these diagnoses would have biased the study results towards the null. Furthermore, when we used doctors' diagnoses of gout combined with antigout drug use (which has previously shown a validity of 90%)^{22,23} as our case definition, our results remained almost identical.

In conclusion, this general population-based study suggests that gout may be independently associated with an increased risk of diabetes and that the magnitude of association is significantly larger in women than in men. These findings support proper recognition and management of risk factors of diabetes in patients with gout, particularly among women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cumulative incidence of diabetes by sex. Cumulative incidence was estimated by adjusting for all-cause death as competing risks.

Table 1

Baseline characteristics according to presence of gout

Variable	Women		Men	
	Gout (n=9693)	No gout (n=37 881)	Gout (n=25 646)	No gout (n=99 175)
Age (years)	67.9±13.7	67.6±13.6	60.7±14.3	60.8±14
BMI (kg/m ²)				
Mean±SD	28±5.1	27.6±4.7	27.7±3.8	27.4±3.4
<18.5	106 (1.1%)	295 (0.8%)	38 (0.1%)	78 (0.1%)
18.5–24.9	2771 (28.6%)	11 530 (30.4%)	5875 (22.9%)	23 608 (23.8%)
25.0–29.9	3737 (38.6%)	15 343 (40.5%)	13 320 (51.9%)	54 194 (54.6%)
30.0	3079 (31.8%)	10 713 (28.3%)	6413 (25.0%)	21 295 (21.5%)
GP visits	5.3±3.9	4.4±3.5	4.2±3.4	3.6±3.1
Smoking				
None	5714 (58.9%)	24 357 (64.3%)	12 279 (47.9%)	46 901 (47.3%)
Past	2373 (24.5%)	7629 (20.1%)	8889 (34.7%)	30 211 (30.5%)
Current	1473 (15.2%)	5207 (13.7%)	4025 (15.7%)	20 107 (20.3%)
Unknown	133 (1.4%)	688 (1.9%)	453 (1.8%)	1956 (2.0%)
Alcohol				
None	2167 (22.4%)	8699 (23.0%)	1799 (7.0%)	10 189 (10.3%)
Past	171 (1.8%)	579 (1.5%)	392 (1.5%)	1803 (1.8%)
Current	6817 (70.3%)	26 083 (68.9%)	22 157 (86.4%)	81 272 (81.9%)
Unknown	538 (5.6%)	2520 (6.7%)	1298 (5.1%)	5911 (6.0%)
Hypertension	5615 (57.9%)	15 351 (40.5%)	10 810 (42.2%)	28 877 (29.1%)
Hyperlipidaemia	2896 (29.9%)	8196 (21.6%)	7587 (29.6%)	22 580 (22.8%)
Glucocorticoids	1219 (12.6%)	3476 (9.2%)	2000 (7.8%)	6616 (6.7%)
Diuretics	5667 (58.5%)	12 153 (32.1%)	8596 (33.5%)	16 798 (16.9%)
Charlson Index	0.34±0.76	0.2±0.58	0.24±0.65	0.17±0.55

Data are represented as mean±SD or number (percentage). Hyperlipidaemia is defined as having either a diagnosis of hyperlipidaemia or a prescription for antihyperlipidemics. Glucocorticoids are oral or injectable steroids. Diuretics are loop or thiazide diuretics. Drug use, the Charlson Index and GP visits were ascertained within 1 year prior to the index date. BMI, body mass index; GP, general practitioner.

Table 2

Incidence rates and HRs for diabetes by Gout status, stratified by sex and age

Sex	Age category	Gout status	N	Diabetes cases	Follow-up time (person-years)	Mean follow-up time (years)	Incidence rate (cases per 1000 person-years)	Age-, sex- and BMI-matched HR* (95% CI)	+GPs visits, smoking and alcohol-adjusted HR* (95% CI)	+Comorbidity and drug use-adjusted HR* (95% CI)
Women	Total	Yes	9693	429	42 503.9	4.4	10.1 (9.2 to 11.1)	1.71 (1.51 to 1.93)	1.65 (1.46 to 1.87)	1.48 (1.29 to 1.68)
		No	37 881	989	176 598.2	4.7	5.6 (5.3 to 6.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	<55	Yes	1700	76	8658.7	5.1	8.8 (6.9 to 11.0)	2.02 (1.49 to 2.74)	1.95 (1.42 to 2.69)	1.77 (1.27 to 2.48)
		No	6683	131	34 942.3	5.2	3.7 (3.1 to 4.4)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	55–69	Yes	3161	176	15 235.8	4.8	11.6 (9.9 to 13.4)	1.64 (1.36 to 1.98)	1.59 (1.32 to 1.93)	1.37 (1.12 to 1.67)
Men		No	12 602	438	63 579.2	5.0	6.9 (6.3 to 7.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	70	Yes	4832	177	18 609.5	3.9	9.5 (8.2 to 11.0)	1.67 (1.38 to 2.03)	1.63 (1.34 to 1.98)	1.52 (1.24 to 1.87)
		No	18 596	420	78 076.7	4.2	5.4 (4.9 to 5.9)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	Total	Yes	25 646	1098	116 083.4	4.5	9.5 (8.9 to 10.0)	1.22 (1.13 to 1.31)	1.24 (1.14 to 1.33)	1.15 (1.06 to 1.24)
		No	99 175	3287	458 406.5	4.6	7.2 (6.9 to 7.4)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	<55	Yes	8973	356	43 538.7	4.9	8.2 (7.3 to 9.1)	1.22 (1.07 to 1.38)	1.24 (1.08 to 1.42)	1.14 (1.00 to 1.31)
		No	34 021	1000	166 116.7	4.9	6.0 (5.7 to 6.4)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	55–69	Yes	9084	500	42 871.3	4.7	11.7 (10.7 to 12.7)	1.24 (1.11 to 1.38)	1.25 (1.12 to 1.39)	1.17 (1.04 to 1.31)
		No	35 960	1526	173 024.0	4.8	8.8 (8.4 to 9.3)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	70	Yes	7589	242	29 673.4	3.9	8.2 (7.2 to 9.3)	1.19 (1.01 to 1.40)	1.21 (1.02 to 1.42)	1.11 (0.93 to 1.31)
		No	29 194	761	119 265.8	4.1	6.4 (5.9 to 6.9)	1.0 (reference)	1.0 (reference)	1.0 (reference)

BMI, body mass index; GP, general practitioner.

* Adjusted for continuous BMI value.