

# Gout and the Risk of Incident Erectile Dysfunction: A Body Mass Index-matched Population-based Study

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**ABSTRACT. Objective.** Gout is the most common inflammatory arthritis. Erectile dysfunction (ED) is common in the general population; however, evidence regarding ED among patients with gout is limited. Our purpose was to study the association between incident gout and the risk of incident ED in the general population.

**Methods.** We conducted a cohort study using The Health Improvement Network, an electronic medical record database in the United Kingdom. Up to 5 individuals without gout were matched to each case of incident gout by age, enrollment time, and body mass index (BMI). Multivariate HR for ED were calculated after adjusting for smoking, alcohol consumption, comorbidities, and medication use.

**Results.** We identified 2290 new cases of ED among 38,438 patients with gout (mean age 63.6 yrs) and 8447 cases among 154,332 individuals in the comparison cohort over a 5-year median followup (11.9 vs 10.5 per 1000 person-years, respectively). Univariate (matched for age, entry time, and BMI) and multivariate HR for ED among patients with gout were 1.13 (95% CI 1.08–1.19) and 1.15 (95% CI 1.09–1.21), respectively. In our sensitivity analysis, by restricting gout cases to those receiving anti-gout treatment (n = 27,718), the magnitude of relative risk was stronger than the primary analysis (multivariate HR 1.31, 95% CI 1.23–1.39).

**Conclusion.** This population-based study suggests that gout is associated with an increased risk of developing ED, supporting a possible role for hyperuricemia and inflammation as independent risk factors for ED. (J Rheumatol First Release July 15 2018; doi:10.3899/jrheum.170444)

## Key Indexing Terms:

GOUT

ERECTILE DYSFUNCTION

BODY MASS INDEX

Gout is the most common inflammatory arthritis in humans, affecting an estimated 8.3 million Americans<sup>1</sup>. The prevalence of gout has increased significantly in many Western countries, including the United Kingdom<sup>2</sup>. Gout is frequently perceived as an acute arthritis of the big toe; however, it is a chronic metabolic condition resulting from hyperuricemia leading to deposition of monosodium urate crystals in joints and soft tissues, as well as to acute attacks. Gout is frequently associated with a number of comorbidities, including hyper-

tension, hyperlipidemia, obesity, chronic kidney disease, diabetes mellitus (DM), as well as a combination of these conditions, known as the metabolic syndrome<sup>3</sup>.

Erectile dysfunction (ED), defined as the “inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse”<sup>4</sup> is common in the general population. An association between ED and cardiovascular disease (CVD) has long been recognized and studies suggest that ED is an independent marker of CVD risk<sup>5</sup>. CVD and ED share mutual risk factors and comorbidities such as DM, obesity, hypertension, advanced age, hyperlipidemia, metabolic syndrome, certain medications, and tobacco abuse<sup>5,6,7</sup>. It has been suggested that there is an increased risk of coronary artery disease (CAD) and peripheral vascular disease associated with gout, independent of traditional CVD risk factors<sup>8</sup>. As the number of CVD risk factors increases, so does the incidence of both CAD and ED<sup>9</sup>.

We have previously reported increased odds of ED in gout patients in a cross-sectional study of arthritis patients (n = 201) from a University Hospital Rheumatology clinic<sup>10</sup>. While common risk factors for, and comorbidities of, gout<sup>11,12</sup> and ED may explain the link between these 2 conditions, chronic inflammation as well as hyperuricemia contribute to an increased risk of ED among patients with gout. Our objective in this study was to confirm the

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independent association between incident gout and the risk of incident ED in a general population context.

## MATERIALS AND METHODS

**Data source.** In the United Kingdom, most general practitioners (GP) record patient data electronically. A subset of general practices has opted to provide anonymous electronic patient records for use in clinical and epidemiological research. This database, The Health Improvement Network (THIN), was set up in 2002 and contains the electronic medical records of 11.1 million patients (3.7 million active patients), equivalent to 75.6 million PY of data collected from 562 general practices in the UK<sup>13</sup>. THIN database is representative of the UK general practice population regarding demographics. Its electronically coded diagnoses have been shown to be accurate when compared with the gold standard (GP questionnaire, primary care medical record, or hospital correspondence)<sup>14</sup>.

Information recorded in the system includes data on prescriptions and health indicators such as height, weight, blood pressure, smoking status, and laboratory test results recorded by GP. Information on symptoms, diagnoses, interventions, and referrals to secondary care are electronically recorded as Read codes, a coding system used in UK general practices<sup>15</sup>. Further, the socioeconomic information available for each patient in the THIN database is the Townsend deprivation index quintile, a measure of material deprivation calculated using census data and linked to area of residence<sup>16</sup>. The study research protocol was approved by the Multicenter Research Ethics Committee (SRC Reference Number: 12-005).

**Study design and cohort definition.** We conducted a cohort study of incident ED among men with incident gout, compared with up to 5 non-gout individuals matched by age, date of study entry, and body mass index (BMI) using data from THIN. We matched on BMI because obesity is a strong risk factor for both gout<sup>17</sup> and ED<sup>18</sup>.

Patients were required to be continuously enrolled in the database for 12 months prior to inclusion in the cohort, and those diagnosed with gout or ED prior to study entry were excluded. Our study period spanned the period from January 1, 1995, through December 31, 2012. 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 ED, died, or until the followup ended, whichever came first.

**Ascertainment of incident gout.** We identified all individuals in THIN who had a Read code diagnosis of gout (Supplementary Table 1, available from the authors on request)<sup>15</sup>. Using Read codes we identified all patients with a first-time 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 ( $n = 38,438$ ). Our primary outcome was the first recorded diagnosis of ED after excluding prevalent ED cases at baseline (i.e., before the index date). Thus, we ascertained incident ED cases that occurred after gout onset.

To evaluate the robustness of our gout case ascertainment, we performed a sensitivity analysis in which we restricted gout cases to those receiving gout treatment ( $n = 27,718$ ), as previously described. For this, we used the following operational definition: we identified within 90 days after the first ever diagnosis of gout any anti-gout treatment (colchicine or urate-lowering drugs such as allopurinol, febuxostat, rasburicase, probenecid, or sulfapyrazone). A similar case definition of gout has been shown to have a validity of 90% in the General Practice Research Database<sup>19</sup>, in which 60% of patients overlap with THIN.

**Ascertainment of ED.** Our primary outcome was the first recorded diagnosis of ED after excluding prevalent ED cases at baseline. We identified all individuals in THIN who had a Read code diagnosis of ED (Read code: E227311)<sup>20</sup>.

**Assessment of covariates.** From the THIN database, we collected data on personal characteristics, socioeconomic status, and lifestyle factors such as alcohol use, smoking, and BMI, as well as healthcare use (i.e., GP visits),

comorbidities [i.e., ischemic heart disease, hypertension, hyperlipidemia (diagnosis or lipid-lowering drug)], and diuretic use (i.e., loop or thiazide) were recorded to the nearest possible measurement prior to the index date. All covariates came before exposure (i.e., incident gout) as well as the endpoint of interest (i.e., ED). Drug use 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 gout and comparison cohorts. We identified incident cases of ED during the followup and calculated incidence rates for ED. Further, we estimated the cumulative incidence of ED in each cohort, accounting for the competing risk of death<sup>21</sup>. Cox proportional hazard regression models were used to calculate HR 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 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 ( $< 50$ , 51–59, 60–69, and  $\geq 70$  yrs) to examine their influence.

Our primary analysis used imputed missing values for covariates (i.e., smoking and alcohol use), with a sequential regression method based on a set of covariates as predictors (IVEware for SAS, version 9.2; SAS Institute). We calculated 95% CI for all HR. All p values were 2-sided.

## RESULTS

The cohort included 38,438 men with gout and 154,332 matched men without gout. The baseline characteristics of the cohorts are shown in Table 1. Men with gout tended to consume more alcohol, to visit the GP more often, not to be current smokers, to have more comorbidities, and to use antihypertensive medications and diuretics more commonly.

The cumulative incidence of ED according to the presence of incident gout is depicted in Figure 1, and the incidence rates for ED according to the presence of incident gout are shown in Table 2.

Overall, new diagnoses of ED occurred among 2290 of men with gout for 192,401 person-years (PY; mean followup 5 yrs), resulting in an incidence rate of 11.90 cases per 1000 PY (95% CI 11.42–12.40). This rate was higher than that in the non-gout male comparison cohort (10.49 cases per 1000 PY, 95% CI 10.27–10.72; Table 2).

Compared with non-gout men, the HR for ED (matched for age and entry time) was 1.13 (95% CI 1.08–1.19). After further adjusting for the number of GP visits during the prior year, socioeconomic deprivation index, smoking, and alcohol use, the corresponding HR was 1.10 (95% CI 1.04–1.15; Table 2). After further adjusting for comorbidities and CVD drug classes, the multivariate HR was 1.15 (1.09–1.21). These HR remain similarly significant in our age subgroup analyses, except for those  $\geq 70$  years, where the frequency of physician-diagnosed ED cases was lowest (likely because of underreporting in elderly men). In our sensitivity analysis restricting gout cases to those receiving anti-gout treatment ( $n = 27,718$ ), the magnitude of relative risk was stronger than the primary analysis (multivariate HR 1.31, 95% CI 1.23–1.39; Table 3).

Table 1. Baseline characteristics according to the presence of gout. Data are represented as mean ± SD or n (%).

Variables	Gout, n = 38,438	Comparison Cohort, n = 154,332
Age, yrs	63.6 ± 12.3	63.6 ± 12.2
BMI, kg/m <sup>2</sup>		
Mean ± SD	28.2 ± 4	27.9 ± 3.7
< 18.5	58 (0.2)	128 (0.1)
18.5–24.9	7929 (20.6)	32,472 (21.0)
25.0–29.9	19,245 (50.1)	81,156 (52.6)
≥ 30.0	11,206 (29.2)	40,576 (26.3)
Smoking		
None	17,944 (46.7)	71,972 (46.6)
Past	14,855 (38.6)	52,232 (33.8)
Current	5098 (13.3)	27,730 (18.0)
Unknown	541 (1.4)	2398 (1.6)
Alcohol		
None	3053 (7.9)	17,623 (11.4)
Past	761 (2.0)	3469 (2.2)
Current	32,717 (85.1)	123,921 (80.3)
Unknown	1907 (5.0)	9319 (6.0)
Socioeconomic deprivation index score*	2.6 ± 1.3	2.6 ± 1.3
GP visits	4.5 ± 3.7	3.9 ± 3.3
Hypertension	19,599 (51.0)	59,456 (38.5)
Hyperlipidemia <sup>†</sup>	14,740 (38.3)	50,279 (32.6)
Stroke	3093 (8.0)	10,304 (6.7)
Ischemic heart disease	8345 (21.7)	26,421 (17.1)
Diabetes	3900 (10.1)	20,043 (13.0)
ACE inhibitors	12,017 (31.3)	33,936 (22.0)
Aspirin	10,286 (26.8)	36,881 (23.9)
Angiotensin II receptor blockers	3571 (9.3)	9503 (6.2)
Beta blockers	10,918 (28.4)	28,928 (18.7)
Calcium channel blockers	8094 (21.1)	28,732 (18.6)
Diuretics	14,403 (37.5)	31,401 (20.3)

<sup>†</sup> Defined as a diagnosis of hyperlipidemia or use of antihyperlipidemics. \* Socioeconomic deprivation index score was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived). GP: general practitioner; ACE: angiotensin-converting enzyme; BMI: body mass index.

## DISCUSSION

In this large general practice cohort representative of the UK population, we found that the risk of ED was higher among men with gout compared with men who do not have gout. Incidence rates and associations between gout and ED per 1000 PY in our cohort were 11.90 (95% CI 11.42–12.40) in gout patients versus 10.49 (95% CI 10.27–10.72) in our comparison group. When restricting gout cases to those receiving anti-gout treatment (multivariate HR 1.31, 95% CI 1.23–1.39), the magnitude of relative risk was stronger than the primary analysis, likely a result of confounding by indication (worse cases got treated). A previous Taiwanese study<sup>22</sup> suggested a potential protective role of anti-gout medication against ED. The increased ED risk associated with our gout definition requiring anti-gout medications or nonsteroidal antiinflammatory drugs should not be viewed as contradictory, because our study aimed to examine the effect of gout, not the drug effect accounting for confounding by indication. For example, a previous THIN study found that proper adjustment using propensity scores that incorporated the major imbalance of baseline serum uric acid levels

between allopurinol users versus nonusers could overcome such confounding by indication and reveal the potential survival benefit of allopurinol in patients with gout<sup>23</sup>.

These findings were independent of BMI, lifestyle factors, and other known risk factors. These findings largely persisted across age categories. Our current study provides the first general population evidence for an independent association between incident gout and the risk of incident ED, to our knowledge.

ED seems to precede CAD in most cases by a mean time interval of 2–3 years<sup>24</sup>. Because the penile arteries are small (1–2 mm) compared with the coronary arteries (3–4 mm), the same level of endothelial dysfunction and atherosclerosis may lead to a more significant decrease in penile artery blood flow compared to that seen in the coronary arteries<sup>25</sup>. Thus, treatment of CVD risk factors commonly seen in our gout patients is warranted.

Hyperuricemia and inflammation may be independent risk factors for ED in addition to the conventional ones. Uric acid can induce endothelial dysfunction<sup>26</sup>, oxidative stress in vascular smooth-muscle cells, inflammation, and microvas-

### Gout and ED

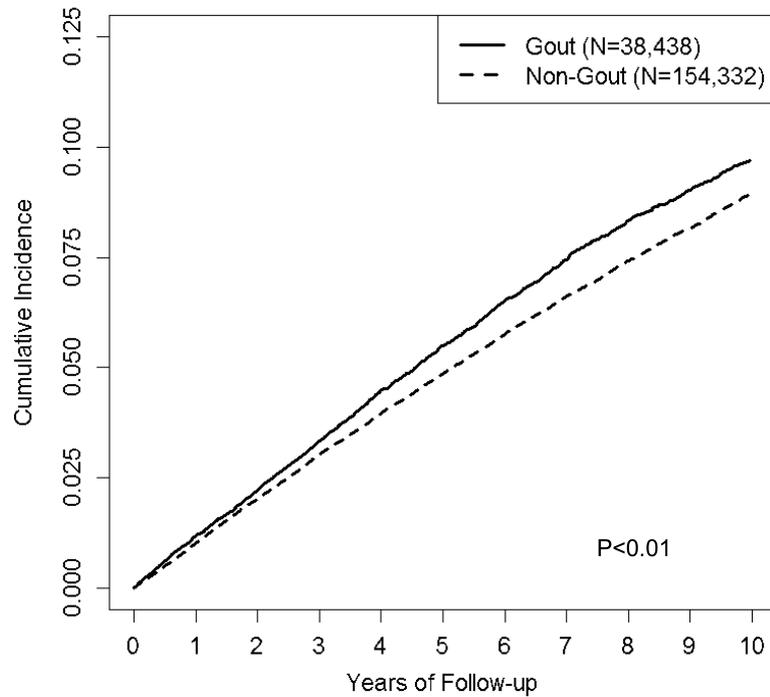


Figure 1. Cumulative incidence of ED according to the presence of gout. ED: erectile dysfunction.

Table 2. Incidence rates and HR for associations between gout and ED according to age groups.

Age Groups	Gout Status	N	ED Cases	Followup Time, PY	Mean Followup, Yrs	Incidence Rate, Cases per 1000 PY (95% CI)	Age-, Sex-, BMI-matched, HR (95% CI)*	+ GP Visits, Socioeconomic Deprivation Index, BMI, Smoking, and Alcohol, Adjusted HR (95% CI)	+ Comorbidity and CVD Drug Classes, Adjusted HR** (95% CI)
Total	Yes	38,438	2290	192,401.1	5.0	11.90 (11.42–12.40)	1.13 (1.08–1.19)	1.10 (1.04–1.15)	1.15 (1.09–1.21)
	No	154,332	8447	804,958.6	5.2	10.49 (10.27–10.72)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
< 50	Yes	6595	451	36,336.2	5.5	12.41 (11.29–13.61)	1.13 (1.01–1.26)	1.10 (0.98–1.23)	1.14 (1.02–1.29)
	No	25,870	1594	143,607.9	5.6	11.10 (10.56–11.66)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
50–59	Yes	8686	817	47,911.3	5.5	17.05 (15.90–18.26)	1.14 (1.05–1.24)	1.11 (1.03–1.21)	1.15 (1.06–1.25)
	No	35,117	2973	201,636.7	5.7	14.74 (14.22–15.28)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
60–69	Yes	10,146	737	53,303.0	5.3	13.83 (12.85–14.86)	1.15 (1.05–1.25)	1.11 (1.02–1.21)	1.18 (1.07–1.28)
	No	41,309	2762	225,662.1	5.5	12.24 (11.79–12.70)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
≥ 70	Yes	13,011	285	54,850.5	4.2	5.20 (4.61–5.84)	1.07 (0.93–1.23)	1.03 (0.89–1.18)	1.14 (0.98–1.32)
	No	52,036	1118	234,051.9	4.5	4.78 (4.50–5.07)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

\* Matched by age, sex, BMI, and entry time. \*\* Comorbidities include hypertension, diabetes, stroke, ischemic heart disease, hyperlipidemia; CVD drugs include angiotensin-converting enzyme inhibitors, aspirin, angiotensin II receptor blockers,  $\beta$  blockers, calcium channel blockers, and diuretics. ED: erectile dysfunction; PY: person-years; BMI: body mass index; GP: general practitioner; CVD: cardiovascular disease.

cular disease<sup>27,28</sup>. In addition to lowering serum urate (SU), treatment with allopurinol improved endothelial dysfunction in subjects with chronic heart failure<sup>29</sup>. This may provide a link between uric acid, ED, CVD, and its risk factors<sup>27,30,31</sup>. Inflammation, too, may play an important role in ED in

patients with gout and may contribute to the association between the metabolic syndrome, ED, and CVD<sup>32,33</sup>. Increased circulating levels of inflammatory and endothelial-prothrombotic compounds are related to the presence and severity of ED<sup>11</sup>. Sexual performance assessed by the Erectile

Table 3. Incidence rates and HR for associations between gout (defined by diagnosis plus anti-gout treatment) and ED according to age groups.

Age Groups	Gout Status	N	ED Cases	Followup Time, PY	Mean Followup, Yrs	Incidence Rate, Cases per 1000 PY (95% CI)	Age-, Sex-, BMI-matched, HR (95% CI)*	+ GP Visits, Socioeconomic Deprivation Index, BMI, Smoking, and Alcohol, Adjusted HR (95% CI)	+ Comorbidity and CVD Drug Classes, Adjusted HR** (95% CI)
Total	Yes	27,718	1787	149,172.7	5.38	11.98 (11.43–12.55)	1.29 (1.22–1.36)	1.25 (1.18–1.33)	1.31 (1.23–1.39)
	No	113,112	5917	635,096.6	5.61	9.32 (9.08–9.56)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
< 50	Yes	4965	360	28,998.32	5.84	12.41 (11.17–13.77)	1.32 (1.16–1.50)	1.31 (1.15–1.49)	1.36 (1.19–1.56)
	No	19,736	1137	117,061.5	5.93	9.71 (9.16–10.29)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
50–59	Yes	6535	624	37,941.81	5.81	16.45 (15.18–17.79)	1.32 (1.20–1.45)	1.29 (1.17–1.42)	1.32 (1.19–1.45)
	No	26,876	2060	164,461.4	6.12	12.53 (11.99–13.08)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
60–69	Yes	7505	592	42,024.17	5.6	14.09 (12.98–15.27)	1.30 (1.18–1.43)	1.25 (1.13–1.38)	1.32 (1.19–1.46)
	No	30,962	1973	180,983.5	5.85	10.90 (10.43–11.39)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
≥ 70	Yes	8713	211	40,208.37	4.61	5.25 (4.56–6.01)	1.12 (0.95–1.32)	1.10 (0.93–1.29)	1.21 (1.02–1.44)
	No	35,538	747	172,590.3	4.86	4.33 (4.02–4.65)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

\* Matched by age, sex, BMI, and entry time. \*\* Comorbidities include hypertension, diabetes, stroke, ischemic heart disease, hyperlipidemia; CVD drugs include angiotensin-converting enzyme inhibitors, aspirin, angiotensin II receptor blockers,  $\beta$  blockers, calcium channel blockers, and diuretics. ED: erectile dysfunction; PY: person-years; BMI: body mass index; GP: general practitioner; CVD: cardiovascular disease.

Function International Index 5 score correlated inversely with circulating levels of the endothelial prothrombotic and inflammatory cytokines interleukin (IL) 1 $\beta$  and IL-6<sup>34,35</sup>. Studies are needed to determine whether improvement in erectile function in gout patients is seen when lowering SU and correcting gouty inflammation.

Our study has several strengths and limitations. Our study was performed using a large UK general practice database; therefore, findings reflect “real life” and are likely to be generalizable to the general population. The THIN data are not subject to recall bias or interviewer bias, because there is no reliance on patient recall or interviewers to collect the data. THIN data were collected from GP medical records and thus may reflect only events deemed to be relevant to the patient’s care, as reflected in the incidence rates of the elderly age group (Table 2). In addition, because the definition of gout was based on doctors’ diagnoses, a certain level of misclassification is possible. However, any nondifferential misclassification of these diagnoses would have biased the study results toward the null. Further, when we used doctors’ diagnoses of gout combined with anti-gout drug use (which has previously shown a validity of 90%)<sup>18,19</sup> as our case definition, our results remained almost identical.

This general population-based study suggests that gout may be independently associated with an increased risk of ED. Sexual function is an important component of quality of life. However, despite its importance, little attention has been paid to the effect of gout on sexual function. Increasing awareness of the presence of ED in patients with gout should in turn lead to earlier medical attention and treatment for this distressing condition.

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