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Original article

Frequency and risk factors of gout flares in a large population-based cohort of incident gout

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Abstract

Objective. So far, few data are available to characterize the flare history of patients with gout. The objective of this study was to describe the frequency and risk factors of gout flares with special consideration of the comorbidity.

Methods. A cohort study was conducted in a UK general practice database (The Health Improvement Network) including all patients aged 20–89 years diagnosed with incident gout between the years 2000 and 2007.

Results. In this study, 23 857 incident gout patients (mean age 61.9 years) were included, overall incidence rate was 2.68 (95% CI 2.65, 2.72) per 1000 person-years. The proportion of patients with at least one flare during the follow-up period (mean 3.8 years) was 36.9% ($n = 8806$). A history of ischaemic heart disease [hazard ratio (HR) 1.12 (95% CI 1.06, 1.19)], hypertension [HR 1.15 (95% CI 1.10, 1.20)] and renal failure [HR 1.33 (95% CI 1.20, 1.48)] were independently associated with a higher risk of a first gout flare. Use of allopurinol at initial gout diagnosis was associated with a lower risk [HR 0.80 (95% CI 0.75, 0.85)].

Conclusions. Gout flares are relatively common among patients with gout. Some of the underlying cardiometabolic comorbid conditions are themselves independent risk factors for flares, which further contribute to the complexity of treatment of gout flares.

Key words: Gout, Flare, Risk factors, Comorbidity, Observational study.

Introduction

Gout is the most common cause of inflammatory arthritis in men, affecting at least 1% of subjects in Western countries [1, 2]. Prevalence of gout in men is much higher than in women and the burden of disease of gout increases with an increase in the number of the underlying risk factors [3]. Several lifestyle-dependent factors such as alcohol consumption, meat consumption and a high BMI increase the risk of gout.

Gout is characterized by acute, often recurrent attacks of arthritis, which are triggered by deposition of monosodium urate (MSU) crystals, predominantly in the joints of the lower limbs. Although the most important single risk factor for developing gout is a raised serum uric acid level, the acute gout process is an inflammatory arthritis induced by the MSU crystals and characterized by inflammatory components of the innate immune system [4]. Acute gouty attacks are painful and, if recurrent, they may lead to disabling arthritis; it is, therefore, important that these manifestations get immediately treated.

Currently, most of the management of gout occurs in primary care and acute gout management is considered suboptimal [5]. The optimal therapy of an acute gout attack is directed at controlling the pain and the inflammation. Colchicine therapy as well as anti-inflammatory drugs and pain medication are part of the standard regimen for acute gout [6, 7]. Current guidelines also advise that urate-lowering treatment (allopurinol) should be initiated if a second attack occurs within 1 year, but should not be initiated during an acute attack, starting with a delay of 1–2 weeks after the inflammation has settled [7]. Despite evidence-based treatment guidelines, several reports discuss inadequacies of management of

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chronic gout and of gout-related inflammation therapy for patients with acute gout attacks [5, 8]. Besides the issues of lack of adherence to suggested treatment, relative or absolute contraindications such as hypertension, metabolic syndrome or chronic kidney disease may be among the reasons that make treatment difficult. As a result, patients may continue to experience clinical manifestations of gout [2, 9]. Few data so far are available to characterize patients with gout and their flare history to determine the risk factors that are associated with recurrent gout attacks, especially under conditions of routine clinical care.

The objective of this study was to describe the frequency of gout flares during the study period and risk factors contributing to first gout flare in a population-based cohort of incident gout with special emphasis on comorbid conditions.

Methods

Study population

Data from The Health Improvement Network (THIN) database in the UK, which currently totals over 4 million patients, were used for this cohort study. Data are systematically recorded and entered by participating primary-care physicians from the UK and sent anonymously to THIN. The computerized information includes demographics, details from general practitioner's (GP) visits, diagnoses from specialist's referrals and hospital admissions, results of laboratory tests and a free-text section. Prescriptions issued by the GP are directly generated from the computer. An additional requirement for participating practices is recording of the indication for new courses of therapy. The READ classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX classification is used to code drugs [10]. THIN has been extensively validated for use in pharmaco-epidemiology [11]. The current study was approved by an ethics committee review board (Multi-centre Research Ethics Committee, REC reference number: 09/H0305/75).

Ascertainment of gout

We identified a cohort population with a first-ever diagnosis of gout recorded in the database using READ codes from January 2000 to December 2007 and who were between 20 and 89 years of age. Subjects with any prescription of anti-gout treatment or any code suggesting gout before the start date were subsequently excluded from the cohort and considered as prevalent patients. All patients with cancer before the start date were also excluded. Finally, we considered 24 768 individuals who developed gout after the start date; the date of gout onset was taken as their index date. The final date of gout diagnosis (index date) was defined as the earliest of the date of the first diagnosis of gout or first anti-gout treatment (allopurinol, colchicine and uricosuric drugs) among individuals with a diagnosis of gout.

Ascertainment of gout flares

All members from the cohort of incident gout were followed from start date, corresponding to 30 days after the first-ever diagnosis of gout, until the earliest occurrence of one of the following endpoints: gout flare, cancer, death, end of practice data collection or 31 December 2008, whichever came first.

The operational definition of gout flare was defined as follows: when there was a recorded prescription of colchicine or when there was a health-care visit recording gout (GP, consultant or emergency visit) together with at least one of the following treatment patterns within 1 week: IA aspiration, IA injection (CS), prescription of NSAIDs or prescription of CS or adrenocorticotropic hormone (ACTH). The final cohort consisted of 23 857 patients: the difference with the initial cohort ($n = 24\,768$) is patients presenting one of the censoring criteria during the first 30 days after the diagnosis of gout (the grace period before starting the ascertainment of flares).

Ascertainment of flares was performed recursively adding in every new follow-up a period of grace of 30 days to the date of the flare detected in each consecutive search (to account for full remission of that attack). The validity of our operational definition of flare was confirmed based on the manual review of a random sample of 100 computerized patient profiles (Fig. 1).

Definition of cormorbid disorders

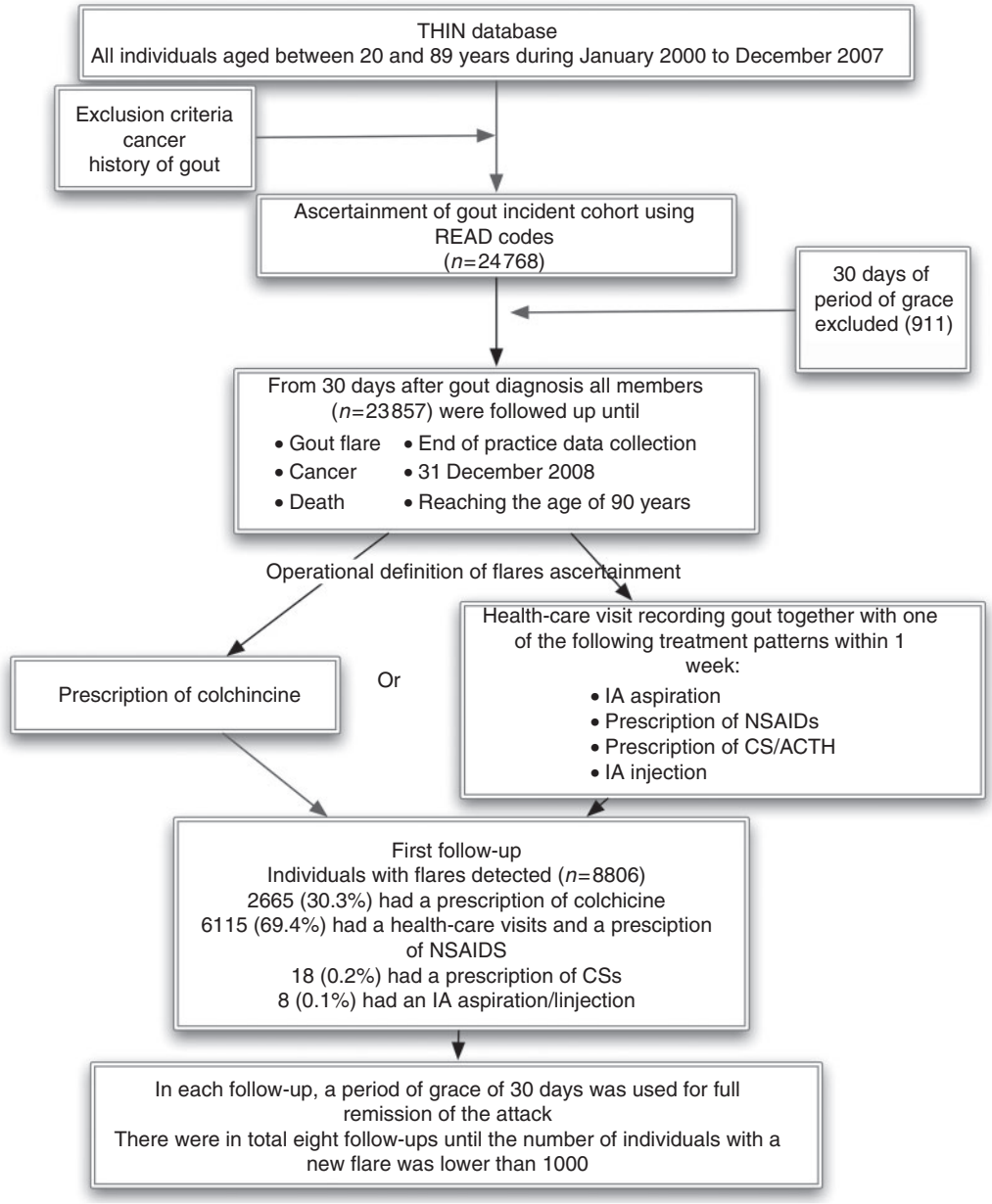
Traditional lifestyle and demographic factors such as alcohol use, smoking and BMI were collected from the database before the index date (defined as the date of onset gout). In a similar way, information about the comorbidities of interest was collected. It comprised cardiometabolic diseases [including a history of congestive heart failure, ischaemic heart disease (IHD), cerebrovascular diseases (stroke, transient ischaemic attack), hypertension, diabetes and chronic renal failure]; digestive diseases (including complicated peptic ulcer, oesophageal complications, chronic hepatic disorders and pancreatic disorders). The numbers of GP visits, referrals and hospitalizations in the year before the index date were also ascertained.

Statistical analysis

The main characteristics of the gout population were described using descriptive statistics. The number of flares within the whole study period and the average number of flares per year of observation were then calculated. The association of various socio-demographic and clinical characteristics with the numbers of flares was assessed by means of a likelihood ratio test.

A survival analysis within the incident gout cohort was used to quantify the occurrence of first post-diagnosis gout flare during the follow-up period between January 2000 and December 2008. The relationship of gender with time to first flare during follow-up was assessed by a Kaplan–Meier plot. We used a Cox proportional hazards model to estimate the hazard ratio (HR) of first post-diagnosis flare associated with various factors

Fig. 1 Study design and ascertainment of gout flares.



in our incident gout population. The following potential confounders were studied in multivariable analyses: sex; age (20–49, 50–59, 60–69, 70–79, 80–89 years); number of GP visits (0–4, 5–9, 10–19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1–9, 10–24, 25–42, >42 U/week); BMI (categories in kg/m^2: 15–19, 20–24, 25–29, ⩾30); history of IHD (no, yes); history of hypertension (no, yes); history of hyperlipidaemia (no, yes); history of renal failure (no, yes); history of diabetes (no, yes); and the use of allopurinol (no, yes; within the first 30 days after initial gout diagnosis). Finally, we investigated the association between the time to first post-diagnosis flare and the number of flares during the follow-up, using the non-parametric Kruskal–Wallis test. All statistical procedures were performed with the Stata package version 11.0 (StataCorp LP, College Station, TX, USA).

Results

Overall, $n = 23\,857$ patients aged 18–89 years with gout were identified in the observation period between the years 2000 and 2007 within THIN. The overall incidence rate of gout per 1000 person-years was 2.68 (95% CI 2.65, 2.72). Table 1 shows the main socio-demographic and medical characteristics of the study gout cohort

Table 1 Main socio-demographic and medical characteristics of the study population with gout ($n = 23\,857$)

Variables	Overall, *n* (%)	Men, *n* (%)	Women, *n* (%)
Sex			
Male	17 358 (72.8)		
Female	6499 (27.2)		
Age, mean (S.D.), years	61.9 (14.5)	59.9 (14.3)	67.6 (13.4)
20–49	5211 (21.8)	4508 (26.0)	703 (10.8)
50–59	4761 (20.1)	3768 (21.7)	993 (15.3)
60–69	5547 (23.3)	4067 (23.4)	1480 (22.8)
70–79	5533 (23.2)	3529 (20.3)	2004 (30.8)
80–89	2805 (11.8)	1486 (8.6)	1319 (20.3)
BMI, kg/m^2			
15–19	297 (1.2)	133 (0.8)	164 (2.5)
20–24	4045 (17.0)	2879 (16.6)	1166 (17.9)
25–29	8799 (36.9)	6832 (39.4)	1967 (30.3)
$\geqslant$30	6945 (29.1)	4548 (26.2)	2397 (36.9)
Unknown	3771 (15.8)	2966 (17.1)	805 (12.4)
Cardiometabolic diseases			
History of hypertension	12 303 (51.6)	8098 (46.7)	4205 (64.7)
History of IHD	4662 (19.5)	3344 (19.3)	1318 (20.3)
History of cerebrovascular disorders	2095 (8.8)	1386 (8.0)	709 (10.9)
History of congestive heart failure	1998 (8.4)	1288 (7.4)	710 (10.9)
History of diabetes	2275 (9.5)	1439 (8.3)	836 (12.9)
History of chronic renal failure	880 (3.7)	573 (3.3)	307 (4.7)
Digestive diseases			
History of peptic ulcer	594 (2.5)	65 (2.7)	129 (2.0)
Oesophageal complications	173 (0.7)	136 (0.8)	37 (0.6)
Chronic hepatic disorders	173 (0.73)	126 (0.7)	47 (0.7)
Pancreatic disorders	147 (0.6)	101 (0.6)	46 (0.7)
Gout-related medication[a]			
Allopurinol	3815 (16.0)	2177 (12.5)	1068 (16.4)
Colchicine	3245 (13.6)	2665 (15.3)	1150 (17.7)

Data are expressed as *n* (%) unless otherwise specified. [a]The drug-use information was collected the first 30 days after gout diagnosis.

($n = 23\,857$) and for males [*n* (%) = 17 358 (72.8)] and females [*n* (%) = 6499 (27.2)] separately. The mean (S.D.) age at start date of the overall population was 61.9 (14.5) years, women were considerably older than men [67.6 (13.4) and 59.9 (14.3) years, respectively]. In the overall population, there were 29.1% of the patients with a BMI of $\geqslant$30 kg/m^2, 51.6% with a history of hypertension, 19.5% with IHD, 9.5% with diabetes, 2.5% with peptic ulcer and 3.7% with chronic renal failure. In general, women had a higher prevalence of cardiometabolic disorders. Use of allopurinol and colchicine within the first 30 days after the first gout diagnosis was recorded for 16.0 and 13.6% of the patients, respectively, and was slightly higher in women.

Incidence and frequency of flares

The incidence rate to develop first flare starting 1 month after the initial diagnosis of gout was 13.7 (95% CI 13.4, 14.0) per 100 person-years. It was higher in men [14.8 (95% CI 14.4, 15.1)] compared with women [11.0 (95% CI 10.5, 11.5)]. The incidence of first flare among men was rather constant across the age groups. In women, the incidence rate increased with age (data not shown). The cumulative proportion of subjects developing a first flare by sex is presented in Fig. 2. Almost 20% of the patients in both genders had a first flare within the first year of follow-up. However, after the first year of follow-up men had a greater cumulative proportion of developing a first flare compared with women.

Table 2 shows the distribution of the number of flares during follow-up (mean follow-up time 3.8 years) among patients with gout. During the follow-up period of this study, 15 051 (63.1%) patients had no flares, 4948 (20.7%) had one flare, 2018 (8.5%) had two flares, 1464 (7.8%) had three to five flares and 376 (1.6%) had six flares or more. In general, women had flares less often compared with men.

Risk factors and determinants of flares

Table 3 shows the association of various factors with the number of flares. Male gender was associated with a higher number of flares ($P < 0.001$). We observed a trend to a lower number of flares among older individuals, i.e. the oldest age category had the highest proportion of

FIG. 2 Cumulative hazard estimates of first post-diagnosis flare stratified by sex.

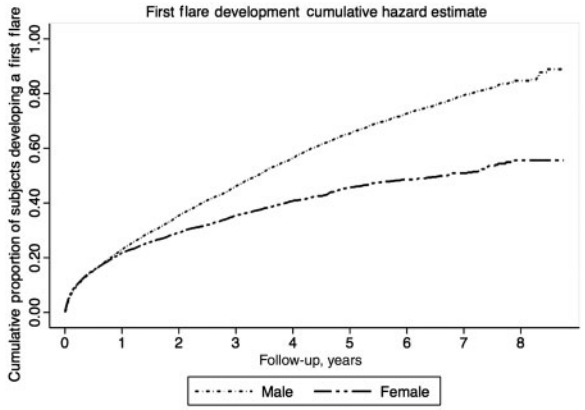


TABLE 2 Number of flares during follow-up among the patients with gout

Number of flares	Number of patients (%) ($n = 23\,857$)	Among patients with flares, %
Over whole observation period (mean 3.8 years)		
Overall		
No flare	15 051 (63.1)	–
1 flare	4948 (20.7)	56.2
2 flares	2018 (8.5)	22.9
3–5 flares	1464 (6.1)	16.6
⩾6 flares	376 (1.6)	4.3
Men only		
No flare	10 522 (60.6)	–
1 flare	3788 (21.8)	55.4
2 flares	1608 (9.3)	23.5
3–5 flares	1146 (6.6)	16.8
⩾6 flares	294 (1.7)	4.3
Women only		
No flare	4529 (69.7)	–
1 flare	1160 (17.8)	58.9
2 flares	410 (6.3)	20.8
3–5 flares	318 (4.9)	16.1
⩾6 flares	82 (1.3)	4.2

individuals with no flares (68.6%). We found that higher BMI ($P < 0.001$), and greater number of GP visits ($P = 0.002$) were also associated with greater number of flares. Both a higher alcohol consumption as well as a history of cardiometabolic diseases were also associated with greater number of flares (both $P < 0.001$). A borderline association was found between the history of digestive diseases and the number of flares ($P = 0.051$).

A multivariable analysis was used to investigate the determinants and risk factors associated with first post-diagnosis flare detected by means of a Cox proportional hazard model (Table 4). Male gout patients presented an HR of 1.36 (95% CI 1.28, 1.43). While older age was associated with a decreased risk of having a first post-diagnosis flare among men, we observed an inverse association among females (P for interaction < 0.001). The overall HR estimate among patients drinking >42 U/week was 1.41 (95% CI 1.26, 1.58) compared with abstainers and 1.22 (95% CI 1.14, 1.30) in individuals with a BMI exceeding 30 kg/m^2. In addition, individuals with a BMI between 15 and 19 kg/m^2 had 27% less likelihood of having a first flare. Also, a history of IHD [HR 1.12 (95% CI 1.06, 1.19)], hypertension [HR 1.15 (95% CI 1.10, 1.20)] and renal failure [HR 1.33 (95% CI 1.20, 1.48)] were independently associated with a higher risk of a first post-diagnosis gout flare. Notably, the HRs associated with obesity and history of hypertension were considerably higher in females compared with males. Use of allopurinol within the first 30 days after gout initial diagnosis was associated with a lower HR of first post-diagnosis flare [in overall population, HR 0.80 (95% CI 0.75, 0.85)].

Time to first flare and clinical manifestation

We investigated the association between the time to first post-diagnosis flare with the number of flares during the follow-up. The median time to first flare in gout patients with one flare, two flares and three or more flares was, respectively, 1.02, 0.78 and 0.62 years ($P < 0.0001$), suggesting that individuals with three or more flares during the whole follow-up period were more likely to have their first post-diagnosis flare earlier.

Discussion

This cohort study, which included 23 857 newly diagnosed patients with gout from a primary-care setting, showed that more than one-third of the patients with gout experienced at least one flare or more as a clinical manifestation of gout over a mean observation period of 3.8 years. Notably, age was an independent risk factor of developing a first post-diagnosis gout flare in women only. In contrast, male gender, obesity, a history of IHD and chronic renal failure as well as lifestyle characteristics such as high alcohol consumption were all associated with increased risk of first post-diagnosis gout flare. Use of allopurinol at baseline was clearly preventive. Notably, a considerable proportion of patients experience flares with prevalent comorbid diseases such as IHDs or hypertension; these conditions may require treatment themselves and, in addition, may make the treatment of acute gout flares more problematic.

Compared with other reports describing frequency of flares in the literature, our patient population comprised the largest number of patients newly diagnosed with gout. In our study, 36.9% of the patients with gout had at least one flare compared with 35% in the study of Sarawate *et al*. [12], 62% in the study of Halpern *et al*. [13] and 41% (within a period of 12 months) in the study of Wu *et al.* [14] (the latter, however, in a population of elderly only). All the aforementioned studies were from the USA and based on claims databases. One study from Europe reported an occurrence of flares of 72 and 41%, among patients with gout from the UK and Germany, respectively [15]. When comparing these numbers, the different

TABLE 3 Association of various socio-demographic and medical characteristics with the frequency of gout flares during follow-up period

Variables	Total	Number of flares (*n*, row%)				
		None	1	2	⩾3	*P*-value
Sex						
Male	17 358	10 522 (60.6)	3788 (21.8)	1608 (9.3)	1440 (8.3)	
Female	6499	4529 (69.7)	1160 (17.9)	410 (6.3)	400 (6.2)	<0.001
Age, (u S.D.), years						
20–49	5211	3199 (61.4)	1077 (20.7)	503 (9.7)	432 (8.3)	
50–59	4761	3011 (63.2)	1029 (21.6)	381 (8.0)	340 (7.1)	
60–69	5547	3489 (62.9)	1123 (20.3)	478 (5.6)	457 (8.2)	
70–79	5533	3428 (62.0)	1179 (21.3)	484 (8.8)	442 (8.0)	
80–89	2805	1924 (68.6)	540 (19.3)	172 (6.1)	169 (6.0)	<0.001
BMI, kg/m^2						
15–19	297	231 (77.8)	38 (12.8)	16 (5.4)	12 (4.0)	
20–24	4045	2691 (66.5)	772 (19.1)	301 (7.4)	281 (7.0)	
25–29	8799	5499 (62.5)	1858 (21.1)	761 (8.7)	681 (7.7)	
⩾30	6945	4271 (61.5)	1509 (21.7)	613 (8.8)	552 (8.0)	<0.001
Unknown	3771	2359 (62.6)	771 (20.5)	327 (8.7)	314 (8.3)	
Number of GP visits						
0–4	6720	4158 (61.9)	1462 (21.8)	586 (8.7)	514 (7.7)	
5–9	6543	4150 (63.4)	1352 (20.7)	563 (8.6)	478 (7.3)	
10–19	7032	4513 (64.2)	1436 (20.4)	568 (8.1)	515 (7.3)	
⩾20	3562	2230 (62.6)	698 (19.6)	301 (8.4)	333 (9.4)	0.002
Smoking						
Never	11 163	6983 (62.6)	2326 (20.8)	972 (8.7)	882 (7.9)	
Current	3673	2406 (65.5)	727 (19.8)	275 (7.5)	265 (7.2)	
Former	7570	4814 (63.6)	1573 (20.8)	627 (8.3)	556 (7.3)	0.041
Unknown	1451	848 (58.4)	322 (22.2)	144 (9.9)	137 (9.4)	
Alcohol, U/week[a]						
Non-use	7306	4818 (66.0)	1403 (19.2)	559 (7.7)	526 (7.2)	
1–9	5705	3655 (64.1)	1178 (20.7)	464 (8.1)	408 (7.2)	
10–24	4922	2970 (60.3)	1087 (22.1)	473 (9.6)	392 (8.0)	
25–42	1990	1177 (59.2)	471 (23.7)	176 (8.9)	166 (8.3)	
>42	723	383 (53.0)	175 (24.2)	82 (11.3)	83 (11.5)	<0.001
Unknown	3211	2048 (63.8)	634 (19.8)	264 (8.2)	265 (8.3)	
History of cardio-metabolic disease[b]						
No	9114	5909 (64.8)	1793 (19.7)	757 (8.3)	655 (7.2)	
Yes	14 743	9142 (62.0)	3155 (21.4)	1261 (8.6)	1185 (8.1)	<0.001
History of digestive diseases[c]						
No	22 822	14 405 (63.1)	4749 (20.8)	1931 (8.5)	1737 (7.6)	
Yes	1035	646 (62.4)	199 (19.2)	87 (8.4)	103 (10.0)	0.051
History of cardiometabolic or digestive diseases						
No	8829	5729 (64.9)	1739 (19.7)	731 (8.3)	630 (7.1)	
Yes	15 028	9322 (62.0)	3209 (21.4)	1287 (8.6)	1210 (8.0)	<0.001
History of cardio-metabolic and digestive diseases						
No	23 107	14 585 (63.1)	4803 (20.8)	1957 (8.5)	1762 (7.6)	
Yes	750	466 (62.1)	145 (19.3)	61 (8.1)	78 (10.4)	0.057
Allopurinol[d]						
No	20 042	12 482 (62.3)	4163 (20.8)	1758 (8.8)	1639 (8.2)	
Yes	3815	2569 (67.3)	785 (20.6)	260 (6.8)	201 (5.3)	<0.001

[a]1 U = 10 ml of pure ethanol (8 g of alcohol). [b]Cardiometabolic diseases include: hypertension, IHD, cerebrovascular disorders, congestive heart failure, diabetes and chronic renal failure. [c]Digestive diseases include: complicated peptic ulcer, oesophageal complications, chronic hepatic disorders and pancreatic disorders. [d]The drug-use information was collected the first 30 days after gout diagnosis.

TABLE 4 Association of various factors at baseline with the time to the first post-diagnosis flare during follow-up by a Cox proportional hazard model

Variables	Adjustment for multiple covariates[a]		
	HR (95% CI) Overall	HR (95% CI) among men	HR (95% CI) among women
Sex			
Female	1 (Reference)		
Male	1.36 (1.28, 1.43)	–	
Age, years	1 (Reference)	1	1
20–49	0.91 (0.85, 0.97)	0.88 (0.82, 0.94)	1.54 (1.24, 1.92)
50–59	0.93 (0.87, 0.99)	0.87 (0.81, 0.93)	1.66 (1.35, 2.06)
60–69	1.01 (0.94, 1.08)	0.91 (0.84, 0.98)	1.92 (1.56, 2.37)
70–79	1.00 (0.91, 1.09)	0.85 (0.76, 0.95)	1.93 (1.55, 2.40)
80–89			
Number of GP visits			
0–4	1 (Reference)	1	1
5–9	1.04 (0.98, 1.10)	1.03 (0.97, 1.10)	1.30 (1.11, 1.52)
10–19	1.08 (1.02, 1.15)	1.11 (1.04, 1.19)	1.24 (1.06, 1.45)
⩾20	1.31 (1.21, 1.41)	1.41 (1.29, 1.55)	1.33 (1.12, 1.58)
Smoking			
Never	1 (Reference)	1	1
Current	0.88 (0.83, 0.94)	0.90 (0.84, 0.97)	0.86 (0.74, 1.00)
Former	1.01 (0.96, 1.06)	1.03 (0.97, 1.09)	0.98 (0.88, 1.09)
Unknown	1.08 (0.96, 1.20)	1.12 (0.99, 1.26)	0.88 (0.66, 1.16)
Alcohol, U/week[b]			
None	1 (Reference)	1	1
1–9	1.02 (0.96, 1.08)	1.05 (0.98, 1.13)	1.00 (0.90, 1.11)
10–24	1.11 (1.05, 1.18)	1.10 (1.03, 1.18)	1.26 (1.08, 1.48)
25–42	1.15 (1.06, 1.25)	1.12 (1.02, 1.22)	1.84 (1.27, 2.66)
>42	1.41 (1.26, 1.58)	1.39 (1.23, 1.57)	0.93 (0.39, 2.25)
Unknown	0.94 (0.86, 1.04)	0.93 (0.84, 1.04)	1.03 (0.85, 1.24)
BMI, kg/m^2			
15–19	0.73 (0.57, 0.94)	0.77 (0.55, 1.08)	0.79 (0.54, 1.15)
20–24	1 (Reference)	1	1
25–29	1.10 (1.03, 1.17)	1.07 (1.00, 1.15)	1.10 (0.96, 1.27)
⩾30	1.22 (1.14, 1.30)	1.12 (1.04, 1.21)	1.43 (1.25, 1.65)
Unknown	1.13 (1.04, 1.24)	1.09 (0.99, 1.20)	1.17 (0.96, 1.42)
History of IHD			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.12 (1.06, 1.19)	1.13 (1.06, 1.21)	1.12 (1.00, 1.25)
History of hypertension			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.15 (1.10, 1.20)	1.08 (1.02, 1.13)	1.45 (1.30, 1.62)
History of hyperlipidaemia			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.01 (0.95, 1.07)	0.98 (0.92, 1.05)	1.03 (0.92, 1.15)
History of diabetes			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.92 (0.85, 0.99)	0.83 (0.75, 0.92)	1.08 (0.94, 1.23)
History of chronic renal failure			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.33 (1.20, 1.48)	1.30 (1.15, 1.48)	1.43 (1.19, 1.73)
Allopurinol[c]			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.80 (0.75, 0.85)	0.80 (0.75, 0.86)	0.77 (0.68, 0.86)

[a]HR adjusted for sex, age (at start date of follow-up), GP visits (1 year before first-ever diagnosis of gout), smoking, alcohol, BMI, IHD, hypertension, hyperlipidaemia, renal failure and diabetes (anytime before first-ever diagnosis of gout). [b]1 U = 10 ml of pure ethanol (8 g of alcohol). [c]The drug-use information was collected the first 30 days after gout diagnosis.

operational conditions of flare definition as well as difference in the methodology and database used have to be considered. While the studies of Halpern *et al*. [13] and Wu *et al*. [14] used similar definitions of flares and an equal period of grace (30 days) to define new occurrences of flares, the latter information was not available in the studies of Sarawate *et al.* [12] and Annemans *et al.* [15]. Altogether, these studies show that a large proportion of patients with gout have clinical manifestations after the initial diagnosis. In all the studies, the likelihood of having flares was related to serum acid level. It has to be considered, however, that some of the studies only had measurements of serum uric acid levels in a small proportion of subjects.

In an Internet-based prospective case–crossover study involving 232 self-selected participants with a mean age of 52 years, the risk of having at least one attack in a year was 69% [16]. Notably, only 54% of participants always consulted a physician for their gout attacks, 24% did so sometimes and 21% never consulted one. About one-quarter of the patients did not receive adequate treatment. Another study from the UK came to a similar conclusion and found that in addition to suboptimal pharmacological treatment of gout, screening for comorbid cardiovascular risk factors was infrequently performed [5].

Chronic hyperuricaemia is the single most important risk factor for gout as well as for acute flares: unfortunately, we could not take this information into account in our study. However, use of allopurinol at baseline, an established means to lower uric acid levels, was clearly reducing the risk for first flare in our study. In addition to the hereditary causes for uric acid excretion and purine metabolism, several lifestyle factors such as high alcohol consumption, intake of purine-rich food such as meat and obesity are considered the main risk factors for gout [3]. Unfortunately, a strict diet only allows a limited reduction of serum acid levels by ~1–2 mg/dl [17], and most patients depend on additional pharmacological treatment.

In our study, the risk of a first post-diagnosis gout flare was independently associated with cardiometabolic diseases such as hypertension and obesity. As demonstrated in a small study including 164 cases of confirmed gout, lifestyle advice and pharmacological treatment seem poorly offered according to the European League Against Rheumatism recommendations [18]. From a clinical perspective, the effort to adequately manage the underlying comorbidities should be emphasized. On one hand, risk factors such as obesity, hypertension or IHD are partly independent risk factors of flares; on the other, the prevalent co-existence of these factors also limits the use of the long-established standard therapy as many of these patients have relative or absolute contraindications. Some examples are the use of: NSAIDs in patients with peptic ulcer; of glucocorticoids in patients with diabetes; or colchicines in patients with gastrointestinal, renal, hepatic or cardiac disorders. In addition, persistence of gouty attacks in patients properly diagnosed and treated may also reflect lack of adherence to recommended treatment.

When looking at the results of our study, the following limitations have to be considered. Although we used a population-based approach to identify all patients with incident gout, the ascertainment of flares had been based on a pragmatic approach. Colchicine was part of the operational definition of flares and could have led to a minor overestimation when used as prophylaxis at the time of starting allopurinol, but as most patients also had a recorded code for gout the same date as that of colchicine prescription, we have evidence that it had been used for therapeutic purposes in the vast majority of patients. In addition, we could only include flares that led to an encounter with the GP. As not all patients with gout flares consult a physician [17], and because many patients were liable to have taken flare medication previously in their possession without seeking a new gout medication prescription, the incidence of gout attacks may be higher: this should, however, not affect the validity of the identified risk factors. In general, several validation studies have, in addition, shown that the internal validity in THIN with respect to recording of data is accurate and complete [11]. Also, we could not include other data such as serum urate levels or SF analysis as these measurements are seldom obtained in general practice and not routinely recorded in the database. Finally, as most of the treatment for gout takes place in primary care [5], we consider the external validity of our study to be acceptable.

In conclusion, our study of a large cohort of patients with incident gout showed that a large proportion of patients with gout also have comorbid diseases. Obesity and hypertension were common comorbidities among patients who developed flares and a small minority had renal impairment. In addition, several lifestyle factors such as obesity and high alcohol intake were also related to risk of a gout flare and the patients should get advice and help for lifestyle modification. The fact that some of these underlying conditions that could impact on treatment are also independent risk factors for flares, further contribute to the complexity of prevention and treatment of gout flares.

Rheumatology key messages

- A large proportion of patients with gout also have comorbid diseases.
- Gout flares are relatively common among patients with gout.
- Several lifestyle factors and comorbid diseases are also independent risk factors for gout flares.

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