Gout and incidence of twelve cardiovascular diseases: A case-control study including 152 663 individuals with gout and 709 981 matched controls

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Abstract

Background: Gout, a common crystal arthropathy, has been associated with increased cardiovascular risk. We aimed to determine how this risk varies by individual cardiovascular disease across a broad spectrum of conditions.

Methods: We used linked primary and secondary electronic health records from 22 million individuals in the Clinical Practice Research Datalink (CPRD) to assemble a cohort of individuals newly diagnosed with gout between 01/01/2000 and 31/12/2017 and free of cardiovascular diseases up to 12 months after diagnosis, and up to five individuals matched on age, sex, socioeconomic status, and geographical region, with follow-up until 30/06/2019. We investigated the incidence of twelve cardiovascular diseases and used Cox proportional hazards models to examine differences in patients with and without gout. In sensitivity analyses, we further adjusted models for known cardiovascular risk factors (blood pressure, BMI, smoking, cholesterol, type 2 diabetes, CKD, and history of hypertension).

Findings: We identified 152 663 individuals with gout and 709 981 matched controls. Of these, 31 479 people with and 106 520 without gout developed cardiovascular disease during a median follow-up of 6.5 years. Patients with gout had a higher risk of cardiovascular disease than controls: hazard ratio (HR) [95% confidence interval (CI)] 1.58 [1.52, 1.63]. Excess cardiovascular risk was greater in women (HR in women: 1.88 [1.75, 2.02], HR in men: 1.49 [1.43, 1.56]), and was highest in the young (HR in people aged 45 years or less: 2.22 [1.92, 2.57]). Excess risk was visible across all 12 cardiovascular diseases investigated. Patients with gout had almost 3 units higher BMI than matched controls and a considerably higher prevalence of chronic kidney disease, dyslipidaemia, and hypertension. Accounting for blood pressure, BMI, smoking, cholesterol, type 2 diabetes, chronic kidney disease, and history of hypertension, attenuated the strength of the association of gout with cardiovascular disease (adjusted HR 1.31 [1.27, 1.36]).

Interpretation: Patients with gout have a higher risk of developing a broad range of cardiovascular diseases that extend beyond atherosclerotic diseases and include heart failure, arrhythmias, valve disease, and thromboembolic diseases. Relative risks are highest in women and younger individuals. These findings suggest that strategies to reduce cardiovascular risk in patients with gout must evolve and be implemented in clinical practice.

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Keywords: Gout, obesity, inflammation, cardiovascular diseases, heart failure, arrhythmia, thromboembolism, atherosclerosis, risk factor, cohort study, epidemiology, CPRD.

Research in Context

Evidence before this study

We searched PubMed for reports published between Jan 1, 2000, and May 14, 2023, in English, using a broad search strategy including the terms “gout”, “hyperuricaemia”, “cardiovascular risk”, “arrhythmias”, “atrial fibrillation”, “valve disease”, “venous thromboembolism”, “heart failure”, “pericarditis”, “myocarditis” and “infective endocarditis”, and reviewed references of relevant studies and clinical practice guidelines. Several studies reported increased cardiovascular risk in patients with gout. Studies were largely focused on coronary heart disease, stroke, and thromboembolic outcomes in gout, of a small sample size compared to the current study, and variably accounted for classic atherosclerotic risk factors. There were few studies assessing cardiac valve disease, pericarditis, myocarditis, or infective endocarditis risk in gout. We found no studies that comprehensively assessed risk across the complete range of cardiovascular diseases in gout.

Added value of this study

In this large observational population-based study, we found that patients with gout have a 58% greater risk of developing cardiovascular diseases than those without gout. Excess cardiovascular risk was higher in women than men and highest in individuals aged 45 years or less at the time of gout diagnosis. Further, excess risk in gout was visible across the whole cardiovascular disease spectrum, beyond classic atherosclerotic disease, including heart failure, cardiac valve disease, arrhythmias, venous thromboembolism, myocarditis, pericarditis, and infective endocarditis.

Patients with gout had about 3 units higher BMI than matched controls, with BMI differences highest in young individuals. Patients with gout also had a considerably higher prevalence of chronic kidney disease, dyslipidaemia, hypertension, and type 2 diabetes. In sensitivity analyses adjusting for these cardiovascular risk factors, the strength of the associations was attenuated, but gout remained an independent cardiovascular risk factor.

Implications of all the available evidence

Patients with gout have a higher risk of developing a broad range of cardiovascular outcomes that extend beyond atherosclerotic diseases and include heart failure, arrhythmias, valve disease, and thromboembolic diseases. Relative risks are highest in women and younger individuals. Current strategies to reduce cardiovascular risk in patients with gout need to be further developed and implemented. Inclusion of gout into routinely used cardiovascular risk scores, such as Q-risk, and into cardiovascular disease prevention guidelines appears warranted.

Introduction

Gout is a common inflammatory arthritis with a worldwide prevalence of 1-4%.[1] It is characterised by deposition of monosodium urate crystals in the joints and adjacent soft tissues that drive acute inflammation. This leads to intensely painful gouty flares, articular damage,[2] chronic arthritis, and joint destruction, and with this to chronic disability and impaired quality of life[3].

Gout is associated with a greater risk of cardiovascular disease.[4] The degree to which this risk is independent of traditional risk factors including hypertension, chronic kidney disease, obesity, and type 2 diabetes, which are more prevalent in people living with gout, remains unclear. The cardiovascular risk conferred by gout may further vary by age and sex, with some evidence of higher relative risk in women and younger individuals, although the reasons for this remain unknown.[5–7]

Another important question is the extent to which gout is associated with individual cardiovascular diseases. While numerous studies have assessed its association with atherosclerotic cardiovascular disease, there are fewer high-quality studies assessing the association between gout and other cardiovascular diseases, including valve disease, venous thromboembolism, heart failure, pericarditis, or infective endocarditis. This is an important gap since such cardiovascular outcomes are now relatively more common in many high-income countries due to reductions in adverse atherosclerotic outcomes from better control of lipids, blood pressure, and smoking cessation, whereas progressive increases in obesity prevalence have occurred.[8] To date, no large-scale study has simultaneously assessed the association between gout and the full spectrum of cardiovascular diseases.

Through analysis of a large longitudinal database of linked primary and secondary care records with long-term follow-up,[9] we assessed the association of gout with the development of 12 cardiovascular diseases and the degree to which traditional cardiovascular risk factors mediated this association.

Methods

Data source

We used electronic health records from the Clinical Practice Research Datalink (CPRD, GOLD and AURUM datasets) from 1 January 1985 to 30 June 2019.[9,10] The CPRD database contains anonymised patient data from approximately 20% of the current UK population and is broadly representative in terms of age, sex, and ethnicity. CPRD is one of the largest databases of longitudinal medical records from primary care in the world and has been validated for epidemiological research for a broad range of conditions.[9] Primary care records from CPRD were linked to secondary care records from Hospital Episodes Statistics (HES admitted patient care and HES outpatient) data as well as death certificates from the Office for National Statistics (ONS). Linkage was available for a subset of English practices from 1 January 1998 onwards, covering approximately 50% of all CPRD records. Scientific approval for this study was given by the CPRD Independent Scientific Advisory Committee (ISAC).

Case identification

To identify patients with gout and for each cardiovascular condition, we created lists of diagnostic codes from the ICD-10 (International Classification of Diseases 10th revision, used in secondary care and on death certificates), OPCS-4 (Classification of Interventions and Procedures version 4, used in secondary care), and Snomed-CT and Read[11,12] (used in primary care) coding schemes (appendix). Incident diagnoses of gout were defined as the first record of that condition in primary or secondary care records from any diagnostic position.

Study endpoints

The primary endpoints for the analysis were the initial presentation of cardiovascular diseases. To best characterize the broad spectrum of cardiovascular diseases, we examined the following twelve conditions: aortic aneurysm; cardiac arrhythmias (atrial fibrillation and flutter, and supraventricular arrhythmias) and conduction system disease; heart failure; ischaemic heart disease; myocarditis and pericarditis (of non-infectious origin); peripheral arterial disease; infective endocarditis; stroke (ischaemic, haemorrhagic) and transient ischaemic attack; valve diseases (excluding congenital and rheumatic); and venous

thromboembolism or pulmonary embolism. Diseases were considered individually and as a composite outcome of all twelve cardiovascular diseases combined. For the combined analyses, the first recorded cardiovascular disease was used. Incident diagnoses were defined as the first record of that condition in primary care or secondary care from any diagnostic position. Diagnoses recorded on death certificates were not included in main analyses, due to the difficulty to reliability ascertain specific individual cardiovascular diseases investigated in this study (e.g. heart failure, myocarditis, or VTE) from death certificates.

Study population

The general population cohort included all men and women with records labelled as 'acceptable' by CPRD quality control[9], approved for HES and ONS linkage, and registered with their general practice for at least 12 months during the study period (01/01/2000 to 30/06/2019). Deduplication between GOLD and Aurum data sources was applied to exclude records from GOLD that were migrated to Aurum, hence ensuring no record was included in our analysis more than once.

Among these, we defined a gout cohort consisting of patients with incident gout between 01/01/2000 and 31/12/2017, up to 80 years of age at diagnosis, and free of cardiovascular disease until 12 months after incident gout. The 12 months cardiovascular disease-free period was defined to minimise risks of reverse causality. The restriction to individuals aged 80 years or less was set because of a comparatively few number of individuals aged 80 years or more and free of cardiovascular disease, which limited the power of analyses. The index date was defined as the date of incident gout diagnosis plus 12 months. To ensure the inclusion of incident gout diagnoses only, we excluded patients with a gout diagnosis before 01/01/2000 or within the first 12 months of registration with their general practice.

A comparison group was defined consisting of up to five individuals matched on age (±5 years), calendar time (individuals contributing to data within ±2 years of the matched individual's incident gout diagnosis), sex, socioeconomic status, and region, randomly selected amongst individuals free of gout at any time. The index date was defined as the latest of the patient's practice registration date + 12 months and the matched individual diagnosis date. Similarly to the gout cohort, individuals with cardiovascular disease before the index date were excluded.

Time at risk was defined to start on the individual's index date and to end on the earliest of the study end date (30/06/2019), patients' transfer out of practice date, practice's last collection date, incident cardiovascular disease, or patient death as listed in the ONS record. Time at risk was calculated separately for each cardiovascular disease investigated.

Covariates

Covariates were selected to account for known cardiovascular risk factors. Baseline characteristics (systolic and diastolic blood pressure, smoking status, cholesterol (total cholesterol/high-density lipoprotein ratio), and body mass index (BMI)) were abstracted from electronic health records as the most recent measurement within 2 years before the index date. We further present the prevalence of chronic kidney disease, dyslipidaemia, hypertension, obesity, and type 2 diabetes, as the percentage of patients with a corresponding diagnosis recorded in their primary care or hospital discharge record, prior to their index date. Socioeconomic status was defined as the Index of Multiple Deprivation (IMD) 2015 quintile,[13] a composite measure of relative deprivation at a small area level, covering an average population of 1500 people, ranked in ascending order of deprivation score and grouped in equal fifths, with quintiles 1 and 5 representing the least and most deprived areas, respectively. Data on sex are as reported by the patient when they registered with their general practitioner. Region refers to geographical region, reflecting the former geographical division of the National Health Service into 10 strategic health authorities in England.[9] Ethnicity was extracted from both primary and secondary care records. When ethnicity differed between primary and secondary care records, secondary care data was used. Finally, we extracted information on cardiovascular prevention therapies, including lipid-regulating drugs, antihypertensives, and diuretics, as the number of patients with at least two prescriptions of that specific drug class prior to the index date.

Statistical analyses

Baseline characteristics are presented as frequencies (%) for categorical data, medians and interquartile range (IQR) for non-normally distributed continuous data, or means and standard deviation (SD) for normally distributed continuous data for each cohort.

Missing values of blood pressure, smoking status, cholesterol, and BMI were imputed using multiple imputation by chained equations (MICE) with 5 imputed datasets.[14] Covariates values outside of the 2 years prior to the index date were used as predictor variables in the imputation model. Considerations on the missing data mechanisms are provided in the supplement. For clinical diagnoses, if no mention of a specific disease was ever recorded, then the patient was assumed to be free from the disease. Other variables (age, sex, socioeconomic status, region, and practice registration dates) were complete in the studied dataset.

Incidence rates of cardiovascular events per 1 000 years at risk were calculated in patients with and without gout, overall as well as by subgroup of age, sex, socioeconomic status, and calendar year. We used Cox proportional hazards models and calculated hazard ratios (HR) and corresponding 95% confidence intervals (CI) to compare the risk of incident cardiovascular disease in patients with gout and matched controls. Models were clustered by matching sets. The proportional hazards assumption was inspected visually. Cumulative incidence plots were created using the Kaplan-Meier method and censored for time at risk. Estimates and standard errors of adjusted analyses were obtained using Rubin's rules to combine the results of the separate analyses of individual imputed data sets.

To test whether observed associations could be due to increased medical attention leading to higher rates of diagnoses in individuals regularly followed up for a chronic condition, we performed sensitivity analyses that restricted cardiovascular diseases to diagnoses recorded as the primary reason for hospital admission as well as mortality with cardiovascular disease listed as the first cause of death. To test whether excess cardiovascular risk associated with gout changed over time, we calculated hazard ratios capping follow-up duration to a maximum of 2 years and investigated differences by time periods. Finally, to test the extent to which known atherosclerotic risk factors might explain the observed associations, we performed further sensitivity analyses, in which we adjusted models for blood pressure, BMI, smoking status, cholesterol, type 2 diabetes, chronic kidney disease, and history of hypertension.

To further examine the association between BMI and gout, we performed post hoc analyses to describe mean differences in baseline BMI between patients with and without gout and 95% t-test confidence intervals, stratified by age and sex. These analyses were performed using imputed BMI measurements. Sensitivity analyses were performed restricting individuals to those with a valid BMI measurement within 2 years of the index date and showed broadly similar trends. Due to the low number of patients with gout under the age of 20 years, these analyses were restricted to individuals aged 20 years and older.

Study findings are reported in accordance with the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) recommendations.[15] Statistical analyses were performed in R, version 4.2.2, and validated with SAS (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among the 22 009 375 individuals included in the study, we identified a total of 292 424 patients with newly diagnosed gout between 01/01/2000 and 31/12/2017. Of those, 152 663 individuals were younger than 80 years of age at diagnosis, free of cardiovascular disease until 12 months after incident gout, and constituted the final gout cohort. Among participants, 355 760 (41.2%) had missing data on blood pressure, 408 986 (47.4%) on smoking status, 529 154 (61.3%) for BMI, and 624 652 (72.4%) for cholesterol. Rates of missing data were higher in the control group compared to those with gout (**Table 1**).

The mean (SD) age at gout diagnosis was 56.4 (13.3) years, and 21% (n = 32 339) were women. The matched cohort comprised 709 981 individuals and presented with similar distributions of age, sex, socioeconomic status, and region. Patients with gout were about three BMI units heavier on average than matched controls

and had a higher prevalence of chronic kidney disease, dyslipidaemia, hypertension, obesity, and type 2 diabetes.

Many baseline characteristics, such as age, comorbidities and BMI, differed significantly between men and women. Women were on average older at the time of diagnosis of gout (mean age at diagnosis was 62.5 (12.8) years in women and 54.6 (12.9) years in men), had more comorbidities, and had greater baseline BMI differences compared to controls than men (at baseline, women were on average 3.9 BMI units (9.9kg) heavier than controls, compared to 2.6 BMI units (8.2kg) in men) (**Table S1**).

Cardiovascular therapies were 2 to 3 times more often prescribed in gout patients than in controls. For example, in women with gout, 46% (n = 14 896) had been prescribed a thiaziade diuretic, compared to 20% (n = 30 154) of female controls. Similar differences were observed for lipid-lowering drugs and other antihypertensives. Men generally had lower baseline rates of cardiovascular therapy, but presented with similarly marked differences between gout and control patients.

Among participants, 31 479 people with and 106 520 without gout developed cardiovascular disease during a median follow-up of 6.5 years. Incidence rates of cardiovascular diseases per 1 000 patient-years were 31.7 among patients with gout and 20.1 among those without gout, resulting in a 58% greater relative risk of all cardiovascular diseases in patients with gout compared to those without (HR: 1.58 [1.52, 1.63]). Higher risks of cardiovascular disease in gout compared to controls was visible across all subgroups of sex, age, socioeconomic status, and time, but the elevated risk was greatest in younger individuals (HR in patients <45 years: 2.22 [1.92, 2.57] vs. HR in patients aged >75 years: 1.40 [1.30, 1.51]). The association between gout and cardiovascular risk was more pronounced in women than men, with women with gout at 88% greater risk of cardiovascular disease compared to women without gout (women: HR 1.88 [1.75, 2.02]; men HR 1.49 [1.43, 1.56]) (**Figure 1**).

Although non-significant, time trend analyses suggest that the elevated risk of cardiovascular disease associated with gout may have declined in later years of the study. Sensitivity analyses capped at two years of follow-up showed that this finding was largely explained by the shorter follow-up duration available for patients diagnosed in later years (**Figure S1**).

In adjusted analyses, traditional cardiovascular risk factors partly explained the observed associations. While data on covariates were partly missing, adjusting for blood pressure, smoking, BMI, cholesterol, type 2 diabetes, chronic kidney disease, and history of hypertension, attenuated but did not eliminate the excess risk related to gout (adjusted HR of cardiovascular disease among patients with gout compared to those without gout: 1.31 [1.27, 1.36]) (**Figure 1**).

Sensitivity analyses further showed that patients with gout also had a higher risk of hospital admissions for cardiovascular causes (unadjusted HR: 1.33 [1.28, 1.38], adjusted HR 1.10 [1.05, 1.15]) as well as higher mortality from cardiovascular causes (HR: 1.41 [1.24, 1.60]), compared to individuals without gout. The higher risk of mortality appeared to be largely explained by traditional risk factors (adjusted HR 1.00 [0.90, 1.11]) (**Figure 1**), particularly hypertension, type 2 diabetes, chronic kidney disease, and smoking.

Cardiovascular risk associated with gout was higher across the full spectrum of cardiovascular diseases (**Figure 2**). Compared to individuals without gout, patients with gout were at 45% greater risk of stroke (HR 1.45 [1.34, 1.57]), 52% greater risk of ischaemic heart disease (HR 1.52 [1.43, 1.61]) and peripheral arterial disease (HR 1.52 [1.37, 1.68]), 57% greater risk of aortic aneurysm (HR 1.57 [1.36, 1.82]), 61% greater risk of myocarditis and pericarditis (HR 1.61 [1.12, 2.32]), and 83% greater risk of infective endocarditis (HR 1.83 [1.38, 2.43]). The risk of cardiac arrhythmias was also elevated with gout associated with 83% greater risk of atrial fibrillation or flutter (HR 1.83 [1.73, 1.93]), 88% greater risk of conduction system disease (HR 1.88 [1.77, 2.00]), and 59% greater risk of supraventricular arrhythmias (HR 1.59 [1.30, 1.95]) compared to those without gout. Venous thromboembolism / pulmonary embolism risk was also higher in gout (HR 1.69 [1.53, 1.88]), as was the risk of heart failure (HR 1.85 [1.74, 1.98]), and valve diseases (HR 1.85 [1.72, 1.98]).

Individuals with gout were on average 2.9kg/m^2 BMI units heavier compared to matched controls. Analysis by age and sex revealed that men diagnosed with gout at a young age (aged 20-24) were on average 4.3kg/m^2 BMI units heavier than their contemporaries without gout, and BMI differences attenuated with increasing

age at gout diagnosis. In contrast, women with gout had an average 3.9 units higher BMI than controls, regardless of which age they were diagnosed at (**Figure S2**).

Discussion

Findings from this large-scale population-based study confirm evidence from previous studies[6,16,17] that gout confers increased cardiovascular risk and extends these by showing that gout is associated with an excess risk across the whole spectrum of cardiovascular diseases - being higher for incident heart failure than incident atherosclerotic disease - and is particularly pronounced in women and younger individuals.

The risks associated with gout were similar in magnitude to those associated with a range of immune-mediated inflammatory conditions in the same dataset.[18] Here too, our results show that gout is associated with increased risk across a broad range of cardiovascular diseases, in addition to atherosclerotic disease. The present findings complement several recent studies that have shown associations between gout flares and cardiovascular events, particularly myocardial infarction and venous thromboembolism[19,20,21].

One surprising finding was that cardiac arrhythmias presented even stronger associations with gout than ischaemic heart disease. In our study, estimates of the association between gout and atrial fibrillation were higher than previously reported,[22,23] yet in line with several recent studies demonstrating an association between inflammation and incident atrial fibrillation or flutter, often suggested to be linked to inflammation-mediated atrial remodelling and fibrosis.[24,25] Higher uric acid levels in the general population, free of cardiovascular disease at baseline, have also recently been associated with increased risk of new-onset atrial fibrillation.[26] Excess adiposity is also causally associated with greater atrial fibrillation risk,[27] as is alcohol,[28] and as both are strong risk factors for gout, these 'upstream' factors are likely relevant to the risk of atrial fibrillation. Even so, further studies are needed to confirm potential mechanistic pathways between gout and AF.

While the absolute risk of cardiovascular disease increases with age, our findings show that gout appears to amplify this risk more in younger individuals, such that a young person with gout has over twice the risk of cardiovascular disease compared to a similarly aged person without gout. Such elevated relative risk has been noted in other inflammatory diseases[18] and may relate to a lower baseline cardiovascular risk in younger individuals compared to older individuals with more cardiovascular disease due to the accumulation of classic risk factors over time. BMI differences between individuals with gout and controls were higher in those diagnosed with gout at a younger age compared to those diagnosed with gout later in life; this may also contribute to enhanced cardiovascular risk in younger individuals with gout. A similar pattern (although somewhat steeper) was reported for type 2 diabetes where younger-onset type 2 diabetes is estimated to lead to far greater loss in life expectancy than when type 2 diabetes develops at older ages.[29,30]

Gout contributed to a greater relative risk of cardiovascular disease in women than men. The reasons for this are not entirely clear but may relate to the phenotype of female patients with gout, who tend to have higher serum urate levels[31] and, as we have shown, more comorbidities, including chronic kidney disease, hypertension, dyslipidaemia, obesity, and type 2 diabetes, likely due, at least in part, to women's older age at the time of gout diagnosis than men (**Table S1**). Our analysis also showed that women with gout have higher baseline BMI rates than men, at any age – a finding that may in part explain the high excess cardiovascular risk observed in women with gout, especially as aggregated exposure to excess weight over years contributes to many chronic complications.[32]

Importantly, the observed excess cardiovascular risk was not fully explained by traditional cardiovascular risk factors, such as age, sex, socioeconomic status, blood pressure, BMI, smoking, cholesterol, or type 2 diabetes. However in our study, many of these risk factors were missing to a significant extent, and other important risk factors (such as activity levels, family history of CVD and alcohol intake) were unavailable, and these findings must be interpreted with caution. Another important aspect is the whether and how the observed association between gout and cardiovascular outcomes is potentially influenced by medications typically used in the treatment of gout. Further studies are needed to investigate cardiovascular side effects of these drugs, such as corticosteroids, NSAIDs or anti-inflammatory drugs, and the complex interplay between beneficial effects, such as on dampening inflammation, and potentially harmful adverse effects.[33]

Our findings are consistent with the hypothesis that chronic inflammation, traditional atherosclerotic risk factors, and associated comorbidities all play a role in cardiovascular risk associated with gout. The role of urate in cardiovascular disease is equivocal. Some speculate that hyperuricaemia contributes to endothelial dysfunction from the generation of reactive oxygen species, inhibition of nitric oxide production[34] and increased blood pressure[35]. However, a review of several Mendelian randomisation studies concluded that serum urate is not causal for hard clinical cardiometabolic renal endpoints, including coronary heart disease, stroke, and type 2 diabetes.[36] Moreover, although some observational studies have suggested that allopurinol, a xanthine oxidase inhibitor that lowers uric acid, could have cardioprotective effects in patients with gout,[37] a recent large scale randomised trial has shown that allopurinol did not reduce cardiovascular risk in patients with ischaemic heart disease and no history of gout.[38]

Finally, the high prevalence of diuretic use in patients with gout in our study, with 46% of women with gout having a history of thiazide prescriptions, is striking and in line with prior evidence of diuretic-induced gout.[39,40] There is evidence to suggest the risk of gout may be lower with calcium channel blockers or losartan, [41] and current guidelines for management of gout from the British Society for Rheumatology (BSR) and the European Society of Hypertension recommend considering an alternative antihypertensive agent to diuretics.[42,43]

A key strength of this study is the selection of a large and representative cohort from primary and secondary care with extensive longitudinal follow-up of a broad range of cardiovascular diseases. Our large sample size allowed us to stratify analyses to assess how cardiovascular risk in gout may vary with age, sex, socioeconomic status, and time, as well as adjust models for traditional risk factors. The use of routinely reported diagnoses captured the burden of disease as experienced by physicians and health services, and increases the generalisability of our findings. We excluded individuals with baseline cardiovascular disease including up to one year after their gout diagnosis to minimise the risk of reverse causality.

Limitations include that we were unable to account for the effect of concomitant medications such as NSAIDs, corticosteroids, colchicine or allopurinol, on the association of gout with cardiovascular risk. Such analyses of non-randomised treatment can be confounded by the indication for treatment, wherein it is difficult to differentiate the effects of the treatment from underlying disease severity. The substantial amounts of missingness in blood pressure, smoking, BMI, and cholesterol measurements, and the unavailability of additional data relevant to cardiovascular risk, such as information on activity levels, family history of CVD, alcohol intake or diet, mean that our adjusted sensitivity analyses must be interpreted with caution. As with other database studies utilising electronic health records, there is a possibility of misdiagnoses or miscoding. However, the validity of diagnoses in the CPRD dataset has been well studied with a meta-analysis of over 200 publications showing an average positive predictive value of 89% for a broad range of conditions.[44] Results from our sensitivity analyses restricted to cardiovascular diseases diagnosed in secondary care (i.e. hospitalisations due to cardiovascular disease and deaths due to cardiovascular disease) further confirm the validity and robustness of our findings.

Finally, the cumulative incidence of some outcomes e.g. myocarditis, pericarditis, and infective endocarditis was low; underlying biological mechanisms are not well understood, and the association of gout with these outcomes should be interpreted with caution and confirmed in future studies.

In conclusion, patients with gout have a higher risk of developing a range of cardiovascular outcomes, with the relative risks being higher in women and younger individuals. Excess risks appear to be only partly explained by traditional cardiovascular risk factors. As such, the addition of gout into routinely used cardiovascular risk scores, such as Q-risk, and its inclusion in cardiovascular disease prevention guidelines appears warranted. Strategies to reduce cardiovascular risk in patients with gout need to be further developed and implemented.

Contributions

NC, NS, LDF and JJVM conceived and designed the study. NC, GM, and GV designed the statistical analysis plan. NC and GM performed the statistical analysis. All authors contributed to interpreting the results, drafting the manuscript, and the revisions. NC, NS, LDF, GM, and GV had full access to the data in the study and had final responsibility for the decision to submit for publication. NC, GM, and GV had permission to access the raw data and NC and GM verified the raw data (CRPD requests that access to raw data is given only as absolutely necessary). All authors gave final approval of the version to be published and accept responsibility to submit the manuscript for publication.

Declarations of interest

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Data sharing

Access to CPRD data is conditional to a license agreement and protocol approval that is overseen by CPRD's Research Data Governance (RDG) Process. A guide to access is provided on the CPRD website (https://cprd.com/data-access).

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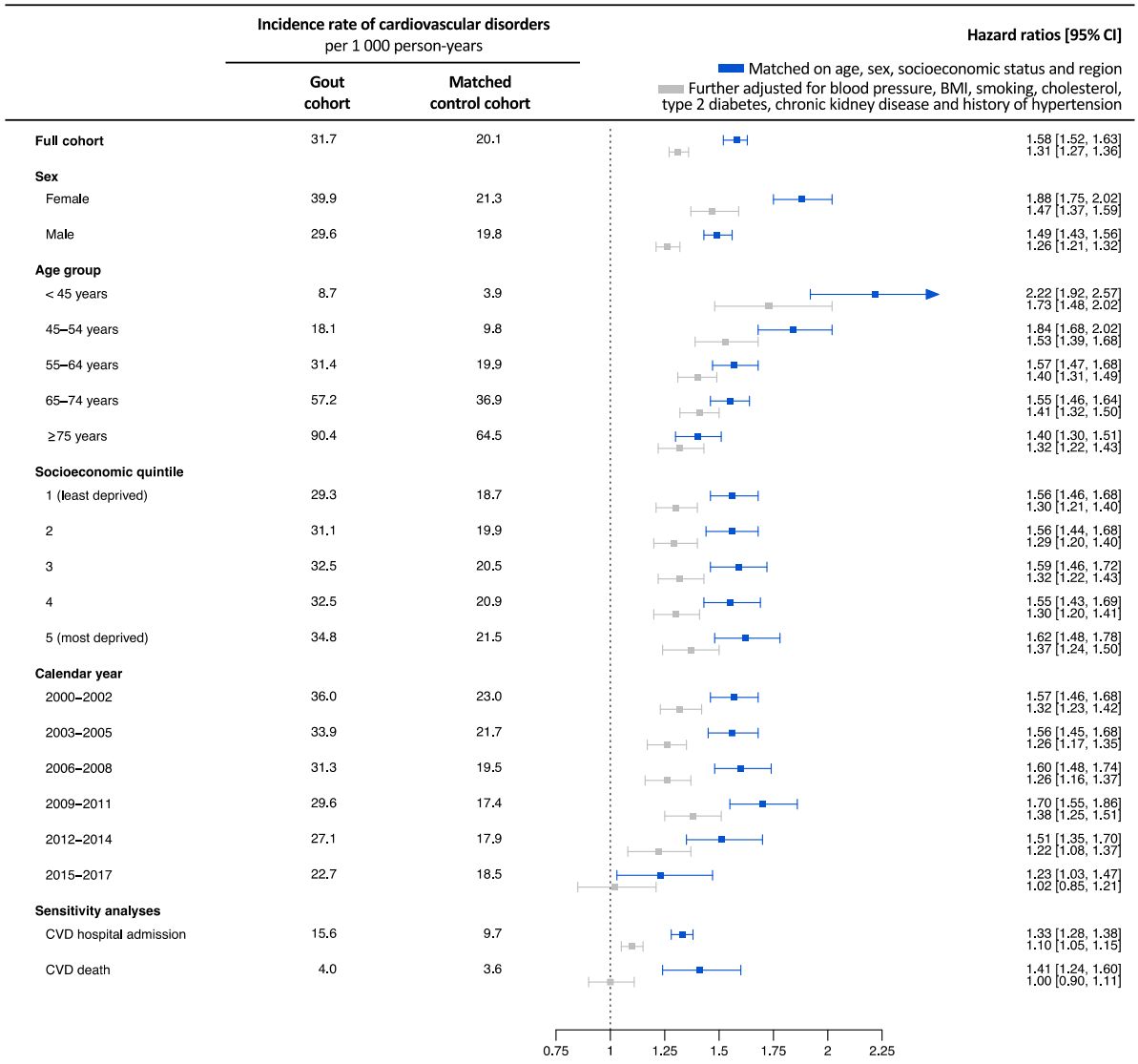
538 **Table1**: Baseline characteristics of patients with incident gout and matched control cohort.
539

	Gout cohort (N= 152 663)	Matched control cohort (N= 709 981)	Overall (N= 862 644)
Age at index (years)			
Mean (SD)	56.2 (13.3)	56.5 (13.2)	56.4 (13.2)
Female sex	32 339 (21.2%)	148 979 (21.0%)	181 318 (21.0%)
Ethnicity			
African/Caribbean	3 270 (2.3%)	11 422 (1.9%)	14 692 (2.0%)
Asian	5 647 (4.0%)	22 309 (3.7%)	27 956 (3.8%)
Mixed or other	11 360 (8.0%)	44 969 (7.5%)	56 329 (7.6%)
White	121 651 (85.7%)	519 129 (86.8%)	640 780 (86.6%)
Missing	10 735 (7.0%)	112 152 (15.8%)	122 887 (14.2%)
Socioeconomic status quintile			
1 (least deprived)	38 107 (25.0%)	178 872 (25.2%)	216 979 (25.2%)
2	33 745 (22.1%)	157 231 (22.1%)	190 976 (22.1%)
3	30 830 (20.2%)	142 916 (20.1%)	173 746 (20.1%)
4	27 136 (17.8%)	125 694 (17.7%)	152 830 (17.7%)
5 (most deprived)	22 845 (15.0%)	105 268 (14.8%)	128 113 (14.9%)
Time at risk (years)			
Mean (SD)	6.46 (4.63)	7.41 (5.03)	7.24 (4.98)
Systolic blood pressure (mmHg)			
Mean (SD)	137 (15.5)	135 (16.1)	135 (16.0)
Missing (%)	40 015 (26.2%)	315 745 (44.5%)	355 760 (41.2%)
Diastolic blood pressure (mmHg)			
Mean (SD)	81.3 (9.78)	79.8 (9.44)	80.1 (9.54)
Missing (%)	40 030 (26.2%)	315 679 (44.5%)	355 709 (41.2%)
Body mass index (kg/m^2)			
Mean (SD)	30.7 (5.77)	27.8 (5.17)	28.4 (5.43)
Missing (%)	84 242 (55.2%)	444 912 (62.7%)	529 154 (61.3%)
Cholesterol (total cholesterol/high-density lipoprotein ratio)			
Mean (SD)	4.24 (1.29)	3.95 (1.24)	4.02 (1.26)
Missing (%)	94 077 (61.6%)	530 575 (74.7%)	624 652 (72.4%)
Smoking status			
Current smoker	17 360 (18.5%)	86 482 (24.1%)	103 842 (22.9%)
Former smoker	30 629 (32.6%)	103 874 (28.9%)	134 503 (29.6%)
Never smoker	46 081 (49.0%)	169 232 (47.1%)	215 313 (47.5%)
Missing (%)	58 593 (38.4%)	350 393 (49.4%)	408 986 (47.4%)
Comorbidities			
Chronic kidney disease	13 042 (8.5%)	16 334 (2.3%)	29 376 (3.4%)
Dyslipidaemia	19 422 (12.7%)	47 570 (6.7%)	66 992 (7.8%)
Hypertension	61 468 (40.3%)	142 502 (20.1%)	203 970 (23.6%)
Obesity	15 542 (10.2%)	27 165 (3.8%)	42 707 (5.0%)
Type 2 diabetes	12 016 (7.9%)	38 531 (5.4%)	50 547 (5.9%)

	Gout cohort (N= 152 663)	Matched control cohort (N= 709 981)	Overall (N= 862 644)
Cardiovascular prevention therapy			
Statins, fibrates or other lipid-regulating drugs	34 306 (22.5%)	88 348 (12.4%)	122 654 (14.2%)
Anti-hypertensives			
ACE- inhibitors or ARB	44 173 (28.9%)	88 742 (12.5%)	132 915 (15.4%)
Alpha adrenoceptor antagonists	8 945 (5.9%)	16 782 (2.4%)	25 727 (3.0%)
Beta blockers	30 552 (20.0%)	67 975 (9.6%)	98 527 (11.4%)
Calcium-channel blockers (dihydropyridines)	30 471 (20.0%)	64 305 (9.1%)	94 776 (11.0%)
Calcium-channel blockers (non-dihydropyridines)	2 238 (1.5%)	4 569 (0.6%)	6 807 (0.8%)
Mineralocorticoid receptor antagonists	996 (0.7%)	1 712 (0.2%)	2 708 (0.3%)
Diuretics			
Loop diuretics	8 217 (5.4%)	13 425 (1.9%)	21 642 (2.5%)
Potassium-sparing diuretics	3 095 (2.0%)	6 135 (0.9%)	9 230 (1.1%)
Thiazides	37 749 (24.7%)	73 049 (10.3%)	110 798 (12.8%)

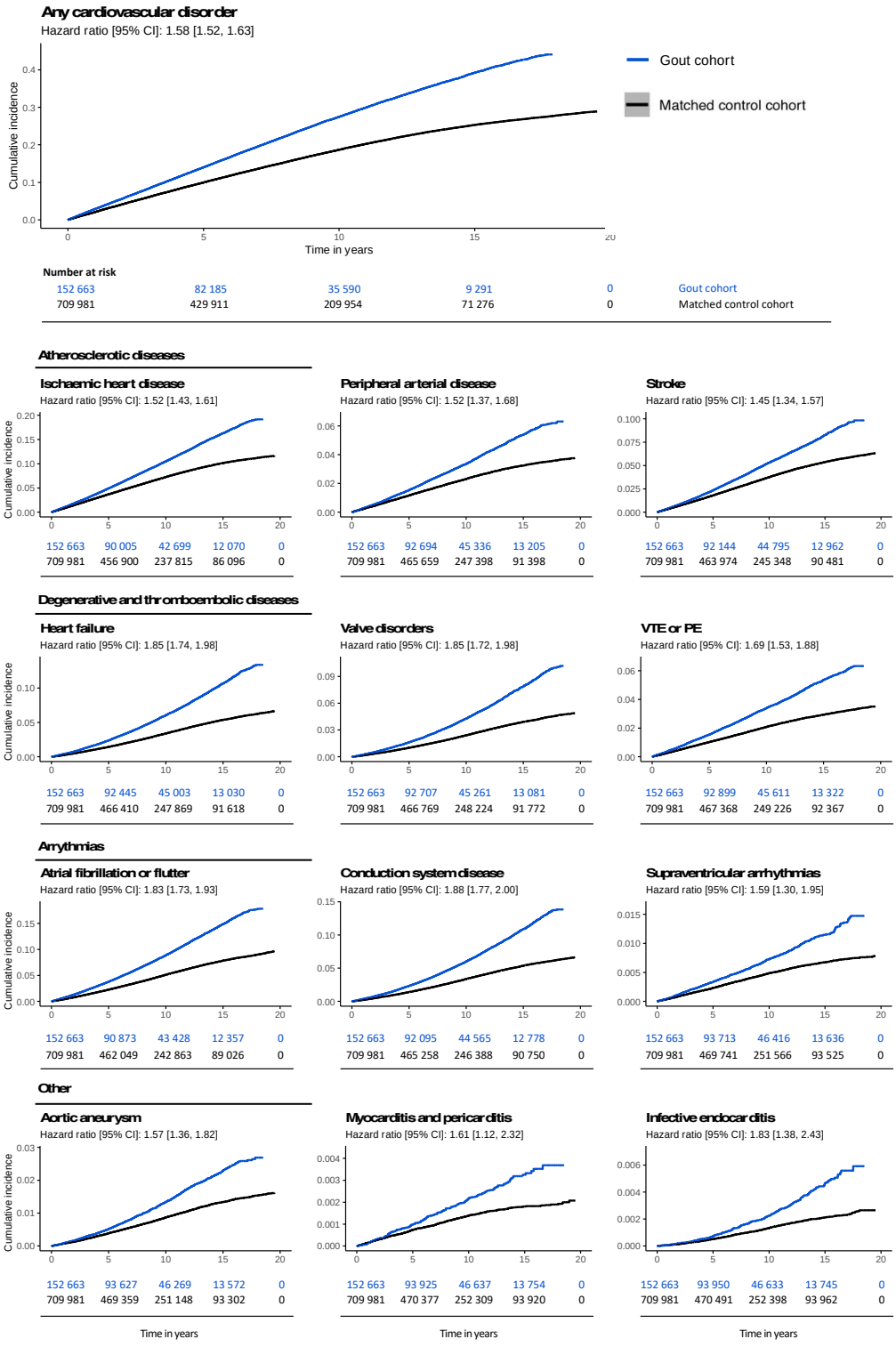
For variables with missing entries, summary statistics present observed values alongside the percentage of missing values (missing within two years prior to index). Socioeconomic status was defined as the Index of Multiple Deprivation (IMD) 2015 quintile. Prevalence of cardiovascular prevention therapies refer to the percentage of patients with at least 2 prescriptions before index date. ACE- inhibitors = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin II Receptor Blockers.

Figure 1: Incidence rates and hazard ratios of cardiovascular disorders among patients with gout and matched controls.



Socioeconomic status (SES) refers to Index of Multiple Deprivation (IMD) 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived quintile. Calendar year refers to the year individuals were included in the study. Cardiovascular hospital admission refers to hospital admissions with cardiovascular disease as the primary admission diagnosis. Cardiovascular death refers to death with cardiovascular disease listed as the primary cause of death. Abbreviations BP = systolic and diastolic blood pressure; BMI = Body Mass Index; T2 diabetes = type 2 diabetes.

Figure 2: Cumulative incidence of cardiovascular disease among patients with gout compared to matched controls. Stratified by individual cardiovascular disorders.



Hazard ratios and corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazards models clustered by matching set, and compared incident cardiovascular disease among patients with gout compared to controls matched for age, calendar year, sex, socioeconomic status, and region.