TITLE PAGE

Title Association Between Gout Flare and Subsequent Cardiovascular Events Among Patients with Gout

Subtitle Gout Flare and Cardiovascular Events

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KEY POINTS

Question

Among patients with gout, is there a transient increase in the risk of cardiovascular events after gout flares?

Findings

In this case-control study that included 62574 participants with gout, those who experienced a cardiovascular event, compared to those who did not experience such an event, had significantly greater odds of a recent gout flare in the prior 0-60 and 61-120 days [adjusted OR (aOR) for 0-60 days, 1.93; aOR for 61-120 days, 1.57].

Meaning

These findings suggest gout flares are associated with a transient increase in cardiovascular events following the flare.

ABSTRACT

Importance

Gout is associated with cardiovascular diseases. The temporal association between gout flares and cardiovascular events has not been investigated.

Objective

To investigate whether there is a transient increase in risk of cardiovascular events after a recent gout flare.

Design, setting and participants

A retrospective observational study was conducted using electronic health records from the Clinical Practice Research Datalink in England between January 1, 1997, and December 31, 2020. A multivariable nested case-control study, and self-controlled case series adjusted for season and age were performed among 62574 patients with gout, and 1421 patients with gout flare and cardiovascular event, respectively.

Exposures

Gout flares were ascertained using hospitalization, primary-care outpatient consultation and prescription records.

Main Outcomes and Measures

The primary outcome was a cardiovascular event, defined as an acute myocardial infarction or stroke. Association with recent prior gout flares was measured using adjusted odds ratios (aOR) and adjusted incidence rate ratios (aIRR) with 95% confidence intervals (95%CI) in a nested case-control study and a self-controlled case series, respectively.

Results

Among patients with a new diagnosis of gout (mean age 76.5 years, 69.3% men), 10475 patients with subsequent cardiovascular events were matched to 52099 patients without cardiovascular events. Patients with cardiovascular events, compared to those without cardiovascular events, had significantly higher odds of gout flare within the prior 0-60 days (204/10475 (2.0%) vs 743/52099 (1.4%); aOR, 1.93 (95%CI, 1.57-2.38)) and 61-120 days (170/10475 (1.6%) vs 628/52099 (1.2%); aOR, 1.57 (95%CI, 1.26-1.96). There was no

significant difference in the odds of gout flare within the prior 121-180 days (148/10475 (1.4%) vs 662/52099 (1.3%); aOR, 1.06 (95%CI, 0.84-1.34)).

In the self-controlled case series (N=1421), cardiovascular event rates (95%CI) were 2.49 (2.16-2.82); 2.16 (1.85-2.47); 1.70 (1.42-1.98)/1000 person-days during 0-60, 61-120, 121-180 days after gout flare compared to 1.32 (1.23-1.41)/1000 person-days during the 150 days before and 181-540 days after the gout flare. Compared with 150 days before and 181-540 days after a gout flare, incidence rate differences (95%CI) and aIRRs (95%CI) for cardiovascular events were 1.17 (0.83-1.52), 0.84 (0.52-1.17), 0.38 (0.09-0.67)/1000 person-days, and 1.89 (1.54-2.30); 1.64 (1.45-1.86); 1.29 (1.02-1.64) within 0-60, 61-120, and 121-180 days after a gout flare, respectively.

Conclusions and Relevance

Among individuals with gout, those who experienced a cardiovascular event, compared with those who did not experience such an event, had significantly higher odds of a recent gout flare in the preceding days. These findings suggest gout flares are associated with a transient increase in cardiovascular events following the flare.

INTRODUCTION Cardiovascular disease is a leading cause of mortality and accounted for 19 million deaths globally in the year 2019 [1]. In addition to traditional cardiovascular risk factors, inflammation is an important risk-factor for cardiovascular diseases [2]. Gout is a common inflammatory condition that affected approximately 4% of the USA general population in 2016 and is particularly prevalent in older age groups [3,4]. Gout is characterized by recurrent episodes of acute inflammatory arthritis [5]. Patients with gout have higher rates of cardiovascular diseases, independent of traditional cardiovascular risk-factors [6–9].

Gout is characterized by low-grade inflammation with elevated concentration of pro-inflammatory cytokines and reactive oxygen species, formation of neutrophil extracellular traps, endothelial dysfunction and platelet hyperactivity that may precipitate atherothrombosis [10]. Gout flares are characterized by inflammation due to activation of the NALP-3 inflammasome. In a randomized clinical trial, blocking the NALP-3 inflammasome prevented recurrent cardiovascular events [10,11]. Therefore, this study assessed whether gout flares were associated with a transient increase in rates of cardiovascular events (i.e., acute myocardial infarction and stroke).

METHODS

Study setting The Clinical Practice Research Datalink is a longitudinal database of anonymized health records of approximately 15 million people across the United Kingdom from over 700 general practices that contains data on socio-demographic and lifestyle factors, diagnoses, investigations, and prescriptions issued in primary-care from people representative of the UK population [12]. Dates and causes of death are available through individual patient linkages with Office for National Statistics data, and for England, linkage with Hospital Episode Statistics provides dates of hospitalization and discharge diagnoses [12].

This study was approved by Clinical Practice Research Datalink's Research Data Governance (protocol 20_000233). Clinical Practice Research Datalink has overarching Research Ethics Committee approval for research studies using anonymous data (Reference 05/MRE04/87). Practices that contributed data to the Clinical Practice Research Datalink consented to using anonymized patient data for approved research projects and additional consent was not required prior to individual studies.

Study design and participants For the analyses reported in this article, data were analyzed using a nested case-control study and also a self-controlled case series, in which patients served as their own controls. Patients with a new diagnosis of gout at age ≥18 years who contributed research-quality data to the Clinical Practice Research Datalink were included. Those with <1-year registration in the database before the first gout diagnosis were excluded. This excluded patients with long-standing gout from entering the study as a patient with newly diagnosed gout [13]. The study period was from January 1, 1997, to December 31, 2020.

Nested case control study

Definition of cases Cases were patients diagnosed with cardiovascular events. Case status was defined as the first cardiovascular event after gout diagnosis. Cardiovascular event was defined as either acute myocardial infarction or stroke (ischemic or hemorrhagic). Cardiovascular events were defined as one or more of the following: cardiovascular event documented in general practice records, hospitalization with cardiovascular event as the primary diagnosis, or death with cardiovascular event as the primary cause of death, using the earliest date as the case event date. Linkage across all was used to improve case ascertainment as 25-50% of cardiovascular events are not recorded in at-least one of the three data

sources [14-16]. The first cardiovascular event after the diagnosis of gout was used to ascertain case status as lifestyle changes after such an event may be associated with fewer subsequent gout flares [17].

Definition, selection and matching of controls Patients with a new diagnosis of gout were followed-up from the date of first diagnosis of gout to the earliest date of: cardiovascular event, transfer-out of practice, last data collection from the practice, death, or study end. Controls were defined as those who did not experience a cardiovascular event during follow-up. Up to five controls were matched to each case based on age (±2 years), sex and length of time since gout diagnosis of gout at first cardiovascular event (±2 years) using time-dependent incidence density sampling. This method assigned equal length of observation to cases and matched controls to ensure equal time windows of exposure [18]. It produced odds ratios that were unbiased estimators of the hazard ratio, with little or no loss in precision [19]. Each control was allocated an index date corresponding to the cardiovascular event date of their matched case. Participants with no primary-care consultation in the 12-months preceding the index date were excluded as they could have moved to a different practice without updating their medical records in the original practice.

Exposure Gout flare was the exposure of interest. It was defined as the presence of one or more of the following: a diagnostic code for gout flare in general practice records, hospitalization with gout as the primary discharge-diagnosis, or primary-care consultation for gout with prescription of either non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or colchicine on the same date. Previous validation studies suggested that this strategy would yield the highest positive predictive value for gout flare ascertainment [20-22] (eMethod 1).

As gout flares typically last for 1-2 weeks, gout-related consultations and prescriptions within 14 days of the first flare consultation were considered part of the same flare. Patients were categorized as experienced gout flares within 0-60, 61-120, 121-180, >180 days or experienced no gout flares prior to cardiovascular event or index date.

Covariates Covariates consisted of age (years), sex (female/male), gout duration (years), body mass index (BMI) in kg/m^2, smoking status (current, past or non-smoker), alcohol intake (current, past or non-drinker), socioeconomic deprivation assessed using the English Index of Multiple Deprivation 2015, Charlson

Comorbidity Index [23], hypertension, atrial fibrillation, hypercholesterolemia, cardiovascular event prior to gout diagnosis, number of hospitalization and primary-care consultations in the 12 months preceding the cardiovascular event or matched index date, European Society of Cardiology cardiovascular risk status (high/very-high or low/moderate) [24]), and prescription of urate-lowering therapy, anti-platelets, statins, diuretics, anti-hypertensives, colchicine, NSAIDs and corticosteroids. Prescriptions were categorized as current (≤60 days), past (>60 days), or not prescribed. Previously published Read code lists were updated to develop code lists in this study (eTable 1). Race and ethnicity data were not included.

Self-controlled case series

Selection of participants Participants with both an exposure (gout flare) and outcome (cardiovascular event) were included [25].

Exposure The exposure period extended from the gout flare consultation date to 180 days divided into three 60-day exposure windows (eFigure 1). There was a 30-day induction period prior to gout flare, and the baseline period comprised of 31 to 180 days pre-exposure and 360 days after the end of the exposure period. Each participant contributed data from their first gout flare. The observation period was restricted to 720 days to minimize confounding from time-varying confounders [25] (eMethods 2).

Outcomes

For both the case-control study and the self-controlled case series, the outcomes were as follows:

- Primary: cardiovascular event defined as either acute myocardial infarction or stroke (ischemic/hemorrhagic).
- Secondary: fatal cardiovascular event, acute myocardial infarction, and stroke (ischemic/hemorrhagic).

Statistical analysis

Nested case control study: Multivariable conditional logistic regression was used to assess the association between recent prior gout flares and cardiovascular events. The odds of a recent prior flare were calculated by comparing patients with flares within a given time period within 180 days of the index cardiovascular event versus either remote or no previous flares, and an OR with 95% confidence interval (95%CI) was

calculated. Unadjusted difference (95%CI) was calculated between cases and controls. The model was adjusted for matching variables to account for residual confounding (model-1), and further adjusted for BMI, smoking status, alcohol intake, and socioeconomic deprivation in model-2. Model-3 included variables in model-2 with additional adjustment for Charlson Comorbidity Index, hypertension, atrial fibrillation, hypercholesterolemia, number of hospitalizations in previous 12 months, number of primary-care consultations in previous 12 months, European Society of Cardiology cardiovascular risk, and drug prescriptions. Model-4 included variables in model-3 with additional adjustment for prescription of colchicine, NSAIDs and corticosteroids. Sensitivity analyses repeated analyses with different outcomes (i.e., acute myocardial infarction, stroke, fatal cardiovascular event), shorter exposure window (i.e., within 0-15, 16-30, 31-60, 61-90, 91-120, 121-150, 151-180 days of index cardiovascular event), patients with gout flares within 180-240 days prior to the cardiovascular event or matched index date as reference, and excluded patients with: cardiovascular event prior to gout diagnosis, moderate or low cardiovascular risk as per European Society of Cardiology, gout diagnosed for <1 year at cardiovascular event or matched index date, no prior gout flares, cardiovascular event or matched index date before January 1, 2010, and cardiovascular event on the same date as gout flare.

BMI, smoking status, alcohol intake status, and socioeconomic deprivation had missing data. The pattern of missingness was compared and missingness at random assumed. Missing data were imputed using chained equations (Stata command “mi impute chained”). BMI was modelled using linear regression. Other variables with missing data were categorical/ordinal and modelled using ordinal regression. The imputation model included all listed confounders, exposure, and case-control indicator [26]. Twenty imputed datasets were derived [27].

Self-controlled case series: A Poisson model was fitted conditioned on the number of cardiovascular events and adjusted Incidence Rate Ratios (aIRR) with 95%CIs for exposure periods compared with the baseline period and adjusted for age (2-year age-bands) and calendar season. The latter accounts for the seasonal change in gout flare incidence [28]. Incidence rate difference (95%CI) was calculated.

196 Sensitivity analyses considered different outcomes (i.e., acute myocardial infarction, stroke, fatal
197 cardiovascular event), short exposure intervals (i.e., flare date to 15, 16-30, 31-60, 61-90, 91-120, 121-150
198 and 151-180 days after the gout flare), excluded patients with fatal cardiovascular event, cardiovascular
199 event on the same date as gout flare, cardiovascular event prior to the first diagnosis of gout, and
200 cardiovascular event or matched index date before January 1, 2010, and evaluated the association of gout
201 flares when restricted to those treated with NSAIDs, corticosteroids or colchicine with cardiovascular
202 events [25].
203 Details of sample size estimation are provided in eMethods 3. $p<0.05$ (2-sided) was considered as
204 statistically significant. Because of the potential for type-I error due to multiple comparisons, findings for
205 secondary outcomes should be interpreted as exploratory. STATA version 17 (StataCorp) was used for data
206 analysis.
207

RESULTS 96153 patients were newly diagnosed with gout during the study period (Figure 1). Of these, 10475 had ≥1 cardiovascular event during 603,923 person-years of follow-up. The incidence (95%CI) of cardiovascular events was 17.34 (17.02-17.68)/1000 person-years. The first cardiovascular event was acute myocardial infarction in 5324 (49.2%) patients and stroke (ischemic or hemorrhagic) in 5151 (50.8%) patients. 3889 (37.1%) patients with gout had a fatal cardiovascular event: 2238 (21.4%) acute myocardial infarction and 1651 (15.8%) stroke.

Nested case-control study The nested case-control study included 62574 patients with gout, either with (n=10475) or without (n=52099) cardiovascular events after the diagnosis of gout (Table 1). Patients with cardiovascular events after a gout diagnosis, compared with patients who did not experience cardiovascular events, had a higher rate of current smoking [1231/9798 (12.6%) vs 4397/49332 (8.9%)], had very high or high cardiovascular risk according to the European Society of Cardiology guidelines [10321/10475 (98.5%) vs. 34856/52099 (66.9%)], a higher rate of prior cardiovascular diseases [5448/10475 (52.0%) vs. 10765/52099 (20.7%)], and a higher Charlson Comorbidity Index (mean (Standard Deviation (SD)) 3.23(2.28) vs. 2.52(2.18)) ($p<0.001$ for all).

Overall, 44.9% (n/N=28119/62574) patients consulted or were hospitalized for gout flares over a mean of 5.3 years (SD 4.5) of follow-up between their initial gout diagnosis and the cardiovascular event date or matched index date for controls. This proportion was similar between cases and controls [4733/10475 (45.2%) vs. 23386/52099 (44.9%)]. The median number of gout flares in both groups was 1.0 (interquartile range (IQR) 1.0-1.0).

In the fully-adjusted model, patients with cardiovascular events, compared to those without cardiovascular events, had significantly higher odds of gout flare within the prior 0-60 days (204/10475 (2.0%) vs 743/52099 (1.4%); aOR, 1.93 (95%CI, 1.57-2.38)) and 61-120 days (170/10475 (1.6%) vs 628/52099 (1.2%); aOR, 1.57 (95%CI, 1.26-1.96), but there was no significant difference in the odds of a gout flare within the prior 121-180 days (148/10475 (1.4%) vs 662/52099 (1.3%); aOR, 1.06 (95%CI, 0.84-1.34) (Figure 2).

Results of sensitivity analyses (e.g., applying shorter exposure window, excluding patients with cardiovascular diseases prior to gout diagnosis, excluding patients without gout flares, changing the

reference period to 180-240 days prior to cardiovascular event, and excluding patients with low/moderate cardiovascular risk) were consistent with the main analysis (Figure 3, eTable 2).

The aOR (95%CI) (n/N, %) for gout flares within 0-60, 61-120 and 121-180 days prior to a fatal cardiovascular event compared to no cardiovascular event were 4.76 (1.69-8.43) (67/3889, 1.7% vs 67/13808, 0.5%), 2.05 (1.19-3.54) (41/3889, 1.1% vs 61/13808, 0.4%), and 1.28 (0.74-2.19) (84/3889, 2.2% vs 221/13808, 1.6%), respectively.

Self-controlled case series 1421 patients with ≥1 gout flare and ≥1 cardiovascular event after the diagnosis of gout were included (eFigure 2). 545 and 876 cardiovascular events occurred during the 180 days after the gout flare (exposed period), and the 150 days before and 181-540 days after the gout flare (baseline period) over a total follow-up time of 256945 and 679476 person-days, at a rate (95%CI) of 2.12 (1.94-2.30) and 1.29 (1.20-1.37)/1000 person-days, respectively, and with an incidence rate difference (95%CI) of 0.83 (0.63-1.03)/1000 person-days. There were significantly more cardiovascular events during the 180 days after the gout flare compared to other time periods (i.e., the 150 days before and 181-540 days after the gout flare) [IRR (95%CI) 1.65 (1.48-1.84)].

Gout flares were associated with significantly more cardiovascular events in the subsequent 0-60, 61-120, and 121-180 days with incidence rates (95%CI) of 2.49 (2.16-2.82), 2.16 (1.85-2.47), 1.70 (1.42-1.98)/1000 person-days, respectively, compared with an incidence rate of 1.32 (1.23-1.41)/1000 person-days during the 150 days before and 181-540 days after the gout flare (Figure 4). Compared with 150 days before and 181-540 days after a gout flare, incidence rate differences (95%CI) and aIRRs (95%CI) for cardiovascular events were 1.17 (0.83-1.52), 0.84 (0.52-1.17), 0.38 (0.09-0.67)/1000 person-days, and 1.89 (1.54-2.30); 1.64 (1.45-1.86); 1.29 (1.02-1.64) within 0-60, 61-120, and 121-180 days after a gout flare, respectively. The results of the sensitivity analyses (e.g., applying shorter exposure window, excluding patients with cardiovascular diseases prior to gout diagnosis, and excluding patients with low/moderate cardiovascular risk) were consistent with those of the main analysis (Figure 4 and eTable 3). The results were similar when the analyses were repeated using only gout flares treated with NSAIDs, colchicine or corticosteroids (eTable 3).

DISCUSSION In the nested case-control study of patients with newly diagnosed gout, patients with cardiovascular events had significantly increased odds of a gout flare during the preceding 120-days compared with patients who did not experience cardiovascular events. These findings suggest that gout flares are associated with a transient increase in cardiovascular events following flares. The increased odds persisted when people with pre-existing cardiovascular diseases were excluded and when shorter exposure periods prior to the cardiovascular event (e.g., within 0-15 and 16-30 days of cardiovascular event) were considered. The self-controlled case series accounted for residual between-person confounding and confirmed the results of the nested case-control study [25].

Gout flares are characterized by neutrophil-rich acute inflammation due to NLRP-3 inflammasome activation [5,29]. Neutrophilic inflammation is associated with atherosclerotic plaque instability and rupture [30-32]. Activated intraplaque inflammatory cells up-regulate host response proteins, including metalloproteinases and peptidases, and promote an oxidative stress, all of which contribute to plaque destabilization [33]. This may explain the association between cardiovascular events and recent prior gout flares. Additionally, acute infection and surgery are associated with atrial fibrillation [34] and the same may be the case for gout flares, providing another potential mechanismClick or tap here to enter text..

The present study had several strengths. It used a large nationwide database representative of the general population [12]. The data used in this study were derived from both primary-care consultations and hospitalizations, and were linked to mortality, and socioeconomic deprivation records. In view of remaining residual confounding in the case-control analysis, a separate self-controlled case series analysis was performed as it removes any between-person confounding, and this yielded similar results. Additionally, gout flares were identified using validated definitions and cardiovascular events were defined using data from general practice, hospitalization, and cause of death to minimize potential bias from misclassification.

Limitations

This study has several limitations. First, data were extracted retrospectively from a prospective database. Second, only association and not causation should be inferred because of the observational study design. Third, although cardiovascular events were ascertained using general practice consultation, hospitalization,

and cause of death records, it was not possible to clinically verify or validate each event. However, this approach has been widely used in cardiovascular research [6,8,9]. Furthermore, the incidence of cardiovascular event was comparable to those reported previously [9]. Fourth, separate analyses with ischemic or hemorrhagic stroke as outcomes could not be conducted because stroke-type was not specified for a considerable proportion of these events [7,16]. Fifth, gout flares for which individuals did not consult were not included in the study as electronic health records only capture interactions with the healthcare service. Sixth, the onset of gout flares likely preceded the date of consultation in general practice or the date of hospitalization. However, this was unlikely to differ between those with and without cardiovascular events. Seventh, this study spanned 24 years. The diagnosis and management of cardiovascular diseases and gout have changed over this period. More remotely collected data may not be relevant to current practice. Eighth, data on severity of gout (e.g., tophi, polyarticular gout flares) [35] were infrequently recorded in the Clinical Practice Research Datalink, and consequently we were unable to control for gout severity in our analyses. Ninth, patients with cardiovascular events before the diagnosis of gout were included in the study and may have introduced surveillance bias. However, the sensitivity analysis excluded such patients and yielded similar significant associations.

CONCLUSION

Among individuals with gout, those who experienced a cardiovascular event, compared to those who did not experience such an event, had a significantly higher odds of a recent gout flare in the preceding days. The findings suggest gout flares are associated with a transient increase in cardiovascular events following the flare.

Acknowledgements

AA conceived the idea for the study, contributed to the study design, supervised and performed data analysis, interpreted the results, and critically reviewed the manuscript. AJA contributed to the study design, interpreted the results and critically reviewed the manuscript. EC contributed to the study design, reviewed the literature, performed data management and analysis, and co-wrote the first draft of the manuscript. GN contributed to the study design, advised on data management, supervised data analysis, interpreted the results and critically reviewed the manuscript. LT contributed to the study design, advised on data analysis, interpreted the results and critically reviewed the manuscript. MM contributed to the study design and critically reviewed the manuscript. All authors approved the submitted manuscript. EC attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

This study used data from the Clinical Practice Research Datalink. These data were provided under licence that does not permit data sharing with third parties. They can be obtained from Clinical Practice Research Datalink. EC and AA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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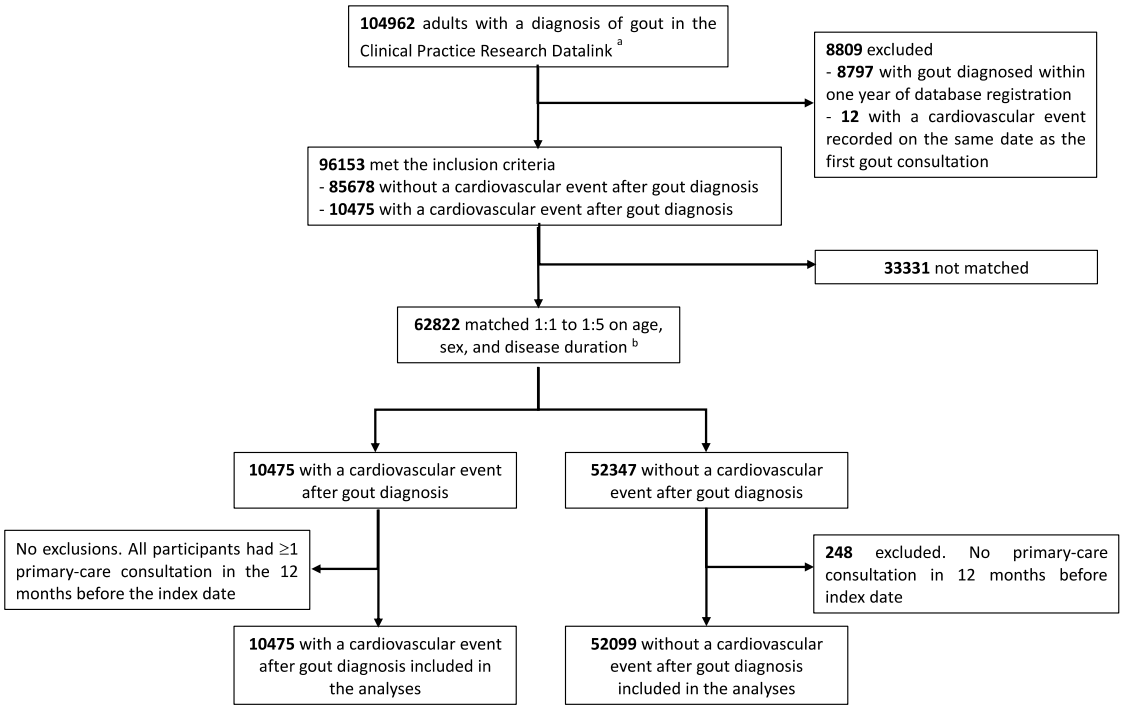
411 **Figure 1**. Cohort development in a nested case-control study of cardiovascular events after new diagnosis
412 of gout.



413

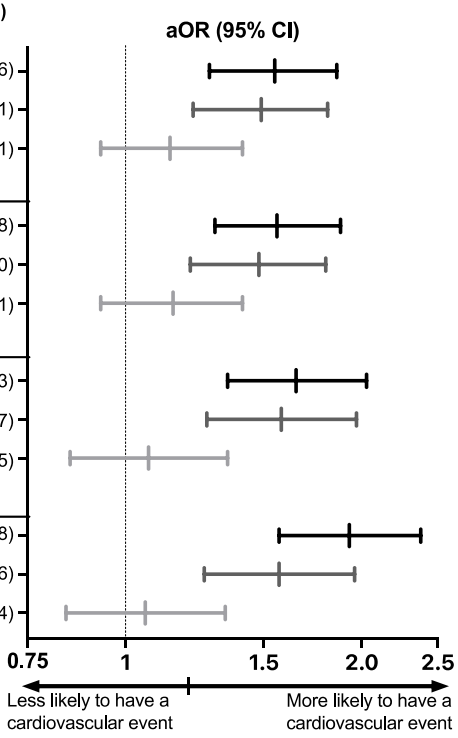
414 [a] Clinical Practice Research Datalink is a longitudinal primary care database of anonymized health records of
415 15 million people across the United Kingdom from over 700 practices. It contains data on socio-
416 demographics, lifestyle factors, diagnoses, consultations, and prescriptions recorded in primary care,
417 hospitalization records, and mortality data.

418 [b] Up to five controls were matched to each case for age (±2 years), sex and duration of gout at first
419 cardiovascular event (±2 years)

420

Figure 2. Association between cardiovascular event and recent prior gout flare in a nested case-control study.

Model	Exposure window	No. (%) of cases [a] (N=10475)	No. (%) of controls [b] (N=52099)	Unadjusted difference % (95% CI)	aOR (95% CI)
1 [d]	0-60 days	204 (2.0)	743 (1.4)	0.5 (0.2-0.9)	1.55 (1.28-1.86)
	61-120 days	170 (1.6)	628 (1.2)	0.4 (0.1-0.8)	1.49 (1.22-1.81)
	121-180 days	148 (1.4)	662 (1.3)	0.1 (-0.2 - 0.5)	1.14 (0.93-1.41)
	>180 days or no flare [c]	9953 (95.0)	50066 (96.1)	-1.1 (-1.7 - -0.5)	1
2 [e]	0-60 days	204 (2.0)	743 (1.4)	0.5 (0.2-0.9)	1.56 (1.30-1.88)
	61-120 days	170 (1.6)	628 (1.2)	0.4 (0.1-0.8)	1.48 (1.21-1.80)
	121-180 days	148 (1.4)	662 (1.3)	0.1 (-0.2 - 0.5)	1.15 (0.93-1.41)
	>180 days or no flare [c]	9953 (95.0)	50066 (96.1)	-1.1 (-1.7 - -0.5)	1
3 [f]	0-60 days	204 (2.0)	743 (1.4)	0.5 (0.2-0.9)	1.65 (1.35-2.03)
	61-120 days	170 (1.6)	628 (1.2)	0.4 (0.1-0.8)	1.58 (1.27-1.97)
	121-180 days	148 (1.4)	662 (1.3)	0.1 (-0.2 - 0.5)	1.07 (0.85-1.35)
	>180 days or no flare [c]	9953 (95.0)	50066 (96.1)	-1.1 (-1.7 - -0.5)	1
4 [g]	0-60 days	204 (2.0)	743 (1.4)	0.5 (0.2-0.9)	1.93 (1.57-2.38)
	61-120 days	170 (1.6)	628 (1.2)	0.4 (0.1-0.8)	1.57 (1.26-1.96)
	121-180 days	148 (1.4)	662 (1.3)	0.1 (-0.2 - 0.5)	1.06 (0.84-1.34)
	>180 days or no flare [c]	9953 (95.0)	50066 (96.1)	-1.1 (-1.7 - -0.5)	1



Abbreviations. 95%CI: 95% confidence interval, **aOR**: adjusted odds ratio, **BMI**: body mass index, **NSAIDs**: non-steroidal anti-inflammatory drugs, **ULT**: urate-lowering therapy.

[a] days before case event date or control index date where 0 is event date/index date.

[b] **Cases**: individuals with cardiovascular events (defined as the first occurrence of acute myocardial infarction or a stroke after gout diagnosis).

[c] **Controls**: matched individuals with gout but without cardiovascular event after diagnosis of gout.

[d] **Reference category:** gout flare >180 days prior to index date or no gout flare.

[e] **Model 1** includes matching variables (age, sex and disease duration).

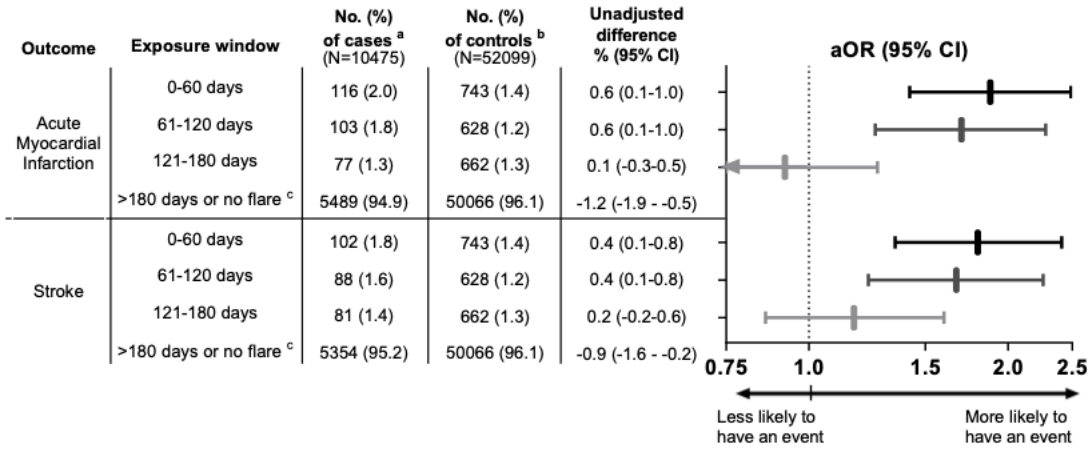
[f] **Model 2** includes matching variables (age, sex and disease duration), demographics and lifestyle factors (BMI, smoking status, alcohol intake status, and English Index of Multiple Deprivation).

[g] **Model 3** includes matching variables (age, sex and disease duration), demographics and lifestyle factors (BMI, smoking status, alcohol intake status, and English Index of Multiple Deprivation), comorbidities (Charlson Comorbidity Index, hypertension, atrial fibrillation, hypercholesterolemia, number of

hospitalisations in the previous year, and number of primary-care consultations in the previous year, European Society of Cardiology individual cardiovascular risk), prescription of anti-platelets, statins, ULT, diuretics, and anti-hypertensives. Prescriptions were categorized as current (≤60 days), past (>60 days), or not prescribed prior to the cardiovascular event date or matched index date.

[h] **Model 4** includes matching variables (age, sex and disease duration), demographics and lifestyle factors (BMI, smoking status, alcohol intake status, and English Index of Multiple Deprivation), comorbidities (Charlson Comorbidity Index, hypertension, atrial fibrillation, hypercholesterolemia, number of hospitalisations in the previous year, and number of primary-care consultations in the previous year, European Society of Cardiology individual cardiovascular risk), prescription of anti-platelets, statins, ULT, diuretics, and anti-hypertensives, prescription of medications used for treating gout flares (colchicine, NSAIDs and corticosteroids). Prescriptions were categorized as current (≤60 days), past (>60 days), or not prescribed prior to the cardiovascular event date or matched index date.

Figure 3 - Association between acute myocardial infarction, stroke and recent prior gout flares in a nested case-control study.



Outcome	Exposure window	No. (%) of cases [a] (N=10475)	No. (%) of controls [b] (N=52099)	Unadjusted difference % (95% CI)
Acute Myocardial Infarction	0-60 days	116 (2.0)	743 (1.4)	0.6 (0.1-1.0)
	61-120 days	103 (1.8)	628 (1.2)	0.6 (0.1-1.0)
	121-180 days	77 (1.3)	662 (1.3)	0.1 (-0.3-0.5)
	>180 days or no flare [c]	5489 (94.9)	50066 (96.1)	-1.2 (-1.9 - -0.5)
Stroke	0-60 days	102 (1.8)	743 (1.4)	0.4 (0.1-0.8)
	61-120 days	88 (1.6)	628 (1.2)	0.4 (0.1-0.8)
	121-180 days	81 (1.4)	662 (1.3)	0.2 (-0.2-0.6)
	>180 days or no flare [c]	5354 (95.2)	50066 (96.1)	-0.9 (-1.6 - -0.2)

Abbreviations. 95%CI: 95% confidence interval, **AMI**: acute myocardial infarction, **aOR**: adjusted odds ratio.

[a] days before case event date or control index date where 0 is event date/index date

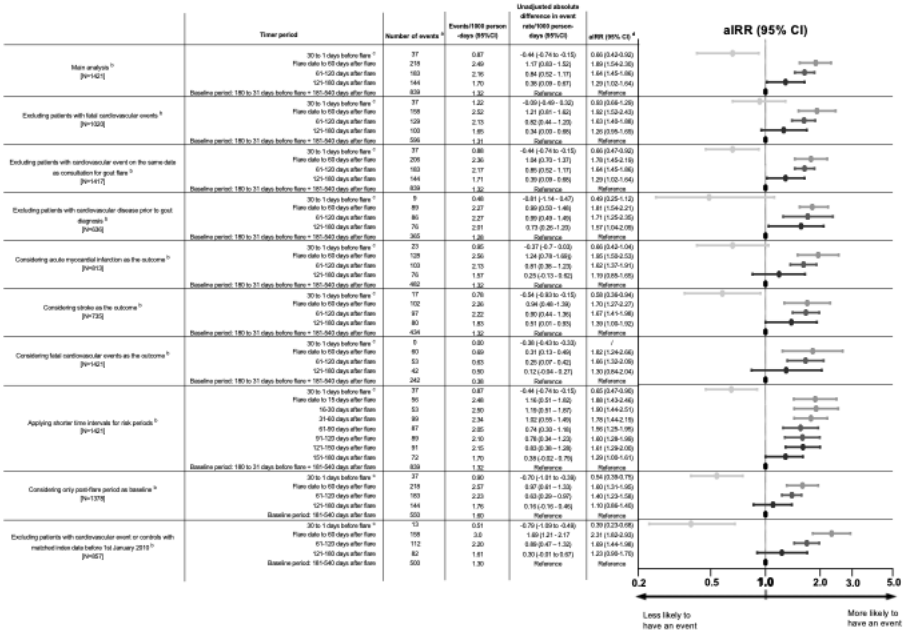
[b] **Cases**: individuals with cardiovascular events (defined as the first occurrence of acute myocardial infarction or a stroke after gout diagnosis).

[c] **Controls**: matched individuals with gout but without cardiovascular event after diagnosis of gout.

[d] **Reference category:** gout flare >180 days prior to index date or no gout flare.

[e] The analyses were adjusted for: age, sex, disease duration, body mass index, smoking status, alcohol intake status, English Index of Multiple Deprivation 2015, Charlson Comorbidity Index, hypertension, atrial fibrillation, hypercholesterolemia, number of hospitalizations in the previous year, number of primary-care consultations in the previous year, European Society of Cardiology cardiovascular risk score, and current, past or no prescription of diuretics, anti-platelets, statins, urate lowering therapy, anti-hypertensives, non-steroidal anti-inflammatory drugs, corticosteroids and colchicine).

Figure 4. Results of the self-controlled case series analysis for patients with a first episode of gout and a cardiovascular event.



Abbreviations. 95%CI: 95% confidence interval, **aIRR**: incidence risk ratio.

[a] **Events:** cardiovascular events were defined as either acute myocardial infarction or a stroke.

[b] The number of individuals included in each analysis is reported in square brackets.

[c] Induction interval.

[d] the analyses were adjusted for age and calendar season.

See eTable 3 for self-controlled case series findings by gout flare treatments

Table 1. Demographic and clinical characteristics of patients with newly diagnosed gout included in the nested case-control study.

	Individuals with gout and cardiovascular events (N=10475)	Matched controls with gout and without cardiovascular events (N=52099)
Age, years - mean (SD)	76.9 (11.4)	76.3 (10.8)
Sex		
Female - n (%)	3213 (30.7)	15979 (30.7)
Male - n (%)	7262 (69.3)	36120 (69.3)
BMI, kg/m^2 - mean (SD) [a]	28.2 (5.1) [N=8893]	28.2 (4.9) [N=44297]
English Index of Multiple Deprivation - mean (SD) [a,b]	3.2 (1.4) [N=9950]	3.1 (1.4) [N=49290]
Smoking habit [a]	[N=9798]	[N=49332]
Current smoker - n (%)	1231 (12.6)	4397 (8.9)
Past smoker - n (%)	3904 (39.8)	19537 (39.6)
Non-smoker - n (%)	4663 (47.6)	25398 (51.5)
Alcohol intake [a]	[N=9474]	[N=47891]
Current drinker - n (%)	7483 (79.0)	39137 (81.7)
Past drinker - n (%)	221 (2.3)	969 (2.0)
Non-drinker - n (%)	1770 (18.7)	7785 (16.3)
Time since since gout diagnosis, years - mean (SD)	5.3 (4.5)	5.3 (4.5)
Gout flare prior to cardiovascular event or marched index date		
Within 0-60 days - n (%)	204 (2.0)	743 (1.4)
Within 61-120 days - n (%)	170 (1.6)	628 (1.2)
Within 121-180 days - n (%)	148 (1.4)	662 (1.3)
>180 days - n (%)	4211 (40.2)	21353 (41.0)
No gout flare – n (%)	5742 (54.8)	28713 (55.1)
Charlson comorbidity index - mean (SD) [c]	3.2 (2.3)	2.5 (2.2)
History of cardiovascular diseases [d]- n (%)	5448 (52.0)	10765 (20.7)
Very high/high cardiovascular risk - n (%) [e]	10321 (98.5)	34856 (66.9)
Diabetes mellitus without target organ damage - n (%) [f]	1537 (14.7)	6689 (12.8)
Diabetes mellitus with target organ damage - n (%) [f]	1050 (10.0)	3944 (7.6)
Chronic kidney disease ≥stage 3 - n(%) [g]	3695 (35.3)	18353 (35.2)
Peripheral artery disease - n (%)	1980 (18.9)	5777 (11.1)
Hypertension - n (%)	7250 (69.2)	35405 (70.0)
Atrial fibrillation - n (%)	2540 (24.3)	10069 (19.3)
Hypercholesterolemia - n (%)	2428 (23.2)	11418 (21.9)
Statins		
Current prescription - n (%) [h]	3430 (32.7)	10897 (20.9)
Past prescription - n (%) [i]	4266 (40.7)	20273 (38.9)
Never prescribed - n (%)	2779 (26.5)	20928 (40.2)
Anti-platelet drugs		
Current prescription - n (%) [h]	3563 (34.0)	9633 (18.5)
Past prescription - n (%) [i]	5372 (51.3)	21842 (41.9)
Never prescribed - n (%)	1540 (14.7)	20624 (39.6)
Urate-lowering therapy		
Current prescription - n (%) [h]	1658 (15.8)	9804 (18.8)
Past prescription - n (%) [i]	3358 (32.1)	15297 (29.4)
Never prescribed - n (%)	5459 (52.1)	26997 (51.8)
Latest urate lowering drug prescription [a]	[N=5016]	[N=25101]
Allopurinol - n (%)	4937 (98.4)	24732 (98.5)
Febuxostat - n (%)	45 (0.9)	226 (0.9)
Uricosurics (probenecid, benzbromarone, sulfinpyrazone) - n (%)	34 (0.7)	143 (0.6)
Diuretics		
Current prescription - n (%) [h]	1959 (18.7)	8306 (15.9)
Past prescription - n (%) [i]	6526 (62.3)	29200 (56.1)
Never prescribed - n (%)	1990 (19.0)	14593 (28.0)

Other anti-hypertensive drugs [j]		
Current prescription - n (%) [h]	2748 (26.2)	11260 (21.6)
Past prescription - n (%) [i]	922 (8.8)	9625 (18.5)
Never prescribed - n (%)	6805 (65.0)	31213 (59.9)
NSAIDs		
Current prescription - n (%) [h]	804 (7.7)	5565 (10.7)
Past prescription - n (%) [i]	7418 (70.8)	36726 (70.5)
Never prescribed - n (%)	2253 (21.5)	9808 (18.8)
Corticosteroids		
Current prescription - n (%) [h]	1389 (13.3)	9084 (17.4)
Past prescription - n (%) [i]	3639 (34.7)	15691 (30.1)
Never prescribed - n (%)	5447 (52.0)	27324 (52.5)
Colchicine		
Current prescription - n (%) [h]	1032 (9.9)	7155 (13.7)
Past prescription - n (%) [i]	2773 (26.5)	12044 (23.1)
Never prescribed - n (%)	6670 (63.7)	32900 (63.2)
Number of primary-care consultations in the previous year - median (IQR)	17 (10-29)	14 (8-23)
Number of hospitalizations in the previous year - median (IQR)	1 (0-2)	0 (0-1)
Time in Clinical Practice Research Datalink, years - mean (SD)	12.0 (5.9)	12.4 (6.0)

Abbreviations. BMI: body mass index, **eGFR**: estimated glomerular filtration rate, **IQR**: interquartile range, **NSAIDs**: non-steroidal anti-inflammatory drugs, **SD**: standard deviation.

[a] The number of individuals with available data is reported in square brackets.

[b] The **English Index of Multiple Deprivation 2015** is a measure of socioeconomic deprivation. It ranks small areas called Lower-layer Super Output Areas from 1 (most deprived) to 32,844 (least deprived). It is analyzed in quintiles, ranging from the 1st (the most deprived) to 5th (the least deprived). Data were provided by Clinical Practice Research Datalink.

[c] The **Charlson Comorbidity Index** predicts mortality by weighting specific comorbidities. It ranges from 0 to 29. Higher score indicates increased risk of mortality. In the current study it was derived from general practice records provided by the Clinical Practice Research Datalink as per Khan et al. [25].

[d] **Cardiovascular disease** was defined as either acute coronary syndrome, ischemic heart diseases, transient ischemic attack, or stroke.

[e] For further information, please see eMethod 4.

[f] Target organ damage with diabetes was defined as primary-care record of microalbuminuria, retinopathy, or neuropathy [26].

[g] Chronic Kidney Disease (CKD), stage ≥3 is eGFR ≤30ml/min/1.73 m^2 or dialysis.

[h] **Current prescription**: most recent prescription within 60 days prior to cardiovascular event date or index date in matched controls.

[i] **Past prescription**: most recent prescription >60 days prior to the cardiovascular event date or index date in matched controls.

[j] Includes angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta blockers, or calcium channel blockers.

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