Gout and Excess Risk of Severe SARS-CoV-2 Infection Among Vaccinated Individuals: A General Population Study

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Objective. Gout patients often have multiple comorbidities, making them susceptible to SARS-CoV-2 infection and poor outcomes. This study was undertaken to examine the association between gout and the risk of SARS-CoV-2 infection and severe outcomes, especially in patients who have received a SARS-CoV-2 vaccine.

Methods. We conducted 2 cohort studies using The Health Improvement Network in the UK. Individuals with gout and those without gout from the general population were followed up from December 8, 2020 to October 31, 2021. We estimated the rate difference (RD) and hazard ratio (HR) of SARS-CoV-2 infection and severe outcomes (i.e., hospitalization and death within 30 days after SARS-CoV-2 infection) for individuals with gout versus those without gout using a Cox proportional hazards model according to SARS-CoV-2 vaccination status. We adjusted for potential confounders by using overlap weighting of exposure scores.

Results. Among the vaccinated cohort, 1,955 cases of breakthrough COVID-19 infection occurred in 54,576 individuals with gout (4.68 cases per 1,000 person-months), and 52,468 cases occurred in 1,336,377 individuals without gout (3.76 cases per 1,000 person-months). The partially adjusted RD of breakthrough infection was 0.91 cases per 1,000 person-months (95% confidence interval [95% CI] 0.62–1.20 cases per 1,000 person-months), and the partially adjusted HR was 1.24 (95% CI 1.19–1.30). Gout was also associated with an increased risk of hospitalization (adjusted HR 1.30 [95% CI 1.10–1.53]) and death (adjusted HR 1.36 [95% CI 0.87–2.13]). Women with gout had an increased risk of hospitalization (adjusted HR 1.55 [95% CI 1.15–2.10]) and death (adjusted HR 2.46 [95% CI 1.12–5.41]). Similar associations with gout were observed in the unvaccinated cohort.

Conclusion. These general population data suggest that individuals with gout, especially women, have higher risks of SARS-CoV-2 infection and severe outcomes, even when vaccinated.

INTRODUCTION

The COVID-19 pandemic has caused devastating economic and social disruption (1). There are few effective therapies for COVID-19, and these therapies remain a scarce resource. As such, vaccination remains the most promising approach at present for controlling this disease (2). Despite the increasing availability of effective vaccines, millions of new COVID-19 cases in both vaccinated and unvaccinated people continue to occur each day worldwide, and new variants are expected to emerge in the future that may evolve immune escape (1). Identifying individuals who are susceptible to breakthrough COVID-19 infection and severe outcomes despite vaccination may identify populations who would benefit from other risk-mitigating strategies (e.g., preexposure prophylaxis).

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Gout is a common inflammatory arthritis (3). Individuals with gout often have multiple comorbidities, including obesity, cardiovascular disease, and chronic kidney disease (4), which have been associated with a higher risk of SARS-CoV-2 infection and poor outcomes (5,6). Furthermore, elevated serum urate levels could contribute to a proinflammatory state that may complicate the COVID-19 course (7). However, unlike other inflammatory rheumatic diseases, such as rheumatoid arthritis and lupus, there is a paucity of data on the risk of SARS-CoV-2 infection among gout patients, particularly on the risk of breakthrough infection after vaccination.

To date, 2 studies have examined the association between gout and the risk of SARS-CoV-2 infection but have yielded conflicting results (8,9). One study using data from the UK Biobank showed no significant difference in the risk of SARS-CoV-2 infection and death between participants with gout and those without gout (9). Using the same data source, a subsequent study reported that gout is a risk factor for SARS-CoV-2 infection and related death (9). However, these studies were conducted before the widespread availability of COVID-19 vaccines—up to August 24, 2020 (8) and up to April 6, 2021 (9)—leaving an important knowledge gap regarding the effectiveness of vaccination against SARS-CoV-2 infection and severe outcomes among individuals with gout (9). Since studies have demonstrated that waning vaccine effectiveness is greater in individuals with underlying medical conditions (10), assessing the effectiveness of COVID-19 vaccination against breakthrough infection and severe outcomes in gout patients has important clinical and public health implications.

We conducted 2 cohort studies to quantify the risk of SARS-CoV-2 infection and severe outcomes (i.e., hospitalization and death) among individuals with gout compared with non-gout individuals from the general population according to their COVID-19 vaccination status.

**METHODS**

**Data source.** The Health Improvement Network (THIN) (now called IQVIA Medical Research Database) is an electronic medical record database that contains general practitioners’ (GPs) records in the UK and is representative of the UK population with regard to demographic characteristics and medical conditions. Details of the THIN database have been described previously (11). It consists of ~17 million individuals from 790 general practices whose health care information is systematically recorded by GPs and sent anonymously to THIN. Because the National Health Service requires residents of the UK to register with a general practice regardless of health status, THIN is considered a population-based cohort representative of the UK general population (12,13). Information in THIN includes sociodemographic characteristics, anthropometric characteristics, lifestyle factors, and details from visits to GPs (i.e., prescriptions, diagnoses and interventions from specialist referrals, hospital admissions, and results of laboratory tests). The Read classification system is used to code specific diagnoses (14), whereas a dictionary based on the Multilex classification system by First Databank is used to code drugs (15). The validity of the database for use in clinical and epidemiologic research studies has been described in a previous study (16).

This study received approval from the ethics committee at Xiangya Hospital (2018091077), with waiver of informed consent, and was approved by the THIN Scientific Review Committee (20SRC003-A2). THIN is a registered trademark of Cegedim in the UK and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This study uses deidentified data provided by individuals as a part of their routine primary care.

**Study design.** We compared the risk of breakthrough infection (i.e., SARS-CoV-2 infection among people who had received a COVID-19 vaccine), hospitalization, and death between individuals with gout and individuals of the general population without gout who had received a COVID-19 vaccine (i.e., vaccinated cohort). The details of vaccination records were based on the Read codes in THIN. Gout diagnosis was also captured using Read codes (see Supplementary Table 1, available on the Arthritis & Rheumatology website at https://onlinelibrary.wiley.com/doi/art.42339) (17,18). Eligible individuals were those 18–90 years of age between December 8, 2020 (when the vaccination campaign began in the UK) and October 31, 2021 who had no previously documented SARS-CoV-2 infection and had at least 2 years of continuous enrollment with a general practice. We then took the same approach to compare the risk of SARS-CoV-2 infection and severe outcomes between individuals with gout and individuals of the general population without gout who had not received a COVID-19 vaccine (i.e., unvaccinated cohort).

**Cohort definition.** Eligible individuals in the vaccinated cohort were followed up starting on the day the first dose of a COVID-19 vaccine was received (i.e., index date) and ending on the day that an outcome of interest occurred (i.e., SARS-CoV-2 infection, hospitalization, or death) or the end of the study period (October 31, 2021), whichever occurred first. Eligible individuals in the unvaccinated cohort were followed up starting on December 8, 2020 (i.e., index date) and ending on the day that the first dose of a COVID-19 vaccine was received, the day that an outcome of interest occurred, or the end of the study period (October 31, 2021), whichever occurred first.

**Assessment of outcomes.** The primary outcome was a confirmed diagnosis of SARS-CoV-2 infection based on Read codes recommended in national guidelines (Supplementary Table 1 [https://onlinelibrary.wiley.com/doi/art.42339]) (19,20). According to National Health Service guidance and standard operating procedures for primary care and UK Faculty of Clinical
Table 1. Baseline characteristics of gout patients and individuals without gout in vaccinated and unvaccinated cohorts*

| Characteristic | Vaccinated cohort | | | | | | Unvaccinated cohort | | | |
|---------------|------------------|-----|-----|-----|-----|------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| | Gout (n = 54,576) | Non-gout (n = 1,336,377) | Standardized difference | Gout (n = 61,111) | Non-gout (n = 1,697,168) | Standardized difference | Gout (n = 61,111) | Non-gout (n = 1,697,168) | Standardized difference |
| Age, mean ± SD years | 66.3 ± 13.1 | 52.1 ± 17.8 | 0.906 | 65.6 ± 13.3 | 56.5 ± 13.8 | 0.001 | 65.7 ± 13.5 | 49.8 ± 17.9 | 0.001 | 64.8 ± 13.6 | 64.8 ± 15.1 | <0.001 |
| Socioeconomic deprivation index score, mean ± SD‡ | 2.6 ± 1.5 | 2.6 ± 1.6 | 0.103 | 2.6 ± 1.5 | 2.6 ± 1.5 | 0.001 | 2.6 ± 1.5 | 2.7 ± 1.6 | 0.046 | 2.6 ± 1.5 | 2.6 ± 1.5 | <0.001 |
| Women, % | 21.2 | 53.1 | 0.699 | 22.9 | 22.9 | 0.001 | 20.9 | 51.1 | 0.664 | 22.5 | 22.5 | <0.001 |
| Body mass index, mean ± SD kg/m² | 30.6 ± 5.9 | 27.9 ± 6.1 | 0.440 | 30.4 ± 6.0 | 30.3 ± 5.8 | 0.017 | 30.5 ± 5.9 | 27.6 ± 6.1 | 0.486 | 30.4 ± 6.0 | 30.2 ± 5.8 | 0.019 |
| Location, % | | | | | | | | | | | | | | |
| England | 14.8 | 14.2 | | | | | | | | | | | |
| Northern Ireland | 11.8 | 13.6 | | | | | | | | | | | |
| Scotland | 35.8 | 41.9 | | | | | | | | | | | |
| Wales | 37.6 | 30.3 | | | | | | | | | | | |
| First dose of COVID-19 vaccine, % | | | | | | | | | | | | | | |
| ChAdOx1-S (AstraZeneca) | 67.7 | 55.2 | 0.265 | 67.7 | 67.7 | 0.001 | – | – | – | – | – | – |
| BNT162b2 (Pfizer-BioNTech) | 31.1 | 42.3 | | | | | | | | | | | |
| Other | 1.1 | 2.4 | | | | | | | | | | | |
| Second dose of COVID-19 vaccine, % | | | | | | | | | | | | | | |
| ChAdOx1-S (AstraZeneca) | 65.5 | 52.4 | 0.288 | 65.4 | 65.2 | 0.013 | – | – | – | – | – | – |
| BNT162b2 (Pfizer-BioNTech) | 29.6 | 38.8 | | | | | | | | | | | |
| Other | 0.5 | 1.8 | | | | | | | | | | | |
| None | 4.4 | 7.0 | | | | | | | | | | | |
| Number of previous SARS-CoV-2 tests, mean ± SD | | | | | | | | | | | | | | |
| | 0.1 ± 0.3 | 0.1 ± 0.4 | 0.101 | 0.1 ± 0.3 | 0.1 ± 0.3 | 0.001 | 0.1 ± 0.3 | 0.1 ± 0.3 | 0.054 | 0.1 ± 0.3 | 0.1 ± 0.3 | <0.001 |
| Influenza vaccination, % | | | | | | | | | | | | | | |
| | 64.4 | 37.7 | 0.553 | 62.8 | 62.8 | 0.001 | 57.9 | 29.0 | 0.609 | 55.8 | 55.8 | <0.001 |
| Lifestyle factors | | | | | | | | | | | | | | |
| Alcohol intake, % | | | | | | | | | | | | | | |
| None | 12.6 | 15.5 | 0.161 | 12.9 | 12.9 | 0.001 | 12.7 | 16.0 | 0.185 | 13.1 | 13.1 | <0.001 |
| Past | 4.0 | 2.6 | | | | | | | | | | | |
| Current | 78.5 | 64.0 | | | | | | | | | | | |
| Missing data | 4.9 | 17.9 | | | | | | | | | | | |
| Smoking, % | 0.301 | | | | | | | | | | | | |
| None | 52.8 | 56.4 | | | | | | | | | | | |
| Past | 36.3 | 23.1 | | | | | | | | | | | |
| Current | 10.5 | 16.5 | | | | | | | | | | | |
| Missing data | 0.4 | 4.0 | | | | | | | | | | | |
| Charlson comorbidity index, mean ± SD | 0.5 ± 1.1 | 0.3 ± 0.8 | 0.296 | 0.5 ± 1.1 | 0.5 ± 1.1 | 0.001 | 0.5 ± 1.1 | 0.2 ± 0.7 | 0.327 | 0.5 ± 1.1 | 0.5 ± 1.1 | <0.001 |
| Comorbidity, % | | | | | | | | | | | | | | |
| Hypertension | 58.9 | 22.5 | 0.798 | 56.0 | 56.0 | 0.001 | 57.7 | 19.6 | 0.849 | 54.5 | 54.5 | <0.001 |
| Diabetes | 26.3 | 11.1 | 0.398 | 24.9 | 24.9 | 0.001 | 25.8 | 9.9 | 0.426 | 24.3 | 24.3 | <0.001 |

(Continued)
| Characteristic                  | Vaccinated cohort | Unvaccinated cohort |
|--------------------------------|-------------------|---------------------|
|                                | Before exposure overlap weighting | After exposure overlap weighting | Before exposure overlap weighting | After exposure overlap weighting |
|                                | Gout (n = 54,576) | Non-gout (n = 1,336,377) | Gout (n = 61,111) | Non-gout (n = 1,697,168) |
| Hyperlipidemia                 | 18.4              | 6.8                 | 0.354            | 17.3              | 6.0                 | 0.378            | 16.8              | 6.8                 | <0.001            |
| Chronic kidney disease         | 17.4              | 3.6                 | 0.462            | 15.1              | 15.1               | <0.001            | 17.1              | 3.1                 | 0.478            | <0.001            |
| Pneumonia or infection         | 9.3               | 6.0                 | 0.123            | 9.0               | 9.0                | <0.001            | 9.2               | 5.6                 | 0.139            | <0.001            |
| Chronic obstructive pulmonary disease | 6.6 | 3.3                 | 0.149            | 6.3               | 6.3                | <0.001            | 6.4               | 2.9                 | 0.168            | <0.001            |
| Cancer                         | 14                | 7.6                 | 0.205            | 13.5              | 13.5               | <0.001            | 13.6              | 6.6                 | 0.233            | <0.001            |
| Venous thromboembolism         | 4.5               | 2.0                 | 0.143            | 4.3               | 4.3                | <0.001            | 4.4               | 1.8                 | 0.152            | <0.001            |
| Atrial fibrillation            | 11.9              | 2.8                 | 0.356            | 10.5              | 10.5               | <0.001            | 11.6              | 2.4                 | 0.367            | <0.001            |
| Ischemic heart disease         | 16                | 5.1                 | 0.361            | 14.9              | 14.9               | <0.001            | 15.7              | 4.4                 | 0.383            | <0.001            |
| Myocardial infarction          | 7.4               | 2.4                 | 0.233            | 6.9               | 6.9                | <0.001            | 7.3               | 2.1                 | 0.249            | <0.001            |
| Congestive heart failure       | 6.7               | 1.4                 | 0.272            | 5.7               | 5.7                | <0.001            | 6.5               | 1.2                 | 0.281            | <0.001            |
| Stroke                         | 5.1               | 2.0                 | 0.171            | 4.8               | 4.8                | <0.001            | 4.9               | 1.7                 | 0.181            | <0.001            |
| Medication, %§                 |                   |                     |                  |                   |                    |                   |                   |                    |                   |                   |
| CCBs                           | 28.3              | 10.5                | 0.460            | 26.9              | 26.9               | <0.001            | 27.5              | 9.0                 | 0.493            | 26.0              | 26.0               | <0.001            |
| ARBs                           | 14.7              | 4.8                 | 0.339            | 13.7              | 13.7               | <0.001            | 14.3              | 4.2                 | 0.357            | 13.2              | 13.2               | <0.001            |
| ACEIs                          | 31.0              | 11.1                | 0.503            | 29.6              | 29.5               | <0.001            | 30.4              | 9.6                 | 0.539            | 28.7              | 28.7               | <0.001            |
| Beta-blockers                  | 26.8              | 10.5                | 0.428            | 24.8              | 24.8               | <0.001            | 26.3              | 9.4                 | 0.454            | 24.2              | 24.2               | <0.001            |
| Glucocorticoids                | 8.7               | 4.1                 | 0.188            | 8.1               | 8.1                | <0.001            | 9.5               | 4.2                 | 0.212            | 8.8               | 8.8                | <0.001            |
| NSAIDs                         | 35.0              | 18.4                | 0.380            | 33.6              | 33.6               | <0.001            | 35.3              | 17.0                | 0.424            | 33.7              | 33.7               | <0.001            |
| Opioids                        | 10.9              | 6.6                 | 0.154            | 10.6              | 10.6               | <0.001            | 11.0              | 6.1                 | 0.177            | 10.7              | 10.7               | <0.001            |
| Antihypertensive drugs         | 62.8              | 26.6                | 0.780            | 60.0              | 60.0               | <0.001            | 61.3              | 23.3                | 0.835            | 58.2              | 58.2               | <0.001            |
| Antidiabetic medicine          | 14.5              | 6.0                 | 0.282            | 14.0              | 14.0               | <0.001            | 14.3              | 5.3                 | 0.307            | 13.6              | 13.6               | <0.001            |
| Statin                         | 46.6              | 18.3                | 0.634            | 44.6              | 44.6               | <0.001            | 45.1              | 15.6                | 0.676            | 42.8              | 42.8               | <0.001            |
| Loop diuretics                 | 11.4              | 2.7                 | 0.344            | 10.0              | 10.0               | <0.001            | 11.4              | 2.4                 | 0.360            | 9.9               | 9.9                | <0.001            |
| Thiazide diuretics             | 8.9               | 4.4                 | 0.180            | 8.9               | 8.9                | <0.001            | 8.7               | 3.8                 | 0.203            | 8.6               | 8.6                | <0.001            |

* CCBs = calcium channel blockers; ARBs = angiotensin II receptor blockers; ACEIs = angiotensin converting enzyme inhibitors; NSAIDs = nonsteroidal antiinflammatory drugs.
† Data were presented after full exposure score overlap weighting.
‡ The socioeconomic deprivation index score was measured by the Townsend deprivation index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).
§ Frequency of medication prescriptions and health care utilization during the past 1 year from the index date.
Informatics guidelines, confirmed SARS–CoV-2 infection codes reflect a positive reverse transcription–polymerase chain reaction test. The secondary outcomes were risk of hospitalization for SARS–CoV-2 infection and death from SARS–CoV-2 infection. Hospitalization for SARS–CoV-2 infection was defined as a hospitalization record in THIN within 30 days after the diagnosis of SARS–CoV-2 infection (21), and death from SARS–CoV-2 infection was defined as a death occurring within 30 days after the diagnosis of SARS–CoV-2 infection.

Assessment of covariates. Covariates included socio-demographic factors (age, sex, Townsend deprivation index), geographic location, body mass index, lifestyle factors (alcohol intake and smoking), number of previous SARS–CoV-2 tests (22), influenza vaccination during the past 1 year before the index date, comorbidities at any time since enrollment in the THIN database (Charlson comorbidity index, as well as individual conditions of hypertension, diabetes, hyperlipidemia, chronic kidney disease, pneumonia or infection, chronic obstructive pulmonary disease, cancer, venous thromboembolism, atrial fibrillation, ischemic heart disease, myocardial infarction, congestive heart failure, and stroke), medication use (calcium channel blockers, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, beta-blockers, glucocorticoids, nonsteroidal antiinflammatory drugs, opioids, antihypertensive drugs, antidiabetic medicine, statins, loop diuretics, and thiazide diuretics), and health care utilization during the past 1 year before the index date. Missing values were treated as a separate category for each variable. The absence of a record of any diagnosis was considered the absence of the condition. Among the vaccinated cohort, we also collected information on the brand of the first dose of vaccine that individuals received (Table 1).

Statistical analysis. For the vaccinated cohort, we divided the baseline study period into monthly time blocks. Eligible individuals were allocated into these blocks according to their index dates. In each monthly time block, we calculated an exposure score for gout and applied overlap weighting of the exposure score to balance baseline characteristics between the comparison groups (23).

The exposure score (analogous to propensity score) for gout at each monthly time block was calculated using a logistic regression model with the covariates described above. We generated 2 sets of exposure scores. First, an exposure score for the probability of gout was generated using a logistic regression model that included the covariates of age, sex, body mass index, Townsend deprivation index score, geographic location, and number of previous SARS–CoV-2 tests (i.e., partially adjusted exposure score). Second, additional covariates, i.e., lifestyle factors, comorbidities (including Charlson comorbidity index score and individual comorbidities), medications, and health care utilization, were added in the logistic regression model to generate an exposure score for the probability of gout in a fully adjusted model. In these partially and fully adjusted models, data on individuals with gout were weighted for the probability of not having gout (i.e., calculated as 1 – the exposure score), and data on individuals without gout (the non-gout general population controls) were weighted for the probability of having gout (i.e., calculated using the exposure score).

We assessed the balance of the distribution of baseline characteristics before and after overlap weighting by calculating the absolute standardized mean differences (24). We calculated the weighted incidence rate for the primary and secondary outcome measures and estimated the weighted absolute rate difference (RD) between the gout group and the non-gout general population control group using overlap weighting of exposure scores to control for confounders. We performed a Cox proportional hazards model to obtain hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of SARS–CoV-2 infection, hospitalization, and death from COVID-19 using overlap weighting of exposure scores to control for confounders. Death from other causes was considered the competing risk in the regression model. We tested the proportional hazards assumption by using a Kolmogorov-type supremum test (25). If the proportional hazards assumption was violated, we used a weighted Cox regression to obtain a nonproportional HR (26).

To assess the robustness of the study findings, we performed 2 sensitivity analyses. First, we restricted gout cases to individuals who had gout Read codes and received medication for gout treatment (i.e., colchicine or urate-lowering drugs). This method for identifying a diagnosis of gout has shown a validity of 90% in the UK General Practice Research Database (27), in which 60% of individuals overlap with THIN. Second, to determine if the severity of gout would affect the risk of SARS–CoV-2 infection, we performed a subgroup analysis according to whether individuals with gout had gout flares during the past year before the index date. A gout flare was defined as follows: 1) having specific Read codes of gout flare, 2) having Read codes of gout and a recorded prescription for colchicine treatment, or 3) having Read codes of gout and having a recorded prescription of at least 1 of the following treatments within 1 week of the gout Read code: intraarticular glucocorticoids, nonsteroidal antiinflammatory drugs, or glucocorticoid or adrenocorticotropic hormone (28,29).

We performed the same analyses for the unvaccinated cohort to assess the risk of SARS–CoV-2 infection, hospitalization within 30 days of infection, and death within 30 days of infection between the gout group and the non-gout general population control group. Sex-specific analyses were conducted to assess for potential differences between men and women in the risk of each of these outcomes.

All P values were 2-sided, and P values less than 0.05 were considered statistically significant in all group comparisons. All statistical analyses were performed with SAS software version 9.4.
RESULTS

A flow diagram depicting the selection process of individuals included in the analyses is shown in Figure 1. The vaccinated cohort included 54,576 individuals with gout and 1,336,377 individuals without gout from the general population. The unvaccinated cohort included 61,111 individuals with gout and 1,697,168 individuals without gout from the general population. Before exposure score overlap weighting, individuals with gout tended to be older, were more likely to be male, had more comorbidities, more frequently took medications, and visited their GPs more often than the general population. However, after exposure score overlap weighting, the baseline characteristics were well-balanced between the gout group and the non-gout general population control group (all standardized differences <0.1) (Table 1).

Vaccinated cohort. In the vaccinated cohort, 1,955 breakthrough infection cases (partially weighted incidence rate 4.68 cases per 1,000 person-months) occurred among individuals with gout during the study period, and 52,468 cases (partially weighted incidence rate 3.76 per 1,000 person-months) occurred among the non-gout general population. The risk of breakthrough infection among individuals with gout was significantly higher compared with individuals without gout in the general population. After adjusting for partial exposure scores, the RD was 0.91 cases per 1,000 person-months (95% CI 0.62–1.20 cases per 1,000 person-months), and the HR was 1.24 (95% CI 1.19–1.30). The corresponding RD after adjusting for full exposure scores was 0.71 cases per 1,000 person-months (95% CI 0.41–1.09 cases per 1,000 person-months), and the HR was 1.18 (95% CI 1.12–1.24) (Table 2 and Figure 2).

Unvaccinated cohort. In the unvaccinated cohort, the risk of SARS–CoV-2 infection was higher among individuals with gout than among non-gout individuals in the general population. As shown in Table 3 and Figure 2, 1,532 cases of SARS–CoV-2 infection occurred in the gout group (partially weighted incidence rate 6.89 cases per 1,000 person-months) and 47,222 cases in the non-gout general population (partially weighted incidence rate 6.89 cases per 1,000 person-months), resulting in a RD of 1.80 cases per 1,000 person-months (95% CI 1.19–2.41 cases per

Figure 1. Flow diagram showing the eligibility criteria applied to recipients of the COVID-19 vaccine (A) and unvaccinated individuals (B) among patients with gout compared to individuals without gout from the general UK population and the final populations included in the analyses. THIN = The Health Improvement Network.

A total of 184 hospitalizations occurred among individuals with gout (partially weighted incidence rate 0.42 hospitalizations per 1,000 person-months) and 1,956 hospitalizations in the non-gout general population (partially weighted incidence rate 0.28 hospitalizations per 1,000 person-months). Gout was associated with an increased risk of hospitalization after adjusting for partial exposure scores (HR 1.54 [95% CI 1.31–1.81]) and adjusting for full exposure scores (HR 1.30 [95% CI 1.10–1.53]). A total of 28 individuals in the gout group died (partially weighted incidence rate 0.06 deaths per 1,000 person-months), and 141 individuals in the non-gout general population died (partially weighted incidence rate 0.04 deaths per 1,000 person-months), resulting in a partial exposure score–adjusted HR of 1.74 (95% CI 1.14–2.67) and full exposure score–adjusted HR of 1.36 (95% CI 0.87–2.13) (Table 2 and Figure 2). When we performed a sensitivity analysis by restricting individuals in the gout group to those who had gout Read codes and had received treatment for gout as well as a subgroup analysis according to whether individuals in the gout group had gout flares during the past year before the index date, the results did not change significantly (see Supplementary Tables 2–4, available on the Arthritis & Rheumatology website at https://onlinelibrary.wiley.com/doi/art.42339).
## Table 2. Association between gout and the risk of breakthrough SARS-CoV-2 infection, 30-day hospitalization, and 30-day death in the vaccinated cohort*  

|                      | Gout (n = 54,576) | Non-gout (n = 1,336,377) |
|----------------------|-------------------|--------------------------|
| **Breakthrough SARS-CoV-2 infection** |                   |                          |
| No. of infections    | 1,955             | 52,468                   |
| Mean follow-up, months | 7.87             | 6.98                     |
| Weighted IR, per 1,000 person-months† | 4.68             | 3.76                     |
| Weighted RD, per 1,000 person-months (95% CI)† | 0.91 (0.62, 1.20) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.24 (1.19, 1.30) | 1.00 (referent)         |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 0.71 (0.41, 1.09) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.18 (1.12, 1.24) | 1.00 (referent)         |
| **30-day hospitalization** |                   |                          |
| No. of hospitalizations | 184              | 1,956                    |
| Mean follow-up, months | 7.85             | 6.98                     |
| Weighted IR, per 1,000 person-months† | 0.42             | 0.28                     |
| Weighted RD, per 1,000 person-months (95% CI)† | 0.15 (0.07, 0.24) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.54 (1.31, 1.81) | 1.00 (referent)         |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 0.10 (0.01, 0.18) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.30 (1.10, 1.53) | 1.00 (referent)         |
| **30-day death** |                   |                          |
| No. of deaths | 28                | 141                      |
| Mean follow-up, months | 7.86             | 6.99                     |
| Weighted IR, per 1,000 person-months† | 0.06             | 0.04                     |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 0.03 (-0.01, 0.06) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.74 (1.14, 2.67) | 1.00 (referent)         |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 0.02 (-0.02, 0.05) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.36 (0.87, 2.13) | 1.00 (referent)         |

* IR = incidence rate; RD = rate difference; 95% CI = 95% confidence interval; HR = hazard ratio.  
† Results obtained after partially adjusted exposure scores.  
‡ Results obtained after fully adjusted exposure scores.

**Figure 2.** Cumulative incidence of SARS-CoV-2 infection, 30-day hospitalization, and 30-day death in gout patients compared to individuals without gout in the vaccinated (A–C) and unvaccinated (D–F) cohorts. Color figure can be viewed in the online issue, which is available at [http://onlinelibrary.wiley.com/doi/10.1002/art.42339/abstract](http://onlinelibrary.wiley.com/doi/10.1002/art.42339/abstract).
Table 3. Association between gout and the risk of SARS–CoV-2 infection, 30-day hospitalization, and 30-day death in the unvaccinated cohort*

|                        | Gout (n = 61,111) | Non-gout (n = 1,697,168) |
|------------------------|-------------------|--------------------------|
| **SARS–CoV-2 infection** |                   |                          |
| No. of infections       | 1,532             | 47,222                   |
| Mean follow-up, months  | 2.86              | 4.20                     |
| Weighted IR, per 1,000 person-months† | 8.69 | 6.89                     |
| Weighted RD, per 1,000 person-months (95% CI)† | 1.80 (1.19, 2.41) | 0.00 (referent)         |
| Weighted HR (95% CI)†   | 1.23 (1.16, 1.30) | 1.00 (referent)         |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 1.15 (0.52, 1.78) | 0.00 (referent)         |
| Weighted HR (95% CI)‡   | 1.14 (1.08, 1.20) | 1.00 (referent)         |
| **30-day hospitalization** |                   |                          |
| No. of hospitalizations | 472               | 5,536                    |
| Mean follow-up, months  | 2.90              | 4.27                     |
| Weighted IR, per 1,000 person-months | 2.57 | 1.71                     |
| Weighted RD, per 1,000 person-months (95% CI) | 0.86 (0.54, 1.17) | 0.00 (referent)         |
| Weighted HR (95% CI) | 1.46 (1.32, 1.62) | 1.00 (referent)         |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 0.47 (0.14, 0.80) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 1.21 (1.09, 1.34) | 1.00 (referent)         |
| **30-day death** |                   |                          |
| No. of deaths | 128              | 842                      |
| Mean follow-up, months | 2.91              | 4.28                     |
| Weighted IR, per 1,000 person-months† | 0.65 | 0.53                     |
| Weighted RD, per 1,000 person-months (95% CI)† | 0.12 (–0.04, 0.28) | 0.00 (referent)         |
| Weighted HR (95% CI)† | 1.18 (0.97, 1.43) | 1.00 (referent)         |
| Weighted RD, per 1,000 person-months (95% CI)‡ | 0.00 (–0.17, 0.17) | 0.00 (referent)         |
| Weighted HR (95% CI)‡ | 0.94 (0.67, 1.34) | 1.00 (referent)         |

* IR = incidence rate; RD = rate difference; 95% CI = confidence interval; HR = hazard ratio.
† Results obtained after partially adjusted exposure scores.
‡ Results obtained after fully adjusted exposure scores.

1,000 person-months) and a HR of 1.23 (95% CI 1.16–1.30) after adjusting for partial exposure scores. The corresponding RD was 1.15 cases per 1,000 person-months (95% CI 0.52–1.78 cases per 1,000 person-months), and the HR was 1.14 (95% CI 1.08–1.20), after adjusting for full exposure scores.

During the follow-up period, 472 hospitalizations occurred in the gout group (partially weighted incidence rate 2.57 hospitalizations per 1,000 person-months) and 5,536 hospitalizations in the non-gout general population (partially weighted incidence rate 1.71 hospitalizations per 1,000 person-months). Compared with the non-gout general population, the HR of hospitalization for individuals with gout was 1.46 (95% CI 1.32–1.62) after adjusting for partial exposure scores and 1.21 (95% CI 1.09–1.34) after adjusting for full exposure scores. No statistically significant difference in death was observed between the gout group and non-gout general population group (Table 3 and Figure 2). Results from the sensitivity analysis and subgroup analysis did not change significantly (see Supplementary Tables 5–7, available on the Arthritis & Rheumatology website at https://onlinelibrary.wiley.com/doi/art.42339).

Sex-specific analyses. Among the vaccinated cohort, men with gout had an increased risk of breakthrough SARS–CoV-2 infection compared with men in the non-gout general population (partial exposure score–adjusted HR 1.30 [95% CI 1.23–1.37], full exposure score–adjusted HR 1.22 [95% CI 1.16–1.29]). However, no apparent association was observed in women. The risk of hospitalization was higher in men with gout (partial exposure score–adjusted HR 1.43 [95% CI 1.19–1.73], full exposure score–adjusted HR 1.22 [95% CI 1.00–1.48]) and women with gout (partial exposure score–adjusted HR 1.91 [95% CI 1.42–2.57], full exposure score–adjusted HR 1.55 [95% CI 1.15–2.10]) compared with the non-gout general population. Women with gout also had a higher risk of death than women without gout in the general population (partial exposure score–adjusted HR 2.46 [95% CI 1.48–6.13], full exposure score–adjusted HR 2.46 [95% CI 1.12–5.41]). However, no such association was observed in men (Figure 3). Similar sex-specific associations between gout and risks of SARS–CoV-2 infection, hospitalization, and death were also observed in the unvaccinated cohort (Figure 3).

**DISCUSSION**

In this large population-based study, we found that the risks of SARS–CoV-2 infection, 30-day hospitalization, and 30-day death were higher among individuals with gout than individuals without gout in the general population, irrespective of COVID-19 vaccination status. These results were consistent with the sensitivity analyses. In addition, women with gout might be more susceptible to severe outcomes of COVID-19 (i.e., hospitalization and death) than men with gout.

Few studies have described the risk of SARS–CoV-2 infection among individuals with gout (30,31). Of 100 studies included...
### Vaccinated cohort

| Subgroup                  | Fully adjusted model | Gout (weighted IR) | Non–gout (weighted IR) | HR (95% CI) |
|---------------------------|----------------------|--------------------|------------------------|-------------|
| **Breakthrough infection**|                      |                    |                        |             |
| Men (n=669,992)           |                      | 4.95               | 3.83                   | 1.30 (1.23, 1.37) |
| Women (n=720,961)         |                      | 3.81               | 3.56                   | 1.06 (0.96, 1.18) |
| **30–day hospitalization**|                      |                    |                        |             |
| Men (n=669,992)           |                      | 0.40               | 0.28                   | 1.43 (1.19, 1.73) |
| Women (n=720,961)         |                      | 0.50               | 0.26                   | 1.91 (1.42, 2.57) |
| **30–day death**          |                      |                    |                        |             |
| Men (n=669,992)           |                      | 0.05               | 0.04                   | 1.42 (0.85, 2.38) |
| Women (n=720,961)         |                      | 0.09               | 0.03                   | 3.01 (1.48, 6.13) |

### Unvaccinated cohort

| Subgroup                  | Fully adjusted model | Gout (weighted IR) | Non–gout (weighted IR) | HR (95% CI) |
|---------------------------|----------------------|--------------------|------------------------|-------------|
| **SARS–CoV–2 infection**  |                      |                    |                        |             |
| Men (n=877,801)           |                      | 8.48               | 6.60                   | 1.26 (1.18, 1.34) |
| Women (n=880,478)         |                      | 9.57               | 8.03                   | 1.53 (0.76, 2.99) |
| **30–day hospitalization**|                      |                    |                        |             |
| Men (n=877,801)           |                      | 2.28               | 1.65                   | 1.34 (1.19, 1.51) |
| Women (n=880,478)         |                      | 3.81               | 1.91                   | 1.91 (1.59, 2.3) |
| **30–day death**          |                      |                    |                        |             |
| Men (n=877,801)           |                      | 0.55               | 0.53                   | 0.99 (0.79, 1.25) |
| Women (n=880,478)         |                      | 1.12               | 0.54                   | 1.92 (1.36, 2.71) |

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**Figure 3.** Subgroup analysis of the incidence of SARS–CoV–2 infection, 30–day hospitalization, and 30–day death in gout patients compared to individuals without gout according to sex in the vaccinated (A) and unvaccinated (B) cohorts. IR = incidence rate, per 1,000 person-months; HR = hazard ratio; 95% CI = 95% confidence interval. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42339/abstract.
GOUT AND SEVERE SARS–COV-2 INFECTION

in a meta-analysis of the risk of SARS–CoV-2 infection among individuals with rheumatic diseases, none of the studies focused on gout (32). Furthermore, no clinical guidelines developed by professional organizations on the management of rheumatic diseases during the COVID-19 pandemic have specifically discussed gout (33).

Recently, one study using data from the UK Biobank showed no significant difference in the risk of SARS–CoV-2 breakthrough infection between individuals with gout and the general population after COVID-19 vaccination (9). The study was conducted shortly after the availability of COVID-19 vaccines; thus, the number of cases of breakthrough infection was relatively small. In addition, the association of gout with severe COVID-19 outcomes was not evaluated among vaccinated individuals.

In this large-scale study, we were able to quantify the respective risk of SARS–CoV-2 breakthrough infection and severe outcomes (i.e., hospitalization and death) among vaccinated individuals. Although vaccination greatly reduced the risk of SARS–CoV-2 infection and severe outcomes among all individuals with or without gout, individuals with gout were still more susceptible to breakthrough infection and severe outcomes than individuals without gout in the general population.

The biologic mechanisms linking gout to the risk of SARS–CoV-2 infection remain unclear and deserve further investigation. A recent study demonstrated that hyperuricemia suppressed neutrophil adhesion and extravasation in mice with coronavirus-related sterile inflammation (34), suggesting that innate immunity may be impaired in gout, leading to increased susceptibility to infections.

Interestingly, the sex-specific analysis in our study showed that women with gout had a higher risk of severe COVID-19–related hospitalization and death than men with gout. In general, women with gout are older and tend to have more comorbidities that are also more severe, which may contribute to more severe COVID-19–related outcomes. Nevertheless, our findings will need confirmation in future studies.

Our study has several strengths. This study was based on a large, electronic medical record database representative of the general population, providing a high level of generalizability. In addition, we controlled for major potential confounders by using the overlap weights of exposure scores, suggesting that the current findings are robust.

Several limitations of our study deserve comment. First, it is possible that individuals with gout may have sought medical care more often and were more likely to be tested for SARS–CoV-2 infection than the non-gout general population controls during the COVID-19 pandemic period. Consequently, their risk of SARS–CoV-2 infection may be overestimated. However, the number of general practice visits and previous COVID-19 tests were well-balanced between the gout cohort and non-gout general population controls, suggesting that such bias, if it exists, is unlikely to fully explain the observed findings.

Second, since we do not have detailed information on the temporal relationship between gout and some covariates, we used 2 exposure scores to control for potential confounding bias. Although the magnitude of associations generated from controlling for the partially adjusted exposure score (which may lead to the residual confounding) (35) was larger than that generated from controlling for the fully adjusted exposure score (which may lead to overadjustment), the direction of the associations from these 2 analyses was consistent, supporting the robustness of the findings.

Third, although patients’ medical information from hospital specialists is usually reported back to their GP, and GPs hold information on significant health-related events (including the diagnosis of COVID-19), we cannot access data that were held in the hospital and not reported back to GPs (e.g., tests performed at the hospital that were not reported back to GPs). As a result, misclassification of COVID-19 diagnosis could occur and bias the study findings. Nevertheless, such bias is likely to be small; if such bias occurred, it is likely to be nondifferential and would bias the observed associations toward the null.

In conclusion, our study findings suggest that individuals with gout, especially women, have a higher risk of severe outcomes of SARS–CoV-2 infection than the non-gout general population, even after COVID-19 vaccination. These findings suggest that additional measures should be considered to mitigate the risk of SARS–CoV-2 infection and potential severe outcomes for individuals with gout, especially women and even after vaccination.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Zhang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Xie, Wei, Lei, Zhang.

Acquisition of data. Xie, Lu, Wei, Lei, Zhang.

Analysis and interpretation of data. Xie, Choi, Dalbeth, Wallace, Sparks, Zeng, Li, Wei, Lei, Zhang.

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