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

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ABSTRACT

Objectives Gout patients often have multiple comorbidities, making them susceptible to SARS-CoV-2 infection and its severe outcomes; however, few studies have examined the association between gout and the risk of SARS-CoV-2 infection and its severe sequelae, especially after COVID-19 vaccination.

Methods We conducted two cohort studies using The Health Improvement Network. Individuals with gout and those without gout from the general population were followed from December 8th, 2020, to October 31st, 2021. We estimated the rate difference (RD) and hazard ratio (HR) of SARS-CoV-2 infection and its severe outcomes (i.e., hospitalization and death over 30 days after SARS-CoV-2 infection) for individuals with gout versus those without gout using Cox proportional hazard model according to COVID-19 vaccination status. We adjusted potential confounders using overlap weighting of exposure score.

Results Among the vaccinated cohort, 1,955 cases of breakthrough infection occurred in 54,576 individuals with gout (4.68/1000 person-months) and 52,468 cases in 1,336,377 individuals without gout (3.76/1000 person-months). The adjusted RD of breakthrough infection was 0.91 (95%CI: 0.62-1.20)/1000 person-months, and the 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 showed 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.

Conclusions These general population data suggest that individuals with gout, especially women, have higher risks of both SARS-CoV-2 infection and severe

sequelae, even with vaccinations.

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has spread around the world, causing devastating economic and social disruption (1). There are few effective therapies for COVID-19 and these remain a scarce resource. As such, vaccination remains the most promising global approach at present for controlling this disease (2). Despite the spreading availability of effective vaccines, millions of new cases in both vaccinated and unvaccinated people continue to occur each day worldwide and new variants are expected to emerge in the future which may have evolved immune escape (1). Identifying individuals who are susceptible to breakthrough infection and its severe sequelae after vaccination may identify populations who remain vulnerable to COVID-19 despite vaccination and therefore benefit from other risk mitigating strategies (e.g., pre-exposure prophylaxis).

Gout is the most 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 pro-inflammatory state that may complicate COVID-19 (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, two 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 found no significant difference in the risk of SARS-CoV-2

infection and death between participants with gout and those without gout (8). Using the same data source, a subsequent study reported that gout is a risk factor for SARS-CoV-2 infection and its related death (9). However, both studies were conducted during the pre-vaccine era (up to August 24, 2020) (8) or the early vaccination era (up to April 6, 2021) (9), leaving an important knowledge gap regarding the efficacy of vaccination against SARS-CoV-2 infection and its severe outcomes among individuals with gout (9). Since studies have found that waning vaccine effectiveness is greater in individuals with underlying medical conditions (10), assessing the effectiveness of COVID-19 vaccination against breakthrough infection and its severe outcomes in gout patients has important clinical and public health implications.

We conducted two cohort studies to quantify the risk of SARS-CoV-2 infection and its severe outcomes (i.e., hospitalization and death) among individuals with gout and compared them 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 represents the UK population regarding demographics and medical conditions. Details of the THIN database have been described previously (11). It consists of approximately 17 million persons from 790 general practices whose health care information is systematically recorded by general practitioners (GPs) and sent anonymously to THIN. Because the National Health Service requires

UK residents 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). The computerized information 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 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).

Study design

First, we compared the risk of breakthrough infection (i.e., SARS-CoV-2 infection among people who were vaccinated), hospitalization, and death between individuals with gout and members of the general population without gout (hereafter referred to as the general population) after COVID-19 vaccination (i.e., vaccinated cohort). The details of vaccination records were based on the Read codes in THIN (**Supplementary Table 1**). Gout diagnosis was also captured using Read codes (**Supplementary Table 1**) (17, 18). Eligible individuals consisted of those who were 18-90 years of age between December 8th, 2020 (i.e., when the vaccination campaign began in the UK) and October 31st, 2021, had no previously documented SARS-CoV-2 infection, and had at least two years continuous enrollment with a general practice. Second, we took the same approach to compare the risk of SARS-CoV-2 infection and its severe outcomes between individuals with gout and the general population among unvaccinated individuals (i.e., unvaccinated cohort).

Cohort definition

For each eligible participant in the vaccinated cohort, follow-up started on the day the first dose of vaccine was received (i.e., index date) and ended on the day that an outcome of the interest occurred (i.e., SARS-CoV-2 infection, hospitalization, or death), or the end of the study period (October 31st, 2021), whichever occurred first. For each eligible participant in the unvaccinated cohort, follow-up started on December 8th, 2020 (i.e., index date) and ended on the day of the first dose of vaccination received, the day that an outcome of the interest occurred or the end of the study period (October 31st, 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**) (19, 20). According to National Health Service Guidance and Standard Operating Procedures for Primary Care, and UK Faculty of Clinical Informatics guidelines, confirmed SARS-CoV-2 infection codes reflects a positive RT-PCR test. The secondary outcomes consisted of the 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 sociodemographic factors (age, sex, Townsend Deprivation Index), geographic location, body mass index (BMI), lifestyle factors (alcohol use and

smoking status), number of previous COVID-19 tests (22), influenza vaccination during the past one year before the index date, comorbidities at any time since enrolment to the index date (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, ischaemic 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 anti-inflammatory drugs, opioids, antihypertensive drugs, antidiabetic medicine, statin, loop diuretics, and thiazide diuretics) and healthcare utilization during the past one year before the index date. Missing values were treated as a separate missing category for each variable. The absence of a record of any diagnosis was considered as the absence of the condition. Among the vaccinated cohort, we also collected information on the brand of the first dose of vaccine that participants received (**Table 1**).

Statistical analysis

Among 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 blocks we calculated 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 the logistic regression model with the covariates described above. We generated two sets of exposure score. First, exposure score for gout was generated using a logistic regression model that included

covariates of age, sex, BMI, socioeconomic deprivation index score, region, and number of previous COVID-19 tests (i.e., exposure score used for partial adjustment). Second, additional covariates, i.e., lifestyle factors, comorbidities (including Charlson comorbidity index score and individual comorbidities), medications, and healthcare utilization, were added in the logistic regression model to generate the exposure score for gout (i.e., exposure score used for full adjustment). Individuals with gout were weighted by the probability of not having gout, i.e., 1-exposure score, and non-gout individuals from the general population were weighted by the probability of having gout, i.e., 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 comparison group using overlap weighting of exposure score to control for confounding. We performed a Cox proportional hazard model to obtain hazard ratios (HR) and 95% confidence intervals (CI) of the risk of breakthrough infection, hospitalization, and death for COVID-19 using overlap weighting of exposure score to control for confounding. Death from other causes was considered as the competing risk in the regression model. We tested the proportional hazard assumption by using the Kolmogorov supremum test (25). If the proportional hazard assumption was violated, we used a weighted Cox regression to obtain a non-proportional HR (26).

To assess the robustness of the study findings, we performed two sensitivity analyses. First, we restricted gout cases to those who had gout Read codes and received medication for gout treatment (i.e., colchicine or urate-lowering drugs). This algorism for diagnosis of gout has shown a validity of 90% in the General Practice Research Database (GPRD) (27), in which 60% of participants 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 gout cases had gout flares during the past year before the index date. We defined a gout flare as follows: having Read codes of gout and a recorded prescription of colchicine; or having Read codes of gout and receiving at least one of the following treatments within one week: intra-articular corticosteroids, prescription of nonsteroidal anti-inflammatory drugs, corticosteroid or adrenocorticotropic hormone; or having Read codes specific for gout flare (28, 29).

We performed the same analyses for the unvaccinated cohort to assess the risk of SARS-CoV-2 infection, 30-day hospitalization, and 30-day death between two comparison groups. Sex-specific analyses was conducted to assess potentially different associations between men and women.

All P values were 2-sided and $P<0.05$ was considered significant for all tests. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The flowchart depicting the selection process of participants is shown in **Figure 1**.

The vaccinated cohort consisted of 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. As shown in **Table 1**, before exposure score overlap weighting, individuals with gout tended to be older, were more likely to be male, had more comorbidities, more frequently used of 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 two comparison groups (all standardized differences<0.1).

Vaccinated cohort

In the vaccinated cohort, 1,955 breakthrough infection cases (partially weighted incidence rate: 4.68/1000 person-months) occurred among the individuals with gout during follow-up, and 52,468 cases (partially weighted incidence rate: 3.76/1000 person-months) occurred among the general population. Compared with the general population, the risk of breakthrough infection among individuals with gout was significantly higher than among the general population. Adjusting for partial exposure score, RD and HR were 0.91 (95% CI: 0.62-1.20)/1000 person-months and 1.24 (95% CI: 1.19-1.30), respectively. The corresponding RD and HR after adjusting for full exposure score were 0.71 (95% CI: 0.41-1.09)/1000 person-months and 1.18 (95% CI: 1.12-1.24), respectively (**Table 2** and **Figure 2**).

A total of 184 hospitalizations occurred in the gout group (partially weighted incidence rate: 0.42/1,000 person-months) and 1,956 in the general population (partially weighted incidence rate: 0.28/1,000 person-months). Gout was associated

with an increased risk of hospitalization after adjusting for either partial exposure score (HR 1.54, 95% CI: 1.31-1.81) or full exposure score (HR 1.30, 95% CI: 1.10-1.53). A total of 28 patients died in the gout group (partially weighted incidence rate: 0.06/1000 person-months) and 141 deaths in the general population (partially weighted incidence rate: 0.04/1000 person-months), resulting in 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 the sensitivity analyses by (1) restricting gout cases to those who had gout Read codes and received treatment for gout, and (2) conducting the subgroup analysis according to whether gout cases had gout flares during the past year before the index date, the results did not change materially (**Supplementary Table 2-4**).

Unvaccinated cohort

In the unvaccinated cohort, the risk of SARS-CoV-2 infection was higher among individuals with gout than among 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: 8.69/1000 person-months) and 47,222 in the general population (partially weighted incidence rate: 6.89/1000 person-months), resulting in an RD of 1.80 (95% CI: 1.19-2.41)/1000 person-months and a HR of 1.23 (95% CI: 1.16-1.30) after adjusting for partial exposure score. The corresponding RD and RR were 1.18 (95% CI: 0.56-1.81)/1000 person-months and 1.14 (95% CI: 1.08-1.20), respectively, after adjusting for full exposure score.

During the follow-up period, 472 hospitalizations occurred in the gout group (partially weighted incidence rate: 2.57/1,000 person-months) and 5,536 in the general

population (partially weighted incidence rate: 1.71/1,000 person-months). Compared with the general population, HR of hospitalization for individuals with gout was 1.46 (95% CI: 1.32-1.62) after adjusting for partial exposure score and 1.21 (95% CI: 1.09-1.34) after adjusting for full exposure score. No statistically significant difference in death was observed between the two comparison groups (**Table 3** and **Figure 2**). Results from the sensitivity analyses did not change materially (**Supplementary Table 5-7**).

Sex-specific analysis

Among the vaccinated cohort, men with gout had an increased risk of breakthrough infection compared with men in the general population (adjusting for partial exposure score: HR 1.30, 95% CI: 1.23-1.37; adjusting full exposure score: HR 1.22, 95% CI: 1.16-1.29). However, no apparent association was observed in women. The risk of hospitalization was higher in both men (adjusting for partial exposure score: HR 1.43, 95% CI: 1.19-1.73; adjusting for full exposure score: HR 1.22, 95% CI: 1.00-1.48) and women with gout (adjusting for partial exposure score: HR 1.91, 95% CI: 1.42-2.57; adjusting for full exposure score: HR 1.55, 95% CI: 1.15-2.10) than that in the general population. Women with gout also had a higher risk of death than the general population (adjusting for partial exposure score, HR 3.01, 95% CI: 1.29-5.75; adjusting for full exposure score, HR 2.23, 95% CI: 0.98-5.08). 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 among 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 among individuals with gout were higher than the general population irrespective of the vaccination status. The results were consistent from the sensitivity analyses. In addition, women with gout are more susceptible to severe sequelae of COVID-19 (hospitalization and death) than men.

Unlike many other inflammatory arthritis, few studies have described the risk of SARS-CoV-2 infection among individuals with gout (30, 31). Of 100 studies included in a meta-analysis of the risk of SARS-CoV-2 infection among rheumatic diseases, none of them focused on gout (32). Furthermore, no clinical guidelines on the management of rheumatic diseases throughout the pandemic developed by professional organizations specifically discussed gout (33).

Recently, one study using the UK Biobank data found 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 during the early vaccination period; thus, the number of cases with breakthrough infection was relatively small. In addition, the association of gout with the severe COVID-19 outcomes was not evaluated among vaccinated individuals. In the current large-scale study, we were able to quantify the respective risk of SARS-CoV-2 breakthrough infection and its severe outcomes (i.e., hospitalization and death) among vaccinated individuals. Although vaccination greatly reduced the risk of SARS-CoV-2 infection and its severe outcomes among individuals with gout and the general population, individuals with gout were still more susceptible to breakthrough infection and its severe outcomes than the general population.

The biological mechanisms linking gout to the risk of SARS-CoV-2 infection remains 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 maybe impaired in gout, leading to enhanced susceptibility to infections. Interestingly, the sex-specific analysis showed that women with gout had a higher risk of severe COVID-19 related hospitalization and death than men. In general, women with gout are older and tended to have a larger number and more severe comorbidities, which may contribute to more severe COVID-19 related outcomes. Nevertheless, our findings will need confirmation in future studies.

Our study has several strengths. The present study was based on a large electronic medical record database representative of the general population, providing a high level of generalizability. In addition, major potential confounders were well-balanced after using the overlap weights of exposure score, suggesting that current findings are robust. Several limitations also deserve comment. First, it is possible that individuals with gout may seek medical care more often and are more likely to have the COVID-19 test than the general population 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 general population cohort, 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 of covariates, we used two exposure scores to control for potential confounding

bias. Although the magnitude of associations generated from controlling for the partial exposure score (which may lead to the residual confounding) (35) was larger than that generated from controlling for the full exposure score (which may lead to over-adjustment), the direction of the associations from these two analyses is consistent, supporting the robustness of the findings. Third, although the medical information from the hospital specialist is reported back to the GP in general, and GPs hold information on significant health-related events (including the diagnosis of COVID-19), we cannot access the data that were held in the hospital and were not reported back to GPs (e.g., tests were performed at the hospital and were not reported back to GPs). As a result, misclassification of the COVID-19 diagnosis could occur and bias the study findings. Nevertheless, such bias is likely to be small; if occurred, it is likely to be non-differential and would bias the observed associations towards 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 general population, even after COVID-19 vaccination. This finding informs individuals with gout, especially women, that additional measures, even after vaccination, should be considered in order to mitigate the risk of SARS-CoV-2 infection and its severe sequelae.

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Contributors

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Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication

Not required.

Ethical approval

This study received approval from the medical ethical committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

The data that support the findings of this study are available within the article and its supplementary information files or from the corresponding author upon reasonable request.

Scientific approval

This study was approved by the THIN Scientific Review Committee (20SRC003-A2).

Statement

THIN is a registered trademark of Cegedim SA 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 work uses de-identified data provided by participants as a part of their routine primary care.

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Figure legends:

Figure 1. Flowchart of eligible participants.

Figure 2. Cumulative incidence of SARS-CoV-2 infection, 30-day hospitalization and death in gout patients as compared with individuals without gout in the vaccinated and unvaccinated cohorts.

Figure 3. Incidence of SARS-CoV-2 infection, 30-day hospitalization and death in gout patients as compared with individuals without gout according to sex subgroups in the vaccinated and unvaccinated cohorts. n, number; IR, incidence rate (/1000 person-months); HR, hazard ratio.

Table 1. Baseline characteristics of gout patients and individuals without gout in vaccinated and unvaccinated cohorts

	Vaccinated cohort						Unvaccinated cohort					
	Before exposure-score overlap weighting			After exposure-score overlap weighting*			Before exposure-score overlap weighting			After exposure-score overlap weighting*		
Variable list	**Gout**	**Non-gout**	**Standard difference**	**Gout**	**Non-gout**	**Standard difference**	**Gout**	**Non-gout**	**Standard difference**	**Gout**	**Non-gout**	**Standard difference**
Number	54,576	1,336,377		54,576	1,336,377		61,111	1,697,168		61,111	1,697,168	
Demographics												
Age, mean (SD), y	66.3 (13.1)	52.1 (17.8)	0.906	65.6 (13.3)	65.6 (13.8)	<0.001	65.7 (13.5)	49.8 (17.9)	1.002	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
BMI, mean (SD), kg/m^2	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
Region, %			0.168			<0.001			0.184			<0.001
England	14.8	14.2		14.9	14.9		17.3	18.5		17.5	17.5	
Northern Ireland	11.8	13.6		12.0	12.0		11.5	13.2		11.7	11.7	
Scotland	35.8	41.9		36.4	36.4		33.9	39.5		34.5	34.5	
Wales	37.6	30.3		36.7	36.7		37.3	28.8		36.4	36.4	
First dose of COVID-19 vaccine			0.265			<0.001			–			–
AstraZeneca	67.7	55.2		67.7	67.7		–	–		–	–	
Pfizer	31.1	42.3		31.2	31.2		–	–		–	–	
Other	1.1	2.4		1.1	1.1		–	–		–	–	

Second dose of COVID-19 vaccine			0.288			0.013			–			–
AstraZeneca	65.5	52.4		65.4	65.2		–	–		–	–	
Pfizer	29.6	38.8		29.7	29.6		–	–		–	–	
Other	0.5	1.8		0.5	0.5		–	–		–	–	
None	4.4	7.0		4.4	4.7		–	–		–	–	
Number of previous COVID-19 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 drinking (%)			0.161			<0.001			0.185			<0.001
None	12.6	15.5		12.9	12.9		12.7	16.0		13.1	13.1	
Past	4.0	2.6		4.0	4.0		4.0	2.5		3.9	3.9	
Current	78.5	64.0		77.7	77.7		78.1	61.3		77.2	77.2	
Missing data	4.9	17.9		5.4	5.4		5.3	20.2		5.8	5.8	
Smoking (%)			0.301			<0.001			0.333			<0.001
None	52.8	56.4		53.0	53.0		52.6	55.0		52.8	52.8	
Past	36.3	23.1		35.4	35.4		35.9	21.7		34.9	34.9	
Current	10.5	16.5		11.2	11.2		11.0	18.2		11.7	11.7	
Missing data	0.4	4.0		0.5	0.5		0.5	5.0		0.6	0.6	
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
Hyperlipidemia	18.4	6.8	0.354	17.3	17.3	<0.001	18.0	6.0	0.378	16.8	16.8	<0.001
Chronic kidney disease	17.4	3.6	0.462	15.1	15.1	<0.001	17.1	3.1	0.478	14.7	14.7	<0.001

Pneumonia or infection	9.3	6.0	0.123	9.0	9.0	<0.001	9.2	5.6	0.139	8.9	8.9	<0.001
Chronic obstructive pulmonary disease	6.6	3.3	0.149	6.3	6.3	<0.001	6.4	2.9	0.168	6.2	6.2	<0.001
Cancer	14	7.6	0.205	13.5	13.5	<0.001	13.6	6.6	0.233	13.0	13.0	<0.001
Venous thromboembolism	4.5	2.0	0.143	4.3	4.3	<0.001	4.4	1.8	0.152	4.2	4.2	<0.001
Atrial fibrillation	11.9	2.8	0.356	10.5	10.5	<0.001	11.6	2.4	0.367	10.1	10.1	<0.001
Ischaemic heart disease	16	5.1	0.361	14.9	14.9	<0.001	15.7	4.4	0.383	14.5	14.5	<0.001
Myocardial infarction	7.4	2.4	0.233	6.9	6.9	<0.001	7.3	2.1	0.249	6.7	6.7	<0.001
Congestive heart failure	6.7	1.4	0.272	5.7	5.7	<0.001	6.5	1.2	0.281	5.6	5.6	<0.001
Stroke	5.1	2.0	0.171	4.8	4.8	<0.001	4.9	1.7	0.181	4.6	4.6	<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	29.5	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
Healthcare utilization, mean (SD)												
Hospitalizations‡	0.4 (1.1)	0.2 (0.8)	0.153	0.3 (1.1)	0.3 (1.1)	<0.001	0.4 (1.1)	0.2 (0.8)	0.176	0.4 (1.1)	0.4 (1.1)	<0.001
General practice visits‡	3.1	1.9	0.275	3.0 (4.9)	3.0	<0.001	3.4	2.0	0.320	3.3	3.3	<0.001

	(5.2)	(3.5)			(5.4)		(5.2)	(3.6)		(4.9)	(5.5)	
Specialist referrals‡	0.3 (0.8)	0.2 (0.6)	0.158	0.3 (0.8)	0.3 (0.8)	<0.001	0.4 (0.9)	0.2 (0.6)	0.189	0.3 (0.8)	0.3 (0.8)	<0.001

*Data were presented after full exposure-score overlap weighting.

†The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

‡Frequency during the past 1 year.

BMI, body mass index; n, number; y, years; SD, standard deviation; CCBs, Calcium channel blockers; ARBs, angiotensin II receptor blockers; ACEIs, angiotensin converting enzyme inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Association between gout and the risk of breakthrough infection, 30-day hospitalization and death in vaccinated cohort

	Breakthrough infection	
	Gout (n= 54,576)	**Non-gout (n= 1,336,377)**
Event (n)	1,955	52,468
Mean follow-up (months)	7.87	6.98
Weighted IR*, /1000 person-months	4.68	3.76
Weighted RD*, /1000 person-months (95% CI)	0.91 (0.62, 1.20)	0.00 (reference)
Weighted HR* (95% CI)	1.24 (1.19, 1.30)	1.00 (reference)
Weighted RD**, /1000 person-months (95% CI)	0.71 (0.41, 1.09)	0.00 (reference)
Weighted HR** (95% CI)	1.18 (1.12, 1.24)	1.00 (reference)
	30-day hospitalization	
	Gout (n= 54,576)	**Non-gout (n= 1,336,377)**
Event (n)	184	1,956
Mean follow-up (months)	7.85	6.98
Weighted IR*, /1000 person-months	0.42	0.28
Weighted RD*, /1000 person-months (95% CI)	0.15 (0.07, 0.24)	0.00 (reference)
Weighted HR* (95% CI)	1.54 (1.31, 1.81)	1.00 (reference)
Weighted RD**, /1000 person-months (95% CI)	0.10 (0.01, 0.18)	0.00 (reference)
Weighted HR** (95% CI)	1.30 (1.10, 1.53)	1.00 (reference)
	30-day death	
	Gout (n= 54,576)	**Non-gout (n= 1,336,377)**
Event (n)	28	141
Mean follow-up (months)	7.86	6.99
Weighted IR*, /1000 person-months	0.06	0.04
Weighted RD*, /1000 person-months (95% CI)	0.03 (-0.01, 0.06)	0.00 (reference)
Weighted HR* (95% CI)	1.74 (1.14, 2.67)	1.00 (reference)
Weighted RD**, /1000 person-months (95% CI)	0.02 (-0.02, 0.05)	0.00 (reference)
Weighted HR** (95% CI)	1.36 (0.87, 2.13)	1.00 (reference)

n, number; IR, incidence rate; RD, rate difference; CI, confidence interval; HR hazard ratio.

*Results obtained from partially adjusted model.

**Results obtained from fully adjusted model.

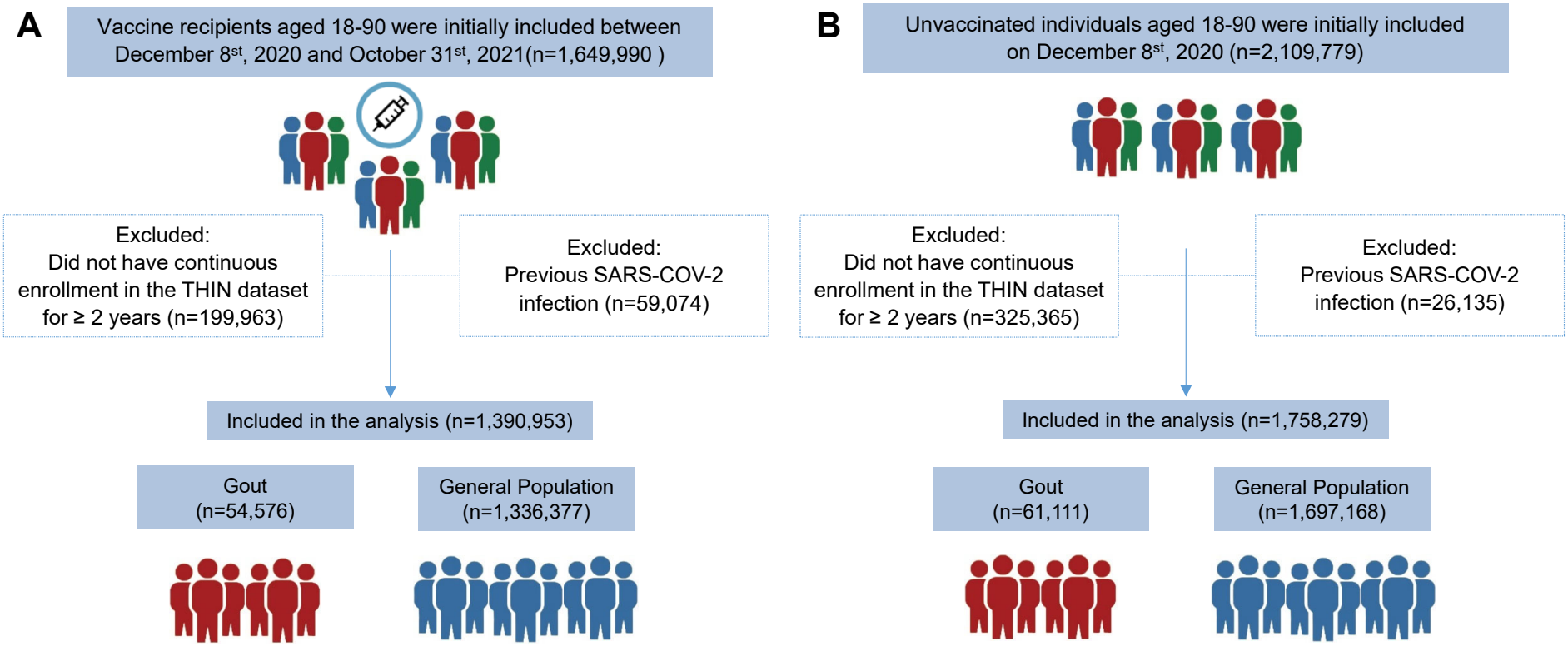
Table 3. Association between gout and the risk of SARS-CoV-2 infection, 30-day hospitalization and death in unvaccinated cohort

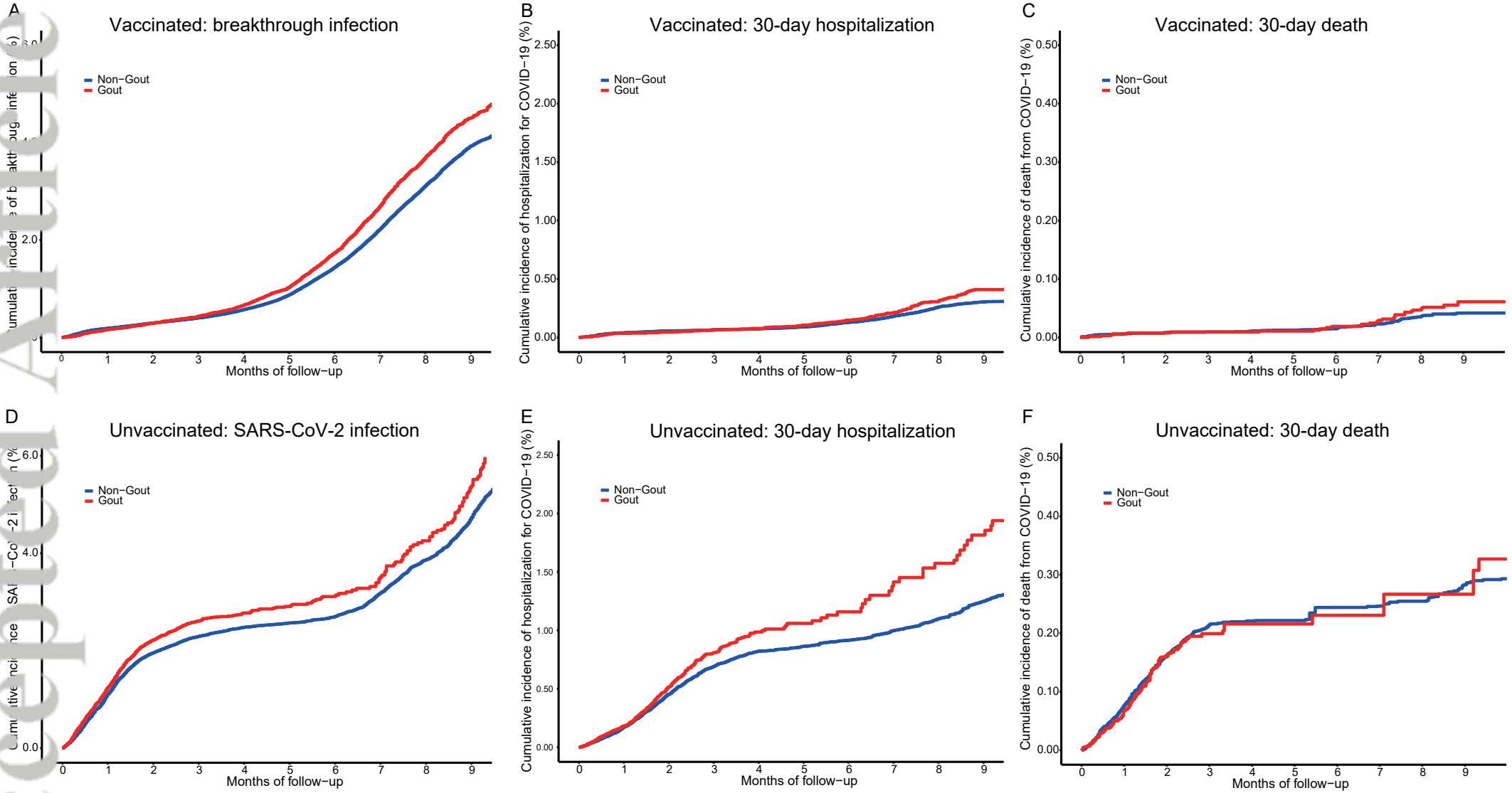
	SARS-CoV-2 infection	
	Gout (n= 61,111)	**Non-gout (n= 1,697,168)**
Event (n)	1,532	47,222
Mean follow-up (months)	2.86	4.20
Weighted IR*, /1000 person-months	8.69	6.89
Weighted RD*, /1000 person-months (95% CI)	1.80 (1.19, 2.41)	0.00 (reference)
Weighted HR* (95% CI)	1.23 (1.16, 1.30)	1.00 (reference)
Weighted RD**, /1000 person-months (95% CI)	1.15 (0.52, 1.78)	0.00 (reference)
Weighted HR** (95% CI)	1.14 (1.08, 1.20)	1.00 (reference)
	30-day hospitalization	
	Gout (n= 61,111)	**Non-gout (n= 1,697,168)**
Event (n)	472	5,536
Mean follow-up (months)	2.90	4.27
Weighted IR*, /1000 person-months	2.57	1.71
Weighted RD*, /1000 person-months (95% CI)	0.86 (0.54, 1.17)	0.00 (reference)
Weighted HR* (95% CI)	1.46 (1.32, 1.62)	1.00 (reference)
Weighted RD**, /1000 person-months (95% CI)	0.47 (0.14, 0.80)	0.00 (reference)
Weighted HR** (95% CI)	1.21 (1.09, 1.34)	1.00 (reference)
	30-day death	
	Gout (n= 61,111)	**Non-gout (n= 1,697,168)**
Event (n)	128	842
Mean follow-up (months)	2.91	4.28
Weighted IR*, /1000 person-months	0.65	0.53
Weighted RD*, /1000 person-months (95% CI)	0.12 (-0.04, 0.28)	0.00 (reference)
Weighted HR* (95% CI)	1.18 (0.97, 1.43)	1.00 (reference)
Weighted RD**, /1000 person-months (95% CI)	0.00 (-0.17, 0.17)	0.00 (reference)
Weighted HR** (95% CI)	0.94 (0.67, 1.34)	1.00 (reference)

n, number; IR, incidence rate; RD, rate difference; CI, confidence interval; HR hazard ratio.

*Results obtained from partially adjusted model.

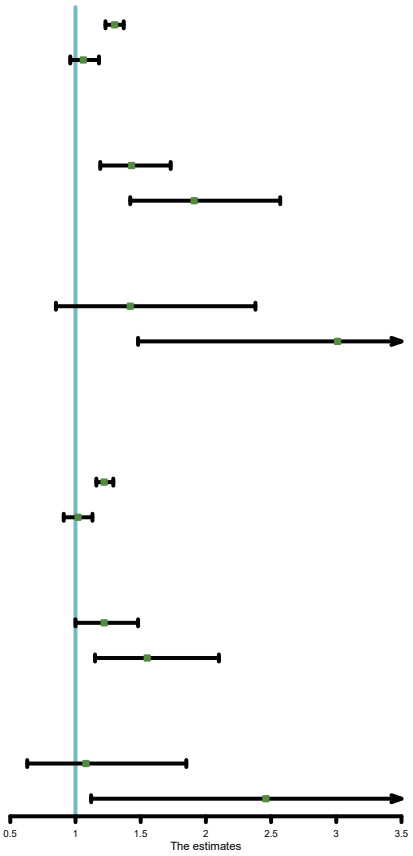
**Results obtained from fully adjusted model.





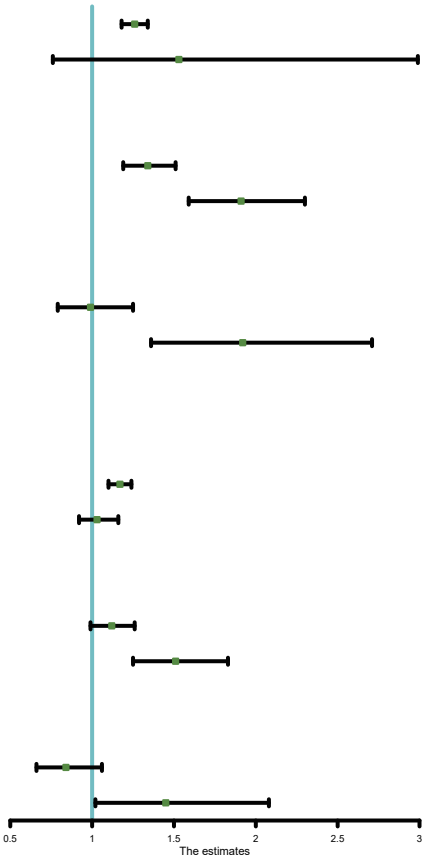
A **Vaccinated cohort**

Subgroup	Gout (weighted IR)	Non−gout (weighted IR)	HR (95%)
Partially adjusted model			
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)
Fully adjusted model			
Breakthrough infection			
Men (n=669,992)	4.95	4.06	1.22 (1.16, 1.29)
Women (n=720,961)	3.82	3.74	1.02 (0.91, 1.13)
30−day hospitalization			
Men (n=669,992)	0.38	0.32	1.22 (1.00, 1.48)
Women (n=720,961)	0.49	0.32	1.55 (1.15, 2.10)
30−day death			
Men (n=669,992)	0.05	0.05	1.08 (0.63, 1.85)
Women (n=720,961)	0.09	0.04	2.46 (1.12, 5.41)



B **Unvaccinated cohort**

Subgroup	Gout (weighted IR)	Non−gout (weighted IR)	HR (95%)
Partially adjusted model			
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)
Fully adjusted model			
SARS−CoV−2 infection			
Men (n=877,801)	8.42	7.16	1.17 (1.10, 1.24)
Women (n=880,478)	9.48	8.72	1.03 (0.92, 1.16)
30−day hospitalization			
Men (n=877,801)	2.18	1.91	1.12 (0.99, 1.26)
Women (n=880,478)	3.72	2.37	1.51 (1.25, 1.83)
30−day death			
Men (n=877,801)	0.50	0.59	0.84 (0.66, 1.06)
Women (n=880,478)	1.07	0.69	1.45 (1.02, 2.08)



Gout and Excess Risk of Severe SARS–CoV-2 Infection Among Vaccinated Individuals

Study cohorts

Vaccinated cohort

Gout
(n = 54,576)

General population
(n = 1,336,377)

Unvaccinated cohort

Gout
(n = 61,111)

General population
(n = 1,697,168)

Methods

The Health Improvement Network
(December 8, 2020 to October 31, 2021)

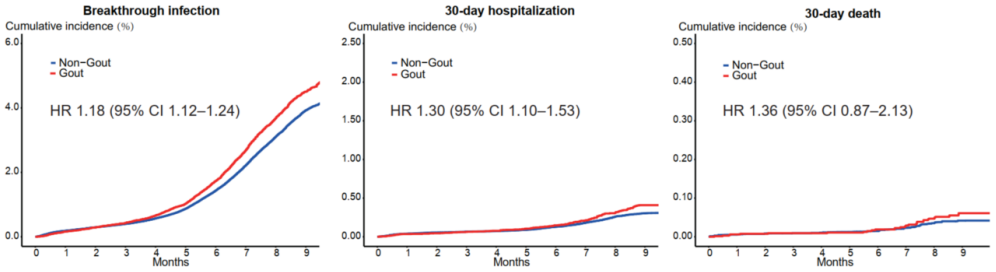
Gout vs. General population

Overlap weighting of exposure score → **Cox proportional hazard model**

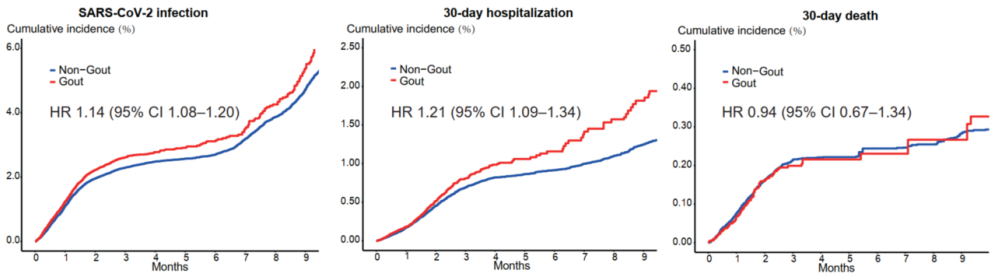
SARS–CoV-2 infection
30-day hospitalization from COVID-19
30-day death from COVID-19

Results

Vaccinated cohort



Unvaccinated cohort



Conclusion

Individuals with gout, especially women, have a higher risk of both SARS–CoV-2 infection and severe sequelae, even with vaccination.

Xie D, Choi HK, Dalbeth N, et al. Gout and excess risk of severe SARS–CoV-2 infection among vaccinated individuals: a general population study. Arthritis Rheumatol 2022.

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