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Running head: COVID-19 among unvaccinated and vaccinated patients with RA

Title: Risk of COVID-19 among unvaccinated and vaccinated patients with rheumatoid arthritis: a general population study

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ABSTRACT

Objective To determine whether the patients with rheumatoid arthritis (RA) are at higher risks for SARS-CoV-2 infection and its severe outcomes before and after COVID-19 vaccination.

Methods Using United Kingdom primary care database, we conducted two cohort studies to compare the risks of SARS-CoV-2 infection, hospitalization and death from COVID-19 between the patients with RA and the general population according to their COVID-19 vaccination status. We used exposure score overlap weighting to balance baseline characteristics between two comparison cohorts.

Results Among the unvaccinated individuals, the weighted incidence rates of SARS-CoV-2 infection (9.21 vs. 8.16/1000 person-months), hospitalization (3.46 vs. 2.14/1000 person-months) and death (1.19 vs. 0.62/1000 person-months) were higher among the patients with RA than the general population over three months of follow-up; the corresponding adjusted HRs were 1.10 (95%CI: 1.00-1.24), 1.62 (95%CI: 1.34-1.96) and 1.88 (95%CI: 1.37-2.60), respectively. Among the vaccinated individuals, the weighted rates of breakthrough infection (4.17 vs. 3.96/1000 person-months; HR=1.10, 95%CI: 1.00-1.20) and hospitalization (0.42 vs. 0.32/1000 person-months; HR=1.29, 95%CI: 0.96-1.75) were higher among the patients with RA than the general population over nine months of follow-up; however, no apparent difference in the risk of these outcomes was observed over three and six months of follow-up between two comparison cohorts.

Conclusion Patients with RA are still at higher risks of SARS-CoV-2 infection and

COVID-19 hospitalization than the general population after receiving COVID-19 vaccines. These findings support booster COVID-19 vaccinations and adherence of other preventive strategies among patients with RA.

Significance and Innovations

- This study shows that the risks of SARS-CoV-2 breakthrough infection or COVID-19 hospitalization is higher among patients with RA than the general population comparators over nine months of follow-up.
- These results support the recent recommendations for booster vaccinations in people with autoimmune inflammatory rheumatic diseases, and other preventive strategies, such as wearing face masks and keeping social distancing, should be encouraged among the patients with RA even after vaccination.

The ongoing COVID-19 pandemic has affected millions of people worldwide and resulted in an unprecedented health and economic toll. As of March 2022, more than 464 million infection cases and more than 6.0 million deaths associated with COVID-19 have been reported globally (1). During the COVID-19 pandemic, a number of studies found that patients with immune-mediated inflammatory diseases had a higher susceptibility to SARS-CoV-2 infection and severe outcomes than the general population (2). Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disease, and patients with RA often use immunosuppressive agents, such as steroids and disease-modifying anti-rheumatic drugs, that contribute to a higher risk for SARS-CoV-2 infection. Moreover, comorbidities caused by RA such as cardiovascular disease and interstitial lung disease has the potential to contribute a high risk of poor responses (3-5). Indeed, several studies have found that patients with RA are at higher risks of SARS-CoV-2 infection and severe outcomes of COVID-19 than non-RA individuals (6-12).

Despite recent introduction of some effective therapies for treating SARS-CoV-2 infection, vaccination remains the most promising approach at present for controlling this pandemic, because of their efficacy at reducing the risk of SARS-CoV-2 infection and severe outcomes in the general population (13). Although the immunogenicity and safety of anti-SARS-CoV-2 vaccines were demonstrated in patients with chronic inflammatory conditions and in those receiving immunosuppressive therapy, immune responses against SARS-CoV-2 after vaccination were blunted (14-16). Moreover, concerns have been raised that the protection provided by vaccines against severe COVID-19 decreases gradually over time (17). A recent systematic review and meta-regression analysis found that COVID-19 vaccine efficacy or effectiveness decreased

somewhat by six months after vaccination, underscoring the importance of evaluating vaccine efficacy or effectiveness against severe outcomes beyond six months (18). However, to date, there is a paucity of data on the risk of SARS-COV-2 infection and severe outcomes (leading to hospitalization or death) after COVID-19 vaccination in patients with RA, leaving knowledge gaps regarding the need for booster vaccinations and adherence to other risk mitigation strategies after vaccination especially beyond six months.

To determine whether patients with RA are at higher risks for SARS-CoV-2 infection and severe outcomes after COVID-19 vaccination, and to inform physicians, other health professionals, vaccine recipients and RA guideline development, we conducted two cohort studies to quantify the risks of SARS-CoV-2 infection, COVID-19 hospitalization, and death among patients with RA compared with non-RA individuals from the general population (hereafter referred to as general population) according to their COVID-19 vaccination status.

PATIENTS AND METHODS

Data source

We used data from The Health Improvement Network (THIN) database (now called IQVIA Medical Research Database). THIN is an electronic medical record database from general practitioners (GPs) in the United Kingdom (UK). It consists of approximately 17 million persons in the UK and represents the UK population regarding patient demographics and the prevalence of medical conditions. During consultation with patients, health information is recorded on site by GP using a computerized system. The computerized information includes socio-demographics,

anthropometrics, lifestyle factors, and details from visits to GPs (i.e., prescriptions, diagnoses from specialist referrals, hospital admissions, and results of laboratory tests). The Read classification system is used to code specific diagnoses (19), whereas a dictionary based on the Multilex classification system is used to code drugs (20). This study was approved by the THIN Scientific Review Committee (20SRC003-A2) and received approval from the medical ethical committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Study design

We conducted two cohort studies to compare the risks of SARS-CoV-2 infection, COVID-19 hospitalization, and death between patients with RA and the general population according to their COVID-19 vaccination status. RA diagnosis was made using Read codes (Supplementary Table 1) (5). This method has been previously validated in the UK General Practice Research Database, with a positive predictive value of ~80% for RA (21). Eligible participants consisted of those who were 18-90 years of age between December 8, 2020 (i.e., when first COVID-19 vaccination open to public in the UK) and October 31, 2021, had no previously documented SARS-CoV-2 infection, and had at least two years of continuous enrollment with a general practice.

Cohort definition

For each eligible individual in the unvaccinated cohort, follow-up started on December 8, 2020 (i.e., index date) and ended on the day of first dose of vaccine received, developing the outcomes of the interest (i.e., SARS-CoV-2 infection, COVID-19 hospitalization, and death), or the end of the study period (October 31,

2021), whichever occurred first. For each eligible individual 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 of developing the outcomes of the interest (i.e., SARS-CoV-2 infection, COVID-19 hospitalization, and death), or the end of the study period (October 31, 2021), whichever occurred first.

Assessment of outcomes

The primary outcome was a documented diagnosis of SARS-CoV-2 infection (22), and the secondary outcomes were hospitalization for COVID-19 and death from COVID-19. Confirmed SARS-COV-2 infection diagnosis was made based on Read codes (Supplementary Table 1) according to previous study using UK general population-based data (22). Hospitalization for COVID-19 was defined as a hospitalization record in THIN within 30 days after documentation of SARS-CoV-2 infection, and death from COVID-19 was defined as a death within 30 days of SARS-CoV-2 infection (23-26).

Assessment of covariates

The covariates included sociodemographic factors (age, sex, Townsend Deprivation Index), geographic location, body mass index (BMI), lifestyle factors (alcohol drinking and smoking status), previous COVID-19 test performed, 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), and healthcare utilization (hospitalizations, general practice visits, and specialist referrals) during the past one year before the index date. Among vaccinated cohort, we also collected information on type of the first dose of vaccine that participants received.

Statistical analysis

For both cohorts, we used exposure score (analogous to propensity score), overlap weighting to balance baseline characteristics between the comparison groups. Specifically, two sets of exposure scores for RA were calculated. First, exposure score for RA was generated using a logistic regression model that included covariates of age, sex, BMI, socioeconomic deprivation index score, region, lifestyle factors, number of previous COVID-19 tests and healthcare utilization (i.e., exposure score for partial adjustment). Second, additional covariates, i.e., comorbidities (including Charlson comorbidity index score and individual comorbidities), were added in the logistic regression model to generate the exposure score for RA (i.e., exposure score for full adjustment). Patients with RA were weighted by the probability of not being RA, i.e., 1-exposure score, and non-RA individuals were weighted by the probability of being RA, i.e., exposure score. Overlap weights were bounded and smoothly reduced the influence of individuals at the tails of the exposure score distribution without making any exclusions (27, 28). We assessed the distribution of the baseline characteristics before and after overlap weights using the standardized mean differences for the comparison groups (29).

Among the unvaccinated cohort, we calculated the incidence rate for the primary and secondary outcomes among RA and the general population using overlap

weighting of exposure score to control for confounders. We performed a Cox proportional hazard model to examine the relation of RA to the risk of SARS-CoV-2 infection, hospitalization and death accounting for the competing risk of death (30) using overlap weighting of exposure score. Since more than 80% unvaccinated subjects received their 1st dose of vaccine within three months after vaccination program began, we restricted our analyses to three months of follow-up time in the non-vaccinated cohort to minimize potential selection bias (30). We tested the proportional hazard assumption by plotting the cumulative incidence curve of each outcome. If the proportional hazard assumption was violated, we conducted a weighted cox regression to obtain a weighted hazard ratio (HR) (31). We took the same approach to compare the risk of COVID-19 breakthrough infection, hospitalization and death from COVID-19 among the vaccinated cohort. However, the follow-up time was extended to nine months. In addition, we conducted a subgroup analysis to compare the risks of breakthrough infection and severe outcomes during the different periods (i.e., SARS-CoV-2 alpha-variant predominance period from January 1, 2021 to May 16, 2021 as well as SARS-CoV-2 delta-variant predominance period from May 17, 2021 to October 31, 2021) between the vaccinated patients with RA and the vaccinated general population (32).

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

RESULTS

The flowchart depicting participant selection is shown in Supplementary Figure 1. We

identified 15,901 patients with RA and 1,558,423 individuals from the general population among the unvaccinated cohort; and 14,330 patients with RA and 1,208,659 individuals from the general population among the vaccinated cohort. As shown in Table 1 and Table 2, before exposure score overlap weighting, patients with RA tended to be older; were more likely to be female; had more hospitalizations and GP visits; and had a lower percentage of influenza vaccination. After exposure score overlap weighting, the baseline characteristics were well-balanced between the comparison groups, with all standardized differences were < 0.1 (Table 1 and Table 2).

Unvaccinated cohort

In the unvaccinated cohort, the risk of SARS-CoV-2 infection (fully weighted incidence rate: 9.21 vs. 8.16/1000 person-months), COVID-19 hospitalization (fully weighted incidence rate: 3.46 vs. 2.14/1000 person-months) and COVID-19 death (fully weighted incidence rate: 1.19 vs. 0.62/1000 person-months) were higher among patients with RA than among the general population over three months (Table 3, Figure 1A-C). The corresponding fully adjusted HRs were 1.11 (95% CI: 1.00-1.24), 1.62 (95% CI: 1.34-1.96) and 1.88 (95% CI: 1.37-2.60), respectively. RA was also associated with an increased risk of SARS-CoV-2 infection, COVID-19 hospitalization and death after using the exposure score for partial adjustment (Table 3).

Vaccinated cohort

Among the vaccinated cohort, there were no apparent differences in the risk of breakthrough infection, COVID-19 hospitalization, and death over three-months. The

fully weighted incidence rates for each outcome were 1.39, 0.22, and 0.00/1000 person-months among the patients with RA, and 1.68, 0.23, and 0.04/1000 person-months among the general population, respectively (Table 4, Figure 2A-C). The corresponding fully adjusted HRs were 1.03 (95%CI: 0.79-1.34) and 0.96 (95%CI: 0.49-1.89) for breakthrough infection and COVID-19 hospitalization, respectively. No increased risk of breakthrough infection (2.19 vs. 2.33/1000 person-months; HR=1.07, 95%CI: 0.92-1.24), COVID-19 hospitalization (0.20 vs. 0.21/1000 person-months; HR=0.93, 95%CI: 0.57-1.52), and death (0.03 vs. 0.03/1000 person-months; HR=0.93, 95%CI: 0.31-2.82) was observed when the analyses were restricted to the six months follow-up period. After using the exposure score for partial adjustment, RA was not associated with an increased risk of SARS-CoV-2 infection and COVID-19 hospitalization over three months of follow-up (Table 4). Similarly, no increased risks of breakthrough infection, COVID-19 hospitalization, and death were observed over six months of follow-up (Table 4).

Over nine months of follow-up, the fully weighted incidence rates of breakthrough infection, COVID-19 hospitalization, and death were 4.17, 0.42, and 0.05/1000 person-months among the individuals with RA; the corresponding rates among the general population were 3.96, 0.32, and 0.04/1000 person-months, respectively. The fully adjusted HRs were 1.10 (95% CI: 1.00-1.20) for breakthrough infection, 1.29 (95% CI: 0.96-1.75) for hospitalization, and 1.41 (95% CI: 0.65-3.05) for death (Table 4, Figure 2A-C). Using the exposure score for partial adjustment did not change the results materially (Table 4).

Results from subgroup analysis showed no increased risk of breakthrough

infection, COVID-19 hospitalization, and COVID-19 death in the patients with RA compared with the general population during the alpha-variant period (Supplementary Table 2). During the delta-variant period, the adjusted HRs of breakthrough infection, COVID-19 hospitalization, and COVID-19 death were 1.12 (95%CI: 1.01-1.23), 1.43 (95%CI: 1.01-2.00), 2.05 (95%CI: 0.89-4.70) for the patients with RA compared with the general population, respectively (Supplementary Table 3).

DISCUSSION

Using data collected from THIN in the UK, we showed that the risks of SARS-CoV-2 infection and its severe outcomes (i.e., COVID-19 hospitalization or death) are higher among individuals with RA than the general population before COVID-19 vaccination. Although COVID-vaccination greatly reduced the risk of breakthrough infection, COVID-19 hospitalization and death, the risk of breakthrough infection and COVID-19 hospitalization is still higher among individuals with RA than the general population over nine months of follow-up.

Several studies have found that patients with RA are at higher risks of SARS-CoV-2 infection and severe outcomes than individuals without RA (6-12). In a study of 33,886 people with RA in the US Veterans Affairs system, the risk of COVID-19 diagnosis and the risk of hospitalization or death was higher for patients with RA than in 33,886 people without RA (8). Using data from the UK Biobank with nearly half a million people, RA was found to be a risk factor for COVID-19 diagnosis and associated death (12). We also found that among non-vaccinated population, individuals with RA are indeed more susceptible to SARS-CoV-2 infection, COVID-19 hospitalization and death than the general population. These findings provide

additional evidence to support European League Against Rheumatism (EULAR) recommendations that patients with rheumatic and musculoskeletal diseases should be strongly advised to comply with all infection prevention and control measures prescribed by public health authorities before SARS-CoV-2 vaccination (17).

Although studies have shown that vaccination for SARS-CoV-2 was immunogenic in the majority of patients with autoimmune inflammatory rheumatic diseases, such immune responses among these patients were often blunted when compared to people without these conditions (14-16). A retrospective cohort study analyzed data from the National COVID Cohort Collaborative (N3C) found that patients with RA had a noticeable higher rate of breakthrough infection than those without immune dysfunction (33). Patients included in that study were recruited from academic medical centers only; thus, the findings may not be generalizable to the general population. In addition, that study did not examine the association between RA and the risk of severe outcomes of COVID-19 sequalae. Using data from a general population-based study, we provided the real-world evidence that both the rates of SARS-CoV-2 infection and COVID-19 hospitalization were higher in individuals with RA than the general population over nine months follow-up after COVID-19 vaccination, providing crucial information for updating COVID-19 vaccine policy.

Our study has several strengths. Our findings are likely generalizable to other populations with similar characteristics since the results were derived from a sample of the general population. Moreover, major potential confounders were well-balanced after exposure overlap weighting. The study also has several limitations. First, we

cannot rule out the residual confounders given the nature of an observational study. Second, because the number of COVID-19 death among the vaccinated patients with RA was relatively small, our study may not have an adequate power to detect a small increased risk of COVID-19 death. Third, owing to the lack of information of biologic disease-modifying anti-rheumatic drugs, we are unable to examine whether the use of these medications by patients with RA may modify their risk of breakthrough infection and COVID-19 severity (34). Fourth, while the effects of current COVID-19 vaccines against the Omicron variant, the current dominant strain in the UK, were not examined in the current study, previous studies have reported that booster dose of currently available COVID-19 vaccines reduced the risk and severity of breakthrough infection due to the Omicron variant (35-39). Thus, until variant-specific vaccines are in use, people should consider receiving booster dose of currently available COVID-19 vaccines to reduce the risk of COVID-19 infection and disease severity. Future studies are needed to examine how variant-specific vaccines impact COVID-19 outcomes for contemporary viral variants among patients with RA. Fifth, in the current study we adopted definitions of hospitalization for COVID-19 and death from COVID-19 occurring within 30 days after documentation of SARS-CoV-2 infection that the previous studies have been used (24-26). Although there is a possibility that the unrelated hospital admission or death could occur within 30 days after documentation of SARS-CoV-2 infection, we believe that such misclassification, if occurred, is probably small and non-differential. As a result, it would bias the effect estimates towards the null. Finally, the patients with RA who are on immunomodulatory treatments may be more likely to be admitted to the hospital than the general population due to medical complexity and immunosuppressed state. However, the risks of breakthrough infection and COVID-19 death were also higher

among the patients with RA than the general population, suggesting that such bias is unlikely to completely explain away the higher risk of COVID-19 infection among the patients with RA than among the general population.

In conclusion, patients with RA are still at higher risks of SARS-CoV-2 infection and COVID-19 hospitalization than the general population after receiving COVID-19 vaccines. These findings support booster COVID-19 vaccinations and adherence of other preventive strategies among patients with RA.

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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 submitted for publication. Professors Lei and 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.

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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.

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. Cumulative incidence of SARS-COV-2 infection, COVID-19 hospitalization and death among the patients with RA as compared with the general population in the unvaccinated cohort over three-month.

A, SARS-COV-2 infection; B, COVID-19 hospitalization; C, COVID-19 death. RA, rheumatoid arthritis.

Figure 2. Cumulative incidence of breakthrough infection, COVID-19 hospitalization and death among the patients with RA as compared with the general population in the vaccinated cohort during the total follow-up.

A, breakthrough infection; B, COVID-19 hospitalization; C, COVID-19 death. RA, rheumatoid arthritis.

Table 1. Baseline characteristics of the patients with RA and the general cohort without RA in the unvaccinated cohort

Characteristics	Before overlap weighting			After overlap weighting		
	RA	General cohort	SMD	RA	General cohort	SMD
Number	15,901	1,558,423		15,286	15,286	
Demographics						
Age, mean (SD), y	64.8 (13.7)	47.9 (17.2)	1.091	64.5 (13.7)	64.5 (15.6)	<0.001
Socioeconomic Deprivation index score (%)[a]			0.097			<0.001
Missing	10.2	12.8		10.2	10.2	
1	15.8	14.9		15.9	15.9	
2	18.6	17.5		18.6	18.6	
3	20.4	19.3		20.4	20.4	
4	19.7	18.9		19.6	19.6	
5	15.3	16.7		15.3	15.3	
Women (%)	70.8	48.9	0.459	70.3	70.3	<0.001
BMI, mean (SD), kg/m^2	28.3 (6.4)	27.5 (6.0)	0.135	28.3 (6.4)	28.3 (6.4)	0.002
Region, %			0.061			<0.001
England	16.7	18.7		16.8	16.8	
Northern Ireland	13.0	13.4		13.0	13.0	
Scotland	39.5	39.0		39.4	39.4	
Wales	30.8	28.8		30.8	30.8	
Number of COVID-19 test, mean (SD)	0.1 (0.3)	0.1 (0.3)	0.024	0.1 (0.3)	0.1 (0.3)	<0.001
Influenza vaccination within previous year (%)	69.7	25.4	0.988	68.9	68.9	<0.001
Lifestyle factors						
Drinking (%)			0.223			<0.001
None	27.0	19.4		26.5	26.5	
Past	5.1	2.9		5.0	5.0	
Current	68.0	77.7		68.5	68.5	
Smoking (%)			0.305			<0.001
None	48.3	58.3		48.6	48.6	
Past	35.6	21.9		35.2	35.2	
Current	16.1	19.8		16.2	16.2	
Charlson omorbidity Index, mean (SD)	0.47 (1.00)	0.20 (0.67)	0.311	0.46 (1.00)	0.46 (0.98)	<0.001
Comorbidity (%)						
Hypertension	42.7	17.2	0.579	42.2	42.2	<0.001
Diabetes	18.5	8.9	0.282	18.4	18.4	<0.001
Hyperlipidemia	12.9	5.0	0.28	12.8	12.8	<0.001
Chronic kidney disease	11.5	2.6	0.354	11.1	11.1	<0.001
Pneumonia or infection	11.5	5.2	0.229	11.1	11.1	<0.001
Chronic obstructive pulmonary disease	9.7	2.4	0.312	9.4	9.4	<0.001
Cancer	12.6	5.7	0.241	12.5	12.5	<0.001
Venous thromboembolism	5.4	1.5	0.214	5.2	5.2	<0.001
Atrial fibrillation	6.3	2.0	0.221	6.2	6.2	<0.001
Ischaemic heart disease	11.1	3.6	0.289	10.9	10.9	<0.001
Myocardial infarction	5.3	1.8	0.189	5.2	5.2	<0.001
Congestive heart failure	3.7	1.0	0.179	3.6	3.6	<0.001
Stroke	3.9	1.5	0.153	3.9	3.9	<0.001

Healthcare utilization within previous year, mean (SD)						
Hospitalizations[b]	0.5 (1.3)	0.2 (0.8)	0.264	0.4 (1.2)	0.4 (1.5)	<0.001
General practice visits[b]	5.3 (6.4)	1.8 (3.3)	0.695	5.1 (5.8)	5.1 (11.3)	<0.001
Specialist referrals[b]	0.4 (0.9)	0.2 (0.6)	0.308	0.4 (0.9)	0.4 (1.1)	<0.001

[a]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).

[b]Frequency during the past year.

RA, rheumatoid arthritis; SMD, standardized mean difference; BMI, body mass index; n, number; y, years; SD, standard deviation; AZ, AstraZeneca.

Table 2. Baseline characteristics of the patients with RA and the general cohort without RA in the vaccinated cohort

Characteristics	Before overlap weighting			After overlap weighting		
	RA	General cohort	SMD	RA	General cohort	SMD
Number	14,330	1,208,659		13,760	13,760	
Demographics						
Age, mean (SD), y	65.3 (13.4)	50.1 (17.2)	0.986	65.1 (13.4)	65.1 (15.1)	<0.001
Socioeconomic Deprivation index score (%)[a]			0.059			<0.001
Missing	10.1	11.8		10.1	10.1	
1	15.8	15.5		15.9	15.9	
2	18.8	18.9		18.9	18.9	
3	20.6	19.8		20.5	20.5	
4	19.5	18.6		19.5	19.5	
5	15.2	15.5		15.2	15.2	
Women (%)	71.0	50.7	0.427	70.5	70.5	<0.001
BMI, mean (SD), kg/m^2	28.4 (6.4)	27.8 (6.1)	0.099	28.4 (6.4)	28.4 (6.5)	0.006
Region, %			0.024			<0.001
England	13.8	14.2		13.9	13.9	
Northern Ireland	13.2	13.9		13.3	13.3	
Scotland	42.0	41.3		41.9	41.9	
Wales	30.9	30.6		30.9	30.9	
Type of first dose vaccination (%)			0.282			<0.001
AZ	67.2	54.1		67.2	67.8	
PFIZER	31.8	43.3		31.8	31.3	
Moderna or Janssen	1.0	2.6		1.0	0.9	
Type of second dose vaccination (%)			0.307			0.064
No second dose	5.1	7.3		5.1	4.4	
AZ	64.4	51.2		64.4	65.2	
PFIZER	30.3	39.5		30.3	30.0	
Moderna or Janssen	0.2	2.0		0.2	0.4	
Number of COVID-19 test, mean (SD)	0.1 (0.3)	0.2 (0.4)	0.090	0.1 (0.3)	0.1 (0.3)	<0.001
Influenza vaccination within previous year (%)	74.4	33.8	0.892	73.8	73.8	<0.001
Lifestyle factors						
Drinking (%)			0.240			<0.001
None	26.4	18.1		26.0	26.0	
Past	5.1	3.0		5.0	5.0	
Current	68.5	78.9		69.0	69.0	
Smoking (%)			0.288			<0.001
None	48.4	59.3		48.7	48.7	
Past	36.0	23.0		35.6	35.6	
Current	15.6	17.7		15.7	15.7	
Charlson comorbidity Index, mean (SD)	0.99	0.71	0.271	0.99	0.96	<0.001
Comorbidity (%)						
Hypertension	43.3	20	0.519	42.8	42.8	<0.001
Diabetes	18.5	10.1	0.242	18.4	18.4	<0.001
Hyperlipidemia	13.1	5.8	0.253	12.9	12.9	<0.001
Chronic kidney disease	11.6	3	0.335	11.2	11.2	<0.001
Pneumonia or infection	11.6	5.6	0.214	11.2	11.2	<0.001

Chronic obstructive pulmonary disease	9.8	2.8	0.293	9.5	9.5	<0.001
Cancer	13.0	6.6	0.214	12.9	12.9	<0.001
Venous thromboembolism	5.2	1.7	0.195	5.0	5.0	<0.001
Atrial fibrillation	6.4	2.3	0.202	6.3	6.3	<0.001
Ischaemic heart disease	11.0	4.3	0.256	10.8	10.8	<0.001
Myocardial infarction	5.2	2.1	0.166	5.1	5.1	<0.001
Congestive heart failure	3.7	1.2	0.161	3.6	3.6	<0.001
Stroke	4.0	1.7	0.139	3.9	3.9	<0.001
Healthcare utilization within previous year, mean (SD)						
Hospitalizations[b]	0.4 (1.2)	0.2 (0.7)	0.229	0.4 (1.7)	0.4 (1.3)	<0.001
General practice visits[b]	4.9 (6.3)	1.7 (3.3)	0.644	4.7 (5.6)	4.7 (10.8)	<0.001
Specialist referrals[b]	0.4 (0. 9)	0.2 (0.6)	0.268	0.4 (0.9)	0.4 (1.0)	<0.001

[a]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).

[b]Frequency during the past year.

RA, rheumatoid arthritis; SMD, standardized mean difference; BMI, body mass index; n, number; y, years; SD, standard deviation; AZ, AstraZeneca.

Table 3. Association between RA and the risk of SARS-COV-2 infection, COVID-19 hospitalization, and death in the unvaccinated cohort over three-month

Outcomes	RA (N=15,901)	General cohort (N=1,558,423)
SARS-COV-2 infection		
Event, N	327	33,889
Mean follow-up, months	2.23	2.60
Weighted IR[a] *, per 1000 person-months	9.21	8.16
Weighted HR[a] * (95% CI)	1.11 (1.00, 1.24)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	9.20	8.31
Weighted HR[a] ** (95% CI)	1.10 (1.00, 1.20)	1.00 (reference)
COVID-19 hospitalization		
Event, N	128	3,299
Mean follow-up, months	2.25	2.64
Weighted IR[a] *, per 1000 person-months	3.46	2.14
Weighted HR[a] * (95% CI)	1.62 (1.34, 1.96)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	3.46	2.08
Weighted HR[a] ** (95% CI)	1.67 (1.38, 2.02)	1.00 (reference)
COVID-19 death		
Event, N	44	561
Mean follow-up, months	2.26	2.64
Weighted IR[a] *, per 1000 person-months	1.19	0.62
Weighted HR[a] * (95% CI)	1.88 (1.37, 2.60)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	1.18	0.64
Weighted HR[a] ** (95% CI)	1.80 (1.30, 2.48)	1.00 (reference)

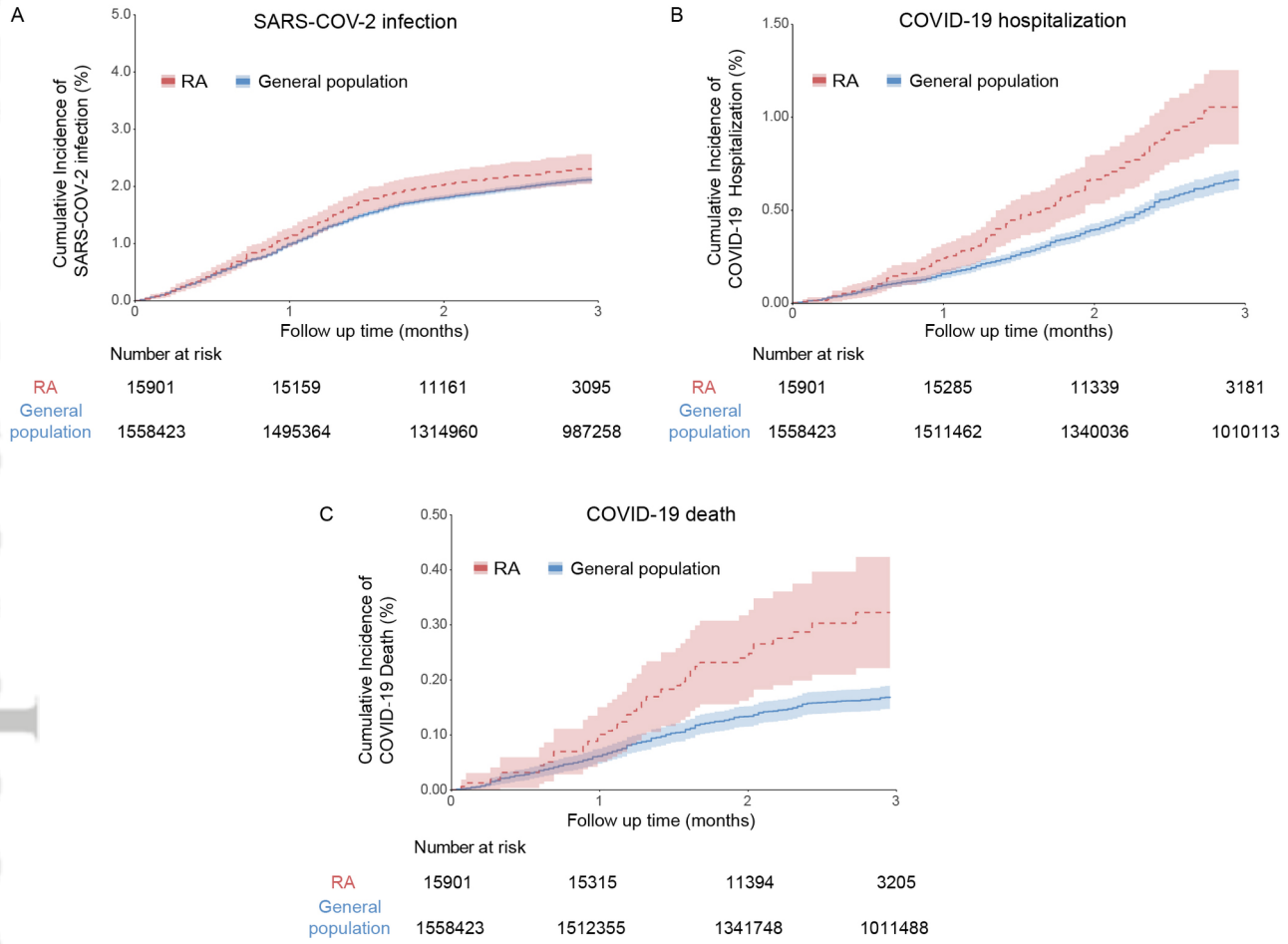
N, number; RA, rheumatoid arthritis; IR: incidence rate; HR hazard ratio; CI, confidence interval.
[a]Estimates were time-stratified overlap weighted of propensity score, weighted cox regression using coxphw method was applied if proportional hazard assumption was violated.
*Results obtained from fully adjusted model.
**Results obtained from partially adjusted model.

Table 4. Association between RA and the risk of breakthrough infection, COVID-19 hospitalization, and death in the vaccinated cohort

Outcomes	RA (N=14,330)	General cohort (N=1,208,659)
Three-month follow-up		
Breakthrough infection		
Event, N	57	13,609
Mean follow-up, months	2.89	2.90
Weighted IR[a] *, per 1000 person-months	1.39	1.68
Weighted HR[a] * (95% CI)	1.03 (0.79, 1.34)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	1.38	1.68
Weighted HR[a] ** (95% CI)	1.01 (0.78, 1.32)	1.00 (reference)
COVID-19 hospitalization		
Event, N	9	478
Mean follow-up, months	2.90	2.92
Weighted IR[a] *, per 1000 person-months	0.22	0.23
Weighted HR[a] * (95% CI)	0.96 (0.49, 1.89)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	0.22	0.23
Weighted HR[a] ** (95% CI)	0.95 (0.49, 1.88)	1.00 (reference)
COVID-19 death		
Event, N	0	39
Mean follow-up, months	2.90	2.92
Weighted IR[a] *, per 1000 person-months	0	0.04
Weighted HR[a] * (95% CI)	-	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	0	0.05
Weighted HR[a] ** (95% CI)	-	1.00 (reference)
Six-month follow-up		
Breakthrough infection		
Event, N	177	32,321
Mean follow-up, months	5.69	5.44
Weighted IR[a] *, per 1000 person-months	2.19	2.33
Weighted HR[a] * (95% CI)	1.07 (0.92, 1.24)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	2.19	2.39
Weighted HR[a] ** (95% CI)	1.07 (0.92, 1.24)	1.00 (reference)
COVID-19 hospitalization		
Event, N	17	1,015
Mean follow-up, months	5.72	5.49
Weighted IR[a] *, per 1000 person-months	0.20	0.21
Weighted HR[a] * (95% CI)	0.93 (0.57, 1.52)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	0.20	0.21
Weighted HR[a] ** (95% CI)	0.95 (0.58, 1.55)	1.00 (reference)
COVID-19 death		
Event, N	3	60

Mean follow-up, months	5.72	5.49
Weighted IR[a] *, per 1000 person-months	0.03	0.03
Weighted HR[a] * (95% CI)	0.93 (0.31, 2.82)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	0.04	0.03
Weighted HR[a] ** (95% CI)	1.08 (0.37, 3.15)	1.00 (reference)
Total follow-up		
Breakthrough infection		
Event, N	475	49,044
Mean follow-up, months	7.99	6.77
Weighted IR[a] *, per 1000 person-months	4.17	3.96
Weighted HR[a] * (95% CI)	1.10 (1.00, 1.20)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	4.17	3.97
Weighted HR[a] ** (95% CI)	1.10 (1.01, 1.21)	1.00 (reference)
COVID-19 hospitalization		
Event, N	50	1,662
Mean follow-up, months	8.06	6.86
Weighted IR[a] *, per 1000 person-months	0.42	0.32
Weighted HR[a] * (95% CI)	1.29 (0.96, 1.75)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	0.42	0.31
Weighted HR[a] ** (95% CI)	1.33 (0.99, 1.81)	1.00 (reference)
COVID-19 death		
Event, N	7	105
Mean follow-up, months	8.07	6.86
Weighted IR[a] *, per 1000 person-months	0.05	0.04
Weighted HR[a] * (95% CI)	1.41 (0.65, 3.05)	1.00 (reference)
Weighted IR[a] **, per 1000 person-months	0.06	0.04
Weighted HR[a] ** (95% CI)	1.45 (0.68, 3.09)	1.00 (reference)

N, number; RA, rheumatoid arthritis; IR: incidence rate; HR hazard ratio; CI, confidence interval.
[a]Estimates were time-stratified overlap weighted of propensity score, weighted cox regression using coxphw method was applied if proportional hazard assumption was violated.
*Results obtained from fully adjusted model.
**Results obtained from partially adjusted model.



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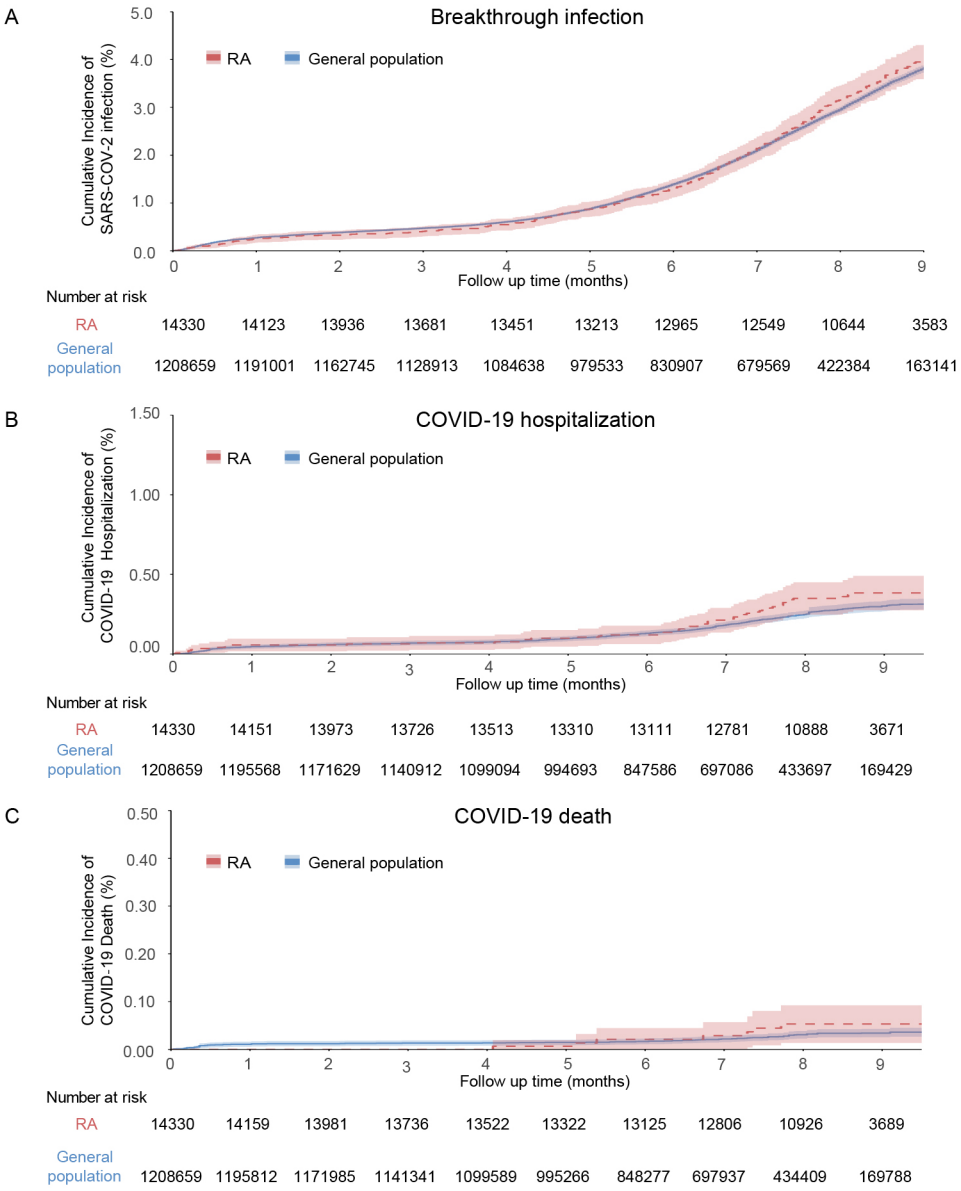

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