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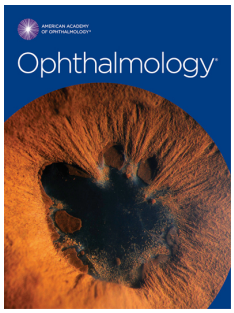

Ocular adverse events after COVID-19 mRNA vaccination: matched cohort and self-controlled case series studies using a large database

Yohei Hashimoto, MD, PhD, Hayato Yamana, MD, PhD, Masao Iwagami, MD, PhD, Sachiko Ono, MPH, PhD, Yoshinori Takeuchi, DVM, PhD, Nobuaki Michihata, MD, PhD, Kohei Uemura, PhD, Hideo Yasunaga, MD, PhD, Makoto Aihara, MD, PhD, Toshikatsu Kaburaki, MD, PhD

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Ocular adverse events after COVID-19 mRNA vaccination: matched cohort and self-controlled case series studies using a large database

Yohei Hashimoto, MD, PhD,[1,2] Hayato Yamana, MD, PhD,[3] Masao Iwagami, MD, PhD,[4] Sachiko Ono, MPH, PhD ,[5] Yoshinori Takeuchi, DVM, PhD,[6,7] Nobuaki Michihata, MD, PhD,[8] Kohei Uemura, PhD,[9] Hideo Yasunaga, MD, PhD,[2] Makoto Aihara, MD, PhD,[1] Toshikatsu Kaburaki, MD, PhD[1]

[1]Department of Ophthalmology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan
[3]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[4]Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[5]Department of Eat-loss Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[6]Division of Medical Statistics, Department of Social Medicine, Faculty of Medicine, Toho University, Tokyo, Japan
[7]Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[8]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[9]Department of Biostatistics and Bioinformatics, Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan

Corresponding author: Yohei Hashimoto, MD, PhD, [2]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
Tel: +81-3-3815-5411; Fax: +81-3-3817-0798
E-mail: youhashi@m.u-tokyo.ac.jp

Running head: Ocular adverse events after Covid-19 vaccination

Abbreviations: HR = hazard ratio; CI = confidence interval; RVO = retinal vein occlusion; SCCS = self-controlled case series

Key Words: COVID-19 vaccines, Drug-Related Side Effects and Adverse Reactions, Uveitis, Scleritis, Retinal Vein Occlusion, Optic Neuritis

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other than the present study. No other potential competing interest relevant to this study is reported.

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Abstract

Purpose: To investigate the risk of ocular adverse events after COVID-19 mRNA vaccination.

Design: Matched cohort and self-controlled case series (SCCS) studies.

Subjects/Controls: We used a population-based database of medical claims and vaccination records in a large city of Japan. In the matched cohort study, we identified individuals who received COVID-19 vaccination (BNT162b2) from February 2021 to September 2021. One control was selected from non-vaccinated individuals by matching time, date of birth, sex, Charlson comorbidity index, and the enrollment period for health insurance. In the SCCS study, we analyzed individuals who developed ocular adverse events from February 2021 to the end of follow-up.

Methods: In the matched cohort study, we applied the Kaplan–Meier estimator to estimate the cumulative incidence of ocular adverse events over 21 days after the first dose and 84 days after the second dose. In the SCCS method, we used conditional Poisson regression to estimate the incidence rate ratio of ocular adverse events during the risk periods (0–21 days after the first dose and 0–84 days after the second dose) compared to the remaining periods.

Main Outcome Measures: Composite outcome of uveitis, scleritis, retinal vein occlusion, and optic neuritis.

Results: There were 99,718 pairs eligible for the matched cohort study after the first dose (mean age, 69.3 years; male, 44%). The vaccinated and control groups developed 29 and 21 events, respectively, over 21 days after the first dose, and 79 and 28 events, respectively, over 84 days after the second dose. The differences in cumulative incidence (reference, the control group) were 2.9 (95% confidence

interval, -14.5 to 19.1) events/100,000 persons and 51.3 (16.2 to 84.3) events/100,000 persons, respectively, for the first and second dose. The SCCS study showed the incidence rate ratios of 0.89 (0.62 to 1.28) and 0.89 (0.71 to 1.11) for the first and second doses, respectively.

Conclusions: The matched cohort analysis found an increased risk for the composite outcome after the second dose; however, the SCCS analysis showed no increased risk. Considering that the SCCS can cancel out time-invariant confounders, the current results suggest that COVID-19 vaccination is unlikely to causally increase the risk of ocular adverse events.

As of June 2022, 536 million COVID-19 confirmed cases, including approximately 6.3 million deaths, have been reported globally[1]. COVID-19 vaccines have shown high efficacy in preventing infection, hospitalization, and death[2,3]. A total of 11.9 billion vaccine doses have been administered so far worldwide[1].

However, previous studies have reported that COVID-19 vaccination may increase the risk of systemic adverse events such as myocarditis, lymphadenopathy, and appendicitis[4,5]. The vaccines may also increase the risk of ocular adverse events such as uveitis[2,4,6–8], scleritis[9], retinal vein occlusion (RVO)[10] and optic neuritis[11,12]. However, because nearly all of these were case reports or case series, the association between vaccination and ocular adverse events has not been established. Only two population-based studies on uveitis have been conducted in Israel, but their results were inconsistent[4,13]; one showed an increased risk of uveitis after vaccination and the other did not.

Thus, we investigated several ocular disorders such as uveitis, scleritis, RVO, and optic neuritis after COVID-19 vaccination by linking health insurance claims data and vaccination records in Japan. We first used the matched cohort design (between-person design) following previous studies[4,13]. Furthermore, we used the self-controlled case series (SCCS) method (within-person design), which can control for time-invariant confounders[14,15].

Methods

Data source

We used the linked database of health insurance claims data and vaccination records of a large city in Japan. Data between April 2014 and September 2021 were used.

The claims database included both outpatient and inpatient information stored at an individual level. Thus, it was possible to perform patient-based tracking of visits and treatment, even for individuals transferred to another hospital. The claims database included the following information: 1) age and sex; 2) diagnoses based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes and Japanese texts; 3) procedures; 4) drugs dispensed based on the Anatomical Therapeutic Chemical Classification System; and 5) the enrollment period for health insurance.

The vaccination record included the following: A) the date of COVID-19 vaccination, B) the dose of the vaccination (first or second), and C) manufacturers (Pfizer–BioNTech, Moderna, or AstraZeneca,).

Using unique identification numbers, vaccine records were linked to health insurance claims data in the city office. All personal information was excluded and de-identified data was provided to the researchers for secondary use. This study was performed following the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Tokyo (2021187NI-(3)). The requirement for informed consent was waived given the anonymous nature of the data.

Outcomes

The outcomes of interest were the occurrence of uveitis, scleritis, RVO, and optic neuritis. We defined the composite of these four diseases as the main outcome and each disease as a secondary outcome. We defined the timing of occurrence as the date of the first diagnosis record. We only included definite diagnoses and

excluded suspected diagnoses. The definitions of outcome are shown in **Supplementary Table 1**.

Exposures

We defined the exposure as the first and second doses of the COVID-19 vaccination. Only BNT162b2 vaccines (Pfizer–BioNTech) were included because they accounted for the majority (83%) in the vaccination record.

Study design and patient selection

We used two types of study design: matched cohort and SCCS studies. The main difference between the two is that the matched cohort design compares individuals with and without exposure (a between-person design), whereas the SCCS method compares different periods within the same individual (a within-person design). The SCCS method is often used to investigate the association between vaccination and adverse events[5,16]. This method only requires the information of individuals with events (e.g. uveitis) during follow-up and can automatically control for time-invariant confounders such as sex, race, socioeconomic status, genetic factors, and geographical location, even when they are unmeasured or unknown[14,15,17]. In the SCCS method, follow-up periods are split into risk and control periods, and incidence rate of the event during the risk periods are compared with control periods (all remaining time within the observation period) within an individual.

<u>Matched cohort study</u>

First, we investigated the risk of the first dose of vaccination on ocular adverse events. The outline of the study design is shown in **Supplementary Figure 1**. We

included individuals who received BNT162b2 vaccines after the vaccination became available in Japan (February 17, 2021). The date of the first dose was defined as the index date. We excluded individuals who a) did not have ≥1 year look-back period before the index date; b) had a history of uveitis, scleritis, retinal vein occlusion, or optic neuritis between the start of the health insurance enrollment and the index date[18]; and c) had a history of COVID-19 infection between the start of the health insurance enrollment and the index date. For each vaccinated person, one control was randomly selected from the non-vaccinated individuals by matching the calendar time (i.e. the date of vaccination for the vaccinated person), date of birth (± 3 years), sex, Charlson comorbidity index (5 categories: 0, 1, 2, 3, and ≥4), and enrollment period for health insurance. Controls matched on a certain day could become eligible vaccinated individuals in the future. Furthermore, because we conducted matching with replacement, a non-vaccinated individual could be selected multiple times.

To examine the risk in dose 1, vaccinated individuals and matched controls were followed from the index date and censored at the earliest of the following: 21 days after vaccination, dose 2 of the vaccination (for vaccinated individuals), dose 1 of the vaccination (for controls), the end of health insurance enrollment, or death. The risk period of 21 days after vaccination was chosen because the second dose is usually administered 21 days after the first dose as recommended by the Centers for Disease Control and Prevention[19]. .

Similarly, we investigated the association between the second dose of vaccination and ocular disorders. We identified the individuals who received the second vaccination and defined the date of the second dose as the index date. Controls were selected from individuals who had not received any vaccination at the index date. Matching was conducted in the same way as above. Censoring was

defined as the earliest of one of the following: 84 days after vaccination, the end of health insurance enrollment, or death. We defined the risk period after the second dose as 84 days to capture longer-term ocular events than previous studies using the risk period of 21 days[4,13].

Moreover, the matching process was repeated for each disease (uveitis, scleritis, RVO, and optic neuritis) separately because each analysis had event-specific exclusion criteria for individuals with a history of that event.

The SCCS method

The outline of the SCCS method is shown in **Supplementary Figure 2**. We included individuals who were diagnosed with uveitis, scleritis, retinal vein occlusion, or optic neuritis during the observation period (from February 17, 2021, to the end of health insurance enrollment). We subsequently excluded individuals who a) did not have ≥1 year look-back period before the index date; b) had a history of uveitis, scleritis, retinal vein occlusion, or optic neuritis between the start of the health insurance enrollment and the index date[18]; c) had a history of COVID-19 infection between the start of the health insurance enrollment and the index date; and d) received COVID-19 vaccines other than BNT162b2. The observation period was split into the risk and control periods. We defined the risk periods as 0–21 and 0–84 days after the first and second doses, respectively, and the control periods as periods other than risk periods. For sensitivity analyses, we split the risk period after the first dose into three (0–7, 8 –14, and 15–21 days) and the risk period after the second dose into four (0–7, 8 –14,15–21, and 22–84 days).

Statistical analysis

Matched cohort design

We applied the Kaplan–Meier estimator to estimate the cumulative incidence of the events over 21 days after the first dose and over 84 days after the second dose. The cumulative incidences of the ocular adverse events between the vaccinated and unvaccinated groups were compared in terms of difference (per 100,000 persons) and ratio.[4] We calculated 95% confidence intervals (CI) of the difference and ratio using the nonparametric percentile bootstrap method with 500 repetitions.

The SCCS method

Conditional Poisson regression was used to estimate the incidence rate ratio (IRR) of events and its 95% CI; that is, the ratio of the incidence rate during the risk periods to that during the control period.

All statistical analyses were conducted using R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). We used an R package 'SCCS' version 1.1 in the SCCS study.

Results

Figure 1 shows the patient selection for the matched cohort design for the composite outcome after the first dose. A total of 99,718 pairs were eligible. The baseline characteristics are shown in **Table 1**. The mean age was 69.3 years and males accounted for 44%. Age, sex, and the Charlson comorbidity index were balanced between the two groups. The patient characteristics for other combinations of exposure and outcome are shown in **Supplementary Tables 2–5**.

Figure 2 and **Figure 3** show the cumulative incidence curves for the composite outcome after first and second doses, respectively. The differences and ratios of the cumulative incidences between the vaccinated and control groups are shown in **Table 2**. Of 99,718 individuals, 29 and 21 cases of the composite outcome occurred in the vaccinated and control groups, respectively, over 21 days after the first dose; the difference in cumulative incidence was 2.9 events/100,000 persons (95% CI, -14.5 to 19.1) and the ratio of cumulative incidence was 1.1 (0.6 to 2.0) (reference, the control group). Of 82,462 individuals, 79 and 28 cases of the composite outcome occurred in the vaccinated and control groups, respectively, over 84 days after the second dose; the vaccinated group showed an increased risk of the composite outcome compared with the control group (the difference in cumulative incidence was 51.3 events/100,000 persons [16.2 to 84.3] and the ratio of cumulative incidence was 1.8 [1.2 to 2.9]). The risk of RVO after the second dose was also higher for the vaccinated group than for the control group (the difference in cumulative incidence was 29.4 events/100,000 persons [8.3 to 48.7] and the ratio of cumulative incidence was 3.3 [1.3 to 16.1]). There were no significant differences in the cumulative incidences of other ocular adverse events between the vaccinated and control groups (**Table 2 and Supplementary Figures 3–10**).

Figure 4 shows the patient selection for the SCCS study for the composite outcome after the first dose. In total, 436 patients were included in the SCCS analysis. **Table 3** shows the results of the SCCS study. Thirty-two composite outcomes occurred between 0 and 21 days after the first dose; the IRR was 0.89 (0.62 to 1.28) compared to the control period, showing no increased risk of the composite outcome during the risk period. Similarly, 115 composite outcomes occurred between 0 and 84 days after the second dose; the IRR was 0.89 (0.71 to

1.11) compared to the control period, with no significant difference. There were neither significantly higher IRRs for each ocular disease nor for the finely-split risk periods (0–7, 8–14, 15–21, and 22–84 days after vaccination).

Discussion

We investigated the risk of ocular adverse events after COVID-19 BNT162b2 vaccination using a health insurance claims database and vaccination records. The matched cohort analysis found an increased risk for the occurrence of RVO and the composite outcome after the second dose; however, the SCCS analysis showed no increase in the risk for any of the ocular events after COVID-19 vaccination.

Of the two previous studies using a database in Israel, one study found an association between COVID-19 vaccination and uveitis[13] while the other did not[4]. This disparity could be caused by differences in population size, the inclusion and exclusion criteria, and the definition of uveitis[13]. In the current study, neither the matched cohort method nor the SCCS method showed an association between COVID-19 vaccination and uveitis. Because we used a population-based database in a Japanese city, we cannot simply compare the current results with the previous ones. Given that few eastern Asians were included in the previous studies, the current studies would add new information to the literature.

Although scleritis has been reported following COVID-19 vaccination, all of the studies were case reports or case series[9,20–22]; the cause-effect relationship was assumed only from temporal order between the COVID-19 vaccination and scleritis. We performed an analytic study using a large database and found there were no significant associations between COVID-19 vaccination and scleritis.

Several case reports and case series reported that COVID-19 vaccination might increase the risk of developing RVO[10,23,24]. In the current matched cohort design, the vaccinated group showed a higher risk for RVO than the control group after the second dose. In contrast, the SCCS study did not show an increased risk of RVO after either the first or second dose. The association found in the matched cohort design may stem from unmeasured confounders such as obesity. We performed the matching process on five variables (the index date, age, sex, Charlson comorbidity index, and the starting year and month of the health insurance) in the matched cohort design, but not on body mass index and waist circumference. Although these variables were reported to be risk factors of RVO[25], they were not available in the database. Since obese individuals were prioritized in the Japanese COVID-19 vaccination, there may have been more individuals with obesity in the vaccinated group. Furthermore, blood pressure values were unavaialble in the database. Given that the risk for developing RVO varied according to the strata based on blood pressure values[26], this may also have caused residual confounding. In contrast to the cohort study (between-person study), the SCCS method compares different time windows within a case that developed an outcome (within-person)[15]. Given that body mass index and other factors do not change drastically over the short study period, the SCCS method may have cancelled out their effects[15].

There have also been several case reports that suggest an increased risk of optic neuritis after COVID-19 vaccination[11,12,27]. A more recent database study indicated that the risk of optic neuritis following COVID-19 vaccination was low[28]. However, the comparator in the previous study was other viral vaccines rather than unvaccinated individuals. Furthermore, because the study used a spontaneous reporting database, the result was subject to reporting bias and the denominator of

the population could not be identified. Our study using claims data and non-vaccinated controls did not find an increased risk of optic neuritis following vaccination.

The analysis for the composite outcome showed similar results to that for RVO: an increased risk after the second dose for the matched cohort analysis and no association for the SCCS analysis. Furthermore, the estimate of the difference in cumulative incidence of RVO after the second dose was 29.4/100,000 persons, which was approximately 60% of that of the composite outcome (51.3). Therefore, the composite outcome was likely influenced by RVO.

The current study has several limitations. First, we could not obtain detailed information on the eyes. For example, the severity of the ocular disorders such as anterior chamber cells for uveitis and macular edema for RVO was not available. Thus, although the risk of developing the ocular adverse events was not increased after COVID-19 vaccination, differences in severity may exist. Second, unmeasured confounders (e.g. body mass index) may have existed in the matched cohort study. Third, because nearly all the individuals were Asians, caution must be exercised in generalizing the findings to other populations. Fourth, we excluded patients with preexisting ocular disorders as our aim was to identify new events associated with the vaccines, whereas we could not distinguish whether such preexisting ocular disorders were stable or not at the index date (vaccination date). The final limitation is the sample size. According to our post hoc power calculation, in the matched cohort study, setting a power of 80% and $\alpha=0.05$, based on the cumulative incidence of the outcome in the unvaccinated group (0.064% over 84 days after the second vaccination), the sample size needed in each group of the matched cohort would be 122,545 to identify the risk ratio of 1.5 (which we believe is clinically meaningful

difference) as “statistically significant” [29]. Therefore, the matched cohort study (n=82,462) may have been underpowered. Meanwhile, in the SCCS analysis, the number of events needed to identify the risk ratio of 1.5 was 214 [14]. Thus, the current study was sufficiently powered for the composite outcome (n=436). Future studies with large sample size or future meta-analyses will be needed to draw a firm inference[30].

A strength of the current study is that we used two designs (matched cohort and SCCS methods) and compared their results, whereas previous studies investigating the association between COVID-19 vaccination and ocular adverse events used only cohort designs. We measured the absolute risk (cumulative incidence) for the occurrence of ocular disorders after vaccination using the matched cohort method. However, this analysis may have been influenced by unmeasured confounders. We compensated for this weakness with the SCCS method, which can automatically control for time-invariant confounders. Second, we used only the period after the COVID-19 vaccination was available in Japan, whereas one of the previous studies used historical reference cohorts before the start of the vaccine campaign[13]. This difference in calendar time may have influenced health-seeking behaviors, leading to a detection bias in their study.

In conclusion, the matched cohort analysis showed an increased risk for RVO and the composite outcome after the second dose of COVID-19 vaccination; however, this association was not observed in the SCCS analysis. Considering that the SCCS design controls for time-invariant confounders, the current results suggest that COVID-19 vaccination does not causally increase the risk of ocular adverse events. Although future studies with a larger sample size will be needed to draw a

307 firm inference, the results support the idea that the benefits of taking the vaccines
308 outweigh the risks.

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Table 1. Patient characteristics of the vaccinated and control groups in the matched cohort design for the composite outcome (uveitis, scleritis, retinal vein occlusion, and optic neuritis).

Variable	Dose 1		Dose 2	
	Vaccinated group (n = 99718)	Control group (n = 99718)	Vaccinated group (n = 82462)	Control group (n = 82462)
Age (year)	69.3±16.6	69.3±16.6	70.9±14.8	70.9±14.9
Male	43453 (43.6)	43453 (43.6)	35335 (42.9)	35335 (42.9)
Charlson comorbidity index				
0	59335 (59.5)	59335 (59.5)	50771 (61.6)	50771 (61.6)
1	8351 (8.4)	8351 (8.4)	6107 (7.4)	6107 (7.4)
2	15483 (15.5)	15483 (15.5)	12556 (15.2)	12556 (15.2)
3	5768 (5.8)	5768 (5.8)	4130 (5.0)	4130 (5.0)
≥4	10781 (10.8)	10781 (10.8)	8898 (10.8)	8898 (10.8)
Follow-up period (days)	20.4±2.9	15.7±6.9	70.9±22.5	42.8±32.0

Data are presented as n (%) or mean ± standard deviation.

Table 2. Cumulative incidences of ocular adverse events after the first and second doses in the matched cohort design.

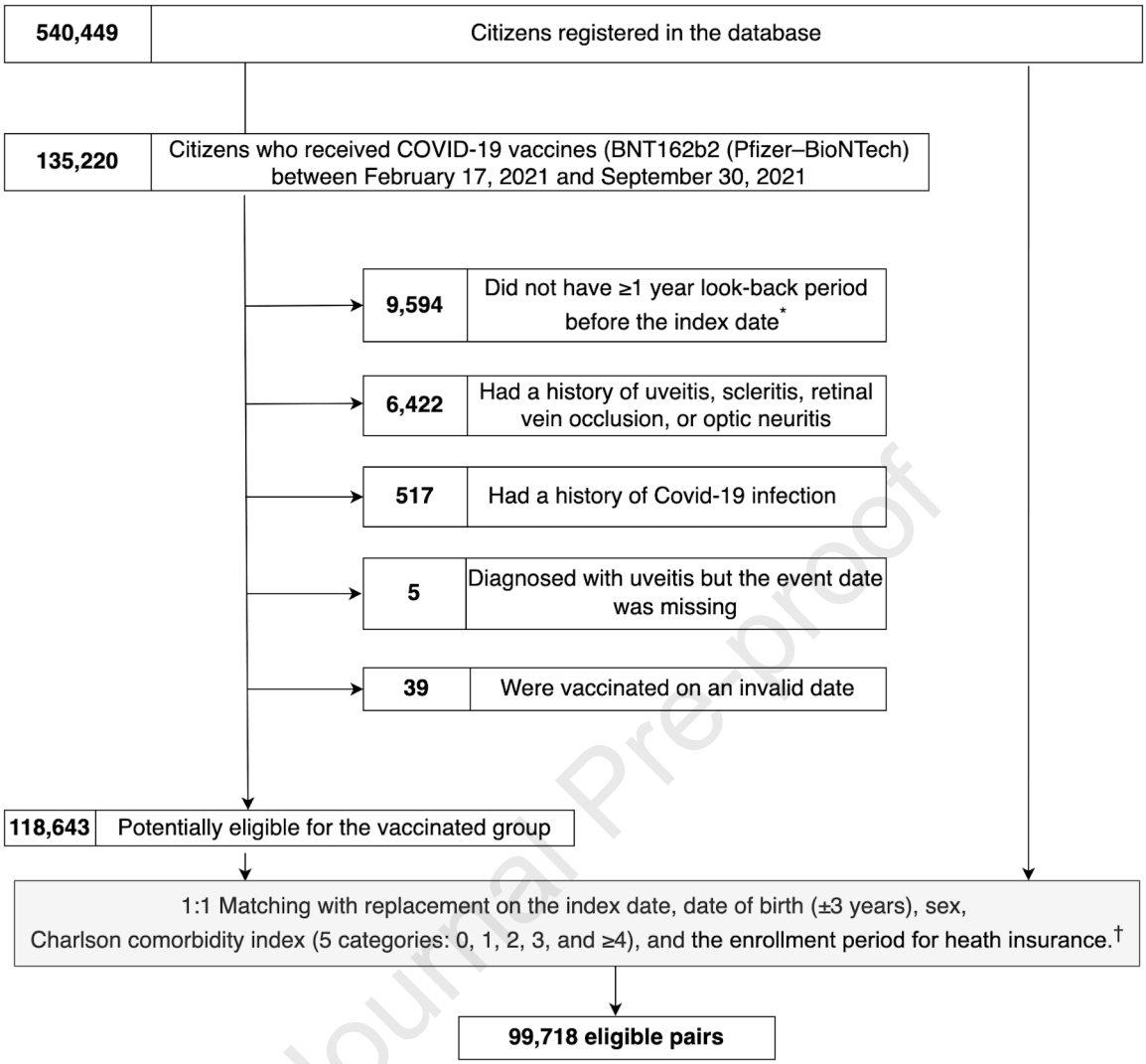
Event	Vaccination dose	Time period (days)	No. of individuals in vaccinated and control groups*	No. of events in vaccinated group	No. of events in control group	Cumulative incidence (No. of events per 100,000 persons)	
						Difference (95% CI)	Ratio (95% CI)
Composite outcome	1	21	99,718	29	21	2.9 (-14.5 to 19.1)	1.1 (0.6 to 2)
	2	84	82,462	79	28	**51.3 (16.2 to 84.3)**	**1.8 (1.2 to 2.9)**
Uveitis	1	21	102,846	19	12	3.5 (-9.6 to 15.8)	1.2 (0.6 to 3)
	2	84	85,286	37	21	7.8 (-19.8 to 32.6)	1.2 (0.7 to 2)
Scleritis	1	21	104,489	6	3	2.6 (-2.8 to 8.3)	1.8 (0.4 to 7.4)
	2	84	86,750	18	7	5 (-13.2 to 23.1)	1.2 (0.6 to 3.9)
Retinal vein occlusion	1	21	103,871	4	6	-4.2 (-12.3 to 2.6)	0.5 (0.1 to 1.8)
	2	84	86,183	30	4	**29.4 (8.3 to 48.7)**	**3.3 (1.3 to 16.1)**
Optic neuritis	1	21	105,484	1	3	-2.7 (-6.8 to 1.9)	0.3 (0 to 1.6)
	2	84	87,647	3	4	-1.8 (-9.5 to 4.5)	0.7 (0 to 3.4)

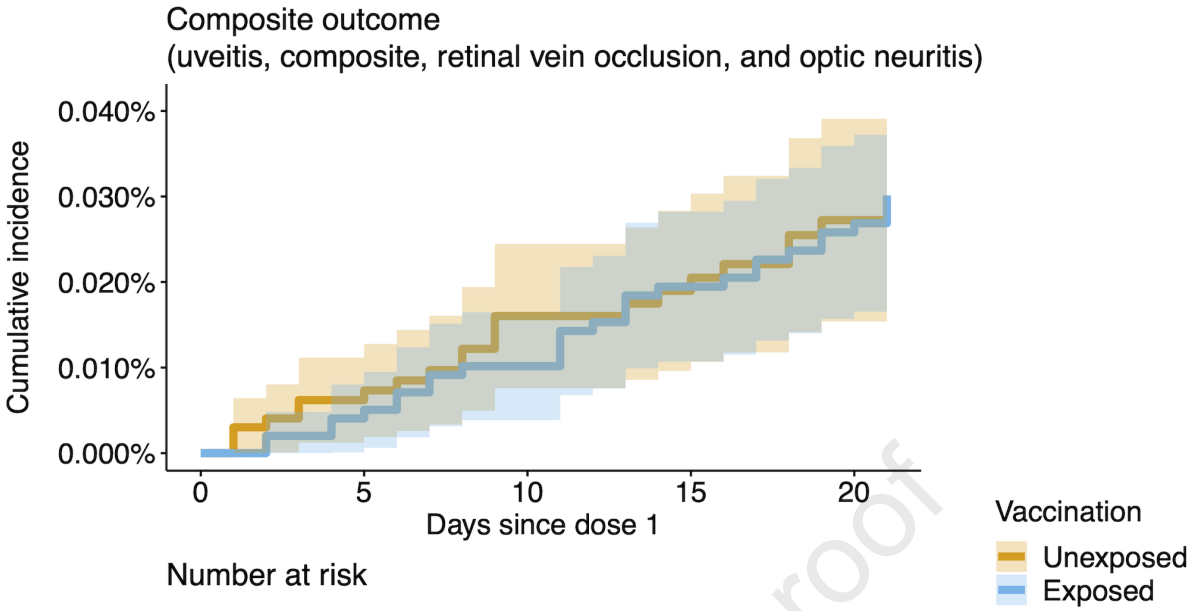
* The number of the study population was different for each adverse event because each analysis had event-specific exclusion criteria for individuals with a history of that event.

Table 3. Incidence rate ratios of ocular adverse events during the risk periods in the self-controlled case series study.

Period	Composite outcome		Uveitis		Scleritis	
	No. of events	IRR (95% CI)	No. of events	IRR (95% CI)	No. of events	IRR (95% CI)
Control period	289	1 (ref)	158	1 (ref)	57	1 (ref)
Days from vaccination dose 1:						
0 to 21 (total)	32	0.89 (0.62 to 1.28)	19	1 (0.63 to 1.59)	8	1.28 (0.60 to 2.73)
0 to 7	13	0.93 (0.53 to 1.63)	9	1.17 (0.59 to 2.30)	2	0.87 (0.21 to 3.62)
8 to 14	10	0.82 (0.44 to 1.55)	4	0.6 (0.22 to 1.62)	3	1.5 (0.46 to 4.86)
15 to 21	9	0.91 (0.50 to 1.68)	6	1.18 (0.58 to 2.41)	3	1.57 (0.48 to 5.09)
Days from vaccination dose 2:						
0 to 84 (total)	115	0.89 (0.71 to 1.11)	66	0.92 (0.68 to 1.25)	22	1.07 (0.63 to 1.83)
0 to 7	13	0.96 (0.55 to 1.69)	9	1.17 (0.60 to 2.31)	2	0.86 (0.21 to 3.58)
8 to 14	14	1.19 (0.69 to 2.04)	8	1.22 (0.60 to 2.50)	0	0 (0.00 to Inf)
15 to 21	10	0.86 (0.46 to 1.62)	4	0.62 (0.23 to 1.68)	3	1.38 (0.43 to 4.42)
22 to 84	78	0.84 (0.65 to 1.09)	45	0.88 (0.62 to 1.24)	17	1.17 (0.65 to 2.11)

Period	Retinal vein occlusion		Optic neuritis	
	No. of events	IRR (95% CI)	No. of events	IRR (95% CI)
Control period	82	1 (ref)	14	1 (ref)
Days from vaccination dose 1:				
0 to 21 (total)	5	0.41 (0.17 to 1.02)	2	1.29 (0.28 to 5.93)
0 to 7	2	0.45 (0.11 to 1.83)	1	1.74 (0.22 to 13.67)
8 to 14	2	0.51 (0.13 to 2.10)	1	2.03 (0.26 to 16.06)
15 to 21	1	0.27 (0.04 to 1.91)	0	0 (0.00 to Inf)
Days from vaccination dose 2:				
0 to 84 (total)	36	0.85 (0.57 to 1.27)	4	0.74 (0.23 to 2.45)
0 to 7	3	0.74 (0.23 to 2.34)	1	2.06 (0.26 to 16.42)
8 to 14	6	1.57 (0.68 to 3.61)	1	2.16 (0.27 to 17.25)
15 to 21	3	0.78 (0.25 to 2.49)	1	2.16 (0.27 to 17.25)
22 to 84	24	0.78 (0.49 to 1.25)	1	0.26 (0.03 to 2.04)



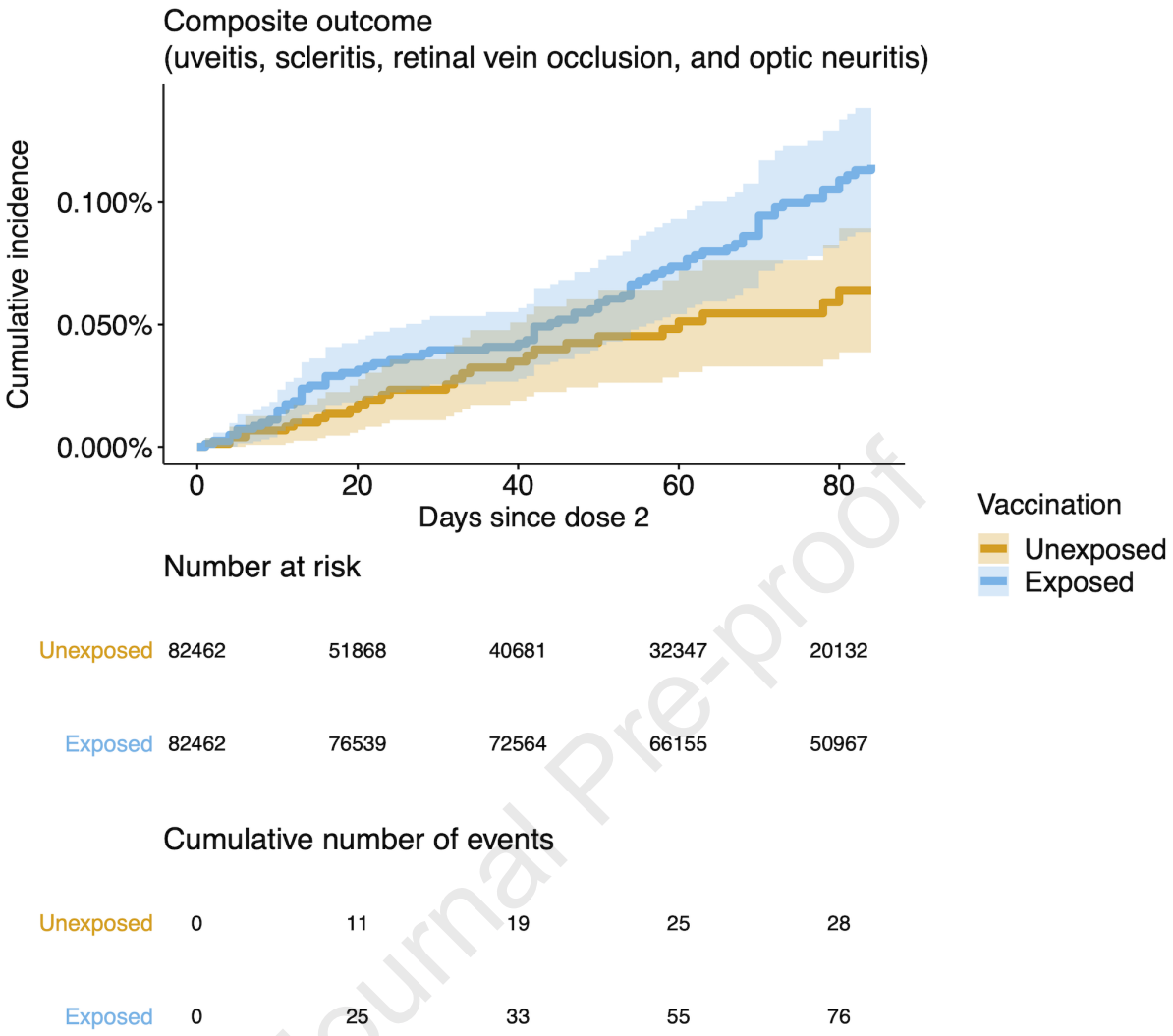


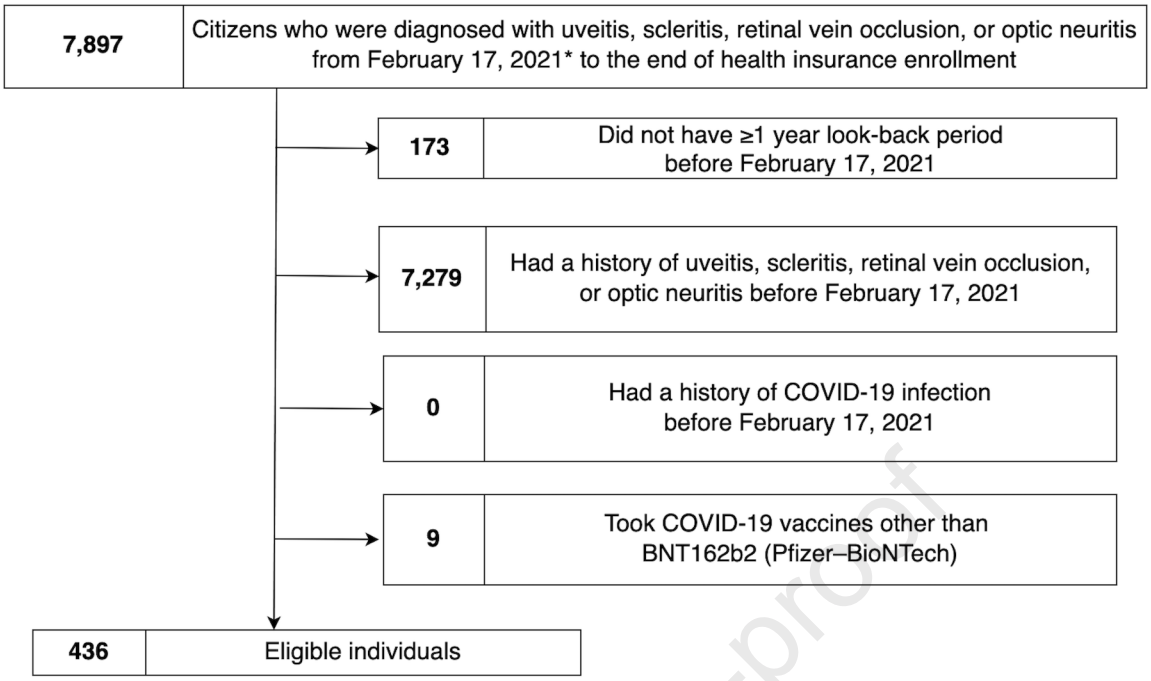
Number at risk

Unexposed	99718	88116	75740	64979	55503
Exposed	99718	98402	97273	95787	93250

Cumulative number of events

Unexposed	0	7	14	17	21
Exposed	0	5	10	19	26





Precis

Matched cohort analysis showed an increased risk for the occurrence of ocular adverse events after the second dose of the COVID-19 vaccine; however, the self-controlled case series analysis showed no increased risk.