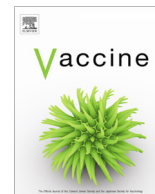




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A post-marketing safety assessment of COVID-19 mRNA vaccination for serious adverse outcomes using administrative claims data linked with vaccination registry in a city of Japan

Yoshinori Takeuchi^{a,b,*}, Masao Iwagami^{c,d}, Sachiko Ono^e, Nobuaki Michihata^f, Kohei Uemura^g, Hideo Yasunaga^h

^a Division of Medical Statistics, Department of Social Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

^b Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

^c Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

^d Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

^e Department of Eat-loss Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

^f Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

^g Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan

^h Department of Clinical Epidemiology & Health Economics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

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ABSTRACT

Introduction: The safety profiles of COVID-19 vaccines are incompletely evaluated in Japan.

Objectives: To examine the risk of serious adverse effects after COVID-19 mRNA vaccination (BNT162b2 and mRNA-1273) in cohort studies and self-controlled case series (SCCS).

Methods: Using an administrative claims database linked with the COVID-19 vaccination registry in a city in Japan between September 2020 and September 2021, we identified health insurance enrollees aged ≥ 18 years. We evaluated the risk of acute myocardial infarction, appendicitis, Bell's palsy, convulsions/seizures, disseminated intravascular coagulation, immune thrombocytopenia, pulmonary embolism, haemorrhagic or ischemic stroke, venous thromboembolism, and all-cause mortality, 21 days following any COVID-19 mRNA vaccination, compared with non-vaccination periods. For the cohort studies, we estimated incidence rate ratios (IRRs) by Poisson regression and rate differences (IRDs) by weighted least-squares regression, adjusting for sex, age, and Charlson comorbidity index. We applied a modified SCCS design to appropriately treat outcome-dependent exposures. For the modified SCCS, we estimated within-subject IRRs by weighted conditional Poisson regression. Subgroup analyses stratified by sex and age were also conducted.

Results: We identified 184,491 enrollees [male: 87,218; mean (standard deviation) age: 64.2 (19.5) years] with 136,667 first and 127,322 s dose vaccinations. The risks of any outcomes did not increase in any analyses, except for the fact that the modified SCCS indicated an increased risk of pulmonary embolism after the first dose in women (within-subject IRR [95%CI]: 3.97 [1.18–13.32]).

Conclusion: The findings suggested that the COVID-19 mRNA vaccine was generally safe, whilst a signal of pulmonary embolism following the first dose of the COVID-19 mRNA vaccine was observed.

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Abbreviations: COVID-19, coronavirus disease 2019; CCI, Charlson comorbidity index; CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; IRD, incidence rate difference; IRR, incidence rate ratio; NA, not available; SCCS, self-controlled case series; SD, standard deviation.

* Corresponding author at: Division of Medical Statistics, Department of Social Medicine, Faculty of Medicine, Toho University, 5-21-16 Ohmori-nishi, Ota-ku, Tokyo 143-8540, Japan.

E-mail address: ytake-tky@umin.ac.jp (Y. Takeuchi).

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1. Introduction

Vaccination against coronavirus disease 2019 (COVID-19) is one of the most fundamental strategies to prevent infection and to reduce the following severe complications. Globally, until December 2021, more than 9 billion doses of the vaccine were administered [1]. Randomised clinical trials showed the high efficacy of the vaccines and low incidence of severe adverse events owing to

their administration [2,3]. However, their small sample sizes and narrow population representativeness are potential limitations of such trials. Thus, post-marketing safety assessment using large real-world data is warranted.

In Japan, BNT162b2 (Pfizer-BioNTech) was first approved in February 2021, followed by mRNA-1273 (Moderna/Takeda), and ChAdOx1-S (Astra-Zeneca) in May 2021 [4]. Until the end of 2021, approximately 80 % of all citizens of Japan had received at least one vaccination [1]. To date, however, the safety monitoring of COVID-19 vaccines has been mostly based on individual case safety reports and the reported adverse reactions at the population level compared with previously recorded data (e.g. recorded diagnosis of myocarditis and pericarditis in the national claims data) between periods before and after the COVID-19 mass vaccination [4]. To our knowledge, no Japanese study directly compared people (or periods) vaccinated against COVID-19 or not for identifying a variety of potentially serious outcomes, although there are several studies of this kind – assessing individual-level data, in other countries such as Israel [5] and the US [6]. Until June 26, 2021, the active surveillance by the US Vaccine Safety Datalink had not found any significant safety signals [6].

In this study, linking administrative claims data and the COVID-19 vaccination registry in an urban city in Japan, we aimed to examine the risk of serious adverse effects after COVID-19 vaccination. In addition to a conventional cohort study design, we conducted self-controlled case series (SCCS) using the same data, because the cohort study design may be affected by unmeasured confounding factors or by the difference of characteristics between those with and without vaccination [7]. We focused on the risk of adverse effects following the first and second dose of mRNA vaccine compared with non-vaccination because COVID-19 mRNA vaccines (BNT162b2 and mRNA-1273) had been dominantly (greater than 99 %) administered in Japan [4].

2. Methods

2.1. Data source

This study was conducted using administrative claims data linked to the COVID-19 vaccine registry and mortality records, in an urban city of Japan, City A between September 2020 and September 2021. The administrative claims data collected from 226,969 insurance enrollees included claims of the National Health Insurance for self-employed individuals, retired individuals, and

their dependants and of the Advanced Elderly Medical Service System for people aged 75 years or older. The data contains information on outpatient clinic visits and hospital admissions, including enrollee's age, sex, diagnoses, medical examinations, and treatments. Diagnoses were established based on the International Classification of Diseases, 10th revision (ICD-10) codes, and disease names in Japanese. The vaccine registry includes information on the types of vaccines administered and the vaccination dates. Using unique identification numbers, the administrative claims data were linked to the vaccine records in the City A Office. All personal information was excluded, and the de-identified data were sent to the researchers for secondary use.

This study was approved by the Research Ethics Committee, Graduate School of Medicine and Faculty of Medicine, the University of Tokyo (approval no. 2021187NI). Because our analyses involved the secondary use of anonymized data that had been routinely collected by the Japanese government, the need for individual informed consent was waived following the current ethical guidelines for medical and health research involving human participants in Japan.

2.2. Study population

Our target population comprised people aged ≥ 18 years who had not received COVID-19 mRNA vaccines, nor had been diagnosed with COVID-19. For each enrollee in the database, we defined his/her observation period from 1st September 2020 or the enrolment date for the insurance, whichever came later, to the withdrawal date for the insurance (including date of death) or 30th September 2021, whichever came first. For each participant, we defined “index date” as the day 180 after the start of the observation, and “look-back period” as the 180 days between the start of the observation and the index date in which covariates were defined. Thus, the study participants were aged ≥ 18 years at the index date, had at least 180 days of observation to ensure sufficient retrospective duration, did not have records of ChAdOx1 vaccines in the look-back period, and did not have a diagnosis record of COVID-19 in the look-back period (Fig. 1). In addition, we censored the follow-up when the participant received a diagnosis of COVID-19, or vaccination of ChAdOx1, whichever occurred earlier, for both study designs and censored the follow-up by the occurrence of serious outcomes only for the cohort study. We defined the diagnosis of COVID-19 based on the claims data (ICD-10 code: U071 or 072).

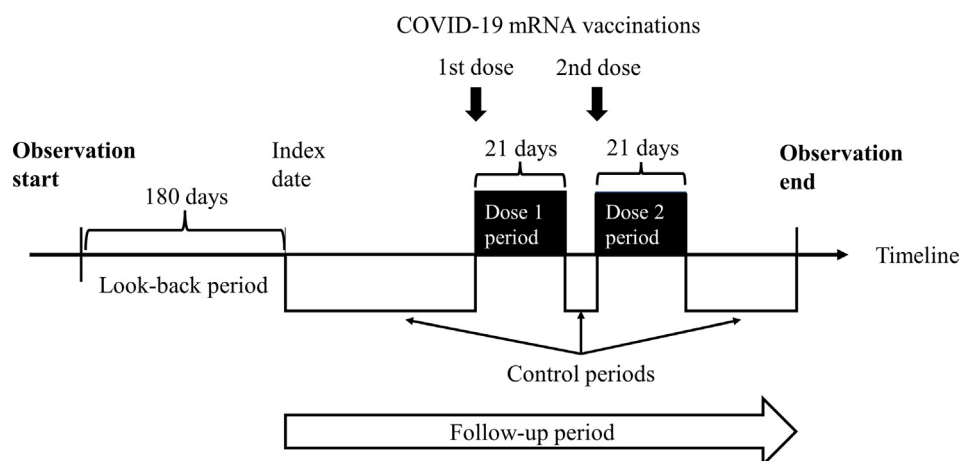


Fig. 1. Graphical representation of the study timeline; definition of the look-back and follow-up periods. The follow-up period was defined as the observation period other than the 180-day look-back period. The follow-up period for each participant was divided into the following 3 categories (at a maximum) according to the COVID-19 mRNA vaccination status: dose 1 risk period (21 days after the first dose), dose 2 risk period (21 days after the second dose), and control period (otherwise). Abbreviation: COVID-19, coronavirus disease 2019.

2.3. Definitions of exposure periods and outcome

In the main analysis, we evaluated the risk of serious outcomes for any COVID-19 mRNA vaccine (BNT162b2 or mRNA-1273). We defined risk periods owing to vaccination as the interval of 21 days after each vaccination dose (i.e., the first dose and the second dose). We selected a 21-day risk period, in line with previous studies [5,6,8] and the recommendations of the Japanese government on the minimal time interval between the first and second dose of the COVID-19 vaccine. If participants received the second vaccine dose within 20 days after the first dose, we censored the period of the first dose on the previous day before the administration of the second dose. We defined control periods as each interval of time during observation other than that within the risk periods (Fig. 1).

We defined serious adverse outcomes as initial hospitalization with acute myocardial infarction, appendicitis, Bell's palsy, convulsions/seizures, disseminated intravascular coagulation, immune thrombocytopenia, pulmonary embolism, haemorrhagic or ischemic stroke, and venous thromboembolism. Among the 19 types of outcomes monitored by the US Vaccine Safety Datalink after COVID-19 mRNA vaccination, we selected those with a frequency of occurrence in our database of over 20 cases [6]. We excluded thrombosis with thrombocytopenia from the outcomes since our database did not collect data on platelet counts. Supplementary Table 1 presents the list of ICD-10 codes for the outcome definition. We set the date of the outcome as the earliest hospitalization date in the claim including the corresponding outcome code. As an additional serious outcome, we evaluated the risk of all-cause death, which was recorded in the basic resident registers in City A. When we evaluated the risk of each outcome, we ignored the other outcomes other than death. When evaluating each outcome, we excluded participants who experienced the same outcomes during the look-back period (i.e., possible history). For example, we excluded the participants who were hospitalized with acute myocardial infarction during the look-back period from the analyses for the risk of acute myocardial infarction, whereas we did not exclude those who experienced other serious outcomes during the look-back period except for death.

2.4. Statistical analyses

First, as a cohort study, we estimated incidence rate ratios (IRRs) on each outcome during the periods of assessment following the first and second dose compared with the control periods by Poisson models adjusting for sex, age at the index date, and Charlson comorbidity index based on the diagnoses recorded during the look-back period [9], using generalized estimating equations. Moreover, to evaluate the absolute risk of each outcome, we estimated incidence rate differences (IRDs) by weighted least-squares regression models adjusting for the same covariates as the IRR model, proposed by Xu et al [10]. To calculate the 95 % confidence intervals (CIs) for estimates of IRRs and IRDs, we employed robust variance estimators.

If the outcome occurrence influenced the probability of receiving the subsequent exposure, the analysis of traditional SCCS would provide a biased effect estimate of the exposure [7]. In this study, because we were interested in the risk of serious outcomes after COVID-19 mRNA vaccination, these outcomes might reduce the probability of subsequent vaccination. Thus, we applied the “modified” SCCS, which can treat such outcome-dependent exposures [11,12]. Some previous studies evaluating the risk of COVID-19 vaccination on some serious outcomes also used the modified SCCS [13,14]. According to the recommendation in the methodological papers for modified SCCS [11,12], we artificially prolonged the follow-up until the end of the study period (30th September 2021) if the follow-up of the participant ended due to death. In the modi-

fied SCCS, we estimated within-subject IRRs and their 95 % CIs by weighted conditional Poisson models. In this study, we did not treat the age and Charlson comorbidity index of the study participants as time-varying covariates because of the short study duration (maximum approximately a half-year follow-up period).

2.5. Subgroup analyses

In both cohort studies and SCCS, subgroup analyses were performed for groups stratified by sex and age at the index date (<75 or ≥ 75 years). All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) or R 4.2.1 (R core team) with the R-package, “SCCS” version 1.6.

3. Results

3.1. Study population

Fig. 2 presents a flow diagram of participant selection for the study cohort. After applying inclusion criteria, we identified 184,5491 participants [male: 87,218; mean (standard deviation) age: 64.2 (19.5) years]. Among 333,655 doses of COVID-19 vaccines (BNT162b2: 310,469; mRNA-1273: 19,044) administered throughout the follow-up period, we identified 136,667 participants receiving the first dose and 127,322 participants receiving the second dose and their corresponding periods. Table 1 shows the baseline characteristics of participants included in each study period. All study periods had slightly higher proportions of women than men. When compared with the control period, those included in the first dose and the second dose periods had higher mean age and Charlson comorbidity index scores.

3.2. Results of the cohort study

Table 2 shows the main results of the cohort study, including the number of outcomes and follow-up lengths in the risk and control periods. Regarding the adjusted IRRs and IRDs for all serious outcomes, we did not find statistically significant elevations of the incidence in any dose-related risk period. Both IRR and IRD models showed lower risk of all-cause mortality in both the first dose (adjusted IRR [95 %CI]: 0.27 [0.21–0.35]; adjusted IRD [95 %CI]: −6.24 [−6.91 to −5.58] /100,000 person days) and the second dose (adjusted IRR [95 %CI]: 0.26 [0.20–0.34]; adjusted IRD [95 %CI]: −6.75 [−7.45 to −6.05] /100,000 person days) compared with control periods.

3.3. Results of self-controlled case series

Table 3 shows the main results of modified SCCS. Weighted conditional Poisson models indicated a higher point estimate (within-subject IRR) for convulsions/seizures (1.11) in the first dose-related risk period and convulsions/seizures (1.22) and immune thrombocytopenia (4.47), and haemorrhagic stroke (1.17) in the second dose-related risk period but the 95 % CIs included a null value (i.e., 1). In the cohort study, a lower risk of all-cause mortalities in both the first dose (within-subject IRR [95 %CI]: 0.38 [0.29–0.49]) and the second dose (within-subject IRR [95 %CI]: 0.43 [0.32–0.56]) were found.

3.4. Results of subgroup analyses

In the subgroup analyses of modified SCCS, there was an increased risk of pulmonary embolism in the first dose-related risk period in women (within-subject IRR [95 %CI]: 3.97 [1.18–13.32]), although no such increased risk was observed in adjusted IRD (0.12

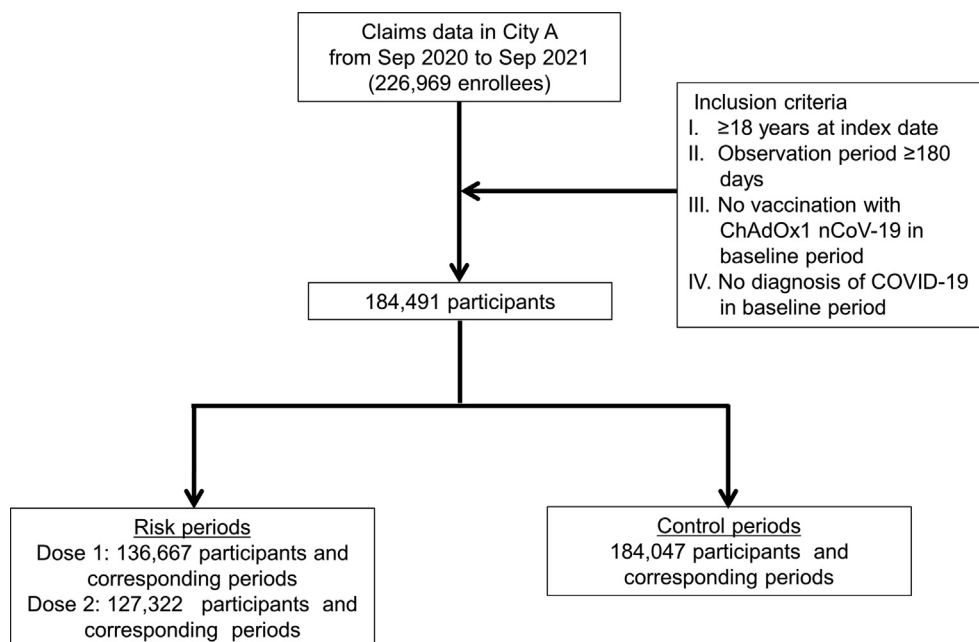


Fig. 2. Flow diagram of participant selection for the study cohort. Abbreviation: COVID-19, coronavirus disease 2019.

Table 1
Participant characteristics of included in each period.

	Period		
	The first dose	The second dose	Control
Participant and corresponding period, N	1,36,667	1,27,322	1,84,047
Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
Sex, n (%)			
Male	60,532 (44.3)	55,622 (43.7)	87,004 (47.3)
Female	76,135 (55.7)	71,700 (56.3)	97,043 (52.7)
Age, years, mean (SD)	69.0 (16.5)	70.7 (14.9)	64.3 (19.5)
Age category, years, n (%)			
18–49	19,611 (14.4)	13,446 (10.6)	44,631 (24.2)
50–64	18,217 (13.3)	16,540 (13.0)	27,074 (14.7)
65–74	39,445 (28.9)	38,880 (30.5)	45,151 (24.5)
75–84	44,073 (32.3)	43,469 (34.1)	48,898 (26.6)
≥85	15,332 (11.2)	14,987 (11.8)	18,293 (9.9)
CCI, mean (SD)	1.15 (1.78)	1.20 (1.80)	0.99 (1.7)

CCI, Charlson comorbidity index; SD, standard deviation.

[−0.17 to 0.40] /100,000 person-days) and adjusted IRR could not be estimated probably due to an insufficient number of outcomes in the cohort study for women (Supplementary Tables 2 and 3). In both the cohort study and modified SCCS, women tended to have higher risk estimates of convulsions/seizures. Participants aged < 75 years tended to have higher risk estimates of acute myocardial infarction than older participants aged ≥ 75 years in both study designs (Supplementary Tables 4 and 5).

4. Discussion

In this analysis, based on data obtained from a cohort study and SCCS using administrative claims data linked with a vaccination registry in an urban city in Japan, we evaluated the risk of serious adverse outcomes within 21 days after the administration of the first and second dose of COVID-19 mRNA vaccine compared with non-vaccination. In addition to IRR, we estimated adjusted IRD as an absolute measure in the cohort study. Safety signal for pulmonary embolism among women (in SCCS only), following the first dose of vaccine, was suggested by our data. The risks of other outcomes were not increased in any analyses.

A signal identified in the modified SCCS included in the current study was pulmonary embolism in women after the first dose (within-subject IRR [95 %CI]: 3.97 [1.18–13.32]) but the 95 % CI was very wide probably due to the small number of outcomes. Adjusted IRR could not be estimated in the cohort study for women owing to the small number of outcomes, whilst adjusted IRD suggested that the risk of the disease tended to be higher in women than in men. Klein et al. showed no increase in the risk of pulmonary embolism after COVID-19 mRNA vaccination, as evidenced by the analysis conditioned on the sex [6]. To our knowledge, although there have been case reports of pulmonary embolism in females following BNT162B2 vaccination [15], sufficient evidence to establish a clear association between the two is absent. Our finding did not lead to any conclusive remark but medical professionals and researchers may need to be cautious of a possibly elevated risk of pulmonary embolism for mRNA COVID-19 vaccination in women at least until further studies confirm otherwise.

Our study did not show an increased risk of haemorrhagic and ischemic strokes in either the cohort study or the SCCS following the administration of the mRNA vaccine compared to no vaccine administration. These findings are consistent with the results of

Table 2

Incidence rate ratios estimated by Poisson regression and incidence rate differences estimated by weighted least-squares regression for each outcome in the cohort studies.

		Period		
		The first dose	The second dose	Control
Acute myocardial infarction	Participant and corresponding period, N	1,36,488	1,27,143	1,83,870
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	13	5	161
	IRR (95 %CI), crude	0.91 (0.52–1.61)	0.38 (0.16–0.93)	1.00
	IRR (95 %CI), adjusted	0.80 (0.46–1.42)	0.32 (0.13–0.78)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−0.05 (−0.31 to 0.22)	−0.32 (−0.51 to −0.13)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−0.11 (−0.38 to 0.16)	−0.41 (−0.61 to −0.22)	0.00
Appendicitis	Participant and corresponding period, N	1,36,606	1,27,268	1,83,990
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	1	3	47
	IRR (95 %CI), crude	0.24 (0.03–1.74)	0.78 (0.24–2.52)	1.00
	IRR (95 %CI), adjusted	0.25 (0.03–1.83)	0.83 (0.25–2.80)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−0.11 (−0.20 to −0.03)	−0.03 (−0.17 to 0.11)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−0.11 (−0.19 to −0.02)	−0.02 (−0.17 to 0.12)	0.00
Bell's palsy	Participant and corresponding period, N	1,36,644	1,27,298	1,84,025
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	2	1	18
	IRR (95 %CI), crude	1.26 (0.29–5.41)	0.68 (0.09–5.10)	1.00
	IRR (95 %CI), adjusted	1.14 (0.27–4.89)	0.60 (0.08–4.49)	1.00
	IRD (95 %CI), crude, / 100,000 person day	0.01 (−0.09 to 0.12)	−0.02 (−0.10 to 0.06)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	0.01 (−0.09 to 0.11)	−0.03 (−0.11 to 0.06)	0.00
Convulsions/seizures	Participant and corresponding period, N	1,36,633	1,27,289	1,84,011
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	3	2	30
	IRR (95 %CI), crude	1.13 (0.35–3.70)	0.82 (0.20–3.42)	1.00
	IRR (95 %CI), adjusted	1.04 (0.32–3.40)	0.73 (0.17–3.14)	1.00
	IRD (95 %CI), crude, / 100,000 person day	0.01 (−0.11 to 0.14)	−0.02 (−0.13 to 0.10)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	0.00 (−0.12 to 0.13)	−0.03 (−0.15 to 0.09)	0.00
Disseminated intravascular coagulation	Participant and corresponding period, N	1,36,588	1,27,246	1,83,948
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	9	5	124
	IRR (95 %CI), crude	0.82 (0.42–1.61)	0.49 (0.20–1.21)	1.00
	IRR (95 %CI), adjusted	0.73 (0.37–1.43)	0.42 (0.17–1.02)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−0.07 (−0.29 to 0.15)	−0.20 (−0.38 to −0.01)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−0.13 (−0.35 to 0.10)	−0.28 (−0.46 to −0.09)	0.00
Immune thrombocytopenia	Participant and corresponding period, N	1,36,656	1,27,311	1,84,034
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	0	3	10
	IRR (95 %CI), crude	NA	NA	NA

Table 2 (continued)

		Period		
		The first dose	The second dose	Control
Pulmonary embolism	IRR (95 %CI), adjusted	NA	NA	NA
	IRD (95 %CI), crude, / 100,000 person day	−0.03 (−0.05 to −0.01)	0.09 (−0.05 to 0.22)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−0.04 (−0.06 to −0.01)	0.08 (−0.06 to 0.21)	0.00
	Participant and corresponding period, N	1,36,594	12,744	1,83,980
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	7	4	62
	IRR (95 %CI), crude	1.28 (0.58–2.79)	0.79 (0.29–2.18)	1.00
	IRR (95 %CI), adjusted	1.09 (0.50–2.38)	0.64 (0.23–1.76)	1.00
	IRD (95 %CI), crude, / 100,000 person day	0.05 (−0.14 to 0.25)	−0.04 (−0.20 to 0.12)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	0.01 (−0.04 to 0.06)	−0.09 (−0.54 to 0.07)	0.00
Stroke, haemorrhagic	Participant and corresponding period, N	1,36,351	1,27,020	1,83,707
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	17	19	206
	IRR (95 %CI), crude	0.93 (0.57–1.53)	1.13 (0.71–1.81)	1.00
	IRR (95 %CI), adjusted	0.82 (0.50–1.34)	0.95 (0.59–1.51)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−0.04 (−0.35 to 0.26)	0.09 (−0.26 to 0.43)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−0.13 (−0.44 to 0.17)	−0.04 (−0.39 to 0.31)	0.00
	Participant and corresponding period, N	1,35,659	1,26,308	1,83,058
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.4)	170.7 (41.7)
	Outcome, N	57	63	762
Stroke, ischemic	IRR (95 %CI), crude	0.85 (0.65–1.11)	1.02 (0.79–1.31)	1.00
	IRR (95 %CI), adjusted	0.72 (0.55–0.94)	0.81 (0.63–1.05)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−0.38 (−0.94 to 0.19)	0.04 (−0.60 to 0.67)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−0.80 (−1.36 to −0.23)	−0.56 (−1.20 to 0.08)	0.00
	Participant and corresponding period, N	1,36,170	1,26,826	1,83,590
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	170.9 (41.5)
	Outcome, N	25	22	363
	IRR (95 %CI), crude	0.78 (0.52–1.17)	0.74 (0.48–1.14)	1.00
	IRR (95 %CI), adjusted	0.67 (0.44–1.00)	0.60 (0.39–0.92)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−0.26 (−0.63 to 0.12)	−0.30 (−0.68 to 0.08)	0.00
Venous thromboembolism	IRD (95 %CI), adjusted, /100,000 person day	−0.46 (−0.84 to −0.09)	−0.58 (−0.97 to −0.20)	0.00
	Participant and corresponding period, N	1,36,667	1,27,322	84,047
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	65	61	2316
	IRR (95 %CI), crude	0.32 (0.25–0.41)	0.32 (0.25–0.42)	1.00
	IRR (95 %CI), adjusted	0.27 (0.21–0.35)	0.26 (0.20–0.34)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−5.02 (−5.67 to −4.38)	−4.99 (−5.66 to −4.33)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−6.24 (−6.91 to −5.58)	−6.75 (−7.45 to −6.05)	0.00
	Participant and corresponding period, N	1,36,667	1,27,322	84,047
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
All-cause mortality	Outcome, N	65	61	2316
	IRR (95 %CI), crude	0.32 (0.25–0.41)	0.32 (0.25–0.42)	1.00
	IRR (95 %CI), adjusted	0.27 (0.21–0.35)	0.26 (0.20–0.34)	1.00
	IRD (95 %CI), crude, / 100,000 person day	−5.02 (−5.67 to −4.38)	−4.99 (−5.66 to −4.33)	0.00
	IRD (95 %CI), adjusted, /100,000 person day	−6.24 (−6.91 to −5.58)	−6.75 (−7.45 to −6.05)	0.00
	Participant and corresponding period, N	1,36,667	1,27,322	84,047
	Length, Mean (SD), days	20.4 (2.8)	20.2 (3.3)	171.0 (41.4)
	Outcome, N	65	61	2316
	IRR (95 %CI), crude	0.32 (0.25–0.41)	0.32 (0.25–0.42)	1.00
	IRR (95 %CI), adjusted	0.27 (0.21–0.35)	0.26 (0.20–0.34)	1.00

CI, confidence interval; IRD, incidence rate difference; IRR, incidence rate ratio; NA, not available; SD, standard deviation.

Table 3

Within-subject incidence rate ratios estimated by weighted conditional Poisson regression for each outcome in the modified self-controlled case series analyses.

		Period		
		The first dose	The second dose	Control
Acute myocardial infarction	Participant and corresponding period, N	131	116	179
	Length, Mean (SD), days*	20.7 (1.6)	20.3 (2.9)	162.8 (44.8)
	Outcome, N	13	5	161
	IRR (95 %CI), within-subject	0.78 (0.42–1.45)	0.35 (0.14–0.87)	1.00
Appendicitis	Participant and corresponding period, N	37	31	51
	Length, Mean (SD), days*	20.2 (3.4)	20.8 (0.8)	180.0 (30.6)
	Outcome, N	1	3	47
	IRR (95 %CI), within-subject	0.23 (0.02–2.71)	0.68 (0.12–3.83)	1.00
Bell's palsy	Participant and corresponding period, N	15	15	21
	Length, Mean (SD), days*	21.0 (0.0)	21.0 (0.0)	181.0 (16.9)
	Outcome, N	2	1	18
	IRR (95 %CI), within-subject	1.03 (0.20–5.31)	0.47 (0.05–4.18)	1.00
Convulsions/seizures	Participant and corresponding period, N	26	20	35
	Length, Mean (SD), days*	20.3 (2.6)	18.8 (5.6)	174.1 (34.7)
	Outcome, N	3	2	30
	IRR (95 %CI), within-subject	1.11 (0.25–4.83)	1.22 (0.27–5.64)	1.00
Disseminated intravascular coagulation	Participant and corresponding period, N	71	59	138
	Length, Mean (SD), days*	20.4 (2.5)	20.5 (2.5)	152.6 (54.8)
	Outcome, N	9	5	124
	IRR (95 %CI), within-subject	0.79 (0.36–1.74)	0.52 (0.20–1.37)	1.00
Immune thrombocytopenia	Participant and corresponding period, N	10	10	13
	Length, Mean (SD), days*	21.0 (0.0)	21.0 (0.0)	163.9 (29.0)
	Outcome, N	0	3	10
	IRR (95 %CI), within-subject	NA	4.47 (0.74–27.18)	1.00
Pulmonary embolism	Participant and corresponding period, N	54	49	73
	Length, Mean (SD), days*	20.5 (2.6)	20.7 (2.1)	156.9 (46.0)
	Outcome, N	7	4	62
	IRR (95 %CI), within-subject	1.01 (0.32–3.16)	1.00 (0.32–3.06)	1.00
Stroke, haemorrhagic	Participant and corresponding period, N	155	130	242
	Length, Mean (SD), days*	20.0 (3.6)	20.4 (2.5)	162.8 (48.4)
	Outcome, N	17	19	206
	IRR (95 %CI), within-subject	1.06 (0.61–1.88)	1.17 (0.67–2.04)	1.00
Stroke, ischemic	Participant and corresponding period, N	655	610	882
	Length, Mean (SD), days*	20.7 (2.0)	20.5 (2.3)	168.5 (37.4)
	Outcome, N	57	63	762
	IRR (95 %CI), within-subject	0.77 (0.58–1.03)	0.89 (0.67–1.19)	1.00
Venous thromboembolism	Participant and corresponding period, N	303	276	410
	Length, Mean (SD), days*	20.6 (2.0)	20.6 (2.5)	167.6 (38.6)
	Outcome, N	25	22	363
	IRR (95 %CI), within-subject	0.78 (0.48–1.28)	0.85 (0.53–1.35)	1.00

Table 3 (continued)

		Period	
All-cause mortality			
Participant and corresponding period, N	672	276	2442
Length, Mean (SD), days*	20.1 (3.0)	20.1 (3.0)	96.7 (54.3)
Outcome, N	65	61	2316
IRR (95 %CI), within-subject	0.38 (0.29–0.49)	0.43 (0.32–0.56)	1.00

CI, confidence interval; IRR, incidence rate ratio; NA, not available; SD, standard deviation.
 *Before artificial extension for the censoring by death

previous observational studies including a modified SCCS for BNT162B2 [13], and cohort studies for BNT162B2 and both mRNA vaccines [5,6]. However, a recent modified SCCS using Hong Kong electric health and vaccine records suggested an increased risk of haemorrhagic stroke within 27 days after COVID-19 mRNA vaccination in the overall population (IRR; 1st dose: 1.67 [1.04–2.69]; 2nd dose: 1.68 [0.99–2.84]) [14]. A large comparative study would be needed to confirm such a risk; however, our analysis did not show any increased risk of these diseases.

For some serious outcomes (e.g., acute myocardial infarction for younger people and haemorrhagic stroke among the elderly), modified SCCS analysis revealed higher point estimates of IRRs compared with the Poisson models in the cohort study. Since SCCS theoretically removes time-invariant confounding factors, the estimates obtained from SCCS rather than those from the cohort studies may be considered closer to causal effect estimates. However, compared with cohort studies, the SCCS model is based on more assumptions that should be met to obtain unbiased estimates. If the assumptions were violated, the conditional Poisson models would produce severely biased estimates [16]. Moreover, the estimates of cohort studies and SCCS are different; the former refers to the effect of the treatment in a population compared to a control group, and the latter to the within-subject effect [17]. Therefore, the comparison between the results obtained from the cohort study and SCCS is useful to examine the violation of the assumptions although we should carefully compare and interpret the estimates obtained from our cohort study and SCCS.

Apart from the signal, the cohort study herein presented demonstrated a substantially lower risk of all-cause mortality within 21 days after either dose of COVID-19 mRNA vaccination when compared to no vaccine. A cohort study conducted by the US Vaccine Safety Datalink demonstrated that within 21 days after vaccinations with BNT162B2 or mRNA-1273 are associated with a substantially lower risk of non-COVID-19 mortality (IRRs: 0.31 to 0.41) compared with non-vaccination periods [18]. Our estimates of IRR in the cohort study were identical to those revealed in the previous study. However, because we focused on the short-term risk (within 21 days) of mRNA vaccination, our findings do not accurately indicate the long-term impact of mRNA vaccination on all-cause mortality. Such substantial decreases in all-cause death after vaccination reported by observational studies may be partially explained by the well-known “healthy vaccinee effect” [19,20]. Overall, based on our findings, we can suggest that there is no increased risk for mortality within 21 days after COVID-19 mRNA vaccination.

This study has several limitations. First, the observational data may have been biased by unmeasured confounders, especially in the cohort study. Particularly, detailed information on socioeconomic status (e.g., income, education level, and job) is not available in the database, and we were unable to account for the influence of this potential risk factor on serious outcomes. Second, we could not evaluate rare outcomes (less than 20 cases in the database) that might be possible adverse effects of mRNA vaccination, such as encephalomyelitis, myocarditis, transverse myelitis, and Guillain-

Barré syndrome. Third, whilst we defined serious outcome occurrence as hospitalization with corresponding inpatient disease diagnosis, it is not hierarchical (i.e., no differentiation between primary and secondary or later inpatient diagnoses) in the Japanese reimbursement claims. Although we excluded participants with the same outcomes during the look-back period to exclude their history and capture only the incident cases, some inpatient diagnoses may have included the history. This misclassification could have diluted the association between vaccination and outcomes. Finally, since the results of polymerase chain reaction tests of SARS-CoV-2 infection were not available, we might have misidentified the censoring time by a faulty COVID-19 diagnosis and also could not exclude the outcome occurrences associated with COVID-19 from the analyses. Based on the expected number of newly SARS-CoV-2 infections in Japan [1], our dataset could capture the majority (approximately 79 %) of new SARS-CoV-2 infections during the study period (detailed calculation for the capture probability is provided in Appendix 1 in Supplementary Materials).

5. Conclusion

To our knowledge, the current study is the first large observational study in Japan that directly compares the risk of occurrence of several serious outcomes between the short-term periods after COVID-19 vaccination and non-vaccination periods. Our results contribute to the assessment of the risk–benefit balance of COVID-19 vaccination and offer information useful for the development of future vaccination strategies. The study suggested that the COVID-19 mRNA vaccine was generally safe. Although our results indicate safety signals of pulmonary embolism for women (only in the SCCS) following the administration of the first dose of COVID-19 mRNA vaccines, further studies using large-scale data or hospital information data, are needed to confirm their extent.

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Availability of data and materials

The database used in this study is maintained by City A, Japan. Restrictions apply to the availability of data, which were used under permission for this study. Accordingly, these data are not publicly available.

Data availability

The data that has been used is confidential.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YT has received consultant fees from Pharmaceuticals and Medical Devices Agency and EPARK, Inc. YT has received lecture fees from SAS Institute Japan Ltd. YT has been conducting a collaborative study, which is not related to this article, with Pfizer Inc. SO is a member of the Department of Eat-loss Medicine, a cooperative program between the University of Tokyo and ITO EN Ltd and received grants from KAKENHI, and Health, Labour, and Welfare Policy Research Grants, not related to the submitted work. No other potential competing interests relevant to this study are reported.

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Appendix A. Supplementary data

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