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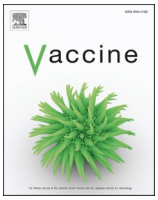

Effect of COVID-19 vaccination on the risk of developing post-COVID conditions: The VENUS study

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ABSTRACT

Introduction: Post-COVID-19 conditions have emerged as a global health challenge. This study examined the long-term effects of COVID-19 vaccination on the incidence and risk of post-COVID-19 conditions in Japan.
Methods: This retrospective cohort study was conducted using a database comprising medical claims, COVID-19 case information, and vaccination records of persons residing in four Japanese municipalities. The cohort included COVID-19 cases diagnosed between August 2020 and December 2022. Participants were classified according to the duration between their most recent COVID-19 vaccination and COVID-19 occurrence (≥365 days, 150–364 days, and 14–149 days). The incidences of 36 post-COVID-19 conditions were monitored for 3, 5, and 8 months after infection. Cox proportional hazards models were used to calculate the risk of developing each post-COVID-19 condition within 8 months after infection according to vaccination status.
Results: From among 84,464 participants, 9642 (11.4 %) developed post-COVID-19 conditions over 8 months. The 8-month risks of developing 28 (including various respiratory conditions, cardiovascular conditions, inflammatory and immune diseases, physical conditions, psychiatric conditions, and endocrine disorders) of the 36 target conditions were significantly lower when individuals had been recently vaccinated (14–149 days) before infection.
Conclusions: COVID-19 vaccination can reduce the incidence and risk of post-COVID-19 conditions if administered within 5 months before infection. Despite having the highest mean age and prevalence of comorbidities, individuals who were most recently vaccinated had a lower risk of developing post-COVID-19 conditions. These results provide important evidence for future COVID-19 vaccination strategies.

1. Introduction

The World Health Organization reported that as of October 2023, there have been over 770 million confirmed cases of COVID-19 worldwide [1]. A meta-analysis by Chen et al. synthesized the results of 50 studies involving nearly 1.7 million individuals, and estimated the global prevalence of post-COVID-19 conditions to be 43% [2]. This means that approximately 331 million individuals throughout the world have previously experienced or are currently experiencing post-acute sequelae of COVID-19. Even with a more conservative estimated prevalence of 10%, this number would be approximately 77 million [3]. More than 200 post-COVID-19 conditions (e.g., fatigue, dyspnea, and cognitive dysfunction) have been reported to date [2,4,5], but most are under-researched. In particular, the duration of these symptoms remains poorly characterized. Because COVID-19 has demonstrated large cross-country variations in pandemic diffusion patterns according to race, government policies, social systems, and medical systems [6], the incidence and characteristics of post-COVID-19 conditions can also be expected to vary greatly. Multinational and multidisciplinary research is needed to understand and formulate countermeasures to these widespread and still-obscure conditions.

Although COVID-19 vaccines have shown to be effective in reducing the risk of severe disease and mortality during acute SARS-CoV-2 infection [7], their impact on the prevalence of post-COVID-19 conditions is less understood. Several studies have reported that vaccination is generally associated with a lower risk of post-COVID-19 conditions after

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breakthrough infection [8–11], while others have indicated that vaccination does not reduce (or even increases) the risk of sequelae [12–15]. Moreover, most of the studies that assessed the effects of COVID-19 vaccines on post-COVID-19 conditions had compared the differences between vaccinated and unvaccinated groups or according to the number of vaccine doses [16]. In addition, many studies had examined patients who were infected within a month after vaccination, and therefore focused on their short-term effects [17]. Previous studies have utilized different study designs, vaccination timings, and definitions of post-COVID-19 conditions. To our knowledge, there are no studies in the literature that have considered the timing of booster vaccinations or most recent vaccination before SARS-CoV-2 infection. The protective effects of COVID-19 vaccines against acute symptoms are reported to decrease approximately 20 weeks after administration [18,19]. To better understand the impact of vaccination on post-COVID-19 conditions, it is necessary to consider the relative timings of vaccination and subsequent COVID-19 occurrence in individuals.

As described above, the evidence on the impact of COVID-19 vaccination on post-COVID-19 conditions remains controversial. Furthermore, there are no reports from Asia that have examined the long-term effectiveness of COVID-19 vaccines against a wide range of post-COVID-19 conditions. Therefore, this study aimed to investigate the long-term effects of COVID-19 vaccination on the incidence and risk of various post-COVID-19 conditions among individuals of all ages in Japan.

2. Materials and methods

2.1. Study design and data collection

This retrospective cohort study was conducted using data from the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) Study [20,21], which is an ongoing longitudinal multi-region database project that supports research on vaccine safety and effectiveness in Japan. As of August 2023, 13 municipalities were participating in the VENUS Study. Among these municipalities, four provided Health Center Real-time Information-sharing System on COVID-19 data, vaccination record system data, and medical claims data from Japan's two public health insurance systems (i.e., National Health Insurance and Latter-Stage Older Persons Health Care System) for this study. These four municipalities are located across Japan (Chugoku, Kanto, and Chubu regions), and have resident populations ranging from 220,000 to 410,000. In the VENUS Study, each individual resident is assigned a unique and anonymous research ID code by data managers, which facilitates their linkage across the various data types. The VENUS Study is a sub-project of the Longevity Improvement & Fair Evidence (LIFE) Study, and its data collection procedures and database construction are described in detail in the LIFE Study's profile paper [22].

Our study cohort comprised residents of the four subject municipalities who were diagnosed with COVID-19 between August 2020 and December 2022. The date on which COVID-19 was confirmed was designated the index date. Participants were assigned into one of three vaccination status groups (distant, intermediate, or recent vaccination) based on the duration between their most recent COVID-19 vaccination and the index date. The distant vaccination group ("distant group") comprised individuals who developed COVID-19 365 days or more after their last vaccine dose (including those who had not received a single dose prior to COVID-19 occurrence). The intermediate vaccination group ("intermediate group") comprised individuals who developed COVID-19 150 to 364 days after their last vaccine dose. The recent vaccination group ("recent group") comprised individuals who developed COVID-19 14 to 149 days after their last vaccine dose. Because Japan's medical claims data are collected on a monthly basis, the month that included the index date was designated the index month. The observation period for the onset of post-COVID-19 conditions was divided into three stages: 3 months, 5 months, and 8 months from the index month.

2.2. Post-COVID-19 conditions

The study outcomes were 36 target post-COVID-19 conditions that were identified using International Classification of Diseases, 10th Revision codes recorded in the medical claims data (Supplementary Table 1). These conditions were broadly categorized into respiratory conditions (pneumonia, acute upper respiratory disease, acute lower respiratory disease, asthma, and respiratory failure), cardiovascular conditions (ischemic heart disease, hypertension, pulmonary circulation disease, pericarditis, myocarditis, arrhythmia, heart failure, stroke, and cerebral infarction), digestive system diseases (appendicitis, noninfective enteritis/colitis, and hernia), inflammatory and immune diseases (arthritis, dermatitis, ear disease, and immune dysfunction), physical conditions (fracture, taste disorder, fatigue, pain, and headache), psychiatric conditions (mood disorders, depression, anxiety disorders, and sleep disorders), and endocrine disorders and other sequelae (diabetes, metabolic disorder, cancer, renal failure, cognitive disorder, and dementia).

As some participants may have had these conditions before SARS-CoV-2 infection, we sought to minimize their possible confounding effects on the impact of COVID-19 vaccination. Therefore, we identified the presence of these conditions as preexisting comorbidities during the year (12 months including the index month) before COVID-19 occurrence in each participant.

2.3. Statistical analysis

First, sex (male and female) and age categories (0–19, 20–39, 40–64, and ≥65 years) were reported as numbers and percentages, and compared using Pearson's chi-squared test. Next, we examined the incidence of new-onset post-COVID-19 conditions over the three follow-up periods (3 months, 5 months, and 8 months after COVID-19 occurrence). To statistically examine the associations between COVID-19 vaccination status and each of the 36 target post-COVID-19 conditions within 8 months after COVID-19 occurrence, we constructed Cox proportional hazards models that adjusted for sex and age. For each post-COVID-19 condition, we excluded cases with a diagnostic history of the same condition during the 12-month period before COVID-19 occurrence. For example, the analysis of incident post-COVID pneumonia excluded cases with preexisting pneumonia during the year before the index month. Schoenfeld residuals were used to assess the proportional hazards assumption. Risks were calculated as hazard ratios (HRs) with 95% confidence intervals (CIs). The analyses were performed using Stata Statistical Software Release 17 (Stata Corp, College Station, TX), and *P*-values below 0.05 were considered significant.

2.4. Ethical clearance

The study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 22114-03), and was conducted in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Participant names and/or identifiers were anonymized to ensure privacy and confidentiality. The data were stored on a computer protected with a password and used specifically for the study.

2.5. Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, manuscript preparation, or decision to submit the manuscript for publication. The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the funding source.

3. Results

3.1. Study cohort characteristics

We identified 84,464 COVID-19 cases during the observation period. Of these, 27,673 were assigned to the distant group, 25,001 to the intermediate group, and 31,790 to the recent group (Table. 1). The entire cohort included 47,244 (55.9%) female participants, who were more likely than male participants to be vaccinated within 364 days before COVID-19 occurrence. The overall mean age was 53 years, and the mean age by group was 36 years for the distant group, 57 years for the intermediate group, and 65 years for the recent group. Supplementary Table 2 presents the proportions of participants with each of the 36 target conditions as preexisting comorbidities during the 12-month period before COVID-19 occurrence. The recent group had the highest prevalence for all comorbidities except acute upper respiratory disease, acute lower respiratory disease, and appendicitis.

3.2. Incidence of post-COVID-19 conditions

Table. 2 presents the incidence of each post-COVID-19 condition over time according to vaccination status. The recent group (vaccinated within 14–149 days before COVID-19 occurrence) had the lowest incidence of pneumonia, acute upper respiratory disease, acute lower respiratory disease, asthma, respiratory failure, noninfective enteritis/colitis, ear disease, fracture, fatigue, headache, mood disorders, depression, anxiety disorders, sleep disorders, and cognitive disorder in all three follow-up periods. The distant group (vaccinated ≥365 days before COVID-19 occurrence) had the highest incidence of acute upper respiratory disease, acute lower respiratory disease, asthma, dermatitis, ear disease, taste disorder, fatigue, and headache in all three follow-up periods. Pulmonary circulation disease, arrhythmia, stroke, hernia, and cancer had the lowest incidence in the distant group during 3 months of follow-up and in the recent group during 8 months of follow-up.

3.3. Associations between vaccination status and incident post-COVID-19 conditions

Table. 3 and Fig. 1 show the adjusted HRs and 95% CIs of the intermediate group and recent group (reference: distant group) for the occurrence of each post-COVID-19 condition during the 8-month period after COVID-19 occurrence.

3.3.1. Respiratory conditions

Respiratory conditions are the most common symptom of COVID-19 in the acute phase, and their incidence were the lowest in the recent group in all three follow-up periods. For pneumonia, the HRs (reference: distant group) were 0.80 (95% CI: 0.55–1.17) for the intermediate group and 0.44 (95% CI: 0.29–0.67) for the recent group. For acute upper respiratory disease (e.g., nasopharyngitis and sinusitis), the HRs were 0.55 (95% CI: 0.46–0.67) for the intermediate group and 0.54 (95% CI: 0.45–0.66) for the recent group. For acute lower respiratory disease (e.g., bronchitis), the HRs were 0.67 (95% CI: 0.54-0.83) for the intermediate group and 0.72 (95% CI: 0.58–0.90) for the recent group. For asthma, the HRs were 0.69 (95% CI: 0.54–0.87) for the intermediate group and 0.59 (95% CI: 0.46–0.76) for the recent group. For respiratory failure, the HRs were 0.74 (95% CI: 0.57–0.97) for the intermediate group and 0.52 (95% CI: 0.39–0.69) for the recent group.

3.3.2. Cardiovascular conditions

The recent group had a significantly lower risk than the distant group for all cardiovascular conditions except pericarditis, myocarditis, and cerebral infarction. The HRs of the recent group (reference: distant group) were 0.55 (95% CI: 0.36–0.84) for ischemic heart disease, 0.60 (95% CI: 0.45–0.79) for hypertension, 0.09 (95% CI: 0.01–0.80) for pulmonary circulation disease, 0.57 (95% CI: 0.38–0.86) for arrhythmia, 0.45 (95% CI: 0.32–0.63) for heart failure, and 0.38 (95% CI: 0.16–0.89) for stroke.

3.3.3. Digestive system diseases

There were no significant differences in the risks of appendicitis and noninfective enteritis/colitis among the three vaccination groups. However, the recent group had a significantly lower risk (HR: 0.27, 95% CI: 0.12–0.63) of developing hernia than the distant group.

3.3.4. Inflammatory and immune diseases

The intermediate group and recent group had significantly lower risks of developing inflammatory diseases, including arthritis, dermatitis, and ear disease (e.g., perichondritis and otitis media). For arthritis, the HRs (reference: distant group) were 0.75 (95% CI: 0.58–0.96) for the intermediate group and 0.66 (95% CI: 0.51–0.86) for the recent group. For dermatitis, the HRs were 0.67 (95% CI: 0.58–0.78) for the intermediate group and 0.56 (95% CI: 0.48–0.66) for the recent group. For ear disease, the HRs were 0.64 (95% CI: 0.52–0.79) for the intermediate group and 0.59 (95% CI: 0.47–0.73) for the recent group. The recent group had the lowest risks for these inflammatory diseases among the vaccination groups. Next, the risk of developing immune dysfunction (e.g., immunodeficiency with predominantly antibody defects, combined immunodeficiencies, and common variable immunodeficiency) was significantly lower in the intermediate group (HR: 0.08, 95% CI: 0.01–0.64), but not the recent group (HR: 0.62, 95% CI: 0.22–1.70).

3.3.5. Physical conditions

The recent group had the lowest risks for all physical conditions. For fracture, the HRs (reference: distant group) were 0.79 (95% CI: 0.59–1.05) for the intermediate group and 0.43 (95% CI: 0.31–0.59) for the recent group. For taste disorder, the HRs were 0.42 (95% CI: 0.20–0.90) for the intermediate group and 0.22 (95% CI: 0.08–0.57) for the recent group. For fatigue, the HRs were 0.64 (95% CI: 0.39–1.07) for the intermediate group and 0.55 (95% CI: 0.32–0.94) for the recent group. For pain, the HRs were 0.94 (95% CI: 0.73–1.20) for the

Table 1
Baseline characteristics of participants according to vaccination status.

Characteristics	Categories	Total	Distant Group	Intermediate Group	Recent Group	P
N		84,464	27,673	25,001	31,790	
Sex	Male (%)	37,220 (44·07)	13,695 (49·49)	10,300 (41·20)	13,225 (41·60)	<0·001
	Female (%)	47,244 (55·93)	13,978 (50·51)	14,710 (58·80)	18,565 (58·40)	
Age, years	Mean [SD]	52·96 [28·84]	35·98 [27·39]	56·78 [27·25]	64·75 [23·90]	
	0–19 (%)	12,048 (14·26)	9021 (32·60)	1546 (6·18)	1481 (4·66)	
	20–39 (%)	17,441 (20·65)	8034 (29·03)	5364 (21·46)	4043 (12·72)	<0·001
	40–64 (%)	17,685 (20·94)	5334 (19·28)	6798 (27·19)	5553 (17·47)	
	≥65 (%)	37,290 (44·15)	5284 (19·09)	11,293 (45·17)	20,713 (65·16)	

Distant group: COVID-19 occurrence ≥365 days after vaccination. Intermediate group: COVID-19 occurrence 150–364 days after vaccination. Recent group: COVID-19 occurrence 14–149 days after vaccination.
SD: standard deviation.

Table 2
Incidence of post-COVID conditions according to vaccination status.

Conditions	Categories	Total	Distant Group	Intermediate Group	Recent Group	P
Pneumonia	N	77,794	25,568 (32.87)	23,158 (29.77)	29,068 (37.37)	
	After 3 months	24 (0.03)	8 (0.03)	9 (0.04)	7 (0.02)	0.633
	5 months	115 (0.15)	35 (0.14)	47 (0.20)	33 (0.11)	0.026
	8 months	175 (0.22)	58 (0.23)	70 (0.30)	47 (0.16)	0.003
Acute upper respiratory disease	N	39,053	13,506 (34.58)	11,873 (30.40)	13,674 (35.01)	
	After 3 months	111 (0.28)	52 (0.39)	28 (0.24)	31 (0.23)	0.025
	5 months	441 (0.13)	223 (1.65)	115 (0.97)	103 (0.75)	<0.001
	8 months	729 (1.87)	397 (2.94)	173 (1.46)	159 (1.16)	<0.001
Acute lower respiratory disease	N	55,938	18,417 (32.92)	16,899 (30.21)	20,622 (36.87)	
	After 3 months	82 (0.15)	41 (0.22)	19 (0.11)	22 (0.11)	0.004
	5 months	360 (0.64)	164 (0.89)	103 (0.61)	93 (0.45)	<0.001
	8 months	574 (1.03)	282 (1.53)	144 (0.85)	148 (0.72)	<0.001
Asthma	N	68,936	22,125 (32.09)	20,788 (30.16)	26,023 (37.75)	
	After 3 months	67 (0.10)	45 (0.20)	15 (0.07)	7 (0.03)	<0.001
	5 months	290 (0.42)	154 (0.70)	75 (0.36)	61 (0.23)	<0.001
	8 months	478 (0.69)	257 (1.16)	121 (0.58)	100 (0.38)	<0.001
Respiratory failure	N	74,839	25,046 (33.47)	22,074 (29.50)	27,719 (37.04)	
	After 3 months	49 (0.07)	21 (0.08)	18 (0.08)	10 (0.04)	0.054
	5 months	218 (0.29)	74 (0.30)	79 (0.36)	65 (0.23)	0.039
	8 months	348 (0.46)	131 (0.52)	120 (0.54)	97 (0.35)	0.002
Ischemic heart disease	N	74,556	26,179 (35.11)	21,898 (29.37)	26,479 (35.52)	
	After 3 months	18 (0.02)	5 (0.02)	6 (0.03)	7 (0.03)	0.807
	5 months	85 (0.11)	17 (0.06)	37 (0.17)	31 (0.12)	0.003
	8 months	143 (0.19)	44 (0.17)	53 (0.24)	46 (0.17)	0.128
Hypertension	N	55,569	23,338 (42.00)	15,974 (28.75)	16,257 (29.26)	
	After 3 months	60 (0.11)	11 (0.05)	27 (0.17)	22 (0.14)	0.001
	5 months	247 (0.44)	63 (0.27)	100 (0.63)	84 (0.52)	<0.001
	8 months	361 (0.65)	108 (0.46)	153 (0.96)	100 (0.62)	<0.001
Pulmonary circulation disease	N	83,956	27,565 (32.83)	24,858 (29.61)	31,533 (37.56)	
	After 3 months	2 (0.00)	0 (0.00)	1 (0.00)	1 (0.00)	0.601
	5 months	10 (0.01)	4 (0.01)	4 (0.02)	2 (0.01)	0.511
	8 months	15 (0.02)	5 (0.02)	9 (0.04)	1 (0.00)	0.014
Pericarditis	N	83,775	27,562 (32.90)	24,797 (29.60)	31,416 (37.50)	
	After 3 months	4 (0.00)	1 (0.00)	2 (0.01)	1 (0.00)	0.669
	5 months	14 (0.02)	2 (0.01)	8 (0.03)	4 (0.01)	0.069
	8 months	18 (0.02)	3 (0.01)	10 (0.04)	5 (0.02)	0.050
Myocarditis	N	84,039	27,589 (32.83)	24,863 (29.59)	31,587 (37.59)	
	After 3 months	1 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0.359
	5 months	3 (0.00)	3 (0.01)	0 (0.00)	0 (0.00)	0.046
	8 months	9 (0.01)	4 (0.01)	2 (0.01)	3 (0.01)	0.749
Arrhythmia	N	77,251	26,573 (34.40)	22,761 (29.46)	27,917 (36.14)	
	After 3 months	23 (0.03)	5 (0.02)	10 (0.04)	8 (0.03)	0.270
	5 months	104 (0.13)	28 (0.11)	47 (0.21)	29 (0.10)	0.002
	8 months	181 (0.23)	56 (0.21)	77 (0.34)	48 (0.17)	<0.001
Heart failure	N	70,771	25,466 (35.98)	20,789 (29.38)	24,516 (34.64)	
	After 3 months	38 (0.05)	11 (0.04)	16 (0.08)	11 (0.04)	0.226
	5 months	163 (0.23)	34 (0.13)	73 (0.35)	56 (0.23)	<0.001
	8 months	254 (0.36)	71 (0.28)	113 (0.54)	70 (0.29)	<0.001
Stroke	N	83,140	27,419 (32.98)	24,589 (29.58)	31,132 (37.45)	
	After 3 months	8 (0.01)	1 (0.00)	5 (0.02)	2 (0.01)	0.118
	5 months	31 (0.04)	8 (0.03)	10 (0.04)	13 (0.04)	0.696
	8 months	42 (0.05)	12 (0.04)	19 (0.08)	11 (0.04)	0.076
Cerebral infarction	N	73,605	26,086 (35.44)	21,679 (29.45)	25,840 (35.11)	
	After 3 months	15 (0.02)	6 (0.02)	6 (0.03)	3 (0.01)	0.443
	5 months	106 (0.14)	26 (0.10)	37 (0.17)	43 (0.17)	0.063
	8 months	175 (0.24)	42 (0.16)	68 (0.31)	65 (0.25)	0.003
Appendicitis	N	84,187	27,607 (32.79)	24,885 (29.56)	31,695 (37.65)	
	After 3 months	2 (0.00)	0 (0.00)	0 (0.00)	2 (0.01)	0.191
	5 months	5 (0.01)	2 (0.01)	1 (0.00)	2 (0.01)	0.886
	8 months	13 (0.02)	7 (0.03)	4 (0.02)	2 (0.01)	0.176
Noninfective enteritis/colitis	N	82,258	27,250 (33.13)	24,327 (29.57)	30,681 (37.30)	
	After 3 months	15 (0.02)	5 (0.02)	4 (0.02)	6 (0.02)	0.964
	5 months	64 (0.08)	24 (0.09)	23 (0.09)	17 (0.06)	0.199
	8 months	92 (0.11)	32 (0.12)	37 (0.15)	23 (0.07)	0.025
Hernia	N	82,615	27,384 (33.15)	24,454 (29.60)	30,777 (37.25)	
	After 3 months	6 (0.01)	1 (0.00)	3 (0.01)	2 (0.01)	0.507
	5 months	24 (0.03)	4 (0.01)	14 (0.06)	6 (0.02)	0.008
	8 months	48 (0.06)	16 (0.06)	23 (0.09)	9 (0.03)	0.007
Arthritis	N	68,349	25,491 (37.30)	20,072 (29.37)	22,786 (33.34)	
	After 3 months	66 (0.10)	18 (0.07)	21 (0.10)	27 (0.12)	0.218
	5 months	264 (0.39)	75 (0.29)	85 (0.42)	104 (0.46)	0.100
	8 months	391 (0.57)	117 (0.46)	140 (0.70)	134 (0.59)	0.003
Dermatitis	N	51,193	18,412 (35.97)	15,388 (30.06)	17,393 (33.98)	
	After 3 months	130 (0.25)	63 (0.34)	28 (0.18)	39 (0.22)	0.009

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Table 2 (*continued*)

Conditions	Categories	Total	Distant Group	Intermediate Group	Recent Group	P
	5 months	681 (1.33)	303 (1.65)	197 (1.28)	181 (1.04)	<0.001
	8 months	1010 (1.97)	452 (2.45)	304 (1.98)	254 (1.46)	<0.001
	N	69,035	22,979 (33.29)	20,829 (30.17)	25,227 (36.54)	
Ear disease	After 3 months	103 (0.15)	62 (0.27)	21 (0.10)	20 (0.08)	<0.001
	5 months	377 (0.55)	196 (0.85)	93 (0.45)	88 (0.35)	<0.001
	8 months	600 (0.87)	311 (1.35)	150 (0.72)	139 (0.55)	<0.001
	N	84,007	27,573 (32.82)	24,858 (29.59)	31,576 (37.59)	
Immune dysfunction	After 3 months	1 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0.359
	5 months	10 (0.01)	5 (0.02)	1 (0.00)	4 (0.01)	0.331
	8 months	19 (0.02)	10 (0.04)	1 (0.00)	8 (0.03)	0.046
	N	74,777	25,988 (34.75)	21,964 (29.37)	26,825 (35.87)	
Fracture	After 3 months	30 (0.04)	13 (0.05)	11 (0.05)	6 (0.02)	0.193
	5 months	177 (0.24)	61 (0.23)	70 (0.32)	46 (0.17)	0.004
	8 months	296 (0.40)	120 (0.46)	109 (0.50)	67 (0.25)	<0.001
	N	83,785	27,446 (32.76)	24,820 (29.62)	31,519 (37.62)	
Taste disorder	After 3 months	10 (0.01)	6 (0.02)	0 (0.00)	4 (0.01)	0.073
	5 months	25 (0.03)	15 (0.05)	5 (0.02)	5 (0.02)	0.014
	8 months	38 (0.05)	21 (0.08)	11 (0.04)	6 (0.02)	0.005
	N	82,400	27,109 (32.90)	24,385 (29.59)	30,906 (37.51)	
Fatigue	After 3 months	11 (0.01)	5 (0.02)	2 (0.01)	4 (0.01)	0.602
	5 months	49 (0.06)	21 (0.08)	13 (0.05)	15 (0.05)	0.324
	8 months	92 (0.11)	40 (0.15)	28 (0.11)	24 (0.08)	0.042
	N	74,096	25,965 (35.04)	21,765 (29.37)	26,366 (35.58)	
Pain	After 3 months	59 (0.08)	21 (0.08)	16 (0.07)	22 (0.08)	0.925
	5 months	235 (0.32)	83 (0.32)	78 (0.36)	74 (0.28)	0.319
	8 months	381 (0.51)	126 (0.49)	153 (0.70)	102 (0.39)	<0.001
	N	72,725	24,691 (33.95)	21,295 (29.28)	26,739 (36.77)	
Headache	After 3 months	65 (0.09)	31 (0.13)	19 (0.09)	15 (0.06)	0.031
	5 months	270 (0.37)	107 (0.43)	86 (0.40)	77 (0.29)	0.017
	8 months	455 (0.63)	209 (0.85)	128 (0.60)	118 (0.44)	<0.001
	N	82,913	27,256 (32.87)	24,513 (29.56)	31,144 (37.56)	
Mood disorders	After 3 months	19 (0.02)	5 (0.02)	7 (0.03)	7 (0.02)	0.744
	5 months	51 (0.06)	19 (0.07)	17 (0.07)	15 (0.05)	0.485
	8 months	79 (0.10)	29 (0.11)	27 (0.11)	23 (0.07)	0.297
	N	78,164	26,349 (33.71)	22,934(29.34)	28,881 (36.95)	
Depression	After 3 months	40 (0.05)	16 (0.06)	13 (0.06)	11 (0.04)	0.455
	5 months	144 (0.18)	51 (0.19)	51 (0.22)	42 (0.15)	0.116
	8 months	213 (0.27)	68 (0.26)	83 (0.36)	62 (0.21)	0.005
	N	72,907	25,142 (34.49)	21,350 (29.28)	26,415 (36.23)	
Anxiety disorders	After 3 months	61 (0.08)	27 (0.11)	16 (0.07)	18 (0.07)	0.266
	5 months	282 (0.39)	107 (0.43)	97 (0.45)	78 (0.30)	0.010
	8 months	416 (0.57)	167 (0.66)	144 (0.67)	105 (0.40)	<0.001
	N	66,589	24,307 (36.50)	19,457 (29.22)	22,825 (34.28)	
Sleep disorders	After 3 months	67 (0.10)	30 (0.12)	18 (0.09)	19 (0.08)	0.355
	5 months	257 (0.39)	95 (0.39)	88 (0.45)	74 (0.32)	0.105
	8 months	387 (0.58)	135 (0.56)	144 (0.74)	108 (0.47)	0.001
	N	64,917	24,370 (37.54)	18,958 (29.20)	21,589 (33.26)	
Diabetes	After 3 months	55 (0.08)	19 (0.08)	18 (0.09)	18 (0.08)	0.831
	5 months	207 (0.32)	62 (0.25)	68 (0.36)	77 (0.36)	0.078
	8 months	329 (0.51)	105 (0.43)	114 (0.60)	110 (0.51)	0.046
	N	52,503	21,965 (41.84)	15,082 (28.73)	15,456 (29.44)	
Metabolic disorder	After 3 months	75 (0.14)	25 (0.11)	23 (0.15)	27 (0.17)	0.287
	5 months	341 (0.65)	123 (0.56)	120 (0.80)	98 (0.63)	0.020
	8 months	530 (1.01)	189 (0.86)	195 (1.29)	146 (0.94)	<0.001
	N	76,211	26,419 (34.67)	22,432 (29.43)	27,360 (35.90)	
Cancer	After 3 months	31 (0.04)	7 (0.03)	11 (0.05)	13 (0.05)	0.367
	5 months	121 (0.16)	28 (0.11)	56 (0.25)	37 (0.14)	<0.001
	8 months	201 (0.26)	62 (0.23)	89 (0.40)	50 (0.18)	<0.001
	N	80,386	26,977 (33.56)	23,743 (29.54)	29,666 (36.90)	
Renal failure	After 3 months	7 (0.01)	4 (0.01)	3 (0.01)	0 (0.00)	0.125
	5 months	52 (0.06)	11 (0.04)	21 (0.09)	20 (0.07)	0.106
	8 months	95 (0.12)	24 (0.09)	42 (0.18)	29 (0.10)	0.007
	N	75,333	26,039 (34.57)	22,171 (29.43)	27,123 (36.00)	
Cognitive disorder	After 3 months	52 (0.07)	18 (0.07)	18 (0.08)	16 (0.06)	0.647
	5 months	208 (0.28)	72 (0.28)	65 (0.29)	71 (0.26)	0.804
	8 months	356 (0.47)	134 (0.51)	119 (0.54)	103 (0.38)	0.019
	N	76,956	26,548 (34.50)	22,669 (29.46)	27,739 (36.05)	
Dementia	After 3 months	10 (0.01)	2 (0.01)	5 (0.02)	3 (0.01)	0.342
	5 months	56 (0.07)	10 (0.04)	30 (0.13)	16 (0.06)	<0.001
	8 months	99 (0.13)	24 (0.09)	47 (0.21)	28 (0.10)	<0.001

Distant group: COVID-19 occurrence ≥365 days after vaccination. Intermediate group: COVID-19 occurrence 150–364 days after vaccination. Recent group: COVID-19 occurrence 14–149 days after vaccination.

Table 3
Results of Cox proportional hazards regression analyses of post-COVID conditions occurring within 8 months of COVID-19.

Conditions	HR [95% CI]	P	Conditions	HR [95% CI]	P	Conditions	HR [95% CI]	P	Conditions	HR [95% CI]	P
Pneumonia			Acute upper respiratory disease			Acute lower respiratory disease			Asthma		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.80 [0.55–1.17]	0.249	Intermediate group	0.55 [0.46–0.67]	<0.001	Intermediate group	0.67 [0.54–0.83]	<0.001	Intermediate group	0.69 [0.54–0.87]	0.002
Recent group	0.44 [0.29–0.67]	<0.001	Recent group	0.54 [0.45–0.66]	<0.001	Recent group	0.72 [0.58–0.90]	0.003	Recent group	0.59 [0.46–0.76]	<0.001
Respiratory failure			Ischemic heart disease			Hypertension			Pulmonary circulation disease		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.74 [0.57–0.97]	0.027	Intermediate group	0.70 [0.47–1.06]	0.091	Intermediate group	0.97 [0.75–1.25]	0.819	Intermediate group	0.98 [0.32–2.98]	0.968
Recent group	0.52 [0.39–0.69]	<0.001	Recent group	0.55 [0.36–0.84]	0.006	Recent group	0.60 [0.45–0.79]	<0.001	Recent group	0.09 [0.01–0.80]	0.031
Pericarditis			Myocarditis			Arrhythmia			Heart failure		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	1.60 [0.44–5.88]	0.475	Intermediate group	0.28 [0.05–1.57]	0.148	Intermediate group	0.99 [0.69–1.42]	0.965	Intermediate group	0.87 [0.64–1.18]	0.318
Recent group	0.60 [0.14–2.57]	0.495	Recent group	0.42 [0.09–1.97]	0.272	Recent group	0.57 [0.38–0.86]	0.007	Recent group	0.45 [0.32–0.63]	<0.001
Stroke			Cerebral infarction			Appendicitis			Noninfective enteritis/colitis		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.85 [0.40–1.79]	0.661	Intermediate group	0.89 [0.60–1.33]	0.580	Intermediate group	0.59 [0.16–2.20]	0.432	Intermediate group	1.07 [0.64–1.77]	0.799
Recent group	0.38 [0.16–0.89]	0.026	Recent group	0.74 [0.49–1.10]	0.139	Recent group	0.29 [0.05–1.54]	0.146	Recent group	0.62 [0.35–1.10]	0.105
Hernia			Arthritis			Dermatitis			Ear disease		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.80 [0.41–1.56]	0.520	Intermediate group	0.75 [0.58–0.96]	0.022	Intermediate group	0.67 [0.58–0.78]	<0.001	Intermediate group	0.64 [0.52–0.79]	<0.001
Recent group	0.27 [0.12–0.63]	0.003	Recent group	0.66 [0.51–0.86]	0.002	Recent group	0.56 [0.48–0.66]	<0.001	Recent group	0.59 [0.47–0.73]	<0.001
Immune dysfunction			Fracture			Taste disorder			Fatigue		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.08 [0.01–0.64]	0.017	Intermediate group	0.79 [0.59–1.05]	0.101	Intermediate group	0.42 [0.20–0.90]	0.027	Intermediate group	0.64 [0.39–1.07]	0.091
Recent group	0.62 [0.22–1.70]	0.354	Recent group	0.43 [0.31–0.59]	<0.001	Recent group	0.22 [0.08–0.57]	0.002	Recent group	0.55 [0.32–0.94]	0.031
Pain			Headache			Mood disorders			Depression		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.94 [0.73–1.20]	0.605	Intermediate group	0.62 [0.49–0.78]	<0.001	Intermediate group	1.07 [0.62–1.84]	0.808	Intermediate group	1.25 [0.89–1.75]	0.190
Recent group	0.58 [0.44–0.77]	<0.001	Recent group	0.57 [0.45–0.73]	<0.001	Recent group	1.02 [0.57–1.81]	0.947	Recent group	0.96 [0.67–1.39]	0.851
Anxiety disorders			Sleep disorders			Diabetes			Metabolic disorder		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.89 [0.70–1.12]	0.320	Intermediate group	1.00 [0.78–1.27]	0.978	Intermediate group	0.75 [0.57–0.98]	0.037	Intermediate group	0.85 [0.69–1.05]	0.126
Recent group	0.66 [0.51–0.86]	0.002	Recent group	0.75 [0.57–0.99]	0.040	Recent group	0.69 [0.52–0.91]	0.010	Recent group	0.62 [0.50–0.78]	<0.001
Cancer			Renal failure			Cognitive disorder			Dementia		
Distant group	Reference		Distant group	Reference		Distant group	Reference		Distant group	Reference	
Intermediate group	0.75 [0.54–1.04]	0.084	Intermediate group	0.83 [0.50–1.38]	0.480	Intermediate group	0.70 [0.54–0.91]	0.008	Intermediate group	0.81 [0.49–1.33]	0.411
Recent group	0.36 [0.25–0.53]	<0.001	Recent group	0.48 [0.28–0.84]	0.010	Recent group	0.57 [0.43–0.75]	<0.001	Recent group	0.37 [0.22–0.65]	<0.001

Distant group: COVID-19 occurrence ≥365 days after vaccination. Intermediate group: COVID-19 occurrence 150–364 days after vaccination. Recent group: COVID-19 occurrence 14–149 days after vaccination. HRs are adjusted for sex and age. CI: confidence interval; HR, hazard ratio.

intermediate group and 0.58 (95% CI: 0.44–0.77) for the recent group. For headache, the HRs were 0.62 (95% CI: 0.49–0.78) for the intermediate group and 0.57 (95% CI: 0.45–0.73) for the recent group.

3.3.6. Psychiatric conditions

The recent group did not have a significantly lower risk of developing mood disorders (HR: 1.02, 95% CI: 0.57–1.81) and depression (HR: 0.96, 95% CI: 0.67–1.39) than the distant group. However, the recent group had a significantly lower risk of developing anxiety disorders (HR: 0.66, 95% CI: 0.51–0.86) and sleep disorders (HR: 0.75, 95% CI: 0.57–0.99).

3.3.7. Endocrine disorders and other sequelae

The recent group had a significantly lower risk of developing endocrine disorders and other sequelae than the distant group. Both the intermediate group (HR: 0.75, 95% CI: 0.57–0.98) and the recent group (HR: 0.69, 95% CI: 0.52–0.91) had a significantly lower risk of developing diabetes than the distant group. The risk of developing metabolic disorder was significantly lower in the recent group (HR: 0.62, 95% CI: 0.50–0.78), but not the intermediate group (HR: 0.85, 95% CI: 0.69–1.05). Similarly, the risk of developing cancer was significantly lower in the recent group (HR: 0.36, 95% CI: 0.25–0.53), but not the intermediate group (HR: 0.75, 95% CI: 0.54–1.04). Also, the risk of developing renal failure was significantly lower in the recent group (HR: 0.48, 95% CI: 0.28–0.84), but not the intermediate group (HR: 0.83,

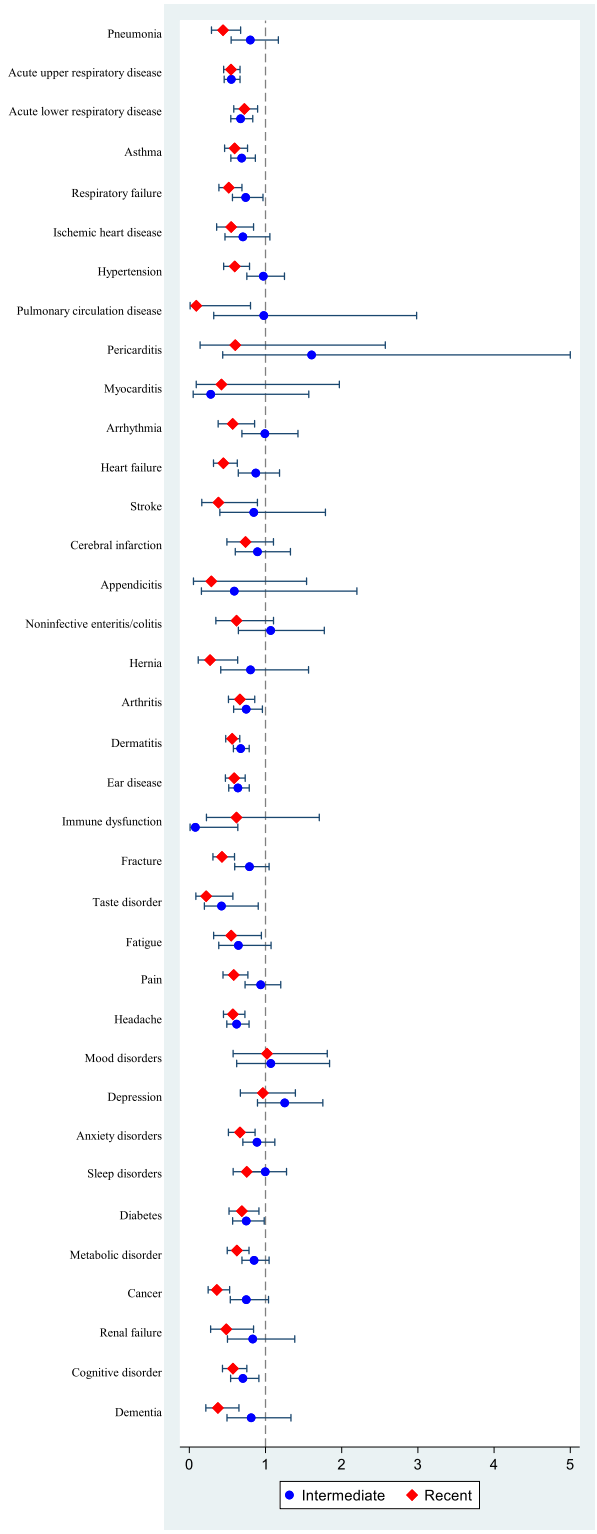

Fig. 1. Risks of incident post-COVID conditions within 8 months of COVID-19 occurrence for the intermediate group (blue circles) and recent group (red diamonds) using the distant group as the reference.
The x-axis presents hazard ratios (95 % confidence intervals) using a base 10 logarithmic scale, and the y-axis shows the 36 target post-COVID conditions. Hazard ratios are adjusted for sex and age. Distant group: COVID-19 occurrence ≥365 days after vaccination. Intermediate group: COVID-19 occurrence 150–364 days after vaccination. Recent group: COVID-19 occurrence 14–149 days after vaccination. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

95% CI: 0.50–1.38). The risk of cognitive disorder was significantly lower for both the intermediate group (HR: 0.70, 95% CI: 0.54–0.91) and recent group (HR: 0.57, 95% CI: 0.43–0.75). For dementia, the recent group had a significantly lower risk (HR: 0.37, 95% CI: 0.22–0.65) than the distant group.

4. Discussion

This is the first study in Asia to explore the impact of COVID-19 vaccination on the incidence of 36 different post-COVID-19 conditions over three different follow-up periods using a large integrated database comprising medical claims, COVID-19 case information, and vaccination records. In addition, our analysis quantified the 8-month risk of developing the target conditions. The results indicated that the risks of various physical and mental conditions occurring after the acute phase of COVID-19 were reduced when infection occurred within 5 months of vaccination, i.e., when the vaccine was most effective. A strength of this study is that the incidence and risk of post-COVID-19 conditions were compared according to the time elapsed since COVID-19 vaccination, and not simply according to the presence of vaccinations or number of vaccine doses. Among the target conditions, dermatitis, acute upper respiratory disease, and acute lower respiratory disease had the highest incidence during the observation period. Respiratory conditions are a characteristic symptom of acute COVID-19, and despite excluding participants with the same preexisting comorbidities, the incidence of these conditions occurring after COVID-19 were found to be highest in the distant group, followed by the intermediate group and recent group at all observation points. These findings indicate that acute respiratory diseases are likely to develop as long-term sequelae after COVID-19, but that vaccination can reduce their risk.

Although the recent group generally had a higher prevalence of the target conditions as preexisting comorbidities before COVID-19 occurrence, our study found that this group had significantly lower risks for developing 28 of the post-COVID-19 conditions within 8 months after infection. Among these, the risks of 27 conditions (excluding acute lower respiratory disease) were highest in the distant group, followed by the intermediate group and the recent group. These results corroborate those of previous studies showing that COVID-19 vaccination can reduce the risk and severity of post-COVID-19 conditions [8–11]. Our study examined vaccine effectiveness by focusing on the duration between each participant's most recent vaccination date and infection date, and suggests that regular booster vaccinations could potentially reduce the risk of post-COVID-19 conditions.

Another major finding of our study is that we detected large age differences among the different groups classified based on the time elapsed since their most recent vaccination. This is likely to be a direct consequence of Japan's health policy to prioritize COVID-19 vaccination for older persons and those with underlying diseases. The recent group was approximately 29 years older than the distant group. Unsurprisingly, the recent (i.e., oldest) group had the highest prevalence of preexisting comorbidities during the 12 months before COVID-19. Accordingly, the fact that the majority of post-COVID-19 conditions were significantly less likely to occur in the recent group (despite their higher probability of having an underlying disease) suggests that vaccination has clear preventive effects against these conditions. In order to explore the age-specific effects of COVID-19 vaccination in more detail, we conducted a subgroup analysis in which participants were divided into "younger adults" (aged 20–39 years), "middle-aged adults" (aged 40–64 years), and "older adults" (aged ≥65 years) (Supplementary Tables 3–11). As age increased, the proportion of women also increased. The differences in mean age among the three vaccination groups were small for each of these age categories. We found that younger adults were more likely to have acute upper respiratory disease as a preexisting comorbidity as well as a post-COVID-19 condition. In addition, younger adults in the distant group had a significantly higher risk of developing taste disorder, headache, and metabolic disorder,

which are common sequelae of COVID-19 [23]. Among middle-aged adults, the recent group had higher incidence of chronic diseases such as hypertension, heart failure, cerebral infarction, metabolic disorder, diabetes, and renal failure as preexisting comorbidities. Similar to the younger adults, the middle-aged adults showed no significant differences in the incidence for most post-COVID-19 conditions among the vaccination groups; however, the distant group had a significantly higher incidence of noninfective enteritis/colitis and anxiety disorders. After adjusting for sex and age, the recent group additionally showed a significantly lower risk of ischemic heart disease and cognitive disorder than the distant group. Older adults in the recent group had the lowest risk for all 36 post-COVID-19 conditions, despite there being no major differences in sex or age among the three vaccination groups (no significant differences in risk were found for pericarditis, myocarditis, immune dysfunction, noninfective enteritis/colitis, taste disorder, fatigue, mood disorders, and depression).

In summary, the results of this study could most clearly be seen in older persons aged ≥65 years, who accounted for the largest proportion (44%) of participants. COVID-19 vaccination was able to significantly reduce the incidence and risk of many post-COVID-19 conditions when breakthrough infection occurred within 5 months after vaccination, regardless of age and comorbidities. As old age and underlying diseases are major risk factors for post-COVID-19 conditions [24,25], the recent group in our study can be regarded to be the most vulnerable to these conditions. Nevertheless, that group had the lowest risk of developing most post-COVID-19 conditions. These findings contribute to our understanding of the effectiveness of COVID-19 vaccines against long-term sequelae, and may provide a starting point for more in-depth analyses on the associations between vaccination and specific conditions.

This study has several limitations. First, the analyses were conducted using claims data, which lack important information on disease severity and health behavior (e.g., tobacco and alcohol consumption). This could have led to residual confounding that biased our results. In addition, the claims data did not allow us to differentiate between diagnoses made within 3 months after COVID-19 occurrence and acute events that occurred during infection. Therefore, the post-COVID-19 conditions identified during the 3-month period after infection may include some acute events. Second, all medical conditions were identified using recorded diagnoses from the outpatient and inpatient claims data. However, there may be coding errors or misclassifications, and the accuracy of these records has not been validated [26]. Third, we did not consider the type, dose, and boosters of COVID-19 vaccines in each individual. However, our study considered the elapsed time between an individual's most recent vaccination and COVID-19 occurrence, which may provide a clearer understanding of vaccine effectiveness than the number of vaccine doses. In Japan, the Pfizer/BioNTech BNT162b2 mRNA vaccine was approved in February 2021, followed by the Moderna mRNA-1273 vaccine and the AstraZeneca ChAdOx1 nCoV-19 adenovirus vector vaccine in May 2021. As of December 2022, approximately 300 million vaccinations had been administered nationwide, with 81% (92% in persons aged ≥65 years) and 69% (90% in persons aged ≥65 years) of the population receiving two and three doses, respectively [27]. Therefore, the vast majority of older persons in Japan had received three doses at the time of this study. Fourth, some of our post-COVID-19 conditions involved groups of diseases, such as cancer and ear disease. Therefore, our analyses do not provide insight into the effects of vaccination on specific diseases. Fifth, we did not adjust for multiple comparisons because we did not wish to overlook potentially important relationships that may require further analysis. Nevertheless, the lack of adjustment increases the risk of detecting spurious associations. Finally, we did not consider COVID-19 reinfections or disease severity due to the lack of data. The cumulative risk of post-COVID-19 conditions is known to increase proportionally to the number of infections, especially in older adults [28]. Accordingly, our findings may have limited generalizability because we could not account for the number of reinfections and severity of individual COVID-19 cases.

In conclusion, this study of a large-scale Japanese cohort provides real-world evidence that recent COVID-19 vaccination can reduce the incidence and risk of a wide range of post-COVID-19 conditions. There is currently insufficient information on the effects of regular booster vaccinations on post-COVID-19 conditions, but our study indicates that the risks of developing these conditions are significantly reduced when vaccinated within 5 months before COVID-19 occurrence. In particular, this effect was more pronounced in older persons. The results of this study may serve as a foundation for formulating future vaccination strategies as COVID-19 transitions from a pandemic to an endemic state.

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CRediT authorship contribution statement

Sung-a Kim: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Megumi Maeda:** Writing – review & editing, Data curation. **Fumiko Murata:** Writing – review & editing, Data curation. **Haruhisa Fukuda:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126497.

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