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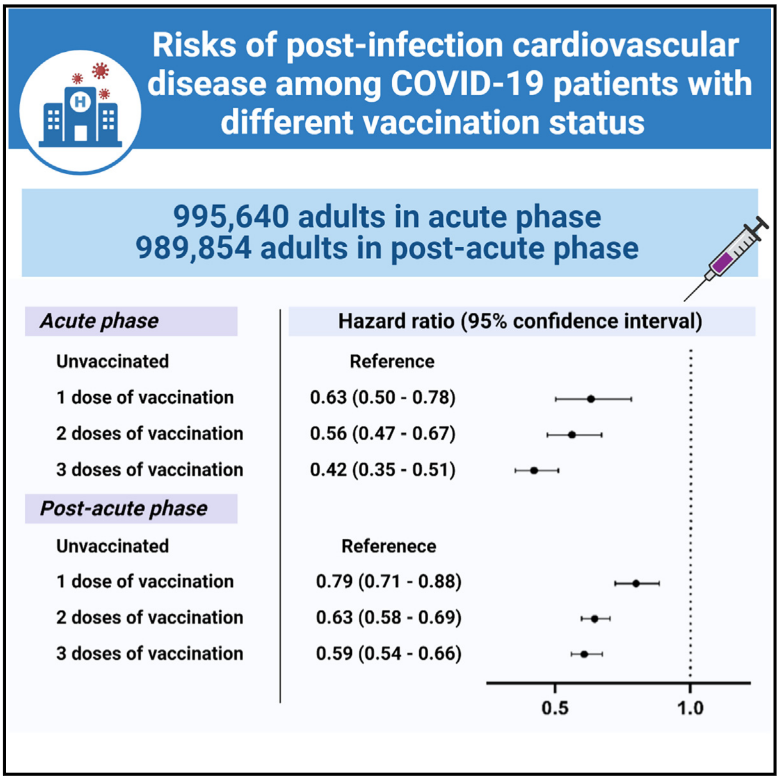
Report

Association between BNT162b2 and CoronaVac vaccination and risk of CVD and mortality after COVID-19 infection: A population-based cohort study

Graphical abstract



Highlights

- BNT162b2 and CoronaVac are associated with lower risks of post-infection incident CVD
- Positive dose-response relationship between risk reduced and number of vaccine doses
- Vaccine protection persists in the post-acute phase (>28 days after infection)

Authors

Eric Yuk Fai Wan, Anna Hoi Ying Mok, Vincent Ka Chun Yan, ..., Chak Sing Lau, Ian Chi Kei Wong, Esther Wai Yin Chan

Correspondence

wongick@hku.hk (I.C.K.W.),
ewchan@hku.hk (E.W.Y.C.)

In brief

It is unknown if vaccination affects the risk of post-COVID-19 cardiovascular diseases (CVDs). Therefore, Wan et al. examine the short-term and long-term risks of post-infection CVD among COVID-19 patients with different vaccination status and observe a positive dose-response relationship between overall CVD risk reduction and the number of vaccine doses received.

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Report

Association between BNT162b2 and CoronaVac vaccination and risk of CVD and mortality after COVID-19 infection: A population-based cohort study

Eric Yuk Fai Wan,[1,2,3,13] Anna Hoi Ying Mok,[3,13] Vincent Ka Chun Yan,[1,13] Cheyenne I. Ying Chan,[3] Boyuan Wang,[3] Francisco Tsz Tsun Lai,[1,2] Celine Sze Ling Chui,[2,4,5] Xue Li,[1,2,6] Carlos King Ho Wong,[1,2,3] Kai Hang Yiu,[6] Hung Fat Tse,[6,7,8] Chak Sing Lau,[6] Ian Chi Kei Wong,[1,2,9,10,11,*] and Esther Wai Yin Chan[1,2,11,12,14,*]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

[2]Laboratory of Data Discovery for Health (D[2]4H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China

[3]Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

[4]School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

[5]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

[6]Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

[7]Centre for Stem Cell Translational Biology, Hong Kong Special Administrative Region, China

[8]Cardiac and Vascular Center, The University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, China

[9]Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK

[10]Aston Pharmacy School, Aston University, Birmingham B4 7ET, UK

[11]Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

[12]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

[13]These authors contributed equally

[14]Lead contact

*Correspondence: wongick@hku.hk (I.C.K.W.), ewchan@hku.hk (E.W.Y.C.)

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SUMMARY

It is unknown if vaccination affects the risk of post-COVID-19 cardiovascular diseases (CVDs). Therefore, this retrospective cohort study examines the short-term and long-term risks of post-infection CVD among COVID-19 patients with different vaccination status utilizing data from electronic health databases in Hong Kong. Cox proportional hazards regression adjusted with inverse probability of treatment weighting is used to evaluate the risks of incident CVD (coronary heart disease, stroke, heart failure) and all-cause mortality in COVID-19 patients. Compared with unvaccinated patients, vaccinated patients have a lower risk of CVD and all-cause mortality, and the lowest risk is observed in those who completed three doses of vaccine. Similar patterns in the subgroups of different vaccine platforms, age, gender, Charlson comorbidity index, and disease severity are observed. These findings highlight a positive dose-response relationship between overall CVD risk reduction and the number of vaccine doses received.

INTRODUCTION

Despite primarily being a respiratory tract infection, coronavirus disease 2019 (COVID-19) can result in systemic inflammation, thereby leading to complications in multiple organ systems, such as cardiovascular and gastrointestinal systems.[1] Among an extensive list of possible complications, acute cardiovascular complications have been frequently discussed because of their significant association with COVID-19-related mortality.[2] Apart from acute myocardial infarction, previously reported cardiovascular complications of COVID-19 include myocarditis, heart failure, venous thromboembolism, and ischemic stroke.[3,4] Higher levels of C-reactive protein and troponin T, and decreased ejection fraction, have been described in patients with severe cardiovascular complications of COVID-19.[5] The mechanism of acute post-infection complications is generally regarded as multifactorial, involving systemic inflammatory response, myocardial cell injury, and hypercoagulability.[4,6] More recently, it was suggested that COVID-19 may also increase the risk of incident cardiovascular diseases (CVDs) beyond the first 30 days after acute infection,[7] and a past history of COVID-19 infection should be regarded as a risk factor for CVD.[8,9] The risk was evident even in individuals who had no baseline CVD before contracting COVID-19.[7] Some regarded post-acute cardiovascular manifestations as part of “long COVID,”[10] which has become a huge burden on healthcare systems in different countries, such as the UK,[11] as the reported incidence of major adverse cardiac events at 12 months post COVID-19 infection was as high as 67 per 1,000 persons.[7] With respect to the exact mechanism of incident CVD after acute COVID-19 infection, it remains to be elucidated, while some authors postulated that chronic inflammation triggered by persistent virus and autoimmune response that damages the heart due to molecular mimicry might have a role.[10]

The effectiveness of COVID-19 vaccines in protecting against severe COVID-19 diseases and mortality has been well studied,[12,13] yet it is uncertain whether vaccination reduces the risk of acute cardiovascular complications and incident CVD in the post-acute phase. Researchers in Korea pointed out that fully vaccinated individuals (i.e., two doses of mRNA vaccine or viral vector vaccine) had a lower risk of acute myocardial infarction and ischemic stroke that occurred 31 to 120 days after contracting COVID-19,[14] thereby supporting the importance of vaccination. Nonetheless, studies regarding other cardiovascular outcomes, such as heart failure and deaths, in people who received inactivated COVID-19 vaccines are lacking. Current evidence mainly focuses on the risk of myocarditis and pericarditis[15,16] or immune dysregulation[17] after receiving mRNA COVID-19 vaccines. Whether vaccination in fact reduces acute cardiovascular complications of COVID-19, and long-term incident CVD in people with or without baseline cardiovascular risk, deserves our attention.

Long COVID is inevitably associated with a huge economic burden.[18] Therefore, it is crucial to evaluate whether vaccination reduces secondary cardiovascular complications in view of the suboptimal COVID-19 vaccine coverage, especially for the booster dose, around the globe. The present study aims to examine the effectiveness of the two COVID-19 vaccines authorized in Hong Kong, namely BNT162b2 from Fosun-BioNTech (Pfizer-BioNTech, mRNA vaccine) and CoronaVac from Sinovac Biotech (HK) Limited (inactivated vaccine) for individuals aged 16 years or above since 23 February 2021 in reducing the risk of acute cardiovascular complications and incident CVD beyond the acute phase of illness. As patients with pre-existing CVD have higher risks of myocardial injury and poor outcome after COVID-19,[19] these patients were excluded from the study.

RESULTS

The analysis in the post-infection acute phase involved 90,607 unvaccinated and 905,033 vaccinated patients (85,703 with one dose, 426,948 with two doses, 392,382 with three doses). After the exclusion of deaths that occurred within the first 28 days post infection, the analysis in the post-acute phase included 87,253 unvaccinated and 902,601 vaccinated patients (84,534 with one dose, 425,965 with two doses, 392,102 with three doses). Table 1 describes the baseline characteristics with standardized mean difference (SMD) before and after weighting. The SMD for all characteristics among the groups was <0.2, indicating a good balance in all characteristics between groups.

The incidence rates (IRs) and the risks of composite CVD, stroke, coronary heart disease, heart failure, cardiovascular mortality, and all-cause mortality among individuals with different vaccination status at acute and post-acute phases are depicted in Figure 1. During the acute phase, the IRs (95% confidence intervals [Cis]) of outcome events were the highest in unvaccinated patients compared to vaccinated patients, and they decrease by number of doses. A similar pattern was observed in the post-acute phase, with higher Irs recorded in unvaccinated patients and lowest at third dose.

A positive dose-response relationship between the magnitude of risk reduction and the number of vaccine doses received was observed. During the acute phase, hazard ratios (HRs) (95% CI) of outcome in first-dose recipients (CVD, 0.63 [0.50–0.78]; stroke, 0.59 [0.43–0.80]; cardiovascular mortality, 0.49 [0.36–0.66]; all-cause mortality, 0.42 [0.39–0.45)) was higher than that in third-dose recipients (CVD, 0.42 [0.35–0.51]; stroke, 0.39 [0.30–0.51); cardiovascular mortality, 0.13 (0.08–0.22); all-cause mortality, 0.08 (0.06–0.09)) compared to unvaccinated patients. A similar pattern was also observed in the individual outcome of coronary heart disease (first-dose recipient, 0.71 [0.47–1.05]; third-dose recipient, 0.59 [0.42–0.83)) and heart failure (first-dose recipient, 0.59 [0.34–1.03]; third-dose recipient, 0.23 [0.13–0.42)) in which insignificant findings were observed. During the post-acute phase, HRs of outcome in first-dose recipients (CVD, 0.79 [0.71–0.88]; stroke, 0.81 [0.68–0.96]; heart failure, 0.64 [0.52–0.78); cardiovascular mortality, 0.49 [0.38–0.62]; all-cause mortality, 0.44 [0.41–0.47)) were also higher than that in third-dose recipients (CVD, 0.59 [0.54–0.66]; stroke, 0.60 [0.51–0.70]; heart failure, 0.34 [0.27–0.43]; cardiovascular mortality, 0.20 [0.15–0.27]; all-cause mortality, 0.17 [0.16–0.19)) compared to unvaccinated patients. Tables S1–S5 show similar results from five sensitivity analyses.

The results of the subgroup analyses stratified by age, gender, Charlson Comorbidity Index (CCI), and disease severity are reported in Figures 2 and S1. Similar to the main analysis, larger risk reductions in terms of all-cause mortality were observed in all subgroups of patients who received three doses of vaccines when compared to those who received fewer doses in both the acute and post-acute phase. This trend was not observed for the outcome of CVD, possibly due to a small number of outcome events recorded, especially in the subgroup of patients with severe COVID-19 who were vaccinated.

DISCUSSION

This study evaluated the association between BNT162b2 or CoronaVac and the risk of CVD and mortality in the acute and post-acute phase after a COVID-19 infection. Both BNT162b2 and CoronaVac were associated with lower risks of post-infection incident CVD. A trend of positive dose-response relationship between the magnitude of overall CVD risk reduction and the number of vaccine doses received was observed, and thus the public were encouraged to get vaccinated and boosted to reduce the burden of CVD and mortality after COVID-19 infection.

Our study produced similar findings to a previous study that demonstrated vaccine effectiveness in lowering the risk of incident CVD within 28 days after COVID-19 infection among a cohort of diabetes patients.[20] At present, similar studies in the COVID-19 setting are scarce, and whether COVID-19 vaccines improve cardiovascular outcome is an important clinical question to be addressed.[21] In terms of the risk reduction of

Table 1. Baseline characteristics before and after weighting among individuals with different vaccination status

(A)	Before weighting					After weighting				
rowhead	Unvaccinated	One dose	Two doses	Three doses	SMD	Unvaccinated	One dose	Two doses	Three doses	SMD
N	90,607	85,703	426,948	392,382	–	1,010,821	1,005,271	995,933	995,907	–
Age, years	56.4 (21.6)	56.8 (19.5)	48.8 (17.1)	50.3 (15.8)	0.269	49.0 (20.4)	49.7 (19.3)	50.8 (17.5)	50.8 (16.2)	0.059
Gender, male	37,731 (41.6)	362,11 (42.3)	184,189 (43.1)	174,584 (44.5)	0.032	443,191 (43.8)	442,844 (44.1)	432,482 (43.4)	433,763 (43.6)	0.007
CCI	0.5 (1.3)	0.4 (1.1)	0.2 (0.7)	0.2 (0.6)	0.201	0.2 (0.8)	0.2 (0.8)	0.3 (0.8)	0.3 (0.8)	0.008
Cancer	5,403 (6.0)	4,086 (4.8)	1,0167 (2.4)	7,919 (2.0)	0.124	27,693 (2.7)	27,982 (2.8)	27,834 (2.8)	28,433 (2.9)	0.004
Chronic kidney disease	2,329 (2.6)	1,591 (1.9)	2,939 (0.7)	2,236 (0.6)	0.099	9,213 (0.9)	9,181 (0.9)	9,267 (0.9)	9,893 (1.0)	0.005
Respiratory disease	3,193 (3.5)	2,473 (2.9)	6,570 (1.5)	5,434 (1.4)	0.085	17,120 (1.7)	17,601 (1.8)	17,747 (1.8)	17,991 (1.8)	0.005
Diabetes	12,386 (13.7)	13,181 (15.4)	40,224 (9.4)	33,243 (8.5)	0.130	96,731 (9.6)	98,648 (9.8)	99,072 (9.9)	100,844 (10.1)	0.010
Dementia	1,289 (1.4)	636 (0.7)	722 (0.2)	261 (0.1)	0.098	2,990 (0.3)	2,952 (0.3)	3,078 (0.3)	3,380 (0.3)	0.004
Renin-angiotensin-system agents	14,167 (15.6)	15,049 (17.6)	45,383 (10.6)	39,505 (10.1)	0.134	111,621 (11.0)	113,673 (11.3)	114,305 (11.5)	115,978 (11.6)	0.010
Beta blockers	9,887 (10.9)	9,631 (11.2)	26,006 (6.1)	20,587 (5.2)	0.139	66,847 (6.6)	67,088 (6.7)	66,324 (6.7)	67,744 (6.8)	0.004
Calcium channel blockers	21,728 (24.0)	22,938 (26.8)	69,729 (16.3)	60,054 (15.3)	0.174	166,207 (16.4)	171,977 (17.1)	174,305 (17.5)	176,088 (17.7)	0.018
Diuretics	4,813 (5.3)	3,491 (4.1)	7,551 (1.8)	5,981 (1.5)	0.129	21,522 (2.1)	21,992 (2.2)	22,015 (2.2)	22,951 (2.3)	0.006
Nitrates	1,620 (1.8)	1,189 (1.4)	2,513 (0.6)	2,124 (0.5)	0.072	7,602 (0.8)	7,605 (0.8)	7,526 (0.8)	7,677 (0.8)	0.001
Lipid-lowering agents										
Statin	16,715 (18.4)	18,758 (21.9)	57,877 (13.6)	54,142 (13.8)	0.131	144,288 (14.3)	145,719 (14.5)	147,781 (14.8)	149,105 (15.0)	0.011
Fibrate	552 (0.6)	605 (0.7)	2,091 (0.5)	1,834 (0.5)	0.018	5,299 (0.5)	5,002 (0.5)	5,093 (0.5)	5,138 (0.5)	0.002
PCSK9 inhibitors	3 (0.0)	9 (0.0)	14 (0.0)	36 (0.0)	0.006	64 (0.0)	62 (0.0)	63 (0.0)	62 (0.0)	<0.001
Insulins	3,122 (3.4)	2,275 (2.7)	5,424 (1.3)	3,836 (1.0)	0.102	15,424 (1.5)	14,922 (1.5)	14,846 (1.5)	15,791 (1.6)	0.005
Antidiabetic drugs										
Sulfonylurea	5,632 (6.2)	6,455 (7.5)	18,728 (4.4)	14,699 (3.7)	0.096	45,436 (4.5)	45,617 (4.5)	45,555 (4.6)	46,425 (4.7)	0.004
Metformin	9,842 (10.9)	11,520 (13.4)	35,950 (8.4)	29,734 (7.6)	0.110	86,960 (8.6)	86,933 (8.6)	87,057 (8.7)	88,364 (8.9)	0.005
DPP-4 inhibitors	2,793 (3.1)	2,500 (2.9)	6,282 (1.5)	4,948 (1.3)	0.079	16,860 (1.7)	16,637 (1.7)	16,632 (1.7)	17,431 (1.8)	0.004
SGLT-2 inhibitors	1,013 (1.1)	1,168 (1.4)	3,909 (0.9)	3,607 (0.9)	0.024	10,771 (1.1)	9,749 (1.0)	9,705 (1.0)	9,933 (1.0)	0.005
GLP-1 agonists	131 (0.1)	140 (0.2)	544 (0.1)	546 (0.1)	0.005	1,800 (0.2)	1,355 (0.1)	1,357 (0.1)	1,388 (0.1)	0.006
Oral anticoagulants	1,589 (1.8)	1,127 (1.3)	2,044 (0.5)	1,669 (0.4)	0.080	6,639 (0.7)	6,549 (0.7)	6,467 (0.6)	6,913 (0.7)	0.003
Antiplatelets	6,399 (7.1)	4,858 (5.7)	10,409 (2.4)	8,717 (2.2)	0.144	30,318 (3.0)	30,276 (3.0)	30,719 (3.1)	31,496 (3.2)	0.005
Immunosuppressants	1,007 (1.1)	703 (0.8)	1,853 (0.4)	1,744 (0.4)	0.047	5,849 (0.6)	5,684 (0.6)	5,488 (0.6)	5,813 (0.6)	0.002
Severe COVID-19	584 (0.6)	353 (0.4)	456 (0.1)	302 (0.1)	0.059	1,786 (0.2)	1,730 (0.2)	1,852 (0.2)	2,211 (0.2)	0.006
BNT162b2 recipients	0 (0.0)	30,269 (35.3)	247,465 (58.0)	218,405 (55.7)	NA	0 (0.0)	436,293 (43.4)	556,019 (55.8)	548,554 (55.1)	NA
CoronaVac recipients	0 (0.0)	55,434 (64.7)	179,483 (42.0)	173,977 (44.3)	NA	0 (0.0)	568,978 (56.6)	439,914 (44.2)	447,353 (44.9)	NA

(B)	Before weighting					After weighting				
	Unvaccinated	One dose	Two doses	Three doses	SMD	Unvaccinated	One dose	Two doses	Three doses	SMD
N	87,253	84,534	425,965	392,102	–	999,740	998,762	990,070	990,046	–

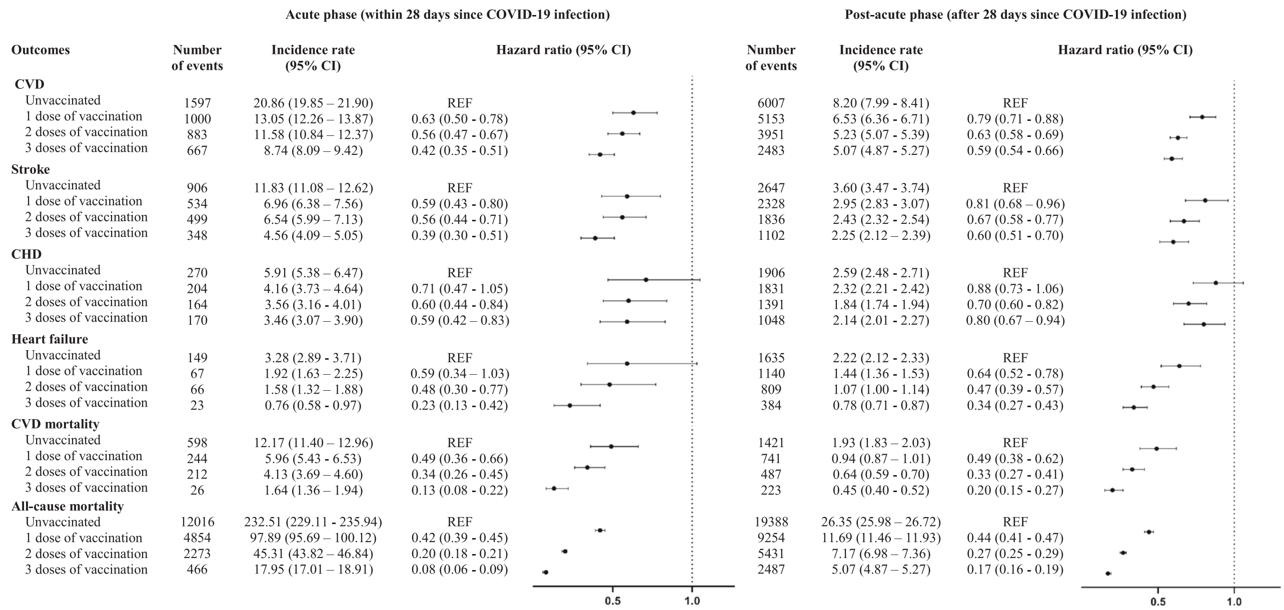
(*Continued on next page*)

Table 1. ***Continued***

(B)	Before weighting					After weighting				
	Unvaccinated	One dose	Two doses	Three doses	SMD	Unvaccinated	One dose	Two doses	Three doses	SMD
Age, years	55.4 (21.1)	56.4 (19.3)	48.8 (17.1)	50.3 (15.8)	0.254	49.2 (20.2)	49.5 (19.2)	50.6 (17.3)	50.6 (16.1)	0.050
Gender, male	35,886 (41.1)	35,561 (42.1)	183,620 (43.1)	174,405 (44.5)	0.037	438,139 (43.8)	439,332 (44.0)	429,225 (43.4)	430,408 (43.5)	0.008
CCI	0.5 (1.2)	0.4 (1.0)	0.2 (0.7)	0.2 (0.6)	0.188	0.2 (0.8)	0.2 (0.8)	0.2 (0.8)	0.3 (0.8)	0.006
Cancer	4,910 (5.6)	3,982 (4.7)	10,002 (2.3)	7,865 (2.0)	0.117	26,941 (2.7)	27,128.5 (2.7)	26,945.8 (2.7)	27,527.9 (2.8)	0.003
Chronic kidney disease	2,013 (2.3)	1,490 (1.8)	2,858 (0.7)	2,215 (0.6)	0.091	8,730 (0.9)	8,659.3 (0.9)	8,691.1 (0.9)	9,238.1 (0.9)	0.004
Respiratory disease	2,863 (3.3)	2,365 (2.8)	6,457 (1.5)	5,414 (1.4)	0.078	16,687 (1.7)	17,025.7 (1.7)	17,123.5 (1.7)	17,369.3 (1.8)	0.004
Diabetes	11,589 (13.3)	12,893 (15.3)	40,000 (9.4)	33,173 (8.5)	0.126	95,750 (9.6)	97,334.8 (9.7)	97,677.4 (9.9)	99,217.4 (10.0)	0.008
Dementia	952 (1.1)	532 (0.6)	638 (0.1)	249 (0.1)	0.084	2,442 (0.2)	2,403.8 (0.2)	2,435.1 (0.2)	2,697.7 (0.3)	0.003
Renin-angiotensin-system agents	13,355 (15.3)	14,756 (17.5)	45,127 (10.6)	39,433 (10.1)	0.132	110,382 (11.0)	112,263 (11.2)	112,787 (11.4)	11,4308 (11.5)	0.009
Beta blockers	9,278 (10.6)	9,435 (11.2)	25,832 (6.1)	20,540 (5.2)	0.136	65,791 (6.6)	66,040 (6.6)	65,225 (6.6)	66,471 (6.7)	0.003
Calcium channel blockers	20,257 (23.2)	22,439 (26.5)	69,318 (16.3)	59,941 (15.3)	0.169	164,969 (16.5)	169,507 (17.0)	171,767 (17.3)	173,382 (17.5)	0.015
Diuretics	4,133 (4.7)	3,305 (3.9)	7,378 (1.7)	5,935 (1.5)	0.116	20,595 (2.1)	20,913 (2.1)	20,860 (2.1)	21,668 (2.2)	0.005
Nitrates	1,465 (1.7)	1,139 (1.3)	2,473 (0.6)	2,116 (0.5)	0.068	7,359 (0.7)	7,362 (0.7)	7,247 (0.7)	7,395 (0.7)	0.001
Lipid-lowering agents										
Statin	15,836 (18.1)	18,404 (21.8)	57,586 (13.5)	54,066 (13.8)	0.129	142,941 (14.3)	144,204 (14.4)	146,082 (14.8)	147,301 (14.9)	0.010
Fibrate	532 (0.6)	597 (0.7)	2,082 (0.5)	1,832 (0.5)	0.018	5,213 (0.5)	4,965 (0.5)	5,054 (0.5)	5,084 (0.5)	0.002
PCSK9 inhibitors	3 (0.0)	9 (0.0)	14 (0.0)	36 (0.0)	0.006	63 (0.0)	62 (0.0)	63 (0.0)	62 (0.0)	<0.001
Insulins	2,770 (3.2)	2,180 (2.6)	5,314 (1.2)	3,808 (1.0)	0.095	14,827 (1.5)	14,314 (1.4)	14,183 (1.4)	14,993 (1.5)	0.004
Antidiabetic drugs										
Sulfonylurea	5,343 (6.1)	6,347 (7.5)	18,640 (4.4)	14,669 (3.7)	0.095	44,878 (4.5)	45,129 (4.5)	45,010 (4.5)	45,794 (4.6)	0.003
Metformin	9,416 (10.8)	11,317 (13.4)	35,795 (8.4)	29,692 (7.6)	0.109	86,058 (8.6)	86,164 (8.6)	86,189 (8.7)	87,388 (8.8)	0.004
DPP-4 inhibitors	2,554 (2.9)	2,423 (2.9)	6,212 (1.5)	4,927 (1.3)	0.075	16,427 (1.6)	16,212 (1.6)	16,179 (1.6)	16,842 (1.7)	0.003
SGLT-2 inhibitors	985 (1.1)	1,153 (1.4)	3,897 (0.9)	3,601 (0.9)	0.025	10,507 (1.1)	9,698 (1.0)	9,643 (1.0)	9,835 (1.0)	0.004
GLP-1 agonists	129 (0.1)	138 (0.2)	544 (0.1)	545 (0.1)	0.005	1,728 (0.2)	1,352 (0.1)	1,353 (0.1)	1,379 (0.1)	0.005
Oral anticoagulants	1,463 (1.7)	1,067 (1.3)	2,014 (0.5)	1,657 (0.4)	0.077	6,400 (0.6)	6,325 (0.6)	6,225 (0.6)	6,635 (0.7)	0.003
Antiplatelets	5,681 (6.5)	4,620 (5.5)	10,219 (2.4)	8,661 (2.2)	0.133	29,231 (2.9)	29,108 (2.9)	29,391 (3.0)	30,121 (3.0)	0.004
Immunosuppressants	948 (1.1)	690 (0.8)	1,837 (0.4)	1,739 (0.4)	0.046	5,692 (0.6)	5,584 (0.6)	5,362 (0.5)	5,623(0.6)	0.002
Severe COVID-19	328 (0.4)	235 (0.3)	336 (0.1)	254 (0.1)	0.042	1,249 (0.1)	1,196 (0.1)	1,222 (0.1)	1,426 (0.1)	0.003
BNT162b2 recipients	0 (0.0)	30,158 (35.7)	247,274 (58.1)	218,344 (55.7)	NA	0 (0.0)	434,877 (43.5)	554,848 (56.0)	547,149 (55.3)	NA
CoronaVac recipients	0 (0.0)	54,376 (64.3)	178,691 (41.9)	173,758 (44.3)	NA	0 (0.0)	563,885 (56.5)	435,222 (44.0)	442,897 (44.7)	NA

(A) Within 28 days since COVID-19 infection; (B) after 28 days since COVID-19 infection

All parameters are expressed in either frequency (percentage) or mean (SD). PCSK9, proprotein convertase subtilisin/kexin type 9; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium/glucose co-transporter 2; GLP-1, glucagon-like peptide-1; NA, not applicable.



Outcomes	Acute: Number of events	Acute: Incidence rate (95% CI)	Acute: Hazard ratio (95% CI)	Post-acute: Number of events	Post-acute: Incidence rate (95% CI)	Post-acute: Hazard ratio (95% CI)
CVD						
Unvaccinated	1597	20.86 (19.85 – 21.90)	REF	6007	8.20 (7.99 - 8.41)	REF
1 dose of vaccination	1000	13.05 (12.26 – 13.87)	0.63 (0.50 - 0.78)	5153	6.53 (6.36 - 6.71)	0.79 (0.71 - 0.88)
2 doses of vaccination	883	11.58 (10.84 – 12.37)	0.56 (0.47 - 0.67)	3951	5.23 (5.07 - 5.39)	0.63 (0.58 - 0.69)
3 doses of vaccination	667	8.74 (8.09 – 9.42)	0.42 (0.35 - 0.51)	2483	5.07 (4.87 - 5.27)	0.59 (0.54 - 0.66)
Stroke						
Unvaccinated	906	11.83 (11.08 – 12.62)	REF	2647	3.60 (3.47 - 3.74)	REF
1 dose of vaccination	534	6.96 (6.38 – 7.56)	0.59 (0.43 - 0.80)	2328	2.95 (2.83 - 3.07)	0.81 (0.68 – 0.96)
2 doses of vaccination	499	6.54 (5.99 – 7.13)	0.56 (0.44 - 0.71)	1836	2.43 (2.32 - 2.54)	0.67 (0.58 - 0.77)
3 doses of vaccination	348	4.56 (4.09 – 5.05)	0.39 (0.30 - 0.51)	1102	2.25 (2.12 – 2.39)	0.60 (0.51 - 0.70)
CHD						
Unvaccinated	270	5.91 (5.38 – 6.47)	REF	1906	2.59 (2.48 - 2.71)	REF
1 dose of vaccination	204	4.16 (3.73 – 4.64)	0.71 (0.47 - 1.05)	1831	2.32 (2.21 - 2.42)	0.88 (0.73 - 1.06)
2 doses of vaccination	164	3.56 (3.16 - 4.01)	0.60 (0.44 - 0.84)	1391	1.84 (1.74 - 1.94)	0.70 (0.60 - 0.82)
3 doses of vaccination	170	3.46 (3.07 – 3.90)	0.59 (0.42 – 0.83)	1048	2.14 (2.01 - 2.27)	0.80 (0.67 – 0.94)
Heart failure						
Unvaccinated	149	3.28 (2.89 - 3.71)	REF	1635	2.22 (2.12 - 2.33)	REF
1 dose of vaccination	67	1.92 (1.63 – 2.25)	0.59 (0.34 – 1.03)	1140	1.44 (1.36 - 1.53)	0.64 (0.52 - 0.78)
2 doses of vaccination	66	1.58 (1.32 – 1.88)	0.48 (0.30 - 0.77)	809	1.07 (1.00 - 1.14)	0.47 (0.39 - 0.57)
3 doses of vaccination	23	0.76 (0.58 - 0.97)	0.23 (0.13 - 0.42)	384	0.78 (0.71 - 0.87)	0.34 (0.27 - 0.43)
CVD mortality						
Unvaccinated	598	12.17 (11.40 – 12.96)	REF	1421	1.93 (1.83 – 2.03)	REF
1 dose of vaccination	244	5.96 (5.43 - 6.53)	0.49 (0.36 - 0.66)	741	0.94 (0.87 – 1.01)	0.49 (0.38 - 0.62)
2 doses of vaccination	212	4.13 (3.69 – 4.60)	0.34 (0.26 - 0.45)	487	0.64 (0.59 - 0.70)	0.33 (0.27 - 0.41)
3 doses of vaccination	26	1.64 (1.36 – 1.94)	0.13 (0.08 - 0.22)	223	0.45 (0.40 - 0.52)	0.20 (0.15 - 0.27)
All-cause mortality						
Unvaccinated	12016	232.51 (229.11 - 235.94)	REF	19388	26.35 (25.98 – 26.72)	REF
1 dose of vaccination	4854	97.89 (95.69 – 100.12)	0.42 (0.39 - 0.45)	9254	11.69 (11.46 – 11.93)	0.44 (0.41 - 0.47)
2 doses of vaccination	2273	45.31 (43.82 – 46.84)	0.20 (0.18 - 0.21)	5431	7.17 (6.98 – 7.36)	0.27 (0.25 - 0.29)
3 doses of vaccination	466	17.95 (17.01 – 18.91)	0.08 (0.06 - 0.09)	2487	5.07 (4.87 – 5.27)	0.17 (0.16 - 0.19)

Figure 1. Incidence rate and risk of cardiovascular outcomes and mortality among individuals with different vaccination status at acute and post-acute phases after weighting

Incidence rate (cases/1,000 person-years) with 95% CI based on Poisson distribution. Hazard ratio with 95% CI was obtained by Cox regression adjusted with weighting. REF, reference level; CVD, cardiovascular disease; CHD, coronary heart disease.

post-acute incident CVD, our findings are consistent with a Korean cohort study that reported reduced risks of acute myocardial infarction and ischemic stroke beyond 30 days after COVID-19 infection in fully vaccinated people who received mRNA or viral vector vaccines during the pre-Omicron era.[14] In addition to their findings, we recruited patients in the period of February 2021 to May 2022, which overlaps with the Omicron-dominant wave, and observed a positive dose-response relationship between vaccine effectiveness against post-infection incident CVD and the number of vaccine doses administered. We noted the strongest protection in those who completed three doses of COVID-19 vaccine. Apart from acute myocardial infarction and ischemic stroke, we also noticed risk reduction in terms of heart failure, cardiovascular deaths, and all-cause mortality. To the best of our knowledge, no study that specifically addresses the effectiveness of inactivated vaccines against incident CVD has been published so far. Although waning effectiveness against COVID-19 infection has been observed in vaccine recipients,[22] the present study reinforces the importance of vaccination, given the possible benefits of reducing cardiovascular complications after COVID-19 infection in the long run. Even though Omicron is associated with less severe disease compared to the earlier delta variant,[23,24] it is unknown whether Omicron causes more cardiovascular complications at the moment. As previous research demonstrated a substantial risk of CVD in people previously infected with COVID-19 even after 1 year,[7] vaccine uptake during the current Omicron outbreak should be promoted.

Our finding of COVID-19 vaccines reducing acute cardiovascular complications is in analogy to the case of influenza vaccine, in which a meta-analysis revealed that preventing influenza infection with vaccination improves cardiovascular outcome in patients with coronary heart disease because influenza infection is considered a risk factor and trigger for acute coronary syndrome.[25] Similarly, with proven effectiveness against COVID-19 infection and severe disease,[20,26–28] COVID-19 vaccines reduce COVID-19-induced myocardial injury, venous thromboembolism, and acute coronary syndrome.[29] Intriguingly, the reduction in major CVD events demonstrated in this study was not mainly contributed by the reduction in coronary heart diseases (including acute coronary syndrome) but rather stroke and heart failure. Indeed, more investigation regarding this topic is needed. On the other hand, cardiovascular complications beyond the acute phase of COVID-19 infection have been inadequately explored, and current studies mainly focused on patients with risk factors and more severe COVID-19 who were hospitalized.[7] A US study reported an increased risk of incident CVD beyond the first 30 days after COVID-19 infection in a cohort of veterans, of whom more than 50% were obese.[7] It was uncertain whether younger people without cardiovascular risk factors are subject to a similar extent of increased CVD risks after contracting COVID-19. In the present study, vaccinated individuals without established CVD had a substantially lower risk of incident CVD, thereby supporting the role of vaccination. It is unclear how COVID-19 is linked to heightened cardiovascular risks in the post-acute phase, and so is the mechanism of vaccination in protecting against longer-term CVD. It was hypothesized that chronic inflammation triggered by continuous viral reservoirs in the heart as post-acute sequelae and autoimmune response as a result of molecular mimicry might have contributed to the development of CVD in the chronic phase.[10] Severe acute

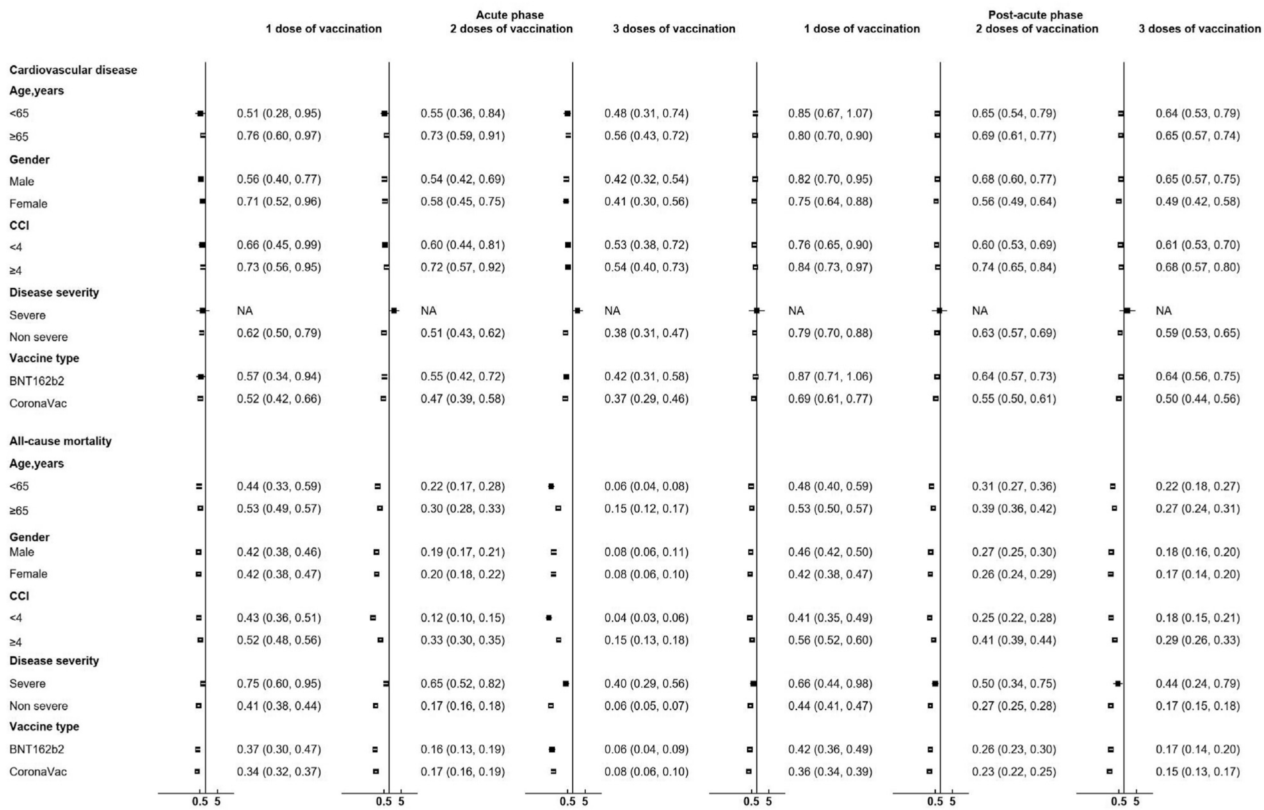


Figure 2. Risk of CVD and mortality among individuals with different vaccination status compared with unvaccinated individuals at acute and post-acute phases by age, gender, Charlson index, disease severity, and vaccine type

HR with 95% CI was obtained by Cox regression adjusted with weighting. NA, not available due to insufficient number of events.

respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific T cells elicited by vaccination, which were shown to be strongly associated with COVID-19 disease severity[30] and longer lasting compared to antibody response,[31] might have potentially played a role in protecting against incident CVD in the post-acute phase, yet further studies are warranted to fill the research gap.

The effectiveness of vaccine in reducing post-infection cardiovascular risks was consistently demonstrated across subgroups of different age, gender, and CCI. The HR of the severe COVID-19 subgroup was apparently high with a large CI compared to patients with mild disease, possibly due to a small number of severe COVID-19 cases recorded among vaccinated patients. Further studies are warranted to confirm our findings. There seemed to be a difference in the post-acute phase between HRs of people receiving one dose of BNT162b2 versus one dose of CoronaVac, but the difference was no longer evident among third-dose recipients, thereby reinforcing the importance of booster shots in protecting against post-infection CVD, irrespective of the type of vaccination.

Strengths of the study

This study enrolled COVID-19 patients with different vaccination status and is one of the studies that provide real-world evidence on the association between mRNA (BNT162b2) and inactivated virus (CoronaVac) vaccine and the risk of incident CVD after acute COVID-19 infection. Our findings highlighted the importance of optimizing vaccine coverage and promoting booster uptake in order to reduce the burden of cardiovascular complications. Another advantage of this study is that we demonstrated both vaccines were associated with lower risks of post-infection incident CVD in individuals without established CVD at baseline.

Limitations of the study

Several limitations were present in this study. First, positive cases in this study were defined by either a positive PCR test or a positive rapid antigen test (RAT) result reported to the Department of Health of Hong Kong. It is possible that some asymptomatic COVID-19 infections were not captured in the current study. Second, the outcome events were solely defined by the diagnosis codes recorded in the electronic database, and, therefore, we could not rule out the possibility of misclassification or underdiagnosis. In the present study, severe COVID-19 was determined by intensive care unit (ICU) admission or the use of ventilatory support only. Both conditions depend on the availability of resources and clinical judgment, and, ideally, more objective parameters should be utilized to determine disease severity. Third, the number of outcome events recorded was small, especially among fully vaccinated patients. Therefore, some HRs could not be estimated in the subgroup analyses. Moreover, the comparison between people who received different numbers of vaccine doses was unavailable due to insufficient events detected within the subgroups. Further study on this comparison is warranted. Theoretically, we were unable to differentiate possible cardiovascular side effects of previous COVID-19 vaccination and the CVD complications of COVID-19. However, most cardiac events related to the vaccine were reported within 1 week of vaccination.[32–34] Hence, the likelihood of side effects of vaccination misinterpreted as COVID-19 complications was minimal. Furthermore, although higher body mass index (BMI) was reported as an independent indicator of the risk of long COVID,[35] data on BMI were not available in the current study. Last, there might be residual confounding, such as lifestyle factors, socioeconomic status, health literacy, and concomitant flu vaccination, which may affect the intention to get vaccinated and the risk of developing CVD.

Conclusions

The risk of CVD and mortality in both the acute and post-acute phase after COVID-19 infection was lower among recipients of BNT162b2 and CoronaVac. There was a positive dose-response relationship between the magnitude of overall risk reduction of CVD and the number of vaccine doses received.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2023.101195.

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AUTHOR CONTRIBUTIONS

Concept and design, E.Y.F.W., A.H.Y.M., V.K.C.Y., I.C.K.W., and E.W.C.; acquisition, analysis, or interpretation of data, E.Y.F.W., A.H.Y.M., V.K.C.Y., C.I.Y.C., B.W., F.T.T.L., C.S.L.C., X.L., C.K.H.W., I.C.K.W., and E.W.C.; drafting of the manuscript, E.Y.F.W., A.H.Y.M., V.K.C.Y., and C.I.Y.C.; critical revision of the manuscript for important intellectual content, all authors; statistical analysis, E.Y.F.W., V.K.C.Y., C.I.Y.C., and B.W.; administrative, technical, or material support, I.C.K.W. and E.W.C.; supervision, I.C.K.W. and E.W.C.

DECLARATION OF INTERESTS

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
original code	This paper	github (https://github.com/kcyan96/hope_vaccine_cvd)
R Version 4.0.3	R Foundation for Statistical Computing	N/A

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact Esther Chan (ewchan@hku.hk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The original code for the main analysis has been deposited on github (https://github.com/kcyan96/hope_vaccine_cvd) and is publicly available as of the date of publication. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

The electronic health records, vaccination records and COVID-19 infection records datasets cannot be deposited in a public repository because these are confidential medical records and the data custodians (the Hospital Authority and the Department of Health of the Hong Kong Special Administrative Region) have not given permission for sharing due to patient confidentiality and privacy concerns. For access, please approach the lead contact to direct your request to the Hospital Authority's data sharing portal. In addition, processed datasets derived from these data which were used in the analyses reported in this paper will be shared by the lead contact upon request. Any additional information required to reanalyze the data reported in this work paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study period and population

This territory-wide retrospective cohort study enrolled patients aged 18 years or above who have a documented COVID-19 infection between 23 February 2021 and 31 October 2022, defined by either a positive Polymerase Chain Reaction (PCR) result or a positive Rapid Antigen Test (RAT). The date of documented COVID infection was defined as the index date. Patients with a history of CVD, including stroke, coronary heart disease, or heart failure, before the index date were excluded from the cohort. Patients were followed up from the index date until the occurrence of study outcome or the end of the study (23 January 2023), whichever occurred first. The baseline characteristics of study participants, including their health status, disease and medication history, are presented in Table 1.

Study design

At the time of publication, two COVID-19 vaccines were provided by the Hong Kong Government, namely BNT162b2 and CoronaVac, and they have been in use since 23 February 2021. Patients in this study were classified into four mutually exclusive groups based on their vaccination status: (i) unvaccinated (reference group); (ii) received one dose of BNT162b2 or CoronaVac; (iii) received two doses of BNT162b2 or CoronaVac; and (iv) received three doses of BNT162b2 or CoronaVac. Since the choice of either heterologous or homologous COVID-19 booster shots were only made available from 11 November 2021 onwards for priority groups and 1 January 2022 for the general population, [36,37] a small proportion of the local population received a heterologous booster after the primary series, and therefore they were excluded from the analysis.

Ethics approval

This study was approved by the Central Institutional Review Board of the Hospital Authority of Hong Kong (CIRB-2021-005-4) and the DH Ethics Committee (LM171/2021). Anonymous data was extracted from the Hospital Authority Clinical Management System, and hence, consent from participants was not required.

METHOD DETAILS

Outcome

The primary outcome of this study was a composite of coronary heart disease, stroke, and heart failure, determined by the primary diagnosis code at hospitalization based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (coronary heart disease: 410.x-414.x, 36.0, 36.1, V45.81; stroke: 430.x-438.x; heart failure: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01–404.03, 404.11–404.13, 404.91–404.93) The secondary outcomes were cardiovascular mortality (International Classification of Diseases, Tenth Revision: I00-99) and all-cause mortality. Information regarding all-cause mortality was extracted from the Hong Kong Death Registry, which is an official registry that records all registered deaths in Hong Kong.

Covariates

Baseline characteristics included age, gender, Charlson Comorbidity Index (CCI),[38] comorbidities (chronic kidney disease, respiratory disease, diabetes and dementia), drug usage (renin-angiotensin-system agents, beta blockers, calcium channel blockers, diuretics, nitrates, lipid lowering agents [statin, fibrate, PCSK9 inhibitor], insulins, antidiabetic drugs [sulphonylurea, metformin, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 agonist], oral anticoagulants, antiplatelets and immunosuppressants), and the severity of COVID-19. Severe COVID-19 was defined by ICU admission or the use of ventilatory support within seven days of infection, identified by the ICD-9-CM procedure codes (39.65, 89.18, 93.90, 93.95, 93.96, 96.04, 96.7x).

QUANTIFICATION AND STATISTICAL ANALYSIS

Weighting

Inverse probability of treatment weighting (IPTW) using propensity score was employed to minimise confounding across comparison groups. The propensity score model included all baseline characteristics mentioned above as covariates. A standardised mean difference (SMD) of less than 0.2 between comparison groups post-weighting was balanced between groups.[39]

Statistical analysis

In order to examine short-term and long-term effects, the observation period was divided into the acute phase (<28 days post-infection) and the post-acute phase ($\geq$28 days post-infection). This cut-off has been used in previous studies.[40,41] The incidence rates of outcome events and their corresponding 95% confidence intervals (CIs) were assessed based on their Poisson distribution. The risks of outcomes were compared between groups using IPTW-weighted Cox proportional hazards regression. Hazard ratios (HRs) and their corresponding 95% CIs were reported. The proportional hazard assumption of the models for CVD outcomes were evaluated using the interaction with time based on Schoenfeld residuals. There was no significant interaction, indicating that the models satisfied the proportional hazard assumption. Five sensitivity analyses were conducted. The first sensitivity analysis only included patients with positive PCR test results as confirmed COVID-19 infection cases. The second sensitivity analysis excluded patients who contracted COVID-19 more than 180 days since the last dose of vaccination, since waning immunity has been described in prior studies.[42] The third sensitivity analysis excluded patients who received additional vaccine doses within 28 days after COVID-19 infection. The fourth sensitivity analysis was adjusted for mortality as a competing risk while evaluating associations. A competing risk Cox regression using the cause-specific cox regression method[43] was conducted. The fifth sensitivity analysis further divided the post-acute phase into two periods (28–89 days and $\geq$90 days). Subgroup analyses stratified by age (<65, $\geq$65 years), gender (male, female), Charlson Comorbidity index (<4, $\geq$4) and disease severity (mild, severe) were conducted.

Two-tailed tests were used when analysing results from this study and a pP-value less than 0.05 was inferred as statistically significant. All statistical analyses were conducted using R version 4.0.3. At least two investigators conducted the statistical analyses independently for quality assurance. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklists were followed to guide transparent reporting of the cohort study.

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Supplemental information

Association between BNT162b2 and CoronaVac vaccination and risk of CVD and mortality after COVID-19 infection: A population-based cohort study

Eric Yuk Fai Wan, Anna Hoi Ying Mok, Vincent Ka Chun Yan, Cheyenne I. Ying Chan, Boyuan Wang, Francisco Tsz Tsun Lai, Celine Sze Ling Chui, Xue Li, Carlos King Ho Wong, Kai Hang Yiu, Hung Fat Tse, Chak Sing Lau, Ian Chi Kei Wong, and Esther Wai Yin Chan

Supplementary figure 1, related to Figure 2. Hazard ratio of cardiovascular outcomes and mortality among individuals with different vaccination status at acute and post-acute phases by age, gender, Charlson index, disease severity, and vaccine type.

	Acute phase			Post-acute phase		
	1 dose of vaccination	2 doses of vaccination	3 doses of vaccination	1 dose of vaccination	2 doses of vaccination	3 doses of vaccination
Stroke						
Age,years						
<65	0.32 (0.13, 0.75)	0.49 (0.29, 0.83)	0.38 (0.22, 0.65)	0.84 (0.59, 1.20)	0.70 (0.53, 0.93)	0.63 (0.47, 0.84)
≥65	0.82 (0.59, 1.15)	0.76 (0.57, 1.01)	0.53 (0.38, 0.74)	0.84 (0.69, 1.02)	0.72 (0.61, 0.86)	0.67 (0.55, 0.82)
Gender						
Male	0.60 (0.39, 0.93)	0.57 (0.40, 0.80)	0.40 (0.28, 0.58)	0.82 (0.65, 1.04)	0.75 (0.62, 0.90)	0.64 (0.52, 0.80)
Female	0.58 (0.38, 0.88)	0.54 (0.38, 0.76)	0.37 (0.25, 0.55)	0.81 (0.63, 1.02)	0.58 (0.47, 0.71)	0.54 (0.42, 0.68)
CCI						
<4	0.60 (0.36, 1.00)	0.54 (0.36, 0.80)	0.45 (0.30, 0.67)	0.77 (0.60, 1.00)	0.68 (0.56, 0.83)	0.61 (0.49, 0.75)
≥4	0.67 (0.46, 0.97)	0.76 (0.55, 1.05)	0.48 (0.32, 0.73)	0.88 (0.70, 1.09)	0.70 (0.57, 0.86)	0.69 (0.53, 0.89)
Disease severity						
Severe	NA	NA	NA	NA	NA	NA
Non severe	0.59 (0.43, 0.81)	0.50 (0.39, 0.64)	0.33 (0.25, 0.44)	0.81 (0.68, 0.96)	0.67 (0.58, 0.77)	0.60 (0.51, 0.70)
Vaccine type						
BNT162b2	0.46 (0.23, 0.92)	0.60 (0.43, 0.84)	0.34 (0.23, 0.50)	0.95 (0.71, 1.29)	0.65 (0.54, 0.78)	0.58 (0.46, 0.73)
CoronaVac	0.50 (0.36, 0.69)	0.45 (0.35, 0.59)	0.36 (0.26, 0.48)	0.71 (0.60, 0.85)	0.61 (0.52, 0.70)	0.54 (0.45, 0.64)
Coronary artery disease						
Age,years						
<65	0.87 (0.29, 2.64)	0.72 (0.31, 1.67)	0.84 (0.36, 1.95)	0.98 (0.68, 1.41)	0.70 (0.52, 0.94)	0.78 (0.57, 1.07)
≥65	0.71 (0.45, 1.10)	0.67 (0.45, 0.99)	0.69 (0.44, 1.07)	0.75 (0.60, 0.94)	0.62 (0.51, 0.75)	0.69 (0.55, 0.86)
Gender						
Male	0.52 (0.30, 0.90)	0.55 (0.37, 0.83)	0.46 (0.30, 0.70)	0.93 (0.73, 1.18)	0.73 (0.60, 0.90)	0.87 (0.70, 1.07)
Female	1.04 (0.59, 1.84)	0.68 (0.40, 1.15)	0.81 (0.46, 1.44)	0.78 (0.58, 1.05)	0.60 (0.47, 0.78)	0.58 (0.43, 0.79)
CCI						
<4	0.73 (0.35, 1.49)	0.68 (0.40, 1.16)	0.71 (0.41, 1.21)	0.79 (0.62, 1.02)	0.59 (0.48, 0.73)	0.72 (0.58, 0.89)
≥4	0.88 (0.56, 1.38)	0.74 (0.48, 1.13)	0.82 (0.50, 1.37)	0.87 (0.66, 1.14)	0.78 (0.60, 1.00)	0.73 (0.54, 1.00)
Disease severity						
Severe	NA	NA	NA	NA	NA	NA
Non severe	0.68 (0.45, 1.04)	0.58 (0.41, 0.81)	0.54 (0.38, 0.78)	0.87 (0.72, 1.06)	0.70 (0.59, 0.82)	0.78 (0.66, 0.93)
Vaccine type						
BNT162b2	0.72 (0.33, 1.59)	0.59 (0.34, 1.02)	0.71 (0.41, 1.23)	0.92 (0.66, 1.29)	0.81 (0.66, 0.99)	0.90 (0.72, 1.12)
CoronaVac	0.59 (0.39, 0.89)	0.54 (0.38, 0.76)	0.48 (0.33, 0.70)	0.83 (0.68, 1.01)	0.61 (0.51, 0.73)	0.66 (0.55, 0.80)
Heart failure						
Age,years						
<65	1.29 (0.26, 6.42)	0.61 (0.17, 2.25)	0.42 (0.11, 1.64)	0.50 (0.25, 0.98)	0.36 (0.22, 0.59)	0.31 (0.17, 0.58)
≥65	0.64 (0.35, 1.15)	0.79 (0.46, 1.36)	0.35 (0.17, 0.71)	0.79 (0.64, 0.98)	0.69 (0.56, 0.84)	0.56 (0.43, 0.73)
Gender						
Male	0.42 (0.17, 1.05)	0.33 (0.15, 0.69)	0.35 (0.16, 0.74)	0.66 (0.49, 0.91)	0.49 (0.37, 0.64)	0.35 (0.25, 0.49)
Female	0.77 (0.38, 1.54)	0.65 (0.36, 1.17)	0.10 (0.03, 0.31)	0.62 (0.47, 0.81)	0.46 (0.36, 0.58)	0.33 (0.24, 0.47)
CCI						
<4	1.04 (0.27, 4.02)	0.90 (0.32, 2.54)	0.61 (0.21, 1.81)	0.65 (0.44, 0.98)	0.41 (0.29, 0.57)	0.32 (0.21, 0.48)
≥4	0.63 (0.34, 1.14)	0.66 (0.37, 1.16)	0.26 (0.11, 0.61)	0.78 (0.62, 0.97)	0.74 (0.59, 0.91)	0.61 (0.46, 0.81)
Disease severity						
Severe	NA	NA	NA	NA	NA	NA
Non severe	0.61 (0.34, 1.09)	0.46 (0.28, 0.75)	0.25 (0.13, 0.46)	0.64 (0.52, 0.78)	0.46 (0.38, 0.55)	0.33 (0.26, 0.42)
Vaccine type						
BNT162b2	0.65 (0.15, 2.84)	0.27 (0.11, 0.65)	0.20 (0.07, 0.54)	0.58 (0.36, 0.93)	0.41 (0.31, 0.55)	0.41 (0.27, 0.61)
CoronaVac	0.47 (0.27, 0.84)	0.46 (0.28, 0.75)	0.21 (0.10, 0.44)	0.52 (0.42, 0.65)	0.41 (0.34, 0.51)	0.27 (0.21, 0.35)
Cardiovascular disease mortality						
Age,years						
<65	0.78 (0.32, 1.92)	0.41 (0.20, 0.84)	0.12 (0.05, 0.34)	0.72 (0.34, 1.52)	0.39 (0.21, 0.71)	0.50 (0.27, 0.93)
≥65	0.57 (0.41, 0.78)	0.51 (0.37, 0.70)	0.23 (0.14, 0.38)	0.60 (0.46, 0.77)	0.51 (0.40, 0.65)	0.28 (0.20, 0.39)
Gender						
Male	0.31 (0.20, 0.48)	0.28 (0.20, 0.40)	0.14 (0.08, 0.24)	0.52 (0.36, 0.76)	0.42 (0.31, 0.57)	0.26 (0.18, 0.36)
Female	0.84 (0.55, 1.29)	0.44 (0.29, 0.68)	0.11 (0.05, 0.24)	0.46 (0.33, 0.63)	0.25 (0.18, 0.35)	0.15 (0.09, 0.24)
CCI						
<4	0.56 (0.31, 1.04)	0.31 (0.19, 0.52)	0.17 (0.07, 0.42)	0.51 (0.29, 0.91)	0.41 (0.27, 0.63)	0.33 (0.20, 0.52)
≥4	0.58 (0.41, 0.81)	0.53 (0.38, 0.74)	0.23 (0.13, 0.40)	0.64 (0.50, 0.83)	0.49 (0.38, 0.63)	0.31 (0.22, 0.45)
Disease severity						
Severe	0.92 (0.47, 1.78)	0.95 (0.50, 1.79)	0.62 (0.28, 1.40)	0.14 (0.02, 1.14)	1.05 (0.34, 3.27)	0.36 (0.07, 1.88)
Non severe	0.45 (0.32, 0.63)	0.28 (0.21, 0.38)	0.08 (0.05, 0.13)	0.49 (0.39, 0.63)	0.32 (0.26, 0.40)	0.20 (0.15, 0.26)
Vaccine type						
BNT162b2	0.51 (0.24, 1.11)	0.37 (0.18, 0.73)	0.23 (0.07, 0.82)	0.36 (0.19, 0.70)	0.36 (0.23, 0.57)	0.33 (0.21, 0.50)
CoronaVac	0.41 (0.30, 0.56)	0.30 (0.22, 0.40)	0.11 (0.07, 0.18)	0.41 (0.32, 0.52)	0.27 (0.21, 0.34)	0.12 (0.09, 0.18)

Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with weighting. NA: Not available due to insufficient number of events.

Supplementary table 1, related to Figure 1. Risk of cardiovascular outcomes and mortality among individuals with different vaccination status among patients with positive PCR results only.

	Within 28 days since COVID-19 infection			After 28 days since COVID-19 infection		
	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)
Cardiovascular disease						
Unvaccinated	1378	30.43 (28.85 - 32.06)	REF	4144	9.16 (8.89 - 9.44)	REF
1 dose of vaccination	938	20.74 (19.44 - 22.09)	0.69 (0.55 - 0.86)	3612	7.71 (7.46 - 7.97)	0.83 (0.73 - 0.94)
2 doses of vaccination	811	18.03 (16.82 - 19.30)	0.60 (0.50 - 0.72)	2717	5.93 (5.71 - 6.16)	0.63 (0.57 - 0.71)
3 doses of vaccination	687	15.25 (14.15 - 16.43)	0.51 (0.41 - 0.62)	1894	5.63 (5.38 - 5.89)	0.59 (0.52 - 0.66)
Stroke						
Unvaccinated	773	17.06 (15.89 - 18.30)	REF	1770	3.90 (3.72 - 4.09)	REF
1 dose of vaccination	504	11.14 (10.21 - 12.16)	0.66 (0.48 - 0.90)	1580	3.37 (3.21 - 3.54)	0.85 (0.70 - 1.04)
2 doses of vaccination	455	10.12 (9.23 - 11.09)	0.60 (0.47 - 0.77)	1220	2.66 (2.51 - 2.81)	0.67 (0.57 - 0.79)
3 doses of vaccination	365	8.09 (7.29 - 8.95)	0.48 (0.36 - 0.63)	841	2.50 (2.33 - 2.67)	0.61 (0.50 - 0.74)
Coronary artery disease						
Unvaccinated	396	8.72 (7.89 - 9.61)	REF	1290	2.84 (2.69 - 3.00)	REF
1 dose of vaccination	299	6.60 (5.88 - 7.38)	0.76 (0.51 - 1.14)	1249	2.66 (2.52 - 2.81)	0.91 (0.73 - 1.14)
2 doses of vaccination	256	5.69 (5.04 - 6.43)	0.66 (0.47 - 0.92)	950	2.07 (1.94 - 2.20)	0.71 (0.59 - 0.85)
3 doses of vaccination	259	5.74 (5.07 - 6.46)	0.66 (0.46 - 0.95)	823	2.44 (2.28 - 2.61)	0.83 (0.68 - 1.01)
Heart failure						
Unvaccinated	221	4.87 (4.25 - 5.53)	REF	1219	2.69 (2.54 - 2.84)	REF
1 dose of vaccination	135	2.99 (2.52 - 3.53)	0.62 (0.35 - 1.08)	909	1.93 (1.81 - 2.06)	0.70 (0.56 - 0.88)
2 doses of vaccination	108	2.40 (1.97 - 2.87)	0.49 (0.30 - 0.81)	600	1.31 (1.21 - 1.41)	0.48 (0.39 - 0.59)
3 doses of vaccination	67	1.49 (1.17 - 1.89)	0.31 (0.16 - 0.58)	275	0.82 (0.72 - 0.92)	0.29 (0.22 - 0.38)
Cardiovascular disease mortality						
Unvaccinated	755	16.65 (15.49 - 17.87)	REF	1079	2.37 (2.24 - 2.52)	REF
1 dose of vaccination	416	9.19 (8.33 - 10.10)	0.55 (0.40 - 0.76)	538	1.15 (1.05 - 1.25)	0.48 (0.36 - 0.63)
2 doses of vaccination	302	6.71 (6.00 - 7.51)	0.40 (0.30 - 0.54)	360	0.78 (0.70 - 0.87)	0.33 (0.26 - 0.42)
3 doses of vaccination	129	2.86 (2.39 - 3.37)	0.17 (0.11 - 0.28)	200	0.59 (0.51 - 0.68)	0.22 (0.16 - 0.30)
All-cause mortality						
Unvaccinated	15032	331.29 (326.01 - 336.61)	REF	15398	33.88 (33.35 - 34.42)	REF
1 dose of vaccination	7080	156.43 (152.83 - 160.12)	0.47 (0.44 - 0.51)	7342	15.61 (15.26 - 15.98)	0.46 (0.42 - 0.49)
2 doses of vaccination	3356	74.56 (72.07 - 77.11)	0.23 (0.21 - 0.24)	4414	9.60 (9.32 - 9.89)	0.28 (0.26 - 0.30)
3 doses of vaccination	1421	31.51 (29.89 - 33.17)	0.10 (0.08 - 0.11)	2289	6.78 (6.51 - 7.07)	0.18 (0.16 - 0.20)

Incidence rate (cases/1000 person-years) with 95% confidence interval based on Poisson distribution. Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with weighting. CI = confidence interval; REF = reference level.

Supplementary table 2, related to Figure 1. Risk of cardiovascular outcomes and mortality among individuals with different vaccination status excluding individuals with COVID-19 onset after 180 days since last dose of vaccination.

	Within 28 days since COVID-19 infection			After 28 days since COVID-19 infection		
	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)
Cardiovascular disease						
Unvaccinated	1354	25.27 (23.96 - 26.65)	REF	1939	11.07 (10.58 - 11.57)	REF
1 dose of vaccination	838	15.54 (14.51 - 16.62)	0.62 (0.50 - 0.77)	1439	8.49 (8.06 - 8.93)	0.74 (0.64 - 0.86)
2 doses of vaccination	764	14.16 (13.18 - 15.18)	0.56 (0.47 - 0.68)	1096	6.47 (6.10 - 6.86)	0.57 (0.49 - 0.66)
3 doses of vaccination	589	10.88 (10.02 - 11.78)	0.43 (0.35 - 0.53)	1009	5.98 (5.62 - 6.36)	0.52 (0.42 - 0.64)
Stroke						
Unvaccinated	757	14.13 (13.15 - 15.16)	REF	817	4.66 (4.34 - 4.98)	REF
1 dose of vaccination	447	8.29 (7.55 - 9.09)	0.59 (0.44 - 0.79)	695	4.09 (3.80 - 4.41)	0.85 (0.67 - 1.06)
2 doses of vaccination	418	7.74 (7.02 - 8.51)	0.55 (0.43 - 0.71)	543	3.21 (2.95 - 3.49)	0.67 (0.53 - 0.83)
3 doses of vaccination	295	5.46 (4.86 - 6.11)	0.39 (0.29 - 0.52)	360	2.13 (1.92 - 2.36)	0.44 (0.34 - 0.57)
Coronary artery disease						
Unvaccinated	389	7.26 (6.57 - 8.01)	REF	628	3.58 (3.31 - 3.87)	REF
1 dose of vaccination	266	4.93 (4.37 - 5.56)	0.68 (0.46 - 1.00)	479	2.82 (2.58 - 3.08)	0.77 (0.59 - 0.99)
2 doses of vaccination	249	4.62 (4.08 - 5.22)	0.64 (0.46 - 0.90)	299	1.76 (1.58 - 1.98)	0.48 (0.36 - 0.63)
3 doses of vaccination	244	4.50 (3.96 - 5.09)	0.62 (0.44 - 0.89)	528	3.13 (2.87 - 3.41)	0.85 (0.62 - 1.15)
Heart failure						
Unvaccinated	219	4.09 (3.58 - 4.66)	REF	511	2.91 (2.67 - 3.18)	REF
1 dose of vaccination	125	2.32 (1.94 - 2.76)	0.57 (0.33 - 0.98)	297	1.75 (1.56 - 1.95)	0.57 (0.42 - 0.78)
2 doses of vaccination	101	1.87 (1.52 - 2.25)	0.46 (0.28 - 0.75)	264	1.56 (1.38 - 1.75)	0.51 (0.38 - 0.69)
3 doses of vaccination	52	0.97 (0.73 - 1.26)	0.24 (0.12 - 0.46)	173	1.03 (0.88 - 1.19)	0.33 (0.16 - 0.71)
Cardiovascular disease mortality						
Unvaccinated	796	14.83 (13.82 - 15.89)	REF	421	2.40 (2.18 - 2.64)	REF
1 dose of vaccination	381	7.06 (6.38 - 7.80)	0.48 (0.35 - 0.64)	178	1.05 (0.90 - 1.21)	0.42 (0.29 - 0.61)
2 doses of vaccination	273	5.05 (4.47 - 5.67)	0.34 (0.26 - 0.46)	164	0.97 (0.83 - 1.13)	0.39 (0.27 - 0.56)
3 doses of vaccination	115	2.13 (1.77 - 2.55)	0.14 (0.08 - 0.25)	94	0.55 (0.45 - 0.67)	0.22 (0.13 - 0.37)
All-cause mortality						
Unvaccinated	15531	289.51 (284.98 - 294.09)	REF	9480	54.01 (52.93 - 55.10)	REF
1 dose of vaccination	6468	119.79 (116.90 - 122.74)	0.41 (0.39 - 0.44)	4353	25.64 (24.89 - 26.41)	0.46 (0.43 - 0.49)
2 doses of vaccination	3054	56.58 (54.60 - 58.62)	0.20 (0.18 - 0.21)	2194	12.95 (12.41 - 13.50)	0.23 (0.21 - 0.25)
3 doses of vaccination	1385	25.58 (24.25 - 26.94)	0.09 (0.07 - 0.11)	1648	9.76 (9.30 - 10.24)	0.17 (0.13 - 0.24)

Incidence rate (cases/1000 person-years) with 95% confidence interval based on Poisson distribution. Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with weighting. CI = confidence interval; REF = reference level.

Supplementary table 3, related to Figure 1. Risk of cardiovascular outcomes and mortality among individuals with different vaccination status excluding individuals who received additional vaccine doses within 28 days after COVID-19 infection.

	Within 28 days since COVID-19 infection			After 28 days since COVID-19 infection		
	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)
Cardiovascular disease						
Unvaccinated	1575	21.14 (20.12 - 22.21)	REF	5848	8.23 (8.02 - 8.45)	REF
1 dose of vaccination	970	13.20 (12.39 - 14.05)	0.63 (0.50 - 0.79)	4779	6.33 (6.16 - 6.52)	0.76 (0.68 - 0.85)
2 doses of vaccination	868	11.62 (10.87 - 12.41)	0.55 (0.46 - 0.66)	3848	5.20 (5.04 - 5.37)	0.62 (0.57 - 0.68)
3 doses of vaccination	667	8.74 (8.09 - 9.42)	0.42 (0.34 - 0.51)	2483	5.07 (4.88 - 5.27)	0.59 (0.53 - 0.66)
Stroke						
Unvaccinated	898	12.04 (11.27 - 12.85)	REF	2565	3.60 (3.47 - 3.74)	REF
1 dose of vaccination	518	7.06 (6.47 - 7.69)	0.59 (0.43 - 0.80)	2143	2.84 (2.72 - 2.96)	0.78 (0.66 - 0.93)
2 doses of vaccination	496	6.64 (6.06 - 7.23)	0.55 (0.43 - 0.71)	1782	2.40 (2.29 - 2.52)	0.66 (0.57 - 0.76)
3 doses of vaccination	348	4.56 (4.10 - 5.05)	0.38 (0.29 - 0.50)	1102	2.25 (2.12 - 2.39)	0.60 (0.51 - 0.71)
Coronary artery disease						
Unvaccinated	450	6.04 (5.50 - 6.62)	REF	1867	2.62 (2.50 - 2.74)	REF
1 dose of vaccination	315	4.29 (3.84 - 4.79)	0.71 (0.48 - 1.06)	1751	2.32 (2.21 - 2.43)	0.87 (0.72 - 1.06)
2 doses of vaccination	260	3.47 (3.07 - 3.91)	0.58 (0.42 - 0.80)	1359	1.83 (1.74 - 1.93)	0.69 (0.59 - 0.81)
3 doses of vaccination	264	3.46 (3.07 - 3.90)	0.58 (0.41 - 0.81)	1048	2.14 (2.01 - 2.27)	0.79 (0.66 - 0.93)
Heart failure						
Unvaccinated	241	3.23 (2.84 - 3.65)	REF	1588	2.23 (2.12 - 2.34)	REF
1 dose of vaccination	136	1.85 (1.57 - 2.19)	0.58 (0.32 - 1.03)	1025	1.36 (1.27 - 1.44)	0.60 (0.48 - 0.74)
2 doses of vaccination	121	1.61 (1.34 - 1.92)	0.50 (0.31 - 0.80)	788	1.06 (0.99 - 1.14)	0.47 (0.39 - 0.57)
3 doses of vaccination	58	0.76 (0.58 - 0.97)	0.23 (0.13 - 0.43)	384	0.78 (0.71 - 0.87)	0.34 (0.27 - 0.43)
Cardiovascular disease mortality						
Unvaccinated	933	12.51 (11.72 - 13.33)	REF	1355	1.90 (1.80 - 2.00)	REF
1 dose of vaccination	457	6.22 (5.68 - 6.82)	0.50 (0.37 - 0.67)	700	0.93 (0.86 - 1.00)	0.49 (0.38 - 0.63)
2 doses of vaccination	315	4.21 (3.76 - 4.69)	0.34 (0.26 - 0.45)	472	0.64 (0.58 - 0.69)	0.33 (0.27 - 0.42)
3 doses of vaccination	125	1.64 (1.36 - 1.94)	0.13 (0.08 - 0.21)	223	0.46 (0.40 - 0.52)	0.20 (0.15 - 0.27)
All-cause mortality						
Unvaccinated	17728	237.72 (234.23 - 241.23)	REF	18728	26.26 (25.89 - 26.64)	REF
1 dose of vaccination	7489	101.92 (99.63 - 104.25)	0.43 (0.40 - 0.46)	8860	11.71 (11.47 - 11.96)	0.45 (0.42 - 0.48)
2 doses of vaccination	3444	46.06 (44.55 - 47.62)	0.19 (0.18 - 0.21)	5342	7.20 (7.01 - 7.39)	0.27 (0.26 - 0.29)
3 doses of vaccination	1370	17.95 (17.02 - 18.92)	0.08 (0.06 - 0.09)	2483	5.06 (4.87 - 5.27)	0.17 (0.16 - 0.19)

Incidence rate (cases/1000 person-years) with 95% confidence interval based on Poisson distribution. Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with weighting. CI = confidence interval; REF = reference level.

Supplementary table 4, related to Figure 1. Risk of cardiovascular outcomes and mortality among individuals with different vaccination status using competing risk method.

	Within 28 days since COVID-19 infection			After 28 days since COVID-19 infection		
	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)
Cardiovascular disease						
Unvaccinated	1597	20.86 (19.85 - 21.90)	REF	6007	8.20 (7.99 - 8.40)	REF
1 dose of vaccination	1001	13.05 (12.26 - 13.87)	0.63 (0.58 - 0.68)	5153	6.53 (6.36 - 6.71)	0.79 (0.76 - 0.82)
2 doses of vaccination	883	11.58 (10.84 - 12.37)	0.56 (0.52 - 0.61)	3951	5.23 (5.07 - 5.39)	0.63 (0.61 - 0.66)
3 doses of vaccination	667	8.74 (8.09 - 9.42)	0.42 (0.39 - 0.46)	2483	5.07 (4.87 - 5.27)	0.59 (0.57 - 0.62)
Stroke						
Unvaccinated	906	11.83 (11.08 - 12.62)	REF	2647	3.60 (3.47 - 3.74)	REF
1 dose of vaccination	534	6.96 (6.38 - 7.56)	0.59 (0.53 - 0.66)	2328	2.95 (2.83 - 3.07)	0.81 (0.77 - 0.86)
2 doses of vaccination	499	6.54 (5.99 - 7.13)	0.56 (0.50 - 0.62)	1836	2.43 (2.32 - 2.54)	0.67 (0.63 - 0.71)
3 doses of vaccination	348	4.56 (4.09 - 5.05)	0.39 (0.34 - 0.44)	1102	2.25 (2.12 - 2.39)	0.60 (0.56 - 0.64)
Coronary artery disease						
Unvaccinated	453	5.91 (5.38 - 6.47)	REF	1906	2.59 (2.48 - 2.71)	REF
1 dose of vaccination	319	4.16 (3.73 - 4.64)	0.71 (0.61 - 0.82)	1831	2.32 (2.21 - 2.42)	0.88 (0.82 - 0.94)
2 doses of vaccination	271	3.56 (3.16 - 4.00)	0.61 (0.52 - 0.71)	1391	1.84 (1.74 - 1.94)	0.70 (0.65 - 0.75)
3 doses of vaccination	264	3.46 (3.07 - 3.90)	0.59 (0.51 - 0.69)	1048	2.14 (2.01 - 2.27)	0.80 (0.74 - 0.86)
Heart failure						
Unvaccinated	252	3.28 (2.89 - 3.71)	REF	1635	2.22 (2.12 - 2.33)	REF
1 dose of vaccination	147	1.92 (1.63 - 2.25)	0.59 (0.48 - 0.72)	1140	1.44 (1.36 - 1.53)	0.64 (0.59 - 0.69)
2 doses of vaccination	121	1.58 (1.32 - 1.88)	0.49 (0.39 - 0.61)	809	1.07 (1.00 - 1.14)	0.47 (0.44 - 0.51)
3 doses of vaccination	58	0.75 (0.58 - 0.97)	0.23 (0.17 - 0.31)	384	0.78 (0.71 - 0.87)	0.34 (0.30 - 0.38)
Cardiovascular disease mortality						
Unvaccinated	933	12.17 (11.40 - 12.96)	REF	1421	1.93 (1.83 - 2.03)	REF
1 dose of vaccination	457	5.96 (5.43 - 6.53)	0.49 (0.44 - 0.55)	741	0.94 (0.87 - 1.01)	0.49 (0.45 - 0.53)
2 doses of vaccination	315	4.13 (3.69 - 4.60)	0.34 (0.30 - 0.39)	487	0.64 (0.59 - 0.70)	0.33 (0.30 - 0.37)
3 doses of vaccination	125	1.64 (1.36 - 1.94)	0.14 (0.11 - 0.16)	223	0.45 (0.40 - 0.52)	0.20 (0.17 - 0.23)

Incidence rate (cases/1000 person-years) with 95% confidence interval based on Poisson distribution. Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with weighting. CI = confidence interval; REF = reference level.

Supplementary table 5, related to Figure 1. Risk of cardiovascular outcomes and mortality among individuals with different vaccination status within 28-90 Days and beyond 90 Days since COVID-19 Infection.

	Within 28-90 Days since COVID-19 infection			After 90 days since COVID-19 infection		
	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)	Events	Incidence rate (95% CI)	Hazard ratio (95% CI)
Cardiovascular disease						
Unvaccinated	1668	9.89 (9.42 - 10.37)	REF	4426	7.82 (7.59 - 8.05)	REF
1 dose of vaccination	1175	6.95 (6.56 - 7.35)	0.70 (0.57 - 0.87)	3984	6.43 (6.23 - 6.63)	0.81 (0.71 - 0.92)
2 doses of vaccination	872	5.20 (4.86 - 5.55)	0.53 (0.44 - 0.63)	3068	5.22 (5.04 - 5.41)	0.66 (0.59 - 0.73)
3 doses of vaccination	934	5.57 (5.22 - 5.94)	0.56 (0.47 - 0.68)	1541	4.79 (4.56 - 5.04)	0.59 (0.52 - 0.67)
Stroke						
Unvaccinated	717	4.25 (3.95 - 4.57)	REF	1969	3.47 (3.32 - 3.63)	REF
1 dose of vaccination	569	3.36 (3.10 - 3.65)	0.79 (0.57 - 1.10)	1762	2.84 (2.71 - 2.97)	0.81 (0.66 - 0.98)
2 doses of vaccination	384	2.29 (2.06 - 2.52)	0.54 (0.41 - 0.71)	1447	2.46 (2.34 - 2.59)	0.70 (0.60 - 0.82)
3 doses of vaccination	379	2.26 (2.04 - 2.49)	0.53 (0.40 - 0.71)	719	2.24 (2.08 - 2.40)	0.62 (0.51 - 0.75)
Coronary artery disease						
Unvaccinated	519	3.07 (2.81 - 3.34)	REF	1409	2.48 (2.36 - 2.61)	REF
1 dose of vaccination	369	2.18 (1.97 - 2.41)	0.71 (0.48 - 1.04)	1463	2.35 (2.24 - 2.48)	0.93 (0.75 - 1.15)
2 doses of vaccination	295	1.75 (1.56 - 1.96)	0.57 (0.42 - 0.78)	1094	1.86 (1.75 - 1.97)	0.73 (0.61 - 0.88)
3 doses of vaccination	393	2.34 (2.12 - 2.59)	0.76 (0.57 - 1.03)	652	2.03 (1.88 - 2.19)	0.78 (0.64 - 0.96)
Heart failure						
Unvaccinated	463	2.74 (2.50 - 3.00)	REF	1200	2.11 (1.99 - 2.23)	REF
1 dose of vaccination	236	1.40 (1.23 - 1.58)	0.51 (0.34 - 0.75)	904	1.45 (1.36 - 1.55)	0.67 (0.53 - 0.85)
2 doses of vaccination	202	1.20 (1.05 - 1.38)	0.44 (0.31 - 0.62)	602	1.02 (0.94 - 1.11)	0.47 (0.38 - 0.59)
3 doses of vaccination	168	1.00 (0.86 - 1.16)	0.36 (0.25 - 0.54)	215	0.67 (0.58 - 0.76)	0.31 (0.23 - 0.42)
Cardiovascular disease mortality						
Unvaccinated	514	3.04 (2.79 - 3.32)	REF	933	1.64 (1.54 - 1.75)	REF
1 dose of vaccination	229	1.35 (1.19 - 1.54)	0.45 (0.29 - 0.68)	512	0.82 (0.75 - 0.90)	0.50 (0.37 - 0.67)
2 doses of vaccination	182	1.09 (0.94 - 1.25)	0.36 (0.25 - 0.51)	302	0.51 (0.46 - 0.57)	0.31 (0.24 - 0.40)
3 doses of vaccination	124	0.74 (0.62 - 0.88)	0.24 (0.16 - 0.36)	98	0.31 (0.25 - 0.37)	0.16 (0.11 - 0.24)
All-cause mortality						
Unvaccinated	7231	42.79 (41.81 - 43.78)	REF	12535	22.04 (21.66 - 22.43)	REF
1 dose of vaccination	2972	17.55 (16.93 - 18.19)	0.41 (0.37 - 0.46)	6271	10.08 (9.83 - 10.33)	0.45 (0.41 - 0.49)
2 doses of vaccination	1686	10.03 (9.56 - 10.52)	0.23 (0.21 - 0.26)	3718	6.31 (6.11 - 6.52)	0.28 (0.26 - 0.30)
3 doses of vaccination	1110	6.61 (6.23 - 7.01)	0.15 (0.13 - 0.18)	1353	4.20 (3.98 - 4.43)	0.18 (0.16 - 0.21)

Incidence rate (cases/1000 person-years) with 95% confidence interval based on Poisson distribution. Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with weighting. CI = confidence interval; REF = reference level.