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Association between COVID-19 vaccination and stroke: a nationwide case-control study in Qatar

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ABSTRACT

Objective: This study investigated the association between Coronavirus Disease 2019 mRNA vaccination and stroke in Qatar.
Methods: Between December 1, 2020, and April 11, 2023, a matched case-control study was conducted to investigate the association between 3036 acute stroke cases and 3036 controls drawn from the entire population of Qatar.
Results: The adjusted odds ratio (aOR) for vaccination among cases compared to controls was 0.87 (95% CI: 0.75-1.00). The aOR was 0.74 (95% CI: 0.45-1.23) for a single vaccine dose, 0.87 (95% CI: 0.73-1.04) for primary-series vaccination (two doses), and 0.91 (95% CI: 0.66-1.25) for booster vaccination (three or more doses). The aOR was 0.87 (95% CI: 0.72-1.04) for BNT162b2 and 0.86 (95% CI: 0.67-1.11) for mRNA-1273. Subgroup analyses, considering different durations since vaccination, also demonstrated no association. Subgroup analyses based on nationality, age, number of coexisting conditions, or prior infection status yielded similar results. Subgroup analysis, stratified by stroke type, suggested an association between vaccination and cerebral venous sinus thrombosis (aOR of 2.50 [95% CI: 0.97-6.44]), but it did not reach statistical significance.
Conclusion: There was no evidence of an increased risk of stroke following vaccination, both in the short term and in the long term, extending beyond a year after receiving the vaccine.
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Introduction

The most recent Global Burden of Disease Study has ranked stroke as the second leading cause of death and the third contributor to disability globally [1]. The Coronavirus Disease 2019 (COVID-19) pandemic introduced an additional complexity by adding a potential risk factor for stroke [2] and accelerating the onset of

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death among individuals susceptible to all-cause mortality, including stroke [3].

Despite established evidence demonstrating the effectiveness of COVID-19 vaccines in reducing COVID-19 severity [4-6], studies have indicated the potential for rare adverse events following vaccination, such as myocarditis, pericarditis, and Guillain-Barré syndrome [7-12]. The association between vaccination and cerebrovascular diseases, particularly stroke, remains inadequately understood [13]. While randomized controlled trials (RCTs) and other vaccine safety analyses assessing vaccine safety did not reveal an increased risk of stroke [14-17], concerns arose following reports of vaccine-induced immune thrombotic thrombocytopenia [18,19].

Subsequent systematic reviews of growing evidence reported mixed findings. A systematic review and meta-analysis of observational studies indicated a decreased risk of ischemic and hemorrhagic strokes within 28 days following COVID-19 vaccination in cohort studies, but contrasting results of increased risk of stroke were reported from self-controlled case series and case-cross-over studies [13]. An additional systematic review of RCTs, observational studies, registries, and case reports found no evidence for an increased risk of stroke relative to the general population among individuals who completed COVID-19 primary-series vaccination, regardless of vaccine type [16]. This conclusion was further supported by another systematic review and meta-analysis which suggested the prevalence of arterial ischemic stroke after any vaccination to be comparable to that in the general population [20]. Recent national studies, not covered in earlier reviews, suggested a protective effect against ischemic stroke within 31-120 days of primary-series vaccination in Korea [21], and no evidence for an increased risk of stroke within 28 days with any COVID-19 vaccination in Norway [20]. However, available studies had a follow-up duration after vaccination of less than 6 months [13,16,20,21,22].

The objective of this study was to assess the risk of stroke in the population of Qatar following COVID-19 vaccination. The investigation considered diverse follow-up durations postvaccination, extending to periods surpassing 1 year.

Methods

Study population and data sources

This study investigated the association between COVID-19 vaccination and the occurrence of stroke in the population of Qatar, utilizing national data spanning from December 1, 2020, just before the commencement of COVID-19 vaccination in Qatar, to April 11, 2023, the study's end date. The data on stroke patients were sourced from the Qatar Stroke Database, a registry that compiles prospectively collected information on all cases of acute ischemic, hemorrhagic, and cerebral venous sinus thrombosis (CVST) strokes admitted to Hamad Medical Corporation (HMC) since February 2013 [23]. HMC, serving as the sole public tertiary care referral institution in Qatar and overseeing a network of 15 hospitals across the country, has captured 98% of all admissions related to acute strokes in Qatar [23].

The collected data on all admitted stroke patients encompass a set of demographic and clinical information, including risk factors, clinical presentation, laboratory tests, radiological imaging results, and the clinical course during hospitalization [23,24]. The severity of symptoms at the time of admission, assessed through the National Institutes of Health Stroke Scale (NIHSS) score, clinical diagnosis following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [25], and Bamford classification [26], along with the length of stay in the hospital, are also recorded. The modified Rankin scale is documented at various points, including preadmission, at discharge, and at 90 days of follow-up. All stroke diagnoses and outcomes undergo thorough verification by licensed neurologists and/or stroke specialists.

The stroke registry was linked to the national federated databases for COVID-19 laboratory testing, vaccination, hospitalization, and mortality to retrieve COVID-19 data and identify study controls. These databases are nested within the integrated nationwide digital health information platform and encompass severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related data with no missing information since the onset of the pandemic.

The national databases include all polymerase chain reaction test results, irrespective of location or facility, and, since January 5, 2022, all medically supervised rapid antigen tests (Supplementary Section S1). Until October 31, 2022, nearly 5% of the population underwent SARS-CoV-2 testing each week, mainly for routine and nonclinical care purposes [5,27]. However, starting from November 1, 2022, the testing rate decreased to close to 1% per week [28]. Most infections in Qatar during the pandemic were diagnosed through routine testing rather than due to the presence of symptoms (Supple mentary Sections S1 and S2) [5,27].

Qatar launched its COVID-19 vaccination program in December 2020, employing mRNA vaccines and prioritizing individuals based on coexisting conditions and age criteria [27]. COVID-19 vaccination was provided free of charge, regardless of citizenship or residency status, and was nationally tracked [5,27]. Demographic details, including sex, age, and nationality, were extracted from the national health registry. Qatar has diverse and mostly working-age demographics, with 89% of the residents being expatriates from over 150 countries [29,30]. Detailed descriptions of Qatar's population and national databases have been previously reported [4-6,27,29,30].

Study design

A case-control study was conducted to assess the odds of prior exposure to COVID-19 vaccination in individuals presenting with acute ischemic, hemorrhagic, or CVST stroke (cases) compared to individuals randomly selected from the wider population of Qatar (controls). Eligible cases included individuals with incident stroke events during the study period, as identified based on medical chart review by licensed neurologists and/or stroke specialists, with only the first stroke event during that period considered.

Eligible controls were individuals with no recorded stroke during the study period. Controls were sampled from all individuals who underwent testing for SARS-CoV-2, as documented in the national SARS-CoV-2 testing database. Considering the diverse testing mandates enforced throughout the pandemic and the large-scale routine testing (Supplementary Section S1) [5,27], it is improbable that any individual residing in Qatar had not been tested for SARS-CoV-2 at least once during the study's duration. Therefore, the national testing database serves as a sampling frame for the population of Qatar.

Cases and controls were matched exactly in a one-to-one ratio based on sex, 10-year age group, nationality, and type of coexisting condition (39 coexisting conditions) using Stata 18.0 *cc-match* command. Exact matching here refers to the pairing of cases and controls based on identical values of the matching factors—the matched pairs shared precisely the same characteristics. Matching was also performed iteratively to ensure that controls had the same prior infection status (no prior infection, or prior infection with either a pre-omicron variant or an omicron subvariant, or prior infections with both a pre-omicron variant and an omicron subvariant) as their match at the time of stroke diagnosis. The matching process aimed to balance observed confounders between study groups, guided by previous epidemiological studies on the same population [4-6,27,29,30].

Coexisting conditions were identified and categorized based on the ICD-10 codes extracted from the electronic health record encounters of each individual in the Cerner-system national database (Supplementary Section S3). This database comprises all citizens and residents registered in the national and universal public healthcare system. The public healthcare system in Qatar offers healthcare services free of charge or at heavily subsidized costs, including prescription drugs.

Oversight

The institutional review boards at HMC (MRC-01-20-1078) and Weill Cornell Medicine—Qatar (20-00017) approved this retrospective study with a waiver of informed consent. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Supplementary Table S1).

Statistical analysis

The eligible and matched study populations were characterized using frequency distributions and measures of central tendency, and their comparability was assessed using standardized mean differences (SMDs). An SMD of $\leq$0.1 indicated adequate matching. Study analyses were carried out on the matched samples.

Adjusted odds ratios (aORs) were calculated through conditional logistic regression to compare the odds of prior COVID-19 vaccination between cases and controls by vaccine dose (with any, one, two, or three or more doses) and by vaccine type (BNT162b2 or mRNA-1273), accounting for the matching factors. Since cases in this study are incident stroke cases, the odds ratios presented in this study, in reality, reflect measures of incidence rate ratios. The associated 95% confidence intervals (CIs) were not adjusted for multiplicity, and interactions were not explored.

Subgroup analyses were conducted to compare the odds of any prior COVID-19 vaccination among cases and controls based on nationality group (Qataris, non-Qataris), age group ($<$40, 40-59, $\geq$60 years), number of coexisting conditions (none, 1, 2, $\geq$3), prior infection types (no prior infection, pre-omicron, omicron, or both), and time since vaccination in the short (14-, 21-, and 28-day cutoffs) and longer terms (90-day, 6-month, and 1-year cutoffs). Subgroup analyses restricting cases based on stroke type were also performed. The reference group for all analyses comprised unvaccinated individuals. Statistical analyses were performed using STATA/SE version 18.0 (Stata Corporation, College Station, TX, USA).

Results

Study population

Between December 23, 2020, date of first COVID-19 vaccination in Qatar, and April 11, 2023, end of study, 2383,116 individuals had received at least one vaccine dose, 2313,678 had received at least two doses, and 740,609 had received at least three doses. The median duration between the first and second doses was 28 days (interquartile range [IQR]: 21-28 days), while the median duration between the second and third doses was 256 days (IQR: 230-294 days).

Figure 1 illustrates the process of selecting the study population. Table 1 describes the baseline characteristics of eligible and matched population groups. Incident stroke patients included individuals diagnosed with stroke based on medical chart review between December 1, 2020, and April 11, 2021. A total of 3036 patients with incident stroke and 3920,386 individuals from the national SARS-CoV-2 testing database met the study inclusion criteria. Matched groups included 2278 individuals from each population group. The majority of stroke cases (81.6%) were males. Nearly 60% fell within the 40-59 age bracket, with the median age estimated at 51 years (IQR: 43-60 years). A quarter of cases were Indians, 15.1% were Bangladeshis, and 14.8% were Qataris. Forty percent of cases had no documented coexisting conditions, and 86.0% had no documented SARS-CoV-2 infection before the stroke diagnosis.

Among stroke cases, 40.7% had not received any COVID-19 vaccination, compared to 38.5% of controls. The median duration between the last vaccine dose and stroke was 262 days (IQR: 122-427 days) among cases. Meanwhile, the median duration between the last vaccine dose and study recruitment (the date of stroke diagnosis of the control's match) was 252.5 (IQR: 121-408 days) among controls. Among cases, 37.3% received BNT162b2, 21.4% received mRNA-1273, and 0.6% received ChAdOx1 nCoV-19 (AZD1222). The corresponding proportions among controls were 40.3%, 20.8%, and 0.4%.

COVID-19 vaccination and stroke

Table 2 shows the aORs comparing the odds of prior COVID-19 vaccination between stroke cases and controls in the main and subgroup analyses.

Main analysis

No statistically significant association was identified between COVID-19 vaccination and the occurrence of stroke (Table 2). The aOR for COVID-19 vaccination among cases compared to controls was estimated at 0.87 (95% CI: 0.75-1.00) with a *P*-value of 0.055.

Furthermore, there was no statistically significant association observed between the number of vaccine doses and the occurrence of stroke (Table 2). The aOR was 0.74 (95% CI: 0.45-1.23) for a single dose, 0.87 (95% CI: 0.73-1.04) for primary-series vaccination (two doses), and 0.91 (95% CI: 0.66-1.25) for booster vaccination (three or more doses).

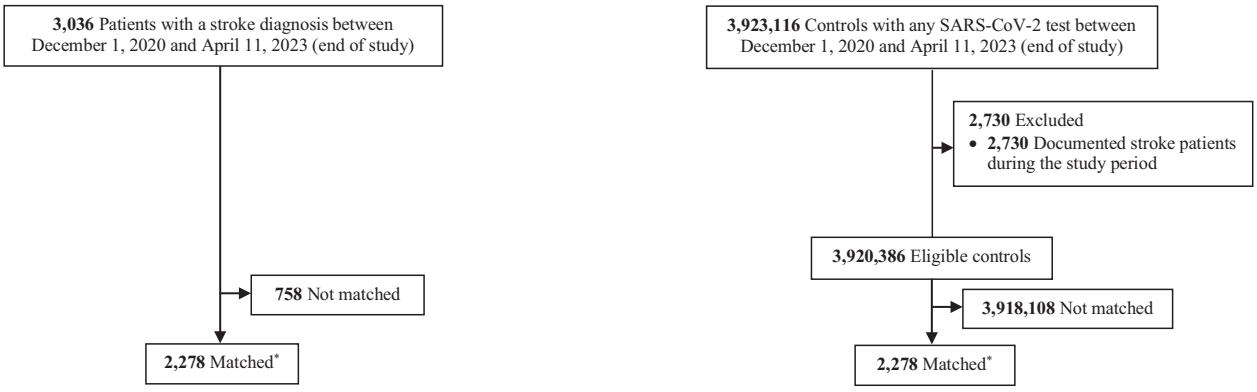
Similarly, no statistically significant association was found between the vaccine type and the occurrence of stroke (Table 2), with the aOR estimated at 0.87 (95% CI: 0.72-1.04) for BNT162b2 and 0.86 (95% CI: 0.67-1.11) for mRNA-1273.

Subgroup analyses

The subgroup analyses, examining nationality status (Qataris vs non-Qataris), age, number of coexisting conditions, or prior infection status, as well as those stratified based on stroke type, consistently indicated either no statistically significant association between COVID-19 vaccination and the occurrence of stroke or suggested a modest protective effect for vaccination against stroke (Table 2). The effect size of this protective effect had a 95% confidence interval that nearly crossed 1, aligning with the null hypothesis of no association.

Similarly, the subgroup analyses by time since vaccination in both the short and long terms demonstrated no statistically significant association between COVID-19 vaccination and the occurrence of stroke or suggested a slight protective effect for vaccination against stroke (Table 2). The effect size of this protective effect also had a 95% confidence interval that nearly crossed with an aOR of 1, aligning with the null hypothesis of no association.

However, the subgroup analysis, stratified based on stroke type, suggested a potential association between vaccination and CVST, with an aOR of 2.50 (95% CI: 0.97-6.44). Yet, the evidence for this association did not reach statistical significance (*P*-value of 0.058).



SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.
*Eligible stroke cases were matched exactly one-to-one by sex, 10-year age group, nationality, and type of coexisting condition to eligible controls who had the same prior infection status as their match at the time of their stroke diagnosis.

Figure 1. Flowchart of the study population selection process.

Discussion

No evidence of an increased risk of stroke following COVID-19 mRNA vaccination was observed, both in the weeks or months after vaccination and in the long term, extending beyond a year after vaccination. This finding remained consistent across all analyses and subgroup assessments, irrespective of the number of vaccine doses, national background, young and old age, number of coexisting conditions, or prior infection status. These results not only align with studies indicating no heightened risk of stroke in the short-term postvaccination [13,16,20-22], but also extend previous findings by demonstrating the absence of any such adverse effect even in the long term, as our investigation spanned durations exceeding 1 year after vaccination.

There was suggestive evidence for an association between vaccination and CVST; however, this evidence did not reach statistical significance. The number of cases of this type of stroke was small, with only 60 cases identified in Qatar throughout the study duration. Therefore, even if such an association existed, vaccination could not have been implicated in more than a very small number of cases despite millions of vaccinations.

While the estimated aORs supported the null hypothesis of no association between COVID-19 vaccination and stroke, the point estimates of the aORs were generally below 1. Some aORs in the subgroup analyses also suggested a statistically significant modest protective effect for vaccination against stroke. This finding remains to be explained. It may hint at a potential protective effect for vaccination against stroke, beyond its known role in preventing SARS-CoV-2 infection—notably, our analyses controlled for prior infection status. A similar protective effect has been observed in several studies examining the association between vaccination and stroke [13,16,20,21].

This potential protective effect, yet to be explained, may be attributed to possible benefits of COVID-19 vaccination against conditions associated with stroke, beyond its direct effect on SARS-CoV-2 infection. For instance, studies have shown that vaccines can induce protective effects against infections other than their intended target, owing to vaccine nonspecific immune activation or trained/bystander immunity [31-36]. The observed protective effect could have also arisen due to residual healthy vaccinee bias [37], where individuals with higher health awareness and in better health conditions (with a lower likelihood of stroke) are more likely to seek vaccination. Although our analyses controlled for documented coexisting conditions, this may not have fully accounted for the severity of individual conditions or the healthy vaccinee bias.

This study has limitations. First, the study was conducted within a particular population, that of Qatar, predominantly comprising healthy working-age adults, and consequently, the generalizability of the findings to other populations remains uncertain. Second, being an observational study, the potential for unmeasured or uncontrolled confounding factors cannot be dismissed. Observational studies, like this one, may be prone to a healthy vaccinee bias, where patients in better health conditions are more likely to receive vaccination, thereby potentially underestimating vaccine-associated adverse effects [37]. Additionally, an indication bias may be present, as individuals with underlying conditions linked to stroke could be more likely to receive vaccination, possibly leading to an overestimation of vaccine-associated adverse effects [37].

Third, despite employing exact matching on various factors, the perfection of matching for specific coexisting conditions may not have been achieved, as these were based on the electronic health records of coexisting conditions. The matching process also only considered a limited set of socioeconomic variables. However, nationality, age, and sex provide a powerful proxy for socioeconomic status in Qatar [29].

Fourth, travel history data were not available for inclusion in the analysis. With expatriates comprising the majority of the population, it is plausible that the rates of travel or leaving the country following the end of employment are higher compared to other countries, potentially introducing differential ascertainment bias for both vaccination and stroke. However, travel or leaving the country was significantly reduced during a substantial portion of the study period due to COVID-19 restrictions. Any under-reporting of vaccination among controls would bias the aOR toward showing a harmful effect for vaccination rather than a protective one. Importantly, when restricting the analysis to only Qatari nationals, representing the stable and nonexpatriate segment of the population, similar results were obtained as in the main analysis for the entire population, indicating no effect for vaccination on the risk of stroke.

Fifth, controls excluded individuals who had a history of stroke during the entire study period. However, proper matched controls should only be free of stroke at the time of the stroke of the matched case. Nevertheless, given the rarity of stroke, this is unlikely to introduce appreciable bias or impact the conclusions of the study. Sixth, theoretically, we cannot exclude the possibility of missing acutely lethal strokes that never led to any hospitalization.

Table 1
Baseline characteristics of eligible and matched population groups.

Characteristics	Full eligible cohorts			Matched cohorts[a]		
	Stroke cases *N* (%) *N* = 3036	Controls *N* (%) *N* = 3920,386	SMD[b]	Stroke cases *N* (%) *N* = 2278	Controls *N* (%) *N* = 2278	SMD[b]
Matching variables						
Median age (IQR)—years	53.0 (44.0-64.0)	32.0 (24.0-40.0)	1.61[c]	51.0 (43.0-60.0)	50.0 (42.0-59.0)	0.09[c]
Age—years						
0-19 years	1 (0.03)	562,456 (14.3)	1.70	1 (0.04)	1 (0.04)	0.00
20-29 years	36 (1.2)	691,380 (17.6)		31 (1.4)	31 (1.4)	
30-39 years	221 (7.3)	1313,096 (33.5)		183 (8.0)	183 (8.0)	
40-49 years	741 (24.4)	838,858 (21.4)		641 (28.1)	641 (28.1)	
50-59 years	857 (28.2)	346,325 (8.8)		702 (30.8)	702 (30.8)	
60-69 years	620 (20.4)	125,903 (3.2)		444 (19.5)	444 (19.5)	
70-79 years	350 (11.5)	33,356 (0.9)		179 (7.9)	179 (7.9)	
≥80 years	210 (6.9)	9012 (0.2)		97 (4.3)	97 (4.3)	
Sex						
Male	2345 (77.2)	2768,060 (70.6)	0.15	1859 (81.6)	1859 (81.6)	0.00
Female	691 (22.8)	1152,326 (29.4)		419 (18.4)	419 (18.4)	
Nationality[d]						
Bangladeshi	398 (13.1)	278,871 (7.1)	0.41	344 (15.1)	344 (15.1)	0.00
Egyptian	117 (3.9)	186,108 (4.7)		82 (3.6)	82 (3.6)	
Filipino	257 (8.5)	291,970 (7.4)		221 (9.7)	221 (9.7)	
Indian	629 (20.7)	1104,353 (28.2)		569 (25.0)	569 (25.0)	
Nepalese	216 (7.1)	365,477 (9.3)		193 (8.5)	193 (8.5)	
Pakistani	171 (5.6)	228,983 (5.8)		123 (5.4)	123 (5.4)	
Qatari	536 (17.7)	321,775 (8.2)		337 (14.8)	337 (14.8)	
Sri Lankan	100 (3.3)	131,711 (3.4)		88 (3.9)	88 (3.9)	
Sudanese	90 (3.0)	79,267 (2.0)		50 (2.2)	50 (2.2)	
Other nationalities[e]	522 (17.2)	931,871 (23.8)		271 (11.9)	271 (11.9)	
Number of coexisting conditions						
None	927 (30.5)	3449,036 (88.0)	1.53	920 (40.4)	920 (40.4)	0.00
1	345 (11.4)	269,983 (6.9)		315 (13.8)	315 (13.8)	
2	463 (15.3)	105,800 (2.7)		366 (16.1)	366 (16.1)	
≥3	1301 (42.9)	95,567 (2.4)		677 (29.7)	677 (29.7)	
Prior infection[f]						
No prior infection	2513 (82.8)	–	–	1959 (86.0)	1959 (86.0)	0.00
Prior pre-omicron infection	327 (10.8)	–		200 (8.8)	200 (8.8)	
Prior omicron infection	172 (5.7)	–		109 (4.8)	109 (4.8)	
Prior pre-omicron & omicron infections	24 (0.8)	–		10 (0.4)	10 (0.4)	
Stroke type						
Ischemic	2515 (82.8)	–		1860 (81.7)	–	
Hemorrhagic	450 (14.8)	–		358 (15.7)	–	
Cerebral venous sinus thrombosis	71 (2.3)	–		60 (2.6)	–	
Vaccination (exposure) variables						
Vaccination[f]						
Unvaccinated	1212 (39.9)	–	–	927 (40.7)	876 (38.5)	0.08
1 dose	86 (2.8)	–		60 (2.6)	64 (2.8)	
2 doses	1261 (41.5)	–		930 (40.8)	915 (40.2)	
≥3 doses	477 (15.7)	–		361 (15.8)	423 (18.6)	
Most recent vaccine type						
Unvaccinated	1212 (39.9)	–	–	927 (40.7)	876 (38.5)	0.07
ChAdOx1 nCoV-19 (AZD1222)	16 (0.5)	–		14 (0.6)	10 (0.4)	
BNT162b2	1229 (40.5)	–		849 (37.3)	918 (40.3)	
mRNA-1273	579 (19.1)	–		488 (21.4)	473 (20.8)	
Bivalent mRNA-1273.214	0 (0.0)	–		0 (0.0)	1 (0.04)	

IQR, interquartile range, *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2, *SMD*, standardized mean difference.
[a] Eligible stroke cases were matched exactly one-to-one by sex, 10-year age group, nationality, and type of coexisting condition to eligible controls who had the same prior infection status as their match at the time of their stroke diagnosis.
[b] SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD ≤ 0.1 indicates adequate matching.
[c] SMD is for the mean difference between groups divided by the pooled standard deviation.
[d] Nationalities were chosen to represent the most populous groups in Qatar.
[e] These comprise up to 183 other nationalities in the unmatched population groups, and 47 other nationalities in the matched population groups.
[f] Ascertained at time of stroke occurrence for cases. Status for controls was determined, after matching, at the time of stroke diagnosis of their matched case.

However, these cases are likely to be very rare in our population and therefore should not introduce bias that could affect the conclusions of the study.

Seventh, although we aimed to control potential bias due to prior infections by matching cases and controls by prior infection status, we cannot exclude the possibility of differential under-ascertainment of infection between cases and controls, leading to imperfect matching. However, SARS-CoV-2 testing was extensive in Qatar until October 31, 2022, covering most of the study duration, with nearly 5% of the population being tested every week, primarily for routine purposes such as screening or meeting travel-related requirements [5,27]. The majority of infections during the pandemic were diagnosed through routine testing rather than symptomatic presentation [5,27]. These points suggest that differential

Table 2
Adjusted odds ratios comparing prior vaccination status between stroke cases and controls in the matched study population.

Analyses	Stroke cases[a]		Controls[a]		Adjusted odds ratio (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Main analysis					
Vaccination status					
Any prior vaccination	1351	927	1402	876	0.87 (0.75-1.00)
Number of vaccine doses					
1 dose	35	583	44	574	0.74 (0.45-1.23)
2 doses	723	813	758	778	0.87 (0.73-1.04)
≥3 doses	226	627	233	620	0.91 (0.66-1.25)
Most recent vaccine type					
BNT162b2	662	791	694	759	0.87 (0.72-1.04)
mRNA-1273	270	679	288	661	0.86 (0.67-1.11)
Subgroup analyses[b]					
By stroke type					
Ischemic	1126	734	1158	702	0.89 (0.76-1.05)
Hemorrhagic	191	167	219	139	0.62 (0.43-0.90)
Cerebral venous sinus thrombosis	34	26	25	35	2.50 (0.97-6.44)
By nationality					
Qataris	234	103	255	82	0.66 (0.44-0.98)
Non-Qataris	1117	824	1147	794	0.91 (0.77-1.06)
By age					
<40 years	117	98	103	112	1.41 (0.91-2.19)
40-59 years	778	565	827	516	0.80 (0.66-0.96)
≥60 years	456	264	472	248	0.84 (0.63-1.12)
By number of coexisting conditions					
None	487	433	491	429	0.98 (0.80-1.20)
1	205	110	208	107	0.93 (0.61-1.42)
2	232	134	240	126	0.84 (0.55-1.27)
≥3	427	250	463	214	0.64 (0.47-0.88)
By prior infection type					
No prior infection	1104	855	1156	803	0.85 (0.73-0.99)
Prior pre-omicron infection	150	50	144	56	1.30 (0.73-2.33)
Prior omicron infection	88	21	94	15	0.63 (0.28-1.38)
Prior pre-omicron & omicron infections	9	1	8	2	2.00 (0.18-22.06)
By time since vaccination					
<90 days	160	652	182	630	0.79 (0.59-1.05)
≥90 days-6 months	103	610	118	595	0.76 (0.52-1.11)
≥6 months-1 year	252	650	256	646	0.96 (0.73-1.27)
≥1 year	327	659	337	649	0.91 (0.69-1.19)
Additional analyses					
Short term					
≤14 days	33	586	45	574	0.68 (0.42-1.13)
>14 days	1259	889	1298	850	0.89 (0.76-1.03)
≤21 days	52	598	69	581	0.66 (0.431.02)
>21 days	1220	877	1254	843	0.90 (0.77-1.05)
≤28 days	63	607	84	586	0.64 (0.43-0.97)
>28 days	1196	868	1226	838	0.91 (0.77-1.06)
Long-term					
<90 days	160	652	182	630	0.79 (0.59-1.05)
≥90 days	1008	823	1037	794	0.89 (0.75-1.06)
<6 months	348	714	385	677	0.78 (0.62-0.98)
≥6 months	751	761	765	747	0.93 (0.77-1.13)
<1 year	791	816	832	775	0.85 (0.71-1.01)
≥1 year	327	659	337	649	0.91 (0.69-1.19)

CI, confidence interval, *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.
[a] Eligible stroke cases were matched exactly one-to-one by sex, 10-year age group, nationality, and type of coexisting condition to eligible controls who had the same prior infection status as their match at the time of their stroke diagnosis.
[b] For subgroup analyses, the exposure was defined as vaccinated (any dose) vs unvaccinated.

under-ascertainment of infection between cases and controls may not have appreciably affected our study.

This study has several strengths. It was conducted on a national scale, encompassing a diverse population based on national backgrounds, and leveraged extensive and validated databases. Stroke diagnoses underwent individual validation by specialized stroke experts. The vaccines used in the country were almost entirely mRNA vaccines, enabling the study to assess the risk of stroke related to this specific type of COVID-19 vaccine platform. The selection of controls was drawn from the entire population of the country, and the use of exact matching facilitated a rigorous pairing of cases and controls. The study was designed to control for prior SARS-CoV-2 infection status, allowing for the differentiation between the effects of vaccination on infection (and thus indirectly on stroke) and the direct impact of vaccination on stroke.

Conclusions

There is no indication of an elevated risk of stroke following COVID-19 mRNA vaccination, whether in the short term within weeks or months postvaccination or in the long term, extending beyond a year after receiving the vaccine.

Author contributions

HC co-conceived and co-designed the study, performed the statistical analyses, and co-wrote the first draft of the article. LJA co-conceived and co-designed the study, led the statistical analyses, and co-wrote the first draft of the article. AAB contributed to study conception and design and facilitated retrieval of data for stroke patients. NA, SA, SK, SJ, DM, RU, and FBA retrieved the data for stroke patients. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and to the writing of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The dataset of this study is a property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly. The data are available under restricted access for preservation of confidentiality of patient data. Access can be obtained through a direct application for data access to Her Excellency the Minister of Public Health (https://www.moph.gov.qa/english/OurServices/eservices/Pages/Governmental-HealthCommunication-Center.aspx). The raw data are protected and are not available due to data privacy laws. Aggregate data are available within the paper and its Supplementary Information.

Ethical approval and consent to participate

Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards approved this retrospective study with a waiver of informed consent.

Consent for publication

Not applicable.

Declarations 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. Dr. Butt has received institutional grant funding from Gilead Sciences unrelated to the work presented in this paper. Otherwise, we declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107095.

References

[1] Global Burden of Disease Stroke CollaboratorsGlobal, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021;**20**(10):795–820.
[2] Libruder C, Hershkovitz Y, Ben-Yaish S, Tanne D, Keinan-Boker L, Binyaminy B. An increased risk for ischemic stroke in the short-term period following COVID-19 infection: a nationwide population-based study. *Neuroepidemiology* 2023;**57**(4):253–9.
[3] Chemaitelly H, Faust JS, Krumholz HM, Ayoub HH, Tang P, Coyle P, et al. Short- and longer-term all-cause mortality among SARS-CoV-2-infected individuals and the pull-forward phenomenon in Qatar: a national cohort study. *Int J Infect Dis* 2023;**136**:81–90.
[4] Abu-Raddad LJ, Chemaitelly H, Ayoub HH, AlMukdad S, Yassine HM, Al-Khatib HA, et al. Effect of mRNA vaccine boosters against SARS-CoV-2 omicron infection in Qatar. *N Engl J Med* 2022;**386**(19):1804–16.
[5] Altarawneh HN, Chemaitelly H, Ayoub HH, Tang P, Hasan MR, Yassine HM, et al. Effects of previous infection and vaccination on symptomatic omicron infections. *N Engl J Med* 2022;**387**(1):21–34.
[6] Chemaitelly H, Ayoub HH, Tang P, Coyle P, Yassine HM, Al Thani AA, et al. Long-term COVID-19 booster effectiveness by infection history and clinical vulnerability and immune imprinting: a retrospective population-based cohort study. *Lancet Infect Dis* 2023;**23**(7):816–27.
[7] Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation* 2021;**144**(6):471–84.
[8] Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. *JAMA—J Am Med Assoc* 2021;**326**(12):1210–12.
[9] Goddard K, Lewis N, Fireman B, Weintraub E, Shimabukuro T, Zerbo O, et al. Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination. *Vaccine* 2022;**40**(35):5153–9.
[10] Hanson KE, Goddard K, Lewis N, Fireman B, Myers TR, Bakshi N, et al. Incidence of Guillain-Barré syndrome after COVID-19 vaccination in the vaccine safety datalink. *JAMA Network Open* 2022;**5**(4):e228879.
[11] Power JR, Keyt LK, Adler ED. Myocarditis following COVID-19 vaccination: incidence, mechanisms, and clinical considerations. *Expert Rev Cardiovasc Ther* 2022;**20**(4):241–51.
[12] Shaheen N, Ramadan A, Nashwan AJ, Shaheen A, Ahmad S, Motawea KR, et al. Guillain-Barre syndrome following COVID-19 vaccination: an updated systematic review of cases. *Clin Case Rep* 2023;**11**(6):e7456.
[13] Liu J, Cao F, Luo C, Guo Y, Yan J. Stroke following coronavirus disease 2019 vaccination: evidence based on different designs of real-world studies. *J Infect Dis* 2023;**228**(10):1336–46.
[14] Klein NP, Lewis N, Goddard K, Fireman B, Zerbo O, Hanson KE, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA* 2021;**326**(14):1390–9.
[15] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020;**383**(27):2603–15.
[16] Rahmig J, Altarsha E, Siepmann T, Barlinn K. Acute ischemic stroke in the context of SARS-CoV-2 vaccination: a systematic review. *Neuropsychiatr Dis Treat* 2022;**18**:1907–16.
[17] Shimabukuro TT. Advisory committee on immunization practices (ACIP): COVID-19 vaccine safety update. 2021. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf [accessed May 2, 2024].
[18] Clerici B, Pontisso E, Aloise C, Peroni B, Perricone R, Pisetta C, et al. Thrombosis and bleeding in patients with vaccine-induced immune thrombotic thrombocytopenia: a systematic review of published cases. *Thromb Haemost* 2024;**124**(5):423–31.
[19] Kim AY, Woo W, Yon DK, Lee SW, Yang JW, Kim JH, et al. Thrombosis patterns and clinical outcome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia: a systematic review and meta-analysis. *Int J Infect Dis* 2022;**119**:130–9.
[20] Stefanou MI, Palaiodimou L, Aguiar de Sousa D, Theodorou A, Bakola E, Katsaros DE, et al. Acute arterial ischemic stroke following COVID-19 vaccination: a systematic review and meta-analysis. *Neurology* 2022;**99**(14):e1465–74.
[21] Kim YE, Huh K, Park YJ, Peck KR, Jung J. Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19 infection. *JAMA* 2022;**328**(9):887–9.
[22] Ihle-Hansen H, Boas H, Tapia G, Hagberg G, Ihle-Hansen H, Berild JD, et al. Stroke after SARS-CoV-2 mRNA vaccine: a nationwide registry study. *Stroke* 2023;**54**(5):e190–3.
[23] Akhtar N, Abid F, Singh R, Kamran S, Imam Y, Al-Jerdi S, et al. Ischemic stroke in patients that recover from COVID-19: comparisons to historical stroke prior to COVID-19 or stroke in patients with active COVID-19 infection. *PLoS One* 2022;**17**(6):e0270413.
[24] Akhtar N, Kamran S, Singh R, Cameron P, Bourke P, Khan R, et al. Prolonged stay of stroke patients in the emergency department may lead to an increased

risk of complications, poor recovery, and increased mortality. *J Stroke Cerebrovasc Dis* 2016;**25**(3):672–8.
[25] Jr Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**(1):35–41.
[26] Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;**337**(8756):1521–6.
[27] Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med* 2021;**385**(24):e83.
[28] Chemaitelly H, Ayoub HH, AlMukdad S, Faust JS, Tang P, Coyle P, et al. Bivalent mRNA-1273.214 vaccine effectiveness against SARS-CoV-2 omicron XBB* infections. *J Travel Med* 2023;**30**(5):taad106.
[29] Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Al Kanaani Z, Al Khal A, Al Kuwari E, et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. *Sci Rep* 2021;**11**(1):6233.
[30] AlNuaimi AA, Chemaitelly H, Semaan S, AlMukdad S, Al-Kanaani Z, Kaleeckal AH, et al. All-cause and COVID-19 mortality in Qatar during the COVID-19 pandemic. *BMJ Glob Health* 2023;**8**(5):e012291.
[31] Benn CS, Netea MG, Selin LK, Aaby P. A small jab – a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol* 2013;**34**(9):431–9.
[32] Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the influenza vaccine on COVID-19 infection rates and severity. *Am J Infect Control* 2021;**49**(6):694–700.
[33] Horns F, Dekker CL, Quake SR. Memory B cell activation, broad anti-influenza antibodies, and bystander activation revealed by single-cell transcriptomics. *Cell Rep* 2020;**30**(3) 905–13.e6.
[34] Netea MG, Dominguez-Andres J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol* 2020;**20**(6):375–88.
[35] Pontiroli AE, Scovenna F, Carlini V, Tagliabue E, Martin-Delgado J, La Sala L, et al. Vaccination against influenza viruses reduces infection, not hospitalization or death, from respiratory COVID-19: a systematic review and meta-analysis. *J Med Virol* 2024;**96**(1):e29343.
[36] Tayar E, Abdeen S, Abed Alah M, Chemaitelly H, Bougmiza I, Ayoub HH, et al. Effectiveness of influenza vaccination against SARS-CoV-2 infection among healthcare workers in Qatar. *J Infect Public Health* 2023;**16**(2):250–6.
[37] Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. *BMC Infect Dis* 2015;**15**:429.