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Stroke Following Coronavirus Disease 2019 Vaccination: Evidence Based on Different Designs of Real-World Studies

Junyu Liu,[1,2] Fang Cao,[3] Chun Luo,[3] Yuxin Guo,[3] and Junxia Yan[3,4]

[1]Department of Neurosurgery, XiangYa Hospital, Central South University, Changsha, China; [2]Department of Pharmacology, Kyoto University Graduate School of Medicine, Kyoto, Japan; [3]Department of Epidemiology and Health Statistics, XiangYa School of Public Health, Central South University, Changsha, China; and [4]Hunan Provincial Key Laboratory of Clinical Epidemiology, XiangYa School of Public Health, Central South University, Changsha, China

Background. We aimed to evaluate whether coronavirus disease 2019 (COVID-19) vaccination was associated with stroke.

Methods. We conducted a systematic meta-analysis of studies using cohort, self-controlled case series (SCCS), and case-crossover study (CCOS) designs to evaluate incidence risk ratios (IRRs) and 95% confidence intervals (CIs) of ischemic stroke (IS), hemorrhagic stroke (HS), and cerebral venous sinus thrombosis (CVST) following COVID-19 vaccination. Risks of stroke were pooled among subpopulations categorized by vaccine type, dose, age, and sex. Sensitivity analysis was performed by different defined risk periods.

Results. Fourteen studies involving 79 918 904 individuals were included. Cohort studies showed decreased risks of IS (IRR, 0.82 [95% CI, .75–.90]) and HS (IRR, 0.75 [95% CI, .67–.85]) postvaccination, but not CVST (IRR, 1.18 [95% CI, .70–1.98]). SCCS identified increased risks 1–21 days postvaccination (IRR_{IS}, 1.05 [95% CI, 1.00–1.10]; IRR_{HS}, 1.16 [95% CI, 1.06–1.26]) or 1–28 days postvaccination (IRR_{IS}, 1.04 [95% CI, 1.00–1.08]; IRR_{HS}, 1.37 [95% CI, 1.15–1.64]), similar to CVST (IRR, 1.58 [95% CI, 1.08–2.32]). CCOS reported an increased risk of CVST after ChAdOx1 vaccination (IRR, 2.9 [95% CI, 1.1–7.2]).

Conclusions. Although different study designs yielded inconsistent findings, considering the relatively low background incidence of stroke and benefits of vaccination, even a potentially increased risk of stroke postvaccination should not justify vaccine hesitancy.

Keywords. COVID-19; meta-analysis; real-world study; stroke; vaccination.

Administration of vaccines against coronavirus disease 2019 (COVID-19) has been shown to be effective against severe infections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. With the rollout of COVID-19 vaccinations, hospitalizations and mortality caused by SARS-CoV-2 infection have been reduced by >90% [2]. However, vaccine hesitancy, which is characterized by a state of indecision and uncertainty, has persisted and continues to affect vaccination coverage [3]. The short development time for these vaccines and a lack of public awareness has contributed to this phenomenon. Side effects after vaccination have significantly tempered public confidence in COVID-19 vaccination, despite the fact that these effects are usually mild and transient [4]. This situation has necessitated a thorough evaluation of the concomitant events occurring postvaccination so that medical workers can promptly assess the risk of vaccination for individuals and rebuild their confidence in COVID-19 vaccines.

Stroke continues to be one of the leading causes of death and disability worldwide, of which ischemic stroke (IS) constitutes the largest proportion (62.4%), followed by 2 subtypes of hemorrhagic stroke (HS), namely, intracerebral hemorrhage (ICH; 27.9%) and subarachnoid hemorrhage (SAH; 9.7%) [5]. The burden of stroke has increased substantially, causing tremendous pressure on families, the government, and society. A French study reported that Pfizer BNT162b2 vaccination as well as SARS-CoV-2 infection were associated with a higher risk of HS within 28 days [6]. Another study focusing on the population of England reported the risk of IS and cerebral venous sinus thrombosis (CVST), a rare acute stroke event, after COVID-19 vaccination [7]. However, the association of COVID-19 vaccination with stroke onset remains unclear. To explore the risks of various subtypes of stroke after administration of different COVID-19 vaccines, we systematically reviewed the existing real-world studies that were conducted, using cohort, self-controlled case series (SCCS) and case-crossover study (CCOS) designs to compare the incidence of stroke events between vaccinated and unvaccinated populations or between the risk and control periods within each self-controlled individual.

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Correspondence: Junxia Yan, MD, Department of Epidemiology and Health Statistics and Hunan Provincial Key Laboratory of Clinical Epidemiology, XiangYa School of Public Health, Central South University, Shang Mayuanling, Changsha 410078, China (20457456@qq.com).

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METHODS

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021258353) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

Search Strategy and Selection Criteria

To identify relevant records, Medline via PubMed and the Cochrane database were searched using the keywords "COVID-19," "SARS-CoV-2," "vaccines," "adverse events," "stroke," "transient ischemia attack," "hemorrhage," and "cerebral venous thrombosis" (Supplementary Appendix 1). We searched for relevant studies published in English up to 24 December 2022 (Supplementary Table 1). Real-world studies included patients with clearly diagnosed stroke confirmed by imaging examinations according to the World Health Organization definition or defined using the *International Classification of Diseases* (Ninth or Tenth Revision) with cohort, CCOS, or SCCS (Figure 1) designs used to report quantitative results, including the incidence risk ratio (IRR) and 95% confidence interval (CI). We excluded reviews, case reports, nonhuman studies, and studies that did not report the findings for national or region-wide populations. The references and citations of the candidate studies were screened to identify other potentially relevant articles that were not identified in the initial search. For studies with overlapping populations, we included the study with the largest sample size.

Data Collection

Record screening, data collection, and methodological quality assessment were independently performed in parallel by J. L., C. L., and F. C., and disagreements were discussed with J. Y. and resolved by consensus. Studies meeting the inclusion criteria were included for data extraction using a prespecified process (Supplementary Appendix 3). The sample size and total events in the stroke subgroups were calculated using the reported number of patients in different periods if the data were not explicit. Since no formal scales are used to assess the methodological quality in CCOS or SCCS designs, and the designs were similar to case-control or cohort studies, quality assessment of the included studies with these designs was performed using the Newcastle–Ottawa Scale (NOS; studies with scores ≥6 were considered to have low bias) [9].

Statistical Analysis

Evidence synthesis was performed using Stata 14.0 software (StataCorp LLC). The IRRs and 95% CIs for outcomes of IS and HS as the primary outcomes, and ICH, SAH, CVST as the secondary outcomes in the risk and control periods (with and without exposure to vaccination) were combined using random-effects models (Mantel–Haenszel heterogeneity). Two-sided P values were considered to indicate significance at $P < .05$. Subgroup analysis was conducted on the basis of vaccine type (Pfizer BNT162b2, AstraZeneca ChAdOx1, Moderna mRNA-1273, Johnson & Johnson/Janssen, and CoronaVac), vaccination dose (first and second), and age (older and younger) and sex (male and female) of the patients. Cochran's Q test and the I^2 statistic were used to assess heterogeneity, and the z test was used to determine the significance of each pooled IRR (P value was set at .05). To identify the potential risk periods, we performed a sensitivity analysis by pooling the IRRs and 95% CIs in different definitions of risk periods (1–7, 1–14, 1–21, and 1–28 days, as well as 1–7, 8–14, 15–21, and 22–28 days), and the secondaryr sensitivity analysis was performed to synthesize the effective value of the remaining studies after excluding each study individually. When the original studies separated the IRRs and 95% CIs under specific conditions (age, sex, doses, or definitions of risk), we initially calculated the values within each included study to obtain the integrated risks and then used these values for overall evidence synthesis. Because of the limited number of studies on each stroke subtype, we did not assess the publication bias.

RESULTS

Of the 983 records, 75 studies (Supplementary Appendix 2) were reviewed for full-text screening, and 14 observational studies [6, 7, 10–21] with a total of 79 918 904 individuals were included in the systematic review and meta-analysis (Figure 2, Supplementary Table 1); these included 9 studies on IS [7, 10, 12–16, 18, 21], 10 on HS [6, 10, 12–19], and 5 on CVST [10–12, 18, 20]. Among the studies, 8 reported the findings for adults aged 16 or 18 years [6, 7, 12, 14, 17, 19–21], 4 did not report their focused populations [10, 11, 16, 18], and 2 [13, 15] reported the findings for adults aged 18–75 years or >75 years. All studies were of good quality (NOS score, ≥7). The details are provided in Table 1 and Supplementary Table S4. The illustration of the comprehensive evidence synthesis is provided in Figure 2.

Ischemic Stroke

The 9 studies on IS included 6 SCCS [7, 10, 13, 15, 16, 21], 1 cohort study [12], and 2 studies using both SCCS and cohort designs [14, 18]. Two studies [7, 12] in England reported that the background incidence of IS was 25.12–27.12 cases per million person-years. Among the 75 587 events in cohort studies [12, 14, 18] (Supplementary Table 1), a decreased risk of IS was identified 1–21 or 1–28 days after COVID-19 vaccination (IRR, 0.82 [95% CI, .75–.90]; $I^2 = 89.1\%$; P^Q [P for Cochran's Q test] < .001). Subgroup analyses (Supplementary Figure 1) showed similar results in males (IRR, 0.84 [95% CI, .76–.92]), females (IRR, 0.78 [95% CI, .70–.88]), and those vaccinated with AstraZeneca ChAdOx1 (IRR, 0.83 [95% CI, .71–.97])

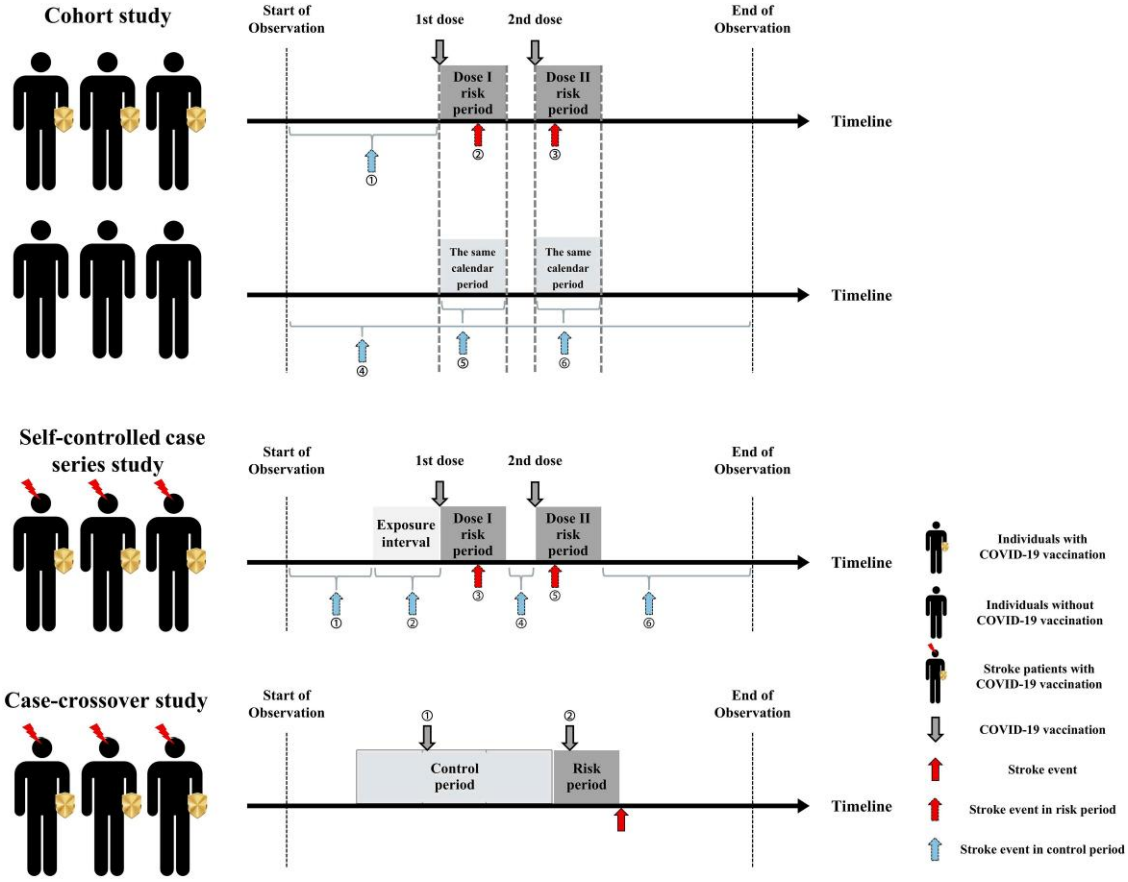

Figure 1. Conceptual diagram of 3 study designs to evaluate the association between coronavirus disease 2019 (COVID-19) vaccination and the risk of stroke. ①②③④⑤⑥ correspond to Control Periods in Table 1.

but not in those vaccinated with Pfizer BNT162b2 (IRR, 0.80 [95% CI, .63–1.01]). Whiteley et al [12]. identified a lower incident risk among individuals aged ≥70 years (IRR, 0.90) than in those aged <70 years (IRR range, 0.71–0.77) receiving AstraZeneca ChAdOx1 or Pfizer BNT162b2 vaccines.

Studies using an SCCS design included >78 490 IS events. These studies reported a reduced risk of IS within 1–7 days after receiving vaccination (IRR, 0.93 [95% CI, .90–.97]; I^2 = 1.0%; P^Q = .455) and for vaccinating with Pfizer BNT162b2 (IRR, 0.85 [95% CI, .77–.93]; I^2 = 0.0%; P^Q = .785) and its first dose (IRR, 0.93 [95% CI, .88–.98]; I^2 = 2.6%; P^Q = .410), with low heterogeneity. No significant associations of IS were obtained with the other vaccines, namely, Moderna mRNA-1273, Johnson & Johnson/Janssen, AstraZeneca ChAdOx1, and CoronaVac (Supplementary Figure 2*A*). When the risk period was defined as 1–14 days, neither each vaccine nor vaccines overall showed a significant association (overall IRR, 0.97 [95% CI, .94–1.01]; I^2 = 35.6%; P^Q = .011; Supplementary Figure 2*B*). An increased incidence rate of IS was observed at 21 days (IRR, 1.05 [95% CI, 1.00–1.10]; I^2 = 20.9%; P^Q = .215; Supplementary Figure 2*C*) or 28 days (IRR, 1.05 [95% CI, 1.01–1.08]; I^2 = 10.1%; P^Q = .330; Supplementary Figure 2*D*) after vaccination with Pfizer BNT162b2, whereas similar results were not observed for AstraZeneca ChAdOx1 or CoronaVac. The populations of different sexes showed similar IS risks within 21 days of vaccination (Supplementary Figure 2*E*). To explore why COVID-19 vaccination converted to a hazard factor of IS over time, we analyzed the fluctuations of IRRs and 95% CIs during the periods of 8–14, 15–21, and 22–28 days after vaccination. Although the 5 vaccines involved in the analysis for the period of 8–14 days (Supplementary Figure 3*A*) were not associated with the onset of IS, statistical significance was identified for the pooled overall vaccination (IRR, 1.04 [95% CI, 1.00–1.08]; I^2 = 8.1%; P^Q = .352). There was a 1.13-fold risk of IS during the period of 15–21 days after vaccination with Pfizer BNT162b2 (95% CI, 1.06–1.21; I^2 = 0.0%; P^Q = .750), whereas similar results were not identified for AstraZeneca ChAdOx1, overall vaccines, or during the period of 22–28 days after receiving Pfizer BNT162b2 (Supplementary Figure 3*B* and 3*C*). Secondary sensitivity analysis were showed in Supplemental Figure S4.

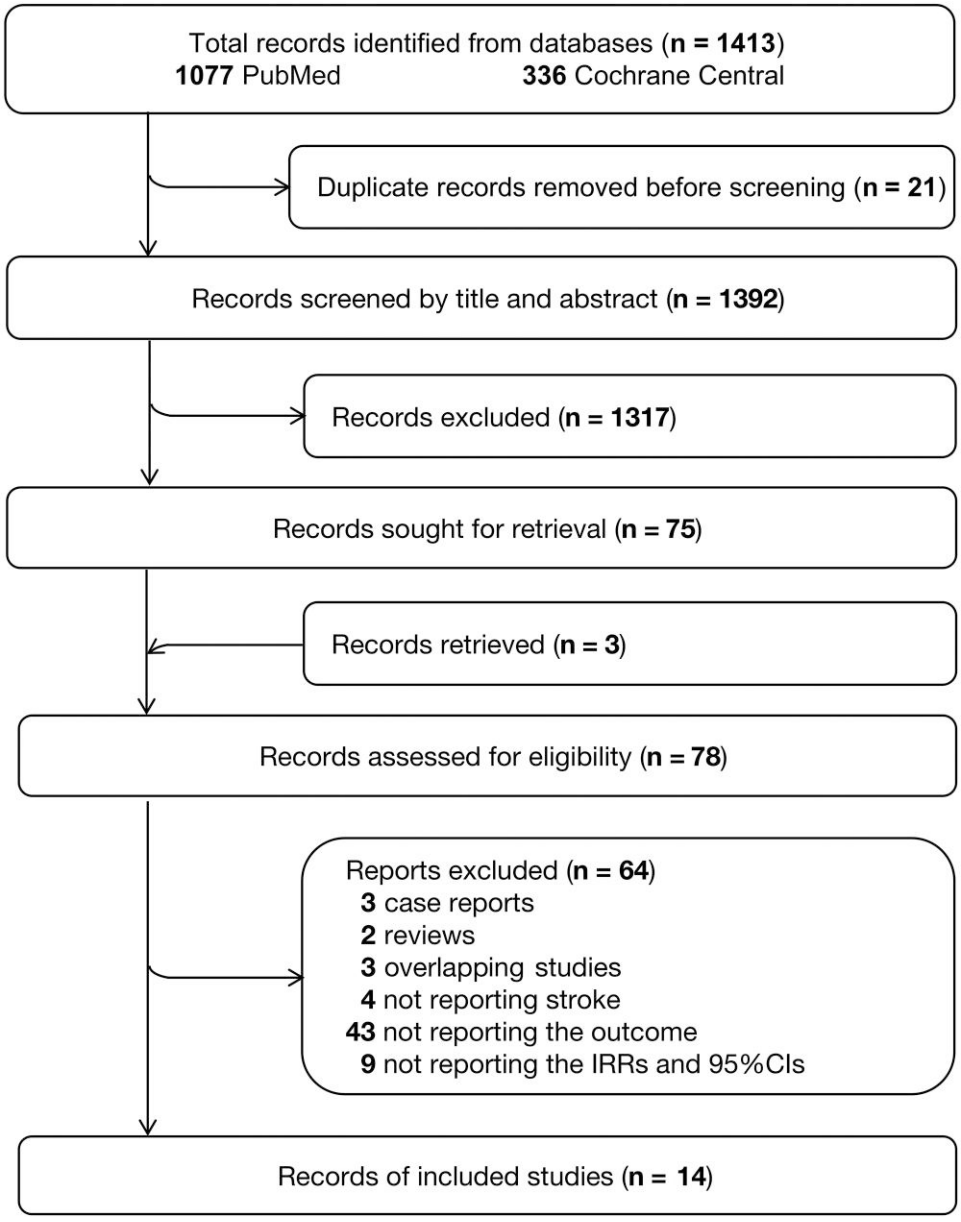

Figure 2. Literature flowchart. Abbreviations: CI, confidence interval; IRR, incidence risk ratio.

Hemorrhagic Stroke

A cohort study [12], 7 SCCS [6, 10, 13, 15–17, 19], and 2 studies using both cohort and SCCS designs [14, 18] reported whether COVID-19 vaccination was associated with the onset of HS, including 3 that focused on either ICH or SAH (Supplementary Table 2). Whiteley et al [12] reported that the background incidence of HS was 3.55 (95% CI, 3.44–3.66) cases per million person-years in an English population. A total of 9920 HS events were included in the cohort studies, which indicated a protective effect of vaccination for HS (IRR, 0.75 [95% CI, .67–.85]; $I^2 = 8.1\%$; $P^Q = .352$; Figure 3), regardless of sex (Supplementary Figure 5*A*). A relatively lower risk of HS was observed among patients receiving Pfizer BNT162b2 vaccination (IRR, 0.68 [95% CI, .59–.78]; $I^2 = 20.5\%$; $P^Q = .284$), but not for those receiving AstraZeneca ChAdOx1 (Supplementary Figure 5*B*).

However, the studies using an SCCS design with >27 862 patients tended to show an increased risk of HS within a specified postvaccination period. For risk periods of 1–14, 1–21, or 1–28 days, the associations between COVID-19 vaccination and the onset of HS showed a gradually increasing risk over time (Figure 3), but this finding was not observed for the risk period of 1–7 days after vaccination (IRR, 1.01 [95% CI, .93–1.08]; Supplementary Figure 6*A*). Although no significant increase was observed in the risk of HS events with any type of vaccine,

Table 1. Characteristics of Included Studies

Study (Year)	Study Period	Region	Design	Sample Size, No.	Sample Size, No. of Doses	Population	Age, y, Mean (SD)	Vaccines	Diseases	Definition of Outcomes	Risk Period	Control Period	NOS
McKeigue et al (2021) [11]	Dec 2020–Jul 2021	Scotland	CCOS	80 905	6 894 008	NA	NA	Pfizer BNT162b2, AstraZeneca ChAdOx1	CVST	Diagnosis by CT, MRV; *ICD-10*	Vaccination at 1–14 d before stroke	Vaccination at 15–84 d before stroke	9
Patone et al (2021) [6]	Dec 2020–May 2021	England	SCCS	32 552 534	32 552 534	Adults ≥16 y	AstraZeneca ChAdOx1: 55.1 (14.8) Pfizer BNT162b2: 55.9 (20.1)	Pfizer BNT162b2, AstraZeneca ChAdOx1	HS	*ICD-10*	1–28 d after vaccination	Observation period: 57 d, ①④⑤⑥[a] (patients only vaccinated first dose)	9
Jabagi et al (2022) [13]	Dec 2020–Apr 2021	France	SCCS	21 818	NA	Adults ≥75 y	NA	Pfizer BNT162b2	IS, HS	*ICD-10*	1–14 d after vaccination	Observation period: 15 d (received only first dose), Observation period: 30 d (received 2 doses), ①②④⑥[a]	8
Takeuchi et al (2022) [14]	Sep 2020–Sep 2021	Japan	Cohort, SCCS	184 491	333 655	Adults ≥18 y	64.2 (19.5)	Pfizer BNT162b2, Moderna mRNA-1273	IS, HS	*ICD-10*	1–21 d after vaccination	Observation period: 21 d (received only first dose), Observation period: 42 d (received 2 doses), ①③④⑥[a,b]	9
Botton et al (2022) [15]	Dec 2020–Jul 2021	France	SCCS	28 717	NA	18–75 y	IS: 62.4 (10.7) HS: 59.9 (12.3)	Pfizer BNT162b2, Moderna mRNA-1273, J&J/Janssen, AstraZeneca ChAdOx1	IS, HS	*ICD-10*	1–21 d after vaccination	Observation period: 22 d (received only first dose), Observation period: 44 d (received 2 doses), ①②④⑥[a]	8
Rahman et al (2022) [16]	Feb 2021–Sep 2021	Malaysia	SCCS	12 383	35 201 509	NA	IS: 63.6 (12.6) HS: 59.9 (16.4)	Pfizer BNT162b2, CoronaVac, AstraZeneca ChAdOx1	IS, HS	*ICD-10*	1–21 d after vaccination	Observation period: 36 d (received only first dose), Observation period: 72 d (received 2 doses), ①④⑥[a]	9
Hippisley-Cox et al (2021) [7]	Dec 2020–Apr 2021	England	SCCS	29 121 633	29 121 633	Adults ≥16 y	Pfizer BNT162b2: 61.5 (18.8) AstraZeneca ChAdOx1: 55.5 (14.9)	Pfizer BNT162b2, AstraZeneca ChAdOx1	CVST, IS	*ICD-10*	1–28 d after vaccination	Observation period: 57 d, ①④⑥[a]	8
Barda et al (2021) [17]	Dec 2020–May 2021	Israel	Cohort	917 598	NA	Adults ≥16 y	Median (IQR): 8 (27–53)	Pfizer BNT162b2	ICH	*ICD-9*	1–21 d after vaccination	The same calendar period for matched unvaccinated control, ⑤⑥[b]	9
Whiteley et al (2022) [12]	Dec 2020–Mar 2021	England	Cohort	46 162 942	21 193 854	Adults ≥18 y	NA	Pfizer BNT162b2, AstraZeneca ChAdOx1	CVST, IS, HS	SNOMED-CT, *ICD-10*	1–28 d after vaccination	Prevaccination or unvaccinated, ①④[b]	7
Klein et al (2022) [18]	Dec 2020–Jun 2021	USA	Cohort, SCCS	12 506 658	NA	NA	49 (NA)	Pfizer BNT162b2, Moderna mRNA-1273	CVST, IS, HS	*ICD-10*	1–21 d after vaccination	SCCS: 22–42 d postvaccination, ④⑥[a] Cohort: the same calendar period in unvaccinated control, ⑤⑥[b]	9
Chui et al (2022) [19]	Feb 2021–Sep 2021	Hong Kong, China	SCCS	4 492 167	8 673 288	Adults ≥16 y	NA	Pfizer BNT162b2, CoronaVac	HS	*ICD-9*	0–27 d after vaccination	Observation period: 28 d (received only first dose); Observation period: 56 d (received 2 doses), ①③⑤[a]	9

Table 1. Continued

Study (Year)	Study Period	Region	Design	Sample Size, No.	Sample Size, No. of Doses	Population	Age, y, Mean (SD)	Vaccines	Diseases	Definition of Outcomes	Risk Period	Control Period	NOS
Berild et al (2022) [10]	Jan 2020–May 2021	Norway, Finland, Denmark	SCCS	92 963	NA	NA	NA	Pfizer BNT162b2, Moderna mRNA-1273, AstraZeneca ChAdOx1	CVST, IS, HS	*ICD-10*	1–28 d after vaccination	Prevaccination period in 2020, ⓘ[a]	9
Kerr et al (2022) [20]	Dec 2020–Jun 2021	England, Scotland, Wales	SCCS	11 637 157	6 808 293	Adults ≥16 y	NA	Pfizer BNT162b2, AstraZeneca ChAdOx1	CVST	*ICD-10*	1–28 d after vaccination	15–104 d before vaccination, ⓘ[a]	9
Torabi et al (2022) [21]	Dec 2020–Dec 2021	Wales	SCCS	2 062 144	3 538 784	Adults ≥16 y	NA	Pfizer BNT162b2, AstraZeneca ChAdOx1	IS	*ICD-10*	0–28 d after vaccination	104 d prior to this date on 25 Aug 2020 or an individual's vaccination date, ⓘ[a]	9

ⓘⓘⓘⓘⓘ correspond to those marked periods in Figure 1.

Abbreviations: CCOS, case-crossover study; CT, computed tomography; CVST, cerebral venous sinus thrombosis; HS, hemorrhagic stroke; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Classification of Diseases, Tenth Revision*; ICH, intracerebral hemorrhage; IS, ischemic stroke; IQR, interquartile range; MRV, magnetic resonance venography; NA, not available; NOS, Newcastle–Ottawa scale; SCCS, self-controlled case series; SD, standard deviation; SNOMED-CT, Systematized Nomenclature of Medicine Clinical Terms.

[a]For SCCS study.

[b]For cohort study.

the pooled result identified an overall mild risk during the post-vaccination period of 1–14 days (IRR, 1.06 [95% CI, 1.00–1.13]; $I^2 = 22.4\%$; $P^Q = .118$; Supplementary Figure 6*B*). The risk existed during 1–21 to 1–28 days (Supplementary Figure 6*C* and 6*D*) after the overall vaccination (IRR_{21days}, 1.16 [95% CI, 1.06–1.26]; IRR_{28days}, 1.37 [95% CI, 1.15–1.64]) and vaccination with Pfizer BNT162b2 (IRR_{21days}, 1.30 [95% CI, 1.14–1.48]; IRR_{28days}, 1.35 [95% CI, 1.25–1.46]), especially for the first dose. A 1.21-fold risk of IS was observed during the period 1–21 days after CoronaVac vaccination (95% CI, 1.03–1.42; $I^2 = 0.0\%$; $P^Q = .446$). According to the defined risk periods (Supplementary Figure 7), a higher risk of HS was noted during the period 8–14 days after overall vaccination (IRR, 1.11 [95% CI, 1.02–1.20]) and CoronaVac vaccination (IRR, 1.30 [95% CI, 1.00–1.70]) and 15–21 days after overall vaccination (IRR, 1.21 [95% CI, 1.05–1.39]) and Pfizer BNT162b2 vaccination (IRR, 1.30 [95% CI, 1.10–1.54]; $I^2 = 5.4\%$; $P^Q = .376$). Subgroup analysis (Supplementary Figure 6*E*) identified a higher risk of HS in older (IRR, 1.35 [95% CI, 1.07–1.72]) rather than younger people (IRR, 1.28 [95% CI, 1.00–1.64]).

ICH, a subtype of stroke, was studied in an Israeli cohort, and the results revealed a protective effect within 21 days of Pfizer BNT162b2 vaccination (IRR, 0.48 [95% CI, .20–.89]) [17]. An SCCS on 2373 Hong Kong ICH patients identified an increased risk after Pfizer BNT162b2 vaccination (IRR within 14–27 days after the first dose, 2.53 [95% CI, 1.34–4.80]; IRR within 0–13 days after the second dose, 3.10 [95% CI, 1.63–5.90]), but not after CoronaVac (Supplementary Table 2) [19]. Two SCCS studies on COVID-19 vaccination and SAH indicated no significant association with Pfizer BNT162b2, AstraZeneca ChAdOx1, or CoronaVac (Supplementary Table 2, Supplementary Figure 8) [6, 19]. Secondary sensitivity analyses were in Supplemental Figure S9.

Cerebral Venous Sinus Thrombosis

A CCOS [11], a cohort study [12], 2 SCCS studies [10, 20], and 1 study [18] using both cohort and SCCS designs attempted to investigate the associations between COVID-19 vaccination and CVST (Supplementary Table 3). Two English studies [7, 12] reported that the baseline incidence of CVST was 0.12–0.20 cases per million person-years. McKeigue et al conducted a CCOS and reported a significantly increased risk of CVST in the Scottish population within 1–14 days after AstraZeneca ChAdOx1 vaccination (IRR, 2.9 [95% CI, 1.1–7.2]) but not after Pfizer BNT162b2 vaccination (IRR, 1.8 [95% CI, .2–8.9]) [11]. Two cohort studies [12, 18] based on English and US populations did not identify a significant association between COVID-19 vaccination and CVST after evidence synthesis (IRR, 1.18 [95% CI, .70–1.98]; $I^2 = 53.5\%$; $P^Q = .072$; Supplementary Figure 10), but Whiteley et al [12] reported a higher rate of acute CVST within 1–28 days after vaccination with AstraZeneca ChAdOx1 (IRR, 2.27 [95% CI,

Risk peroid	Study design	Vaccines	Included studies	Total events	IRR (95% CI)	I^2	P^Q
-	Cohort	Total	3 [12,14,18]	46948	0.82(.75-.90)	89.1%	<.001
		Pfizer BNT162b2	1 [12]	37484	0.80(.63-1.01)	96.1%	<.001
		Astra-Zeneca ChAdOx1	1 [12]	35512	0.83(.71-.97)	91.6%	<.001
1-7 days	SCCS	Total	4 [7,15,16,21]	72240	0.93(.90-.97)	1.0%	.445
		Pfizer BNT162b2	4 [7,15,16,21]	35296	0.93(.88-.98)	2.6%	.410
		Moderna mRNA-1273	1 [15]	1491	0.93(.62-1.40)	65.6%	.088
		Johnson & Johnson Jassen	1 [15]	196	0.78(.43-1.41)	-	-
		Astra-Zeneca ChAdOx1	4 [7,15,16,21]	17286	0.92(.85-1.00)	14.4%	.317
		CoronaVac	1 [16]	4244	0.96(.90-1.12)	23.3%	.253
1-14 days	SCCS	Total	5 [7,13,15,16,21]	75445	0.97(.94-1.01)	35.6%	.011
		Pfizer BNT162b2	5 [7,13,15,16,21]	52682	0.96(.92-1.01)	41.4%	.031
		Moderna mRNA-1273	1 [15]	1491	0.92(.74-1.16)	42.2%	.158
		Johnson & Johnson Jassen	1 [15]	196	0.95(.64-1.39)	0.0%	.400
		Astra-Zeneca ChAdOx1	4 [7,15,16,21]	17286	0.98(.91-1.06)	41.5%	.042
		CoronaVac	1 [16]	4244	1.02(.93-1.12)	0.0%	.451
1-21 days	SCCS	Total	5 [7,14,16,18,21]	69744	1.02(.99-1.06)	37.1%	.014
		Pfizer BNT162b2	3 [7,16,21]	24014	1.05(1.00-1.10)	20.9%	.215
		Astra-Zeneca ChAdOx1	3 [7,16,21]	14703	0.98(.91-1.05)	47.8%	.024
		CoronaVac	1 [16]	4244	1.06(.97-1.16)	0.0%	.834
1-28 days	SCCS	Total	3 [7,19,21]	>29529	1.05(1.01-1.08)	10.1%	.330
		Pfizer BNT162b2	3 [7,19,21]	>29529	1.05(1.01-1.08)	10.1%	.330

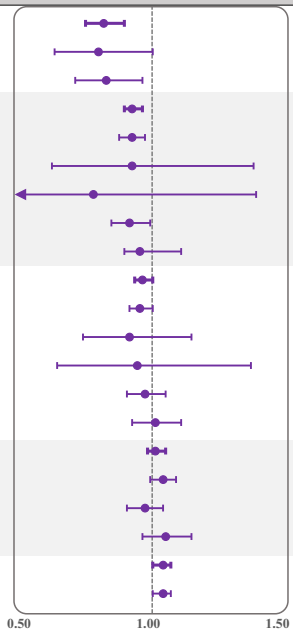

Figure 3. Incidence risk ratio for ischemic stroke following coronavirus disease 2019 vaccination. Abbreviations: CI, confidence interval; IRR, incidence risk ratio; SCCS, self-controlled case series.

Risk peroid	Study design	Vaccines	Included studies	Total events	IRR (95% CI)	I^2	P^Q
-	Cohort	Total	3 [12,14,18]	46948	0.82(.75-.90)	89.1%	<.001
		Pfizer BNT162b2	1 [12]	37484	0.80(.63-1.01)	96.1%	<.001
		Astra-Zeneca ChAdOx1	1 [12]	35512	0.83(.71-.97)	91.6%	<.001
1-7 days	SCCS	Total	4 [7,15,16,21]	72240	0.93(.90-.97)	1.0%	.445
		Pfizer BNT162b2	4 [7,15,16,21]	35296	0.93(.88-.98)	2.6%	.410
		Moderna mRNA-1273	1 [15]	1491	0.93(.62-1.40)	65.6%	.088
		Johnson & Johnson Jassen	1 [15]	196	0.78(.43-1.41)	-	-
		Astra-Zeneca ChAdOx1	4 [7,15,16,21]	17286	0.92(.85-1.00)	14.4%	.317
		CoronaVac	1 [16]	4244	0.96(.90-1.12)	23.3%	.253
1-14 days	SCCS	Total	5 [7,13,15,16,21]	75445	0.97(.94-1.01)	35.6%	.011
		Pfizer BNT162b2	5 [7,13,15,16,21]	52682	0.96(.92-1.01)	41.4%	.031
		Moderna mRNA-1273	1 [15]	1491	0.92(.74-1.16)	42.2%	.158
		Johnson & Johnson Jassen	1 [15]	196	0.95(.64-1.39)	0.0%	.400
		Astra-Zeneca ChAdOx1	4 [7,15,16,21]	17286	0.98(.91-1.06)	41.5%	.042
		CoronaVac	1 [16]	4244	1.02(.93-1.12)	0.0%	.451
1-21 days	SCCS	Total	5 [7,14,16,18,21]	69744	1.02(.99-1.06)	37.1%	.014
		Pfizer BNT162b2	3 [7,16,21]	24014	1.05(1.00-1.10)	20.9%	.215
		Astra-Zeneca ChAdOx1	3 [7,16,21]	14703	0.98(.91-1.05)	47.8%	.024
		CoronaVac	1 [16]	4244	1.06(.97-1.16)	0.0%	.834
1-28 days	SCCS	Total	3 [7,19,21]	>29529	1.05(1.01-1.08)	10.1%	.330
		Pfizer BNT162b2	3 [7,19,21]	>29529	1.05(1.01-1.08)	10.1%	.330

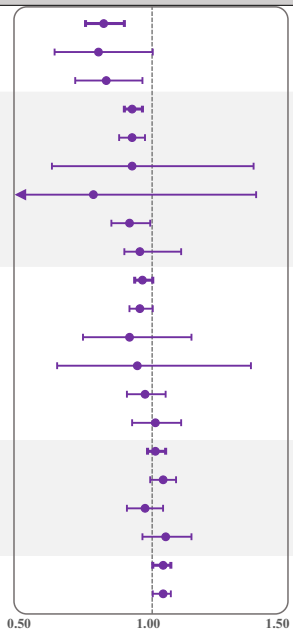

Figure 4. Incidence risk ratio for hemorrhagic stroke following coronavirus disease 2019 vaccination. Abbreviations: CI, confidence interval; IRR, incidence risk ratio; SCCS, self-controlled case series.

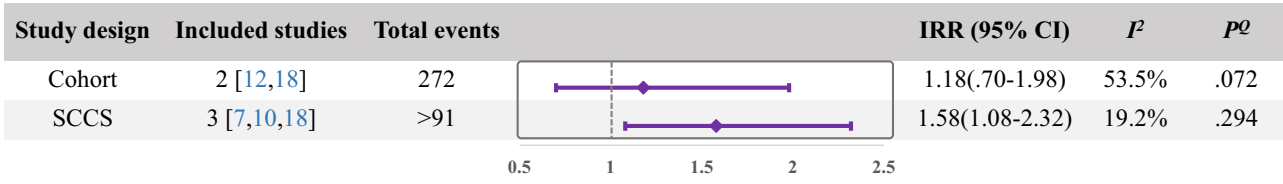

Figure 5. Incidence risk ratio for cerebral venous sinus thrombosis following coronavirus disease 2019 vaccination. Abbreviations: CI, confidence interval; IRR, incidence risk ratio; SCCS, self-controlled case series.

1.33–3.88]). The pooled results from the SCCS studies [10, 18, 20] showed an increased CVST risk associated with COVID-19 vaccination, but with large heterogeneity (IRR, 2.24 [95% CI, 1.00–5.03]; I^2 = 83.3%; P^Q < .001; Supplementary Figure 11*A*). According to the sensitivity analysis, this heterogeneity may have originated from the study by Berild et al on AstraZeneca ChAdOx1 [10], which identified a larger number of patients with CVST than the other cohorts (Supplementary Figure 11*B*). After omitting the results of this study, the heterogeneity reduced abruptly (IRR, 1.58 [95% CI, 1.08–2.32]; I^2 = 19.2%; P^Q = .294; Supplementary Figure 11*C*).

DISCUSSION

This study systematically reviewed real-world studies using 3 different designs to identify the association between COVID-19 vaccination and acute stroke events. Discrepant results were observed in relation to the study designs: Cohort studies showed a reduced risk of IS and HS in individuals who received COVID-19 vaccines during the risk period of 1–21 or 1–28 days postvaccination in comparison with the risk in people without vaccination or that before the vaccination, whereas SCCS indicated that vaccination was associated with an increased risk of acute IS or HS. A slightly elevated risk of CVST was associated with vaccination in SCCS but not in cohort studies. We identified a protective effect of COVID-19 vaccination against stroke in cohort studies, but this finding was inconsistent with the potential hazard risk identified in the SCCS or CCOS designs because of several differences among the 3 designs (Figure 1).

Cohort studies recruited vaccinated and unvaccinated individuals and compared the incidence of outcomes in matched comparators within the same calendar period of the risk interval [17, 18]. This design stems from the perspective of populations, where the compared variables were the incidence of outcome events after receiving COVID-19 vaccination and the background incidence. Given that confounders often occur in cohort studies and distort the results [22], Barda et al [17] matched the important factors to avoid confounders as much as possible, and Whiteley et al [12] regarded the incidence of outcomes in 2018–2020 among the whole target population as the control to ensure comparability. Although the comparability in sex, age, or race between vaccinated and control groups was not sufficient enough in the other cohort studies [14, 18], multiple factors were adjusted to reduce the influence from the bias. Additionally, despite the fact that the original studies excluded SARS-CoV-2–positive patients from the cohorts, a proportion of patients were still included due to lack of tests or false-negative polymerase chain reaction results. Therefore, it is reasonable to obtain a protective effect, as vaccines can significantly protect populations from both SARS-CoV-2 infection and related stroke during the pandemic period [17].

Compared to cohort studies, SCCS and CCOS designs focus on each individual to treat patients themselves as controls, minimizing confounding as much as possible while assessing exposure risks and diseases [23, 24]. The main distinction is that SCCS are more concerned about the risk of stroke pre- and postinoculation, whereas CCOSs assess different exposures to vaccines between risk and control periods before the outcome of an acute stroke event.

During the 21/28-day postinoculation period, COVID-19 vaccination was associated with an elevated risk of stroke subtypes in SCCS studies, and sensitivity analysis also showed an adverse tendency 2–4 weeks postvaccination, which was consistent with the physiological process wherein vaccines trigger innate immune activation and adaptive responses [25]. Both the generation of neutralizing antibody titers and the response of virus-specific T cells were also rapidly induced during the same period [26, 27]. Vaccine-induced immune thrombotic thrombocytopenia is a potential pathophysiological mechanism [28–30]. Different types of vaccines would induce anti-PF4 antibodies through various pathways, which may accelerate both thrombosis and thrombocytopenia [28]. Meanwhile, the induced systemic inflammation could damage endothelial cells [28, 29], possibly explaining why COVID-19 vaccination was associated with both IS and HS.

A range of platforms have been used for different types of vaccines, and comparisons showed that messenger RNA (mRNA) vaccines and Novavax protein subunit vaccines could induce higher antibody responses than inactivated virus or viral-vector vaccines [31]. mRNA-based vaccines deliver mRNA of the pathogen to the host's cytoplasm for quick

translation of the antigen, mimicking natural infections to stimulate the immune system against infection, whereas inactivated virus or viral-vector vaccines stimulate the immunity respectively by using dead viruses or cloning antigen encoding gene into the low toxic viral vectors as the immunogen [32]. Thus, based on the assumption that the levels of inflammatory responses may trigger the onset of stroke to varying degrees, an analysis was conducted among subpopulations that received the respective vaccines. For Pfizer BNT162b2, a widely used mRNA vaccine, SCCS-designed studies reported significantly increased risks of both IS and HS 1–21 or 1–28 days postvaccination, whereas a potential hazard of HS could be identified earlier, within 14 days. This implies a hemorrhagic tendency at the early stage after vaccination, but the detailed mechanisms underlying this tendency require further investigation. In comparison, the inactivated virus vaccine CoronaVac showed an association with HS within 2–3 weeks but at a lower risk than mRNA vaccines. The results were consistent to the difference in immune response after receiving different platforms of vaccines. However, no significant association was identified between vaccination of the viral-vector vaccine of AstraZeneca ChAdOx1 and stroke.

It should be noted, the SCCS-designed studies were based on the assumption that the occurrence of events and exposure do not influence each other, evaluating the changes in stroke risk before and after COVID-19 vaccination within each patient, which seems unlikely in real-world scenarios [23]. During the limited observational period, patients were relatively likely to refuse vaccines soon after suffering a stroke; thus, the potential selection bias led to a decreased incidence in the control period and induced an overestimated risk. As such, the results of cohort studies had relatively less bias and seemed closer to real-world scenarios, whereas SCCS-designed studies tended to limit the applicable populations to those without any vaccine contraindication. Thus, populations at high risk of stroke should choose an appropriate vaccine to acquire immunity against SARS-CoV-2. In addition, in the risk period, reducing the exposure to other trigger factors of stroke, such as physical exertion, anger, and several Valsalva maneuvers, could also contribute to prevention of the disease [33].

The main strengths of this study are as follows: First, the sample size of approximately 80 million cases of acute stroke provided robustness to the quantification of the risk of stroke postvaccination. In addition, the summarized evidence was relatively comprehensive, because the included studies evaluated whether COVID-19 vaccines increase the incidence risk of stroke from different aspects using 3 study designs. Third, the synthesized results had less heterogeneity to maintain reliability, and the analyses of subpopulations receiving different types of vaccines helped distinguish the trigger effect of specific vaccines. This would contribute to a better policy on guidance and suggestions for those at high risk of stroke.

Nevertheless, this study had several limitations. First, the original data were not available; therefore, individual patient meta-analysis could not be performed to obtain more reliable results. Second, as a limited number of studies were included, most of them recruited populations in developed countries, possibly resulting in selection bias, which could not be assessed. Detailed data were not reported in some of the studies, which limited the analyses of subpopulations, risk periods, and different vaccines and doses to explore the potential sources of heterogeneity. Additionally, due to the extremely low incidence rate of CVST, a limited number of cases were included to obtain relatively wide 95% CIs for the pooled estimate of vaccines, simultaneously with large heterogeneity. Finally, this review could not provide a reference for the disease burden or severity of stroke, and other adverse effects that may have led to individual decisions regarding vaccine hesitancy were not considered.

In conclusion, our meta-analysis of real-world studies on 80 million individuals indicated that studies with cohort, SCCS, or CCOS designs yielded contradictory results for the association between COVID-19 vaccination and acute stroke events. Considering the integrated effect of the assessed risks and the relatively low background incidence rates, significantly increased reporting of acute stroke events may not be observed in the context of COVID-19 vaccination, which may help reduce vaccine hesitancy in a proportion of populations. Nevertheless, individuals in populations at a high risk of stroke should deliberate whether to vaccinate and which type of vaccine should be received. Weighing the benefits and adverse effects of vaccination, as well as the risk of exposure to COVID-19, is still necessary before making the decision.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. L.: data curation, statistical analysis, investigation, validation, resources and software, writing of the original draft, review and editing. F. C.: data curation, statistical analysis. C. L.: data curation, validation. Y. G.: data curation. J. Y.: project administration and supervision, methodology, funding acquisition, statistical analysis, writing of the original draft, review and editing.

Data availability. Data in the manuscript and supplemental files make use of publicly available data from included studies, and there are no original data for sharing.

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