Review Article

COVID-19 Vaccination and Cardiovascular Events: A Systematic Review and Bayesian Multivariate Meta-Analysis of Preventive Benefits and Risks

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Abstract

Background: To provide a detailed understanding and apply a comprehensive strategy, this study examines the association between COVID-19 vaccination and cardiovascular events. We conducted a Bayesian multivariate meta-analysis using summary data across multiple outcomes including myocardial infarction, stroke, arrhythmia, and CAD, considering potential dependencies in the data. Markov chain Monte Carlo (MCMC) methods were detected for easy implementation of the Bayesian approach. Also, the sensitivity analysis of the model was done by using different priors. **Methods:** Fifteen studies were included in the systematic review, with eleven studies comparing the results between the vaccine group and the unvaccinated group. Additionally, six studies were used for further analysis to compare mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna). **Results:** Bayesian meta-analysis revealed a link between vaccines and CAD risk (OR, 1.70; 95% CrI: 1.11–2.57), particularly after BNT162b2 (OR, 1.64; 95% CrI: 1.06–2.55) and second dose (OR, 3.44; 95% CrI: 1.99–5.98). No increased risk of heart attack, arrhythmia, or stroke was observed post-COVID-19 vaccination. As the only noteworthy point, a protective effect on stroke (OR, 0.19; 95% CrI: 0.10–0.39) and myocardial infarction (OR, 0.003; 95% CrI: 0.001–0.006) was observed after the third dose of the vaccine. **Conclusions:** Secondary analysis showed no notable disparity in cardiovascular outcomes between BNT162b2 and mRNA vaccines. The association of COVID-19 vaccination with the risk of coronary artery disease should be considered in future vaccine technologies for the next pandemic.

Keywords: *Arrhythmias, cardiac, coronary artery disease, COVID-19 vaccines, myocardial infarction, SARS-CoV-2, stroke*

Introduction

As of November 8, 2023, the World Health Organization reported that there have been over 771820937 confirmed cases of COVID-19 worldwide, resulting in 6978175 deaths.[1] Vaccines have played a crucial role in controlling and preventing the spread of COVID-19 by helping develop immunity in individuals, thus lowering the risk of severe illness and infection.[2,3] To date, more than 11.8 billion vaccine doses have been distributed globally.[4]

However, despite the success of vaccination campaigns, several issues have been linked to the COVID-19 vaccines, particularly worries regarding cardiovascular complications, which have garnered attention.[5-8] It is essential to tackle these allegations and provide clarity on the true effects of the vaccines on heart health, as well as ease individuals' anxieties related to such worries. Concerns regarding the potential health risks linked to vaccines may overshadow a logical evaluation of the advantages of vaccination and result in skepticism towards vaccines in upcoming pandemics. Hence, it is crucial to address these claims and offer scientific clarifications to alleviate worries and regain public trust in COVID-19 vaccines.

The findings of several studies in this field have reported conflicting results about the effect of COVID-19 vaccines on cardiovascular events. Some findings show that the use of these vaccines may increase the incidence of stroke, myocardial infarction, and arrhythmia.[5,9,10] On the other hand, specific research has shown that vaccines can have significant protective effects on cardiovascular events such as myocardial infarction and stroke.[11-13] Also, some studies have shown that there is no significant association between COVID-19 vaccines and cardiovascular events.[14,15] Therefore, a

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comprehensive review or meta-analysis is needed to draw reliable conclusions regarding the effects of the coronavirus vaccine on cardiovascular health.

Several systematic reviews and meta-analyses have assessed the cardiovascular event risk following COVID-19 vaccination. However, the focus has mainly been on issues like myocarditis and pericarditis.[16-19] Uncertainty remains regarding other complications such as arrhythmia, stroke, coronary artery disease (CAD), and myocardial infarction (MI).[20,21] Furthermore, many of these studies are based on case reports and case series without control group comparisons. It is difficult to assess the link between vaccination and cardiovascular events solely through case reports, and population-based data could offer more accurate estimates. Additionally, no research has explored the connection between CAD events. A thorough study is required to analyze various cardiovascular outcomes concurrently and contrast the findings with those of a control group.

In this study, our goal is to present a strong Bayesian multivariate meta-analysis model to examine the link between vaccine-related cardiovascular events in controlled studies, taking into account correlations between outcomes. This method enables people to make informed decisions about their health and enhances public confidence in vaccination programs, thereby supporting public health and the management of infectious diseases.

Methods

Objectives

The primary goal is to examine the possible presence of cardiovascular events, specifically myocardial infarction, CAD, arrhythmia, and stroke, linked to COVID-19 vaccination. Additionally, the aim is to provide comprehensive details on the demographic and clinical characteristics of both vaccinated and unvaccinated groups, in order to perform subgroup analysis to more effectively explore the main objective. In this study, we compared BNT162b2 and mRNA vaccines, with a focus on cardiovascular complications as a Secondary Analysis.

Protocol

The review adheres to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines for systematically reviewing the existing literature.[22]

Search strategy

The registration number for this study in PROSPERO is (CRD42024559390). A thorough search of prominent electronic databases (such as PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar) was performed until October 22, 2023, to retrieve all relevant publications [Table S1 in the Supplementary materials]. The literature review carried out with the predetermined search terms: ("SARS-CoV-2 "2019 Novel Coronavirus" OR "Coronavirus Disease 2019") AND ("COVID-19 vaccines" OR "mrna COVID-19 vaccin" OR "Pfizer" OR "moderna" OR "mRNA-1273" OR "mRNA 1273" OR "messenger RNA vaccine" OR "ChAdOx1" OR "ChAdOx1 nCoV 19" OR "AstraZeneca, COVID-19 Vaccine") AND ("inflammatory heart disease*" OR "inflammatory cardiac disease*" OR "heart failure" OR "cardiac manifestation*" OR "stroke" OR "ischemic heart disease" OR "Coronary Artery Disease" OR "myocardial infarction" OR "arrhythmia" OR "myocardial damage"). Moreover, we thoroughly examined the references of all relevant articles to identify any additional studies meeting our criteria.

Inclusion and exclusion criteria

We included all studies on humans and focused on adverse events specifically cardiovascular events occurring after COVID-19 vaccination. Information of individuals who experienced cardiovascular events following any COVID-19 vaccine, regardless of the vaccine type or dosage was extracted. We excluded narrative and systematic reviews, case reports studies, or original papers that lacked available data. Additionally, articles written in languages other than English were excluded from the review.

Data screening procedure

The study followed the PRISMA 2020 guidelines for data extraction, adhering to a standardized process. Two authors independently screened abstracts and full-text articles based on pre-defined inclusion and exclusion criteria, with any disagreements resolved through discussion. Microsoft Excel spreadsheets were used to collect the necessary information from the extracted studies. This included 1) essential details such as the first author, publication year, and study design; 2) information on the study population, including sample sizes, age, gender, follow-up duration, and locations; 3) information on COVID-19 vaccine types, number of doses administered, and reported cardiovascular events in each study; and 4) information needed for data analysis includes the frequency of cardiovascular events following COVID-19 vaccination and in the control group (unvaccinated or inactive vaccine) during the study period. The study's outcomes centered on myocardial infarction, arrhythmia, stroke, and coronary artery disease (CAD) or coronary heart disease (CHD). These outcomes were identified using the 10th edition of the International Classification of Diseases, as detailed in Table S2 in the Supplementary materials.

Quality assessment

The quality of the included articles was assessed by the two reviewers independently using two checklists. NHLBI quality assessment tools were used for case-series studies,[23] and the Newcastle-Ottawa Scale assesses explicitly the quality of cohort studies.[24] The cohort tool includes eight questions,

and the prevalence tool includes nine questions, each scoring 0 or 1, to determine the potential flaws in study methods or implementation. The overall methodological quality judgments will be determined by the total score for each article as follows: low quality (≤ 50% of overall score), moderate rate (50-70% of overall score), and high quality (≥70% of overall score). Tables are available in Tables S3 and S4 in the Supplementary materials.

Data synthesis and analysis

In this investigation, we examined *N* studies that evaluated the desired outcomes following the COVID-19 vaccine. Since the multivariate approach enables us to estimate correlations in treatment effects among studies as an integral part of a random-effects model, we applied this method to combine the results. As the studies may not report all the events we were interested in, to address this limitation, we employed multivariate normal models with different dimensions, $1 \le p_i \le p$. Where pi represents the number of effects reported by the study i, $(i = 1, 2, \ldots, N)$.

We modeled the data as follows:

- y_i (The observation vector of the study i) ~$MVN\ (\theta_i, \sum_i)$.

- θ_i (Effect sizes for each outcome in the study).~ $MVN\left(X_i\mu, X_i \Delta X_i^T\right)$.

The primary goal in the multivariate random-effects meta-analysis is to estimate the mean treatment effects $\theta = (\theta_1, \theta_2, \ldots, \theta_m)$ and the between-study covariance matrix, Δ.[25,26] To achieve this goal, we utilized Bayesian methods and considered prior distributions for these parameters.[27] We employed three different priors, Inverse-Wishart, Cholesky, and Spherical for the variance-covariance matrix of the between-study, along with a multivariate normal distribution for the mean vector, μ. The inverse-Wishart prior serves as the conjugate prior distribution for the variance-covariance matrix of the between-study component in multivariate normal models.[28,29] The Cholesky parameterization allows for assumptions of homogeneity in between-study correlations, while the Spherical parameterization incorporates a prior assumption of positive between-study correlation. Subsequently, we presented the findings corresponding to the structure or prior that yielded the best overall fit for the model.[25]

By running The Markov Chain Monte Carlo MCMC in parallel with a substantial number of iterations for each chain and including a burn-in period, the algorithm can converge to the target distribution and produce reliable results. The convergence was evaluated using visual diagnostics for specific parameters of interest within the models. It is essential to note that we did not have information about Within-study covariances. So we estimated it with methods developed by Wei and Higgins.[30] To ensure the robustness of our results, we conducted a subgroup analysis, considering factors such as dose, type of vaccine, and geographical region.

Model execution

The multivariate Bayesian meta-analysis models were run using R version 4.3.2 and the "rjags" package version 4-14. The MCMC model output was summarized using the "coda" package.[31] Four parallel MCMC chains were run, each consisting of 100,000 iterations with a burn-in period of 10,000 iterations. The datasets (studies) used and analyzed during the current study are available in Table 1 and the JAGS code for the model is provided in a Supplementary materials.

Results

Selection of studies

Upon searching major databases (PubMed, Web of Science, Embase, Cochrane Library, and Google Scholar) on October 22, 2023, we identified 1266 articles related to search criteria. 493 studies were automatically removed due to duplicate content by utilizing Endnote as a citation manager tool. After examination of the titles and abstracts of 496 articles meticulously, 175 studies were not related and did not meet our inclusion requirements. Finally, after an examination of 85 remaining studies, 15 studies remained. Out of the 15 studies, 11 were controlled studies chosen for the primary analysis, while 4 studies did not have a control group and were included in the secondary analysis [Figure 1]. More details about the studies can be found in Table 1. In the assessment of study quality using quality assessment tools, two out of the seven cohort studies and nine self-control case series studies reviewed were rated as medium-quality, as shown in Tables S3 and S4. The remaining studies were determined to be of high quality based on the evaluation criteria specified in the quality assessment tools. This indicates that the majority of the reviewed studies demonstrated a high level of methodological rigor and reliability in their design and execution.

Feature of the extracted studies

Eleven studies were included in the primary analysis: four were conducted in Hong Kong, two were related to England, and the remaining studies took place in the United States, Malaysia, Thailand, Israel, France, and Korea. A total of 37774228 individuals received the first dose of the vaccine, 8076761 received the second dose, and 199021 received the third dose. Additionally, 39898214 individuals either did not receive any vaccine or were given an inactive vaccine in the control group. Four studies analyzed the outcomes of the first and second doses of vaccine. Two studies looked at the effects of the first, second, or third doses, while the remaining studies focused on either the first dose or any dose of the vaccine. All studies analyzed the BNT162b2 vaccine, four studies looked into the ChAdOx1, and two studies investigated other vaccines in addition to BNT162b2.

Table 1: Characteristics and outcomes of patients with cardiovascular events related to COVID-19 vaccine related to 15 last articles

First author	Study design	Country	Study period	Dose Vaccine	Follow up	Age	Type of vaccine, n	Control group, *n*	Outcome
Carlos King Ho Wong (2022)[13]	Retrospective cohort	Hong Kong	Dec 14, 2021 to Jan 1, 2022	Dose 1 Dose 2	21 days after the first and second doses	>18 years old	BNT162b2: The first dose: 1308820 The second dose: 1116677	Inactivated vaccine: The first dose: 955859 The Second dose: 821560	Arrhythmia CAD MI
Norazida Ab Rahman (2022)[48]	Self-controlled case-series (SCCS)	Malaysia	February 1, 2021 to September 30, 2021	Dose 1 Dose 2	21 days after the first and second doses	>18 years old	BNT162b2: 15488664 ChAdOx1: 2816121	Unvaccinated: 16896724	Arrhythmia MI Stroke
Maria Elena Flacco (2022)[49]	Retrospective cohort	Italian	2 January 2021 to 31 July 2022	Dose 1 Dose 2 Dose 3	6 months after the first and second doses	>6 years old	BNT162b2 The first dose: 8106 The second dose: 34422 The third dose: 73845 mRNA-1273 The first dose: 7504 The seconded dose: 8011 The third dose: 22884 Janssen The second dose: 1085 ChAdOx1 The first dose: 190 The second dose: 6719	Unvaccinated: The first dose: 56494 The second dose: 56494	Arrhythmia MI Stroke
Noam Barda (2021[5]	Retrospective cohort	Israel	December 20, 2020 to May 24, 2021	Dose 1 Dose 2	21 days after the first or second dose	≥ 16 years old	BNT162b2 mRNA: 884828	Unvaccinated: 884828	Arrhythmia MI
Jeremie Botton (2022)[50]	Self-controlled case-series (SCCS)	France	December 27 2020 to July, 20 2021	Dose 1 Dose 2 Dose 3	21 days after each of the first, second, and third doses	18–74 years	BNT162b2 The first dose: 38393 The second dose: 31385 mRNA-1273 The first dose: 5343 The second dose: 4099 Janssen The first dose: 593 ChAdOx1 The first dose: 8358 The second dose: 4887	Unvaccinated: The first dose: 20640 The seconded dose: 32947	MI Stroke
Young-Eun Kim (2022)[10]	Retrospective cohort	Korea	July 2020 and December 2021	Dose 1	84 days after vaccination	>18 years old	BNT162b2: 168 310	Unvaccinated: 62 727	MI Stroke

Contd...

Table 1: Contd...

First author	Study design	Country	Study period	Dose Vaccine	Follow up	Age	Type of vaccine, n	Control group, *n*	Outcome
William N. Whiteley (2022)[12]	Retrospective cohort	England	December 8, 2020 to March 18, 2021	Dose 1	28 days after vaccination	>18 years old	BNT162b2: 8712477 ChAdOx1: 12481337	Unvaccinated: 10563566	MI Stroke
Eric Yuk Fai Wan (2022)[51]	Self-controlled case-series	Hong Kong	23 February 2021 and 31 January 2022	Dose 1 Dose 2	21 days after the first or second dose	≥ 16 years old	BNT162b2: 141224	Inactivated vaccine: 209739	Arrhythmia CAD
Francisco Tsz Tsun Lai (2022)[52]	Retrospective cohort	Hong Kong	to September 30, 2021	Dose 1 Dose 2	28 days following the first and second doses	12–18 years	BNT162b2 The first dose: 138141 The seconded dose: 119664	Unvaccinated: The first dose: 136743 The second dose: 118300	Arrhythmia CAD
Barbara H. Bardenheier (2021)[53]	Cohort study	US	December 18, 2020 to March 7, 2021	Dose 1 Dose 2	15 days	Average age≥60 years	BNT162b2 The first dose: 8553 The second dose: 8371	Unvaccinated: 11,072	MI Stroke
Julia Hippisley-Cox (2021)[54]	Self-controlled case-series	England	December 20, 2020 to May 24, 2021	Dose 1	28 days	≥16 years old	BNT162b2: 19608008	Unvaccinated: 19608008	MI Stroke
Anne M. Hause (2022)[55]	Retrospective, observational study	US	August 31,2022–October 23, 2022	Booster dose	7 days	≥12 years old	BNT162b2: 122953 mRNA-1273: 89006	-	Arrhythmia MI Stroke
Soonok Sa (2022)[56]	Observational study	US	14 December, 2020 to 30 September, 2021	-	-	≥18 years old	BNT162b2: 205436 mRNA-1273: 237158	-	MI Stroke
Barbra A. Dickerman (2022)[57]	Observational study	US	January 4, 2021 to September 20, 2021	Dose 1	14 days after the first dose and 42 days after the first dose	≥18 years old	BNT162b2: 216836 mRNA-1273: 216836	-	Arrhythmia MI Stroke
Hannah G Rosenblum (2022)[6]	Observational study	US	December 14, 2020 to June 14, 2021	Dose 1 Dose 2	7 days	≥16 years old	BNT162b2: 167177332 mRNA-1273: 131639515	-	MI Stroke

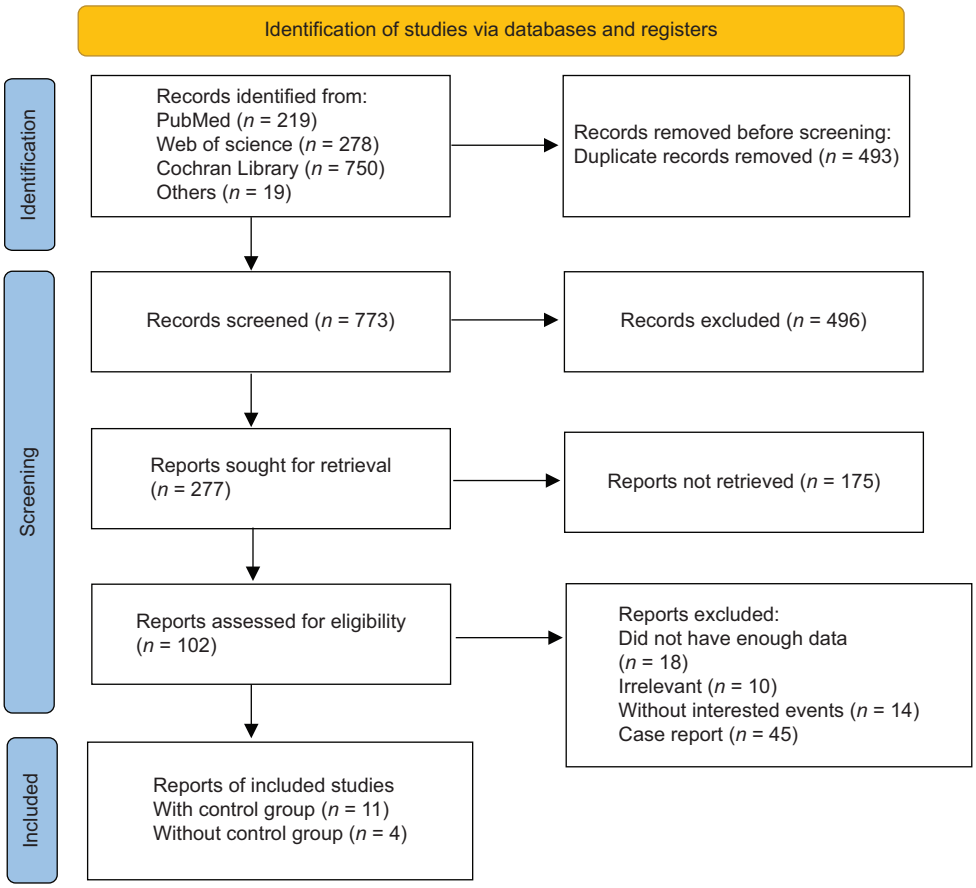

Figure 1: Article identification flow chart following the PRISMA guidelines

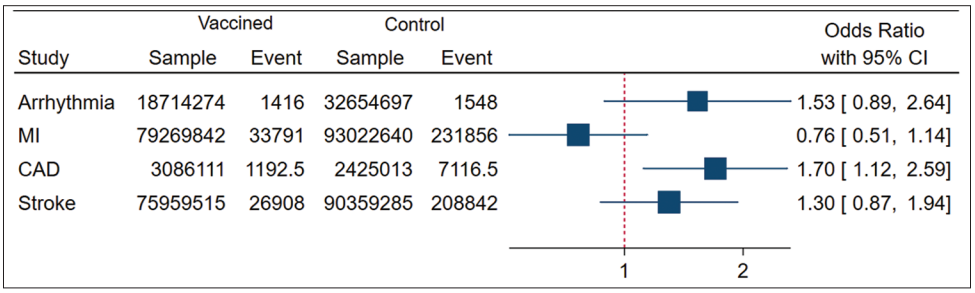

Figure 2: Odds ratio for arrhythmia, MI, CAD, and Stroke events following COVID-19 vaccination

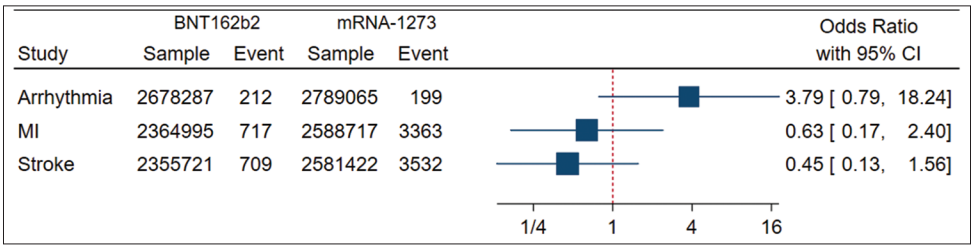

Figure 3: Odds ratio for comparing arrhythmia, MI, and Stroke events following BNT 162b2 and mRNA-1273 vaccination

In the secondary analysis, four studies from the United States were included, with 167722557 individuals in the BNT162b2 (Pfizer) vaccine group and 132182515 individuals in the mRNA-1273 (Moderna) vaccine group. The age of participants in all studies was above 16 years old, except for one study, which focused on individuals aged between 12 and 18 years.

Bayesian multivariate and univariate results

Primary analysis

Based on the Bayesian multivariate meta-analysis, among the examined cardiovascular events, only CAD was notable.

Vaccine dose	Event		Total		Odds Ratio with 95% CrI
First	**vaccine**	**Control**	**Vaccine**	**Control**	
Arrythmia	921	1683	9991274	17120385	2.99 (1.20-7.44)
MI	27863	128993	70351319	77273410	1.24 (0.76-2.03)
CAD	149	190	1588185	1302141	1.01 (0.61-1.66)
Stroke	21048	105050	68157664	75432923	3.40 (1.98-5.86)
Second					
Arrythmia	661	1412	8788707	15929770	0.65 (0.33-1.29)
MI	5516	21364	8717912	15921383	3.86 (2.28-6.60)
CAD	103	129	1236341	939860	3.44 (1.99-5.98)
Stroke	5262	23275	7601210	15099823	1.35 (0.83-2.20)
Third					
MI	123	21616	103381	291839	0.003 (0.001-0.006)
Stroke	168	21106	103440	291839	0.19 (0.10-0.39)
Vaccine type					
BNT162b2					
Arrythmia	1525	1726	17325353	18060245	1.75 (0.79-3.85)
MI	17858	70880	45503649	47978447	1.87 (1.22-2.89)
CAD	251	318	2824526	2242001	1.64 (1.06-2.55)
Stroke	14698	65096	42193365	45316400	2.09 (1.36-3.21)
ChAdOx1					
Arrythmia	58	927	1509194	14876922	8.11 (3.67-17.99)
MI	14660	75860	33616701	45135030	1.11 (0.33-3.74)
Stroke	11025	62241	33616685	45135030	0.47 (0.19-1.95)
Others					
Arrythmia	55	884	42195	225976	0.96 (0.39-2.41)
MI	984	25232	52262	373155	1.73 (0.72-4.18)
Stroke	754	22094	52264	373155	0.50 (0.24-1.03)
Geographical location					
Asia					
Arrythmia	1416	1548	18714274	32654697	2.23 (0.99-4.97)
MI	1063	1541	18483555	32252642	0.27 (0.07-1.53)
CAD	251	318	2824526	2242001	1.60 (1.03-2.46)
Stroke	1303	1877	15173230	29590595	0.29 (0.05-1.83)
Europe					
Arrythmia	222	1989	162468	508446	1.36 (0.72-2.58)
MI	32439	170431	60689057	61233990	0.80 (0.54-1.20)
Stroke	25174	147554	60689084	61233990	1.33 (0.89-2.00)

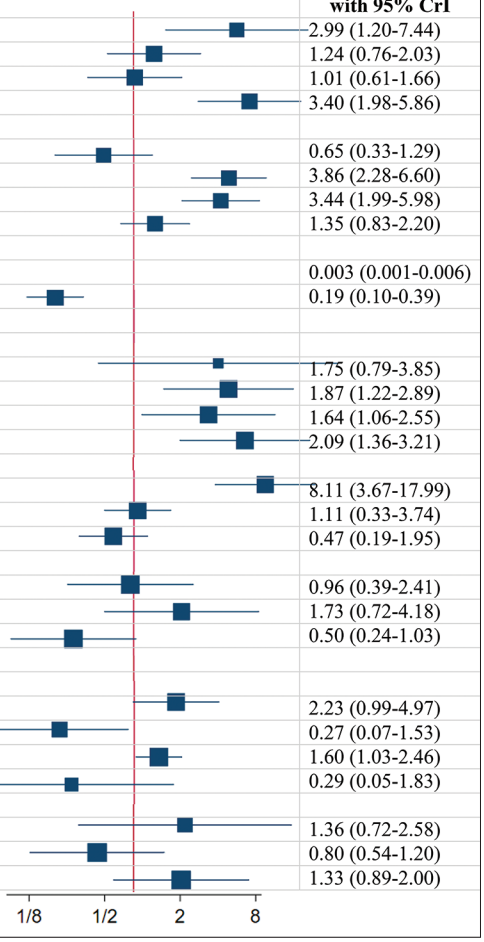

Figure 4: Subgroup analysis for arrhythmia, MI, CVD and Stroke events following COVID-19 vaccination

As evident from the findings indicate in Figure 2, the overall odds of CAD events in the vaccine group exceeded than the control group (OR, 1.70; 95% CrI: 1.11–2.57). Five studies reported CAD, all of which were BNT162b2 (OR, 1.64; 95% CrI: 1.06–2.55) and from Asian countries. Moreover, examining the results by vaccine dose, we observed that the odds of CAD were not significant for the first dose (OR, 1.01; 95% CrI: 0.61–1.65), but significant for the second dose (OR, 3.44; 95% CrI: 1.99–5.98). However, no significant relationship was detected between vaccination and stroke, myocardial infarction, and arrhythmia. And just a protective effect on stroke (OR, 0.19; 95% CrI: 0.10–0.39) and myocardial infarction (OR, 0.003; 95% CrI: 0.001–0.006) was observed after the third dose of the vaccine.

Subgroup analyses were conducted to further investigate these findings by considering vaccine type, dose, and geographical location [Table 2 and Figure 4]. Results based on vaccine type revealed a link between the BNT162b2 vaccine and an increased risk of myocardial infarction (OR, 1.87; 95% CrI: 1.22–2.89) and stroke (OR, 2.09; 95% CrI: 1.36–3.21). These findings were significant for stroke following the first dose (OR, 3.69; 95% CrI: 2.13–6.37) and for myocardial infarction after the second dose of BNT162b2 (OR, 3.84; 95% CrI: 2.21–6.66). The ChAdOx1 vaccine, in general, showed no significant association with any of the events. Just a notable link between the increased risk of arrhythmia and the ChAdOx1 was observed in relation to the first dose (OR, 4.89; 95% CrI: 1.21–19.38).

Examining the results by dose, irrespective of the vaccine type, revealed that the first dose was linked to a higher risk of arrhythmia (OR, 2.98; 95% CrI: 1.41–6.32) and stroke (OR, 3.40; 95% CrI: 1.98–1.98). As mentioned in the subgroup findings on vaccine type indicated that arrhythmia was associated with the first dose of the ChAdOx1, while stroke was associated with the first dose of BNT162b2. In contrast, the second dose exhibited a higher risk of myocardial infarction (OR, 3.86; 95% CI: 1.99–5.98) and CAD (OR, 3.44; 95% CrI: 1.99–5.98). Interestingly, the third dose had no impact on myocardial infarction (OR, 0.003; 95% CI: 0.001–0.006) and decreased the risk of stroke (OR, 0.20; 95% CI: 0.10–0.39).

Except for the case of CAD related to Asian countries, no significant findings were noted based on geographical region for any of the outcomes.

Table 2: Results of Bayesian multivariate meta-analyses and subgroup analyses. Odds Ratio (95%CI)

	Arrythmia	MI	CAD	Stroke
Total	1.53 (0.89-2.63)	0.76 (0.51-1.14)	1.70 (1.12-2.59)	1.29 (0.87-1.93)
Dose				
Dose 1	2.99 (1.20-7.44)	1.24 (0.76-2.03)	1.01 (0.61-1.66)	3.40 (1.98-5.86)
Dose 2	0.65 (0.33-1.29)	3.86 (2.28-6.60)	3.44 (1.99-5.98)	1.35 (0.83-2.20)
Dose 3	-	0.003 (0.001-0.006)	-	0.19 (0.10-0.39)
Vaccination				
BNT162b2	1.75 (0.79-3.85)	1.87 (1.22-2.89)	1.64 (1.06-2.55)	2.09 (1.36-3.21)
Dose 1	2.30 (0.62-5.71)	1.13 (0.69-1.87)	1.07 (0.64-1.77)	3.69 (2.13-6.37)
Dose 2	1.54 (0.36-6.65)	3.84 (2.21-6.66)	2.98 (1.64-5.37)	1.34 (0.81-2.21)
ChAdOx1	8.11 (3.67-17.99)	1.11 (0.33-3.74)	-	0.47 (0.19-1.95)
Dose 1	4.89 (1.21-19.38)	16.18 (2.46-3.08)	-	9.37 (0.96-91.25)
Dose 2	0.36 (0.12-1.03)	3.22 (0.29-3.08)	-	0.80 (0.07-9)
Others	0.96 (0.39-2.41)	1.73 (0.72-4.18)	-	0.50 (0.24-1.03)
Dose 1	0.29 (0.03-3.04)	1.10 (0.12-10.27)	-	0.39 (0.04-3.73)
Dose 2	0.97 (0.30-3.22)	3.99 (1.06-15.19)	-	1.58 (0.38-6.43)
Geographical location				
Asia	2.23 (0.99-4.97)	0.27 (0.07-1.53)	1.60 (1.03-2.46)	0.29 (0.05-1.83)
Europe	1.36 (0.72-2.58)	0.80 (0.54-1.20)	-	1.33 (0.89-2.00)

MI: Myocardial infarction; CAD: Coronary Artery Disease

Secondary analysis

To compare BNT162b2 and mRNA vaccines as a secondary objective, we merged the findings of 6 studies, all conducted in the United States. Among these, four studies compared BNT162b2 and mRNA vaccines, while two studies compared these vaccines with an unvaccinated group. Ultimately, upon consolidating the results of these studies, we observed no significant difference between the two vaccines regarding the odds of cardiovascular consequences. The result is shown in Figure 3.

Discussion

To the best of our knowledge, this is the first meta-analysis that represents the pioneering effort in conducting a multivariate analysis of COVID-19 vaccine-related cardiovascular events. Distinguishing our study from previous meta-analyses, we exclusively focused on controlled observational studies, which are recognized for providing more robust evidence than case reports or non-controlled observational studies. Concentrating on controlled observational studies, we aimed to mitigate biases and confounding factors that could influence the association between the vaccines and cardiac complications. Prior systematic review and meta-analysis studies predominantly relied on case reports, case series, or a combination of these with observational or cohort studies, lacking direct comparisons with control groups.[16-21] Furthermore, the present study differs from most meta-analyzes that primarily focused on myocarditis and pericarditis as common post-vaccine cardiac side effects.[17,18]

Our primary analysis, conducted through Bayesian multivariate meta-analysis, uncovered notable insights regarding the impact of COVID-19 vaccines on cardiovascular health. Specifically, we found that the administration of COVID-19 vaccines, particularly BNT162b2, was associated with increased odds of CAD following the second dose. However, it's important to highlight that the odds of experiencing myocardial infarction, stroke, and arrhythmia did not exhibit significant elevation due to the administration of COVID-19 vaccines. Subgroup analysis revealed a significant increase in arrhythmia and stroke risk after the first vaccine dose, a rise in myocardial infarction and CVD risk post-second dose, and no significant association after the third dose. Some outcomes even exhibited a protective effect, possibly due to higher stress levels during the early phases of vaccination, contrasting with reduced stress and increased vaccine confidence in the third phase. Analysis by vaccine type indicated that the BNT162b2 vaccine was notably linked to increased risk for all events except arrhythmia. In contrast, the ChAdOx1 vaccine primarily affected arrhythmia risk, especially after the first dose, while other vaccines showed no significant effects.

A secondary objective of our research involved comparing the BNT162b2 vaccine with mRNA-1273 vaccine to assess any differences in their effects on cardiovascular health. To achieve this, we synthesized the findings of six independent studies, all of which were conducted in the United States. After meticulous analysis and consolidation of the results from these studies, our investigation yielded an intriguing finding. Despite variations in study methodologies and populations, there was a consistent observation: no

significant difference was observed between the Pfizer BioNTech vaccine and mRNA-1273 vaccine concerning the odds of cardiovascular consequences. This implies that both types of mRNA vaccines were similarly effective or lacked substantial variance in their impact on cardiovascular health. mRNA vaccines encode the prefusion stabilized full-length spike protein of SARS-CoV-2, but they use slightly different systems for intracellular delivery. Yet, the specific mechanisms behind any observed differences in safety profiles remain unclear.

Two meta-analyzes examining the relationship between cardiovascular events and COVID-19 vaccination were recently published. A study by Chang *et al*.,[20] published in 2023, investigated not only myocarditis but also myocardial infarction and arrhythmia. The study found no significant association between COVID-19 vaccination and the incidence of myocardial infarction or arrhythmia, which aligns with the findings of our research. Contrary to our study, subgroup analysis in this research did not yield significant results regarding vaccine dose or type. Similarly, Khaity *et al*.,[21] did not find a significant relationship between arrhythmia and the vaccine. The study analyzed published cases and did not examine results based on vaccine dosage. Anyway, the consistent results of these two studies regarding arrhythmia and myocardial infarction support the findings of the multivariate model in our research. The assessment of myocardial infarction risk post-COVID-19 vaccination was also examined in a systematic review conducted by Petrudi *et al.* Their analysis of case report studies concluded that instances of myocardial infarction after COVID-19 vaccination are infrequent.[32] Likewise, the analysis by Baqi *et al.*, which scrutinized 10 case reports and 5 case series studies, underscored that myocardial infarction associated with COVID-19 vaccination is an uncommon yet severe and potentially life-threatening occurrence.[33]

In terms of stroke, our multivariate results align with a previously conducted meta-analysis conducted in England using the self-controlled case series design,[34-36] and population studies from France, the United States, and Israel.[5,37,38] All of the studies found no increased incidence of stroke following vaccination. In contrast, a recent and comprehensive analysis conducted by Jiang in 2023,[39] revealed a 41% reduction in the risk of post-COVID heart attack or stroke among fully vaccinated individuals. The study mentioned that even partial vaccination was associated with a decreased risk of adverse cardiovascular events, consistent with the findings from our subgroup meta-analysis about myocardial infarction and stroke after the third dose.

To compare our findings on CAD, we have not come across any research examining the connection between CAD and the coronavirus vaccine. The results from this study consist of 5 studies, all focusing on the BNT162b2 vaccine in Asia, indicating a need for further research and exploration in this area.

The concerns regarding a potential link between adverse cardiovascular events and COVID-19 vaccines have prompted various hypotheses to explain the underlying mechanism, although the exact pathogenesis remains unclear. One hypothesis suggests a correlation between vaccine-induced immune syndrome and CVD.[40] One of the particular concerns is the autoimmune reaction following vaccination, especially for individuals with a complex medical history.[41] This is because the immune system plays a crucial role in both cardiac composition and function, which can potentially trigger an excessive immune response in certain individuals, leading to autoimmune cardiac injury.[42] Additionally, the immune system has various effects on ischemic injuries, such as MI and ischemic stroke, involving both innate and adaptive immune cells.[40] Proposed mechanisms for COVID-19 vaccine-induced myocardial infarction may be attributed to vaccine-induced thrombotic thrombocytopenia (VITT), a condition akin to heparin-induced thrombocytopenia.[43,44] Another hypothesis posits that following vaccination, there may be a mismatch between the supply and demand of oxygen in a cardiovascular system already affected by disease.[45] Additionally, there is a possibility that COVID-19 vaccines may trigger a vasospastic allergic myocardial infarction, a condition known as Kounis syndrome.[46,47]

Overall, our study contributes to the existing literature by employing a comprehensive analysis approach and emphasizing controlled observational studies. While acknowledging potential side effects, our findings support the overall safety of the COVID-19 vaccine concerning cardiovascular complications such as myocardial infarction, stroke, and arrhythmia. However, it is crucial to note that ongoing surveillance and research are essential to continually monitor the safety and efficacy profiles of vaccines, including their potential cardiovascular effects, particularly as new variants emerge and vaccination strategies evolve. This underscores the importance of robust and continuous post-marketing surveillance systems to promptly identify and address any emerging safety concerns associated with vaccines.

Limitations

Among the limitations of our study, one noteworthy factor is the limited number of included studies. This restriction arises from the scarcity of studies available in the field that possess a control group. Consequently, due to the small sample sizes within subgroups, specific subgroup analyses could not be conducted. In addition, the absence of reported data on the 3rd dose of the vaccine, except for just two studies, prohibited further analyses related to this aspect. Furthermore, to gain a more comprehensive understanding, future investigations should encompass age

and gender subgroups. Nevertheless, the potential impact of this discrepancy on the precision of the findings may be minimal.

Conclusions

This is the first meta-analysis focusing on COVID-19 vaccine-related cardiovascular events in controlled observational studies, aiming to reduce biases. The study found BNT162b2 linked to increased CAD risk after the second dose. Various risks were analyzed post-vaccination doses, with different impacts based on vaccine type. Comparison between BNT162b2 and mRNA-1273 vaccines showed no significant difference in cardiovascular effects.

The findings of the present study may help public health policy for future pandemics, consider CAD in the context of COVID-19 vaccination, and assess the cardiac condition before the choice of vaccine is offered to adults. To minimize such risks, it is recommended that comprehensive preclinical and clinical studies be conducted to assess the cardiovascular safety of new vaccines, including large-scale trials involving diverse populations.

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Ethical considerations

Ethical considerations are not relevant to this study.

Author contributions

RK contributed substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; MM contributed to drafting the work or revising it critically for important intellectual content; H.RM contributed to the final approval of the version to be published; MN, and FE contributed in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary material

Table S1: Search strategy used with the five databases

Database	Step	Search strategy	Number of results
PubMed	#1	(SARS-COV 2[MeSH Terms]) OR (SARS-COV 2[Title/Abstract]) OR (COVID-19[MeSH Terms]) OR (COVID-19[Title/Abstract]) OR ("Coronavirus Disease 2019"[Title/Abstract]) OR ("SARS COV 2"[Title/Abstract]) OR (2019-nCoV[Title/Abstract]) OR ("2019 Novel Coronavirus"[Title/Abstract])	393,147
	#2	(COVID-19 Vaccines[MeSH Terms]) OR (COVID-19 Vaccines[Title/Abstract]) OR (SARS-CoV-2 Vaccines[Title/Abstract]) OR (Vaccine, COVID19 Virus[Title/Abstract]) OR (COVID19 Vaccine*[Title/Abstract]) OR (COVID 19 Virus Vaccines[Title/Abstract]) OR ("Corona Vac"[Title/Abstract]) OR ("Vaccine, BNT162"[Title/Abstract]) OR ("BNT162B2"[Title/Abstract]) OR (BNT162 Vaccine[MeSH Terms])) OR (BNT162 Vaccine*[Title/Abstract]) OR ("COVID-19 Vaccine Pfizer-BioNTech"[Title/Abstract]) OR ("Pfizer COVID 19 Vaccine*"[Title/Abstract]) OR ("BNT162B2"[Title/Abstract]) OR ("ChAdOx1 COVID 19 Vaccine*"[Title/Abstract]) OR ("messenger RNA vaccine*"[Title/Abstract]) OR ("mRNA Vaccine*"[Title/Abstract]) OR ("AstraZeneca, COVID-19 Vaccine*"[Title/Abstract]) OR ("COVID-19 Vaccine AstraZeneca"[Title/Abstract]) OR ("ChAdOx1 nCoV 19"[Title/Abstract]) OR (ChAdOx1 nCoV-19[MeSH Terms])	31,779
	#3	(Myocardial Infarction[MeSH Terms]) OR ("Myocardial Infarction") OR (Infarctions, Myocardial) OR ("Cardiovascular Stroke") OR (Stroke, Cardiovascular) OR (Arrhythmias, Cardiac[MeSH Terms]) OR (Arrhythmias, Cardiac) OR (Cardiac Arrhythmias) OR (Arrhythmia) OR (stroke[MeSH Terms]) OR (stroke) OR (Ischemic Stroke[MeSH Terms]) OR (Ischemic Stroke) OR (Carditis) OR (Cardiovascular events)) OR (Cardiovascular Diseases[MeSH Terms]) OR ("inflammatory heart disease") OR ("inflammatory cardiac disease ") OR ("ischemic heart disease") OR (Coronary Artery Disease[MeSH Terms]) OR (Coronary Artery Disease) OR (Myocardial Ischemia[MeSH Terms]) OR (Myocardial Ischemia) OR (Heart Attack)	3,026,311
	#4		
	#5	1# AND #2 AND #3	219
Web of Science	#1	TS=(SARS-CoV-2 OR "SARS COV 2" OR "SARS-COV 2" OR "2019 Novel Coronavirus" OR COVID-19 OR 2019-nCoV OR "Coronavirus Disease 2019")	480,652
	#2	TS=("SARS-CoV-2 Vaccine" OR "COVID-19 vaccines" OR "Vaccine, SARS-CoV-2" OR "CoronaVac" OR "BNT162 Vaccine" OR "Vaccine, BNT162" OR "Vaccine, BNT162" OR "COVID-19 Vaccine Pfizer-BioNTech" OR "Pfizer Covid 19 Vaccine" OR "BNT162B2"OR "ChAdOx1 COVID 19 Vaccine" OR "ChAdOx1 nCoV 19" OR "COVID-19 Vaccine AstraZeneca" OR "AstraZeneca, COVID-19 Vaccine")	51,998
	#3	TS=(Myocardial Infarction)) OR TS=("Infarctions, Myocardial")) OR TS=("Cardiovascular Stroke")) OR TS=("Stroke, Cardiovascular")) OR TS=("Arrhythmias, Cardiac")) OR TS=(Arrhythmias)) OR TS=("Cardiac Arrhythmias")) OR TS=(Ischemic Stroke)) OR TS=(Stroke)) OR TS=(Carditis)) OR TS=(Cardiovascular events)) OR TS=("Cardiovascular Diseases")) OR TS=(Coronary Artery Disease)) OR TS=(Myocardial Ischemia)) OR TS=(Heart Attack)) OR TS=("ischemic heart disease")	1,113,355
	#4	1# AND #2 AND #3	278
Google scholar		("SARS-CoV-2" OR "COVID-19") AND ("COVID-19 vaccines" OR "SARS-CoV-2 Vaccine") AND ("Ischemic stroke" OR "Myocardial Ischemia" OR "Carditis" OR "Myocardial Infarction" OR "Cardiovascular events" OR Arrhythmia OR "coronary artery disease" OR "cardiovascular diseases")	179
Cochrane Library		(SARS-CoV-2 Vaccines):ti, ab, kw OR (COVID-19 Vaccines):ti, ab, kw AND (Cardiovascular events):ti, ab, kw OR (adverse events):ti, ab, kw OR (Cardiac events):ti, ab, kw" Time=(2020-01-01/2022-12-30)	750

Table S2: 10th ed..ition of the International Classification of Diseases for variables used in the analysis

Variable	Functional form	Values	Codes
Acute myocardial infarction	Indicator	Yes/No	ICD10: I21.%, I22.%
Coronary artery disease	Indicator	Yes/No	ICD10: I20.%, I21.%, I24.%, I25.10, I25.110, I25.2, I25.3, I25.41, I25.42, I25.5, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9
Arrythmia	Indicator	Yes/No	ICD10: I44, I45, I46, I47, I48, I49
Stroke	Indicator	Yes/No	I64

Table S3: Newcastle–Ottawa scale (NOS) scale for checking quality assessment of cohort studies

	Wong (2022)	Flacco (2022)	Kim (2022)	Whiteley (2022)	Wan (2022)	Lai (2022)	Bardenheier (2021)
Selection of study groups							
Representativeness of the exposed cohort							
Selection of the non-exposed cohort							
Ascertainment of exposure							
Demonstration that outcome of interest was not present at start of study							
Comparability							
Comparability of patients on the basis of the study design or analysis							
Management of confounders (data collection and investigation of impact)							
Outcomes							
Assessment of outcome							
Was follow-up long enough for outcomes to occur							
Adequacy of follow up of cohorts							
Total score	9	9	7	9	8	8	9

Table S4: Joanna Briggs Institute Checklist for checking quality assessment of prevalence studies

	Ab Rahman (2022)	Ye (2022)	Barda (2021)	Botton (2022)	Dickerman BA (2022)	Hippisley-Cox J (2021)	Hause AM (2022)	Rosenblum HG (2022)	Sa (2022)
Was the study question or objective clearly stated?									
Was the study population clearly and fully described, including a case definition?									
Were the cases consecutive?									
Were the subjects comparable?									
Was the intervention clearly described?									
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?									
Was the length of follow-up adequate?									
Were the statistical methods well-described?									
Were the results well-described?									
Total score	8	8	9	9	9	9	7	9	