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Risk of myocarditis and pericarditis in mRNA COVID-19-vaccinated and unvaccinated populations: a systematic review and meta-analysis

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ABSTRACT

Objective To summarise the available evidence on the risk of myocarditis and/or pericarditis following mRNA COVID-19 vaccination, compared with the risk among unvaccinated individuals in the absence of COVID-19 infection.

Design Systematic review and meta-analysis.

Data sources Electronic databases (Medline, Embase, Web of Science and WHO Global Literature on Coronavirus Disease), preprint repositories (medRxiv and bioRxiv), reference lists and grey literature were searched from 1 December 2020 until 31 October 2022.

Study selection Epidemiological studies of individuals of any age who received at least one dose of an mRNA COVID-19 vaccine, reported a risk of myo/pericarditis and compared the risk of myo/pericarditis to individuals who did not receive any dose of an mRNA COVID-19 vaccine.

Data extraction and synthesis Two reviewers independently conducted screening and data extraction. The rate of myo/pericarditis among vaccinated and unvaccinated groups was recorded, and the rate ratios were calculated. Additionally, the total number of individuals, case ascertainment criteria, percentage of males and history of SARS-CoV-2 infection were extracted for each study. Meta-analysis was done using a random-effects model.

Results Seven studies met the inclusion criteria, of which six were included in the quantitative synthesis. Our meta-analysis indicates that within 30-day follow-up period, vaccinated individuals were twice as likely to develop myo/pericarditis in the absence of SARS-CoV-2 infection compared to unvaccinated individuals, with a rate ratio of 2.05 (95% CI 1.49–2.82).

Conclusion Although the absolute number of observed myo/pericarditis cases remains quite low, a higher risk was detected in those who received mRNA COVID-19 vaccinations compared with unvaccinated individuals in the absence of SARS-CoV-2 infection. Given the effectiveness of mRNA COVID-19 vaccines in preventing severe illnesses, hospitalisations and deaths, future research should focus on accurately determining the rates of myo/pericarditis linked to mRNA COVID-19 vaccines, understanding the biological mechanisms behind these rare cardiac events and identifying those most at risk.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data included in our quantitative synthesis came from several very well-conducted observational studies, and mostly from population-based cohort studies, demonstrating racial and ethnic diversity, with the majority spanning similar time frames.
⇒ All myocarditis and pericarditis cases were adjudicated by at least two methods, minimising the risk of misclassification that can arise from relying on diagnosis codes alone.
⇒ Due to insufficient data, we could not evaluate the possibility of sex differences, or variations in the risk according to the number of doses of mRNA COVID-19 vaccines received.
⇒ Confounding by indication and healthy vaccinee bias may be present in the studies included in our analysis, and it is difficult to determine to what extent these biases may have influenced our risk estimates.

INTRODUCTION

SARS-CoV-2 vaccines have proven to be highly effective in protecting against serious illness and death associated with COVID-19.[1–5] Nevertheless, there have been reports of cardiac complications following mRNA SARS-CoV-2 vaccination, including reports of myocarditis and pericarditis.[6–13]

The aetiology of these conditions is broad and can include infectious triggers such as viral, bacterial and fungal infections, as well as non-infectious triggers such as autoimmune disease and drug induced.[14 15] Additionally, myocarditis and pericarditis can also occur as an adverse event following immunisation. In the past, such cases have been reported after smallpox, influenza and

hepatitis B vaccination.[16] While people experiencing these conditions will fully recover, in rare cases, patients may develop heart failure or asymptomatic left ventricular dysfunction.[17]

There has been an increase in reports of myocarditis and pericarditis following COVID-19 vaccination shortly after several countries expanded immunisation to children and young adolescents.[18 19] According to several studies and case series, the highest incidence of myo/pericarditis was found among adolescents aged 12–17 years, and mainly affecting males following the second vaccine dose.[9 20 21] The remarkable clinical similarities in patients presenting with myo/pericarditis, the onset of symptoms within a few days following the mRNA COVID-19 vaccine inoculation and the absence of other known aetiologies suggest a possible link between mRNA vaccination and these cardiac adverse events.[22] Nonetheless, it is important to point out that occurrence of myo/pericarditis in vaccinated individuals does not immediately imply that the vaccine was the causative agent; it could also be the result of an adjuvant that promoted, reactivated or accelerated naturally occurring myocarditis caused by viral or immune-mediated factors.[23]

Less information is available regarding the risk of myo/pericarditis among unvaccinated individuals. Before the COVID-19 pandemic, inflammatory myocarditis was known to be mediated predominantly by viral infections, among other causes.[24 25] However, appreciable underdiagnosis is likely to be made in secondary care settings.[26 27] It remains unclear how the risk of myocarditis and pericarditis compares between unvaccinated individuals and those who have received an mRNA vaccination in the absence of COVID-19 infection.

A direct comparison of the risk of myo/pericarditis among vaccinated individuals compared with unvaccinated individuals would allow for a more thorough benefit-risk analysis of COVID-19 vaccination programmes. To inform this comparison, a systematic review and meta-analysis was conducted to address the following research question: what is the risk of myocarditis or pericarditis among individuals who received an mRNA COVID-19 vaccine, compared with those who did not receive an mRNA injection, in the absence of COVID-19 infection?

METHODS

Eligible studies

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines were followed in conducting and reporting our review.[28] All epidemiological studies satisfying the following criteria were eligible for inclusion: (1) observational studies that included individuals of any age who received at least one dose of an mRNA SARS-CoV-2 vaccine (BNT162b2 or mRNA-1273); (2) studies that reported a risk of myocarditis and/or pericarditis; and (3) compared the risk of myocarditis or pericarditis to individuals who did not receive any dose of an mRNA SARS-CoV-2 vaccine. Since we anticipated that the criteria for case definition would differ across studies, all reported clinical or laboratory-confirmed myocarditis or pericarditis cases were considered, and the methods used for case identification and confirmation in each study are reported in our summary.

Table 1 Inclusion criteria for eligible studies

Population	Individuals of any age and any sex
Intervention	Individuals who received at least one dose of an mRNA COVID-19 vaccine: Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273)
Comparator	Unvaccinated individuals
Outcome	Myocarditis and/or pericarditis
Time frame	December 2020 to October 2022

We excluded vaccine clinical trials (as no occurrences of myocarditis or pericarditis were reported in these studies),[29 30] systematic reviews or observational studies that focused on only a single group of patients (such as studies examining risk among vaccinated patients only), studies that limited their study sample to patients with cardiac events of interest prior to vaccination and studies in which patients received non-mRNA vaccines. We also excluded studies that relied on rates calculated from historical cohorts in a pre-COVID-19 vaccination period to approximate the expected rates in unvaccinated individuals. Case series, case reports, editorials, letters, viewpoints, commentaries, abstracts and narrative reviews, along with any other non-quantitative studies, were also excluded. Our search was restricted to human studies; however, we did not include limits for language of publication, research setting or country of study (table 1).

Search strategy

To provide adequate and efficient coverage of the relevant literature,[31] Ovid Medline, Embase and Web of Science were searched for studies published between 1 December 2020 and 30 October 2022 examining the risk of myo/pericarditis following mRNA vaccination, and comparing this risk between vaccinated and non-vaccinated groups. Our search strategy was developed in consultation with an experienced health information librarian and employed the combined keywords ‘COVID-19’, ‘myocarditis’, ‘pericarditis’ and ‘COVID-19 mRNA vaccine’. Detailed search terms are attached in supplementary material (online supplemental table S1a Ovid Medline, online supplemental table S1b Ovid Embase, online supplemental table S2 Web of Science), and the list of literature used for the construction of the study search terms (online supplemental table S3).

We supplemented our search by systematically searching the two preprint repositories medRxiv and bioRxiv using the medRxiv R package, which allowed us to perform a reproducible search using complex search strings and download preprint metadata for all identified studies (online supplemental table S4).[32] We also conducted

manual searches of OpenGrey, WHO's COVID-19 Global Literature on Coronavirus Disease database (online supplemental table S5) and Google Scholar to identify relevant papers. Additionally, we examined the websites of four major national public health sites for unpublished studies relevant to our research question: the Centers for Disease Control and Prevention (CDC), the Public Health Agency of Canada, the European Centre for Disease Prevention and Control and the UK's Medicines and Healthcare Products Regulatory Agency. Furthermore, the reference lists of all included papers were checked to identify additional relevant studies.

Study selection

All records identified in our search were exported to EndNote for deduplication using the method described by Bramer *et al*.[33] Deduplicated records were then exported to the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for review and screening. Two reviewers (AA, NF) independently screened eligible studies using a two-level process. In level 1, titles and abstracts were screened for inclusion against the predefined inclusion and exclusion criteria. In level 2, the two reviewers independently screened and evaluated the full-text articles that were retained from level 1 screening. Disagreements regarding eligibility were resolved by discussion, with consultation with a third investigator (DK) where needed.

Data extraction

For each included study, information on study characteristics (design, setting and data source) and participant data (total number of participants, case ascertainment criteria, total number of cases, follow-up period, incidence rate reported, percentage of males, median age of participants and history of SARS-CoV-2 infection) was extracted using a piloted data extraction form. Data extraction was performed independently by two reviewers and extracted data were compared for discrepancies.

Since both myocarditis and pericarditis can occur concurrently in clinical settings, we recognised that studies included in this review reported and aggregated cases of both cardiac conditions in varying ways, as may have used the terms myopericarditis and perimyocarditis interchangeably. Due to the significant overlap in signs and symptoms, pathology and clinical manifestations of the two conditions, cases of myocarditis and pericarditis were pooled into one outcome 'myo/pericarditis', which is used here to refer to myocarditis, pericarditis or myopericarditis (a term used to describe primarily pericarditis, with some evidence of myocarditis).

Data synthesis

Several observational studies have indicated that COVID-19 infection is linked with a statistically significant increase in the risk of myocarditis-related hospitalisation, even among those with no history of cardiovascular illnesses.[34–39] Hence, when computing the rate ratios (RR), we excluded all cases that had a prior record of COVID-19 infection in both vaccinated and unvaccinated groups. For each included study, we extracted the numeric rates of myo/pericarditis (per person-year of follow-up) occurring in vaccinated and unvaccinated groups, and then calculated the RRs for this condition. When multiple risk estimates were given in the original study, we selected the estimate with the longest follow-up period.

Where a study did not report the RR, associated CI or the follow-up time, we used the formula below[40] to estimate the RRs:

$$RR = \frac{E_1/T_1}{E_0/T_0} \quad (1)$$

Here, E_1 and E_0 are the number of events in the exposed (vaccinated) and unexposed (unvaccinated) groups, respectively, and T_1 and T_0 are the person-time at risk for each group. The standard error (SE) of the (natural) logarithm of the RR is given by:

$$SE\left[ln(RR)\right] = \sqrt{\frac{1}{E_1} + \frac{1}{E_0}} \quad (2)$$

For a sufficiently large number of events in both the vaccinated and unvaccinated groups, the 95% CI for the RR is then given by:

$$\left(e^{\ln(RR)-1.96SE[\ln(RR)]}, e^{\ln(RR)+1.96SE[\ln(RR)]}\right) \quad (3)$$

We used a forest plot to visualise the distribution of the RR and the 95% CI derived across all included studies. To obtain the overall RR accounting for between-study heterogeneity, the log of the RR and its corresponding 95% CI were computed for each study, and then summarised using the random-effects inverse-variance model with DerSimonian-Laird method.[41] Cochran's Q, the Higgins' I^2 statistic and tau-squared (τ^2) were used to assess heterogeneity among the included studies. Cochran's Q provides a statistical test of heterogeneity, and we considered a p value <0.05 to indicate statistically significant heterogeneity. The I^2 statistic measures the proportion of total variability in effect sizes that is due to between-study heterogeneity rather than chance. I^2 values above 50% were considered indicative of moderate heterogeneity, while values above 75% reflecting high heterogeneity.[42] Lastly, τ^2 was used to estimate the between-study variance, providing a quantitative measure of the heterogeneity in our analysis.

We evaluated the possibility of publication bias using Egger's test for asymmetry in funnel plots, when feasible.[43] We also conducted an influence analysis, leaving out one study at a time from the meta-analysis to determine the influence of individual studies on the overall effect size estimate.[44] Planned subgroup analyses were performed by study setting (inpatient only or inpatient and outpatient) and duration of follow-up (incidence of myo/pericarditis within a maximum of 30 days following vaccination). All analyses were performed using STATA V.16.1.[44]

Study quality

Two reviewers independently assessed study quality using the Office of Health Assessment and Translation (OHAT) risk of bias rating tool, incorporating the assessment of seven bias domains: selection, confounding, attrition/exclusion, detection, selective reporting and other sources of bias, with a rating scale for each domain ranging from 'definitely low', 'probably low', 'probably high' and 'definitely high' risk of bias.[45] This quality assessment instrument is one of the risk of bias assessment tools currently recommended over scales that produce a summary score (such as the Newcastle-Ottawa Scale and Downs and Black tools), which focus on the methodological quality of studies.[46] We used the OHAT method for risk of bias assessment and a tiered approach to assess study quality, as outlined in the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, to classify studies as 1st tier, 2nd tier or 3rd tier.[47]

Patient and public involvement

None.

RESULTS

The meta-analysis and report of the results were carried out according to the PRISMA criteria (online supplemental table S6). Our initial search method retrieved 2147 records from Embase, Medline and Web of Science, with additional records identified through manually searching the grey literature. Of these, 953 records were excluded after deduplication and before screening. Following title-abstract screening, 147 citations were retained for full-text screening, following which 140 were further excluded, leaving a total of seven studies that met the inclusion criteria. The PRISMA flow chart (figure 1) illustrates the study screening and selection process.[28]

In total, 11 papers were initially eligible for extraction in our analysis,[48–58] however, four papers were excluded due to overlapping patient data with other included studies (based on authors' list, institution, data source, country and study period). This left us with seven studies for qualitative analysis. Two studies by Lai and colleagues—a case–control study[54] and a cohort study[55]—were likely to have overlapping patient data using the same electronic health records: we included the more recent study with the longer study period.[55] Likewise, we included the most recent of the two overlapping cohorts published by Simone and colleagues.[57 58] Similarly, two cohorts had overlapping patient populations: a study by Barda *et al*[48] examined data from Clalit Health Services (Israel's largest healthcare provider), while another study by Mevorach *et al*[56] used national surveillance data from Israel's Ministry of Health, which includes cases of myo/pericarditis considered by Barda and colleagues: we therefore excluded the smaller study by Barda and colleagues for the quantitative analysis. Finally, we excluded a cohort study published by Husby and colleagues[50] since patient data overlapped with a recently published study that included patients from all four Nordic countries.[51]

The present review focused on the remaining seven studies that met the inclusion criteria, totalling more than 47 million individuals across the seven cohorts examined. Five of the seven included studies employed concurrent comparators to reduce the likelihood of bias, while only two studies used cohort controls consisting of historical data from the same subjects 1–2 years prior to COVID-19 pandemic. To avoid misclassification based on diagnosis code alone, six of the seven studies used at least two methods for ascertainment of myocarditis diagnosis: three studies had suspected cases adjudicated by one to two cardiologists and rheumatologists, two studies used International Classification of Diseases codes in addition to medical records review and expert medical diagnostic criteria, while only one study relied solely on hospital diagnostic codes. The characteristics of the seven scientific articles included in our meta-analyses are summarised in table 2.

Of the seven included studies, two did not report on the verification of absence of positive SARS-CoV-2 infection among confirmed cases. This is significant since SARS-CoV-2 infection can confound the association between our exposure and outcomes of interest as it has been linked to long-term cardiac complications including myo/pericarditis.[59] The remaining four of the seven studies used medical records and negative SARS-CoV-2 PCR test results to verify that cases of myo/pericarditis had no history of COVID-19 infection. One study reported 29 cases with confirmed COVID-19 infection solely among the unvaccinated group,[56] while another study excluded patients with active COVID-19 disease at the time of diagnosis of myo/pericarditis but reported two cases with history of COVID-19 infection in the vaccinated group.[49] All of these reported positive SARS-CoV-2-infected cases were excluded from our quantitative analyses. There were a total of 3727 myo/pericarditis cases in all included studies, with 1192 cases occurring among the vaccinated groups compared with 2535 cases in the unvaccinated comparator groups. Denmark, Finland, Norway and Sweden accounted for 77.7% (2896) of the cases, the USA for 16.15% (602) and Hong Kong and Israel for the remaining 6.1% (229). Numeric rates of confirmed cases of myo/pericarditis were extracted or estimated for each study based on the number of cases and follow-up time, along with their corresponding 95% CIs. As risk estimates were reported differently in the included studies—some provided aggregate incidence rates, while others stratified only by dosage number, gender or vaccination type (BNT162b2 and mRNA-1273)—we aggregated and standardised the results using data extracted from each study. A summary of the number of cases, overall follow-up time and RRs retrieved from each study is provided in table 3.

Six studies were included in the meta-analysis of the risk of myocarditis in COVID-19-vaccinated versus unvaccinated individuals: Lai *et al*'s[55] study was not included since the follow-up time for the reported RR was not

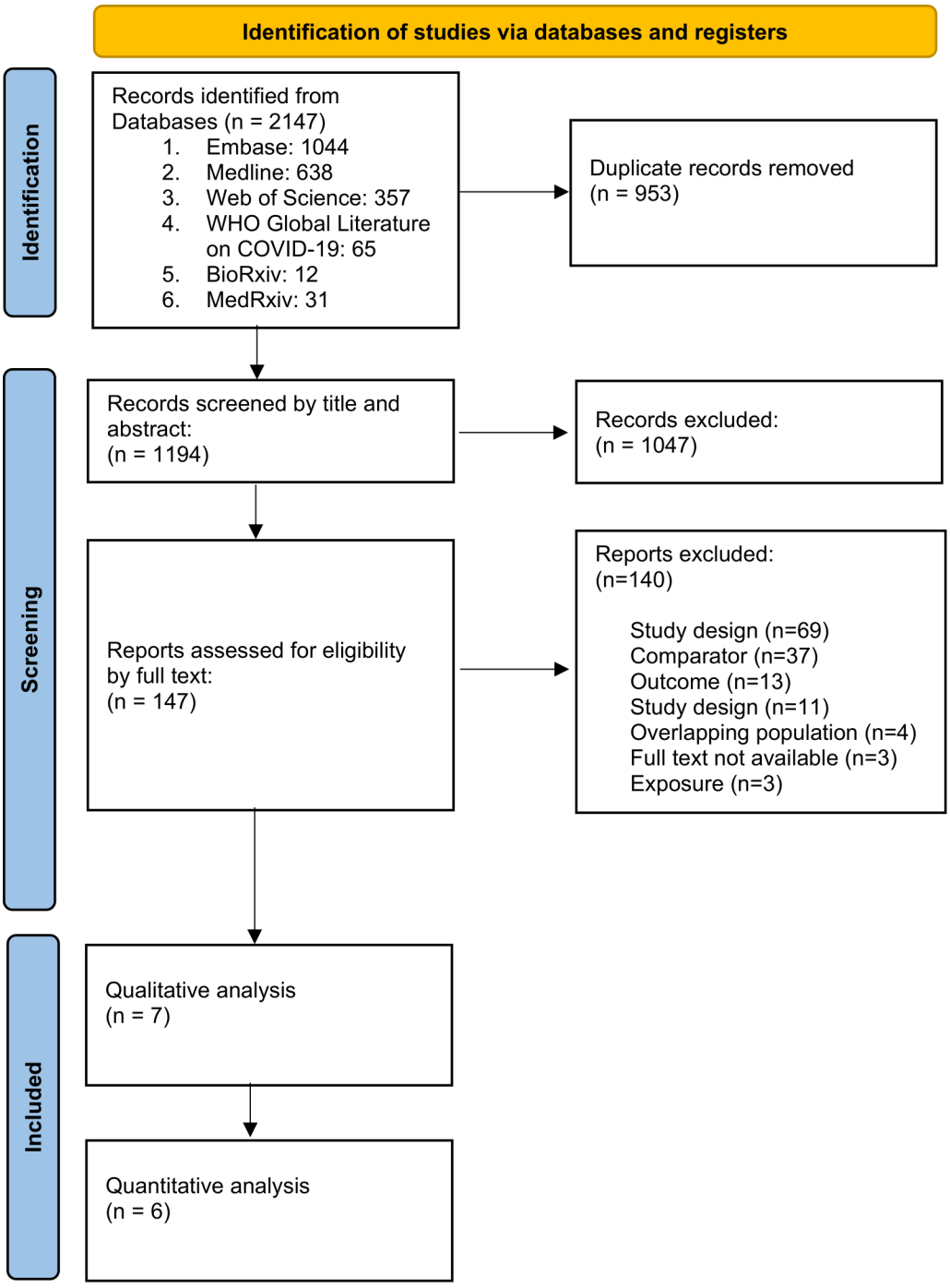

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart summarising the process to identify studies that met the eligibility criteria for inclusion in the systematic review.

available. Overall, three out of the seven studies were considered to have a low risk of bias and were classified as being in the first tier (high quality). These studies had either a 'definitely low' or 'probably low' risk of bias for key items and for most other applicable criteria. The other four studies were rated to have a 'probably high' risk of selection (Lai and Farahmand) or confounding bias (Simone and Knowlton) and were classified as being in the second tier, meaning that they did not meet the criteria for either the first or third tier. A summary of the assessment method and approach used to determine the tiers of study quality can be found in online supplemental table S7.

To further explore the results of our meta-analysis, consider the forest plot shown in figure 2. The risk of myo/pericarditis among those who received the mRNA COVID-19 vaccine relative to those who did not receive the vaccine was higher, with a RR of 2.06 and a 95% CI of 1.60–2.67. The studies included in the meta-analysis demonstrated a high degree of heterogeneity, as reflected

Table 2 Summary of characteristics of included studies

Study	Period of observation	Study design and data source	Sample size	Males (%)	Age (years)	Myocarditis diagnostic criteria	Risk of bias
Farahmand *et al* [49]	3 Aug 2020 to 21 May 2021	Self-controlled cohort using Massachusetts Immunization Information System, USA	Exposed: 268 320 Unexposed: 235 343	40	≥18	ICD-10 codes+ European Society of Cardiology diagnostic criteria	2nd Tier
Karlstad *et al* [51]	27 Dec 2020 to 5 Oct 2021	Cohort study using nationwide health registers from four Nordic countries: Denmark, Finland, Norway and Sweden	23 122 522	49.8	≥12	ICD-10 codes+ independent ascertainment of vaccinations and diagnoses from nationwide registers	1st Tier
Klein *et al*[52]	14 Dec 2020 to 26 Jun 2021	Cohort study using Vaccine Safety Datalink, USA	10 162 227	47.6	≥12	ICD-10 codes+clinical expert medical review	1st Tier
Knowlton *et al*[53]	15 Dec 2020 to 15 Jun 2021	Cohort study using Intermountain Healthcare, Utah, USA	1 695 514	NR	≥18	ICD-9 codes+ Brighton Collaboration criteria+ adjudication by 3 exposure-blinded cardiologists and 1 cardiovascular physician assistant	2nd Tier
Lai *et al*[55]	14 Jun 2021 to 30 Sep 2021	Cohort study using electronic health records from Department of Health and Hospital Authority of the Hong Kong Government	First dose cohort: 274 884 Second dose cohort: 237 964	First dose cohort: 50.3 Second dose cohort: 51.0	12–18	ICD-9 codes	2nd Tier
Mevorach *et al*[56]	20 Dec 2020 to 31 May 2021	Cohort study using the Israeli Ministry of Health database	9 289 765	49	≥16	ICD-9 codes+ Brighton Collaboration criteria+ adjudication by one of four cardiologists and rheumatologist	1st Tier
Simone *et al*[58]	14 Dec 2020 to 18 Feb 2022	Self-controlled cohort using Kaiser Permanente Southern California database, USA	3 076 660	46.4	≥18	ICD-10 codes+ adjudication by two cardiologists	2nd Tier

ICD, International Classification of Diseases; NR, not reported.

Table 3 Summary of number of myo/pericarditis cases and incidence rate ratio from included studies

Study	Vaccinated		Unvaccinated				
	Events	Follow-up time (person-years)	Events	Follow-up time (person-years)	RR	LB	UB
Farahmand *et al* [49]	7	46744	5	55952	1.68	0.53	5.28
Karlstad *et al*[51]	883	2520700	2013	10282500	1.79	1.65	1.94
Klein *et al*[52]	87	660766	293	3093220	1.39	1.09	1.77
Knowlton *et al*[53]	19	185248	29	659387	2.33	1.31	4.16
Lai *et al*[55]	8 (1st dose cohort) 30 (2nd dose cohort)	NR NR	1 (1st dose cohort) 1 (2nd dose cohort)	NR NR	9.15 29.6	1.14 4.04	73.16 217.1
Mevorach *et al*[56]*	117	410373	72	811994	3.22	2.40	4.31
Simone *et al*[58]†	41	428035	121	3076660	2.44	1.71	3.47

*Total vaccinated cases pertain to only second dose of an mRNA vaccine.
†Baseline cohort of individuals who received first, second or third dose of an mRNA vaccine.
LB, lower bound for RR; NR, not reported; RR, rate ratio; UB, upper bound for RR.

by I^2=78.0% (p<0.001), Cochran's Q=22.72 (df=5, p<0.001) and τ^2=0.0652.

We found no evidence of publication bias, as visual inspection of the funnel plot (comprising six data points) did not indicate any asymmetry (online supplemental figure S1), with most of the studies randomly scattered within the confidence limits region resembling the inverted funnel shape, indicating that publication bias is unlikely. The Cochrane Collaboration recommends caution when interpreting funnel plots with fewer than 10 studies included, as the precision of the estimates may be insufficient to identify any potential publication bias.[60] In such cases, it may be difficult to draw firm conclusions about the presence or absence of publication bias based on the funnel plot alone. While statistical methods may fail to detect publication bias when the number of relevant published articles is small, regression tests such as Egger's test may still be used and are more likely than other methods to detect publication bias.[61] With a p value of 0.466, Egger's test did not indicate the presence of publication bias in this meta-analysis. Nonetheless, the lack of asymmetry of the funnel plot and the results of Egger's test should be interpreted with caution.

Considering that most low-risk patients with myocarditis can be effectively managed in an ambulatory setting,[62] and that high-risk patients are generally hospitalised to initiate therapy and referred to a cardiologist to continue the diagnostic evaluation, myocarditis diagnosed in ambulatory clinic visits may be under-represented in cohorts that only include inpatient data. To address this issue, we conducted a subgroup analysis by grouping studies based on patient settings (inpatient or inpatient and outpatient combined) (figure 3). The overall RR was lower for studies that included inpatients and outpatients (RR 1.90, 95% CI 1.64 to 2.21) compared with studies that included inpatients only (RR 2.10, 95% CI 0.93 to 4.79). For studies that included inpatients only, Cochran's Q was 18.83 (df=1, p<0.001), I^2 was 94.7% and τ^2 was 0.333, indicating the presence of heterogeneity among the studies. For studies that included inpatients and outpatients, Cochran's Q was 3.50 (df=3, p=0.321), I^2 was 14.3% and τ^2 was 0.006, indicating a low to moderate heterogeneity

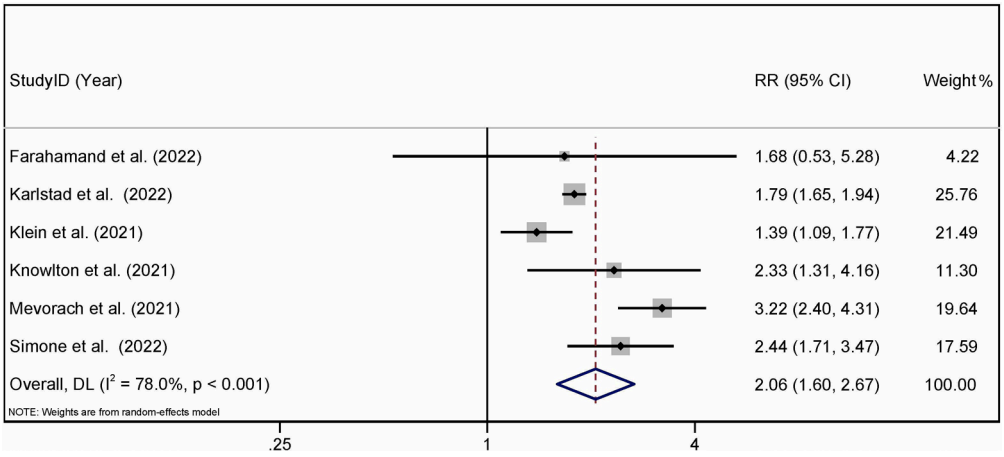

Figure 2 Meta-analysis of the rate ratios (RR) of myo/pericarditis in vaccinated relative to unvaccinated individuals. DL, DerSimonian-Laird.

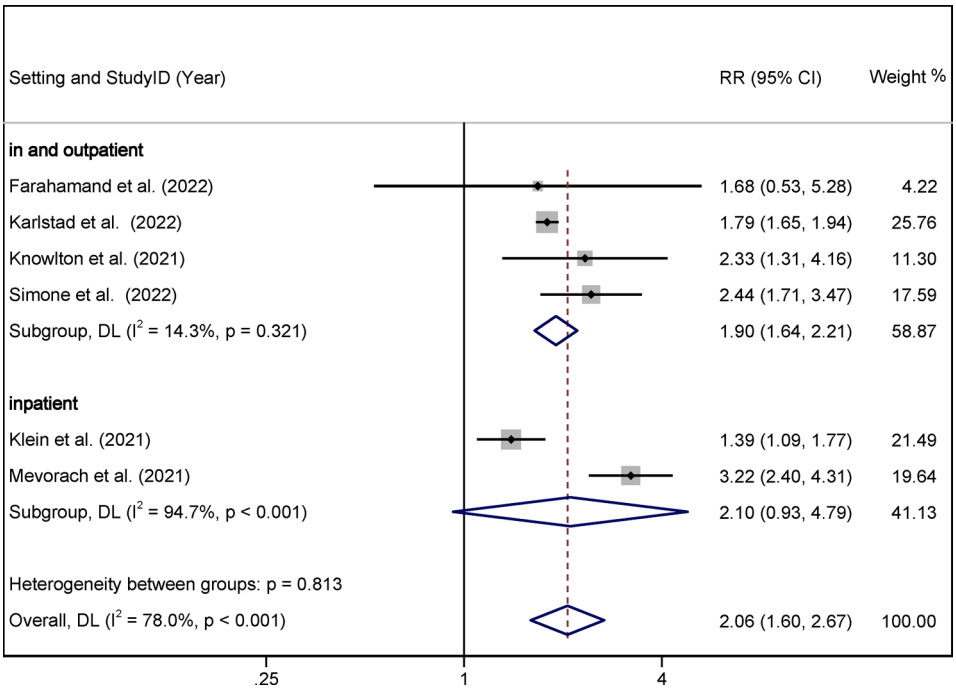

Figure 3 Rate ratio (RR) of myo/pericarditis in vaccinated relative to unvaccinated individuals by study setting. DL, DerSimonian-Laird.

among the studies. Overall, there was a higher degree of heterogeneity among the studies that included inpatients only compared with the studies that included inpatients and outpatients based on Cochran's Q, I^2 and τ^2.

Mean age, region, number of cases, total number of individuals included and overall person-year time of follow-up were not identified as significant sources of heterogeneity in the meta-regression analysis. However, given the limited number of studies (n = 6) included, we cannot conclusively rule these factors out as potential sources of heterogeneity. To determine if the results of our meta-analysis were unduly influenced by any one study, we applied the leave-one-out meta-analysis using the random model, and excluded one study at a time while performing a meta-analysis on the remaining papers. As can be seen in table 4, the study by Karlstad *et al*[51] had a relatively high influence on the overall results; when this study was excluded from the meta-analysis, the overall risk estimate shifted from 2.06 (95% CI 1.60 to 2.67) to 2.17 (95% CI 1.45 to 3.25). Nevertheless, no substantial change from any of the pooled RR was observed, with exclusion of a single study leading to a significantly elevated overall RR ranging from 1.45 to 3.25, depending on the study omitted from the meta-analysis.

Table 4 Influence analysis showing rate ratios based on meta-analysis omitting one study at a time

Study omitted	Rate ratio	LB	UB
Farahmand *et al* [49]	2.09	1.60	2.73
Karlstad *et al*[51]	2.17	1.45	3.25
Klein *et al*[52]	2.30	1.69	3.14
Knowlton *et al*[53]	2.03	1.53	2.70
Mevorach *et al*[56]	1.80	1.49	2.18
Simone *et al*[58]	1.99	1.48	2.68

LB, lower bound for rate ratio; UB, upper bound for rate ratio.

Lastly, to assess the effects of the duration of follow-up time and the inclusion of concurrent unvaccinated comparator cohorts on the risk of myocarditis, we conducted a sensitivity analysis by analysing the distribution of RRs derived from each study with shorter follow-up times, including only studies that reported cases of myo/pericarditis within 30 days following vaccination, and excluding studies that used prepandemic historical records rather than providing risks estimated of concurrent unvaccinated cohorts during the same period. This approach was motivated by the potential impact of the COVID-19 pandemic on the number of patients seeking medical care and the possible underreporting of myocarditis. The RRs and associated 95% CIs derived from each study are shown in figure 4. The overall risk of myo/pericarditis, RR of 2.05 (95% CI 1.49 to 2.82), was not appreciably different from that in our main analysis. All three heterogeneity statistics (I^2=85.5%, Cochran's Q=20.74 (df=3, p<0.001), τ^2=0.0824) reflected appreciable variability among the studies included in this sensitivity analysis.

DISCUSSION

Our review is the first systematic review and meta-analysis comparing the risk of myo/pericarditis among vaccinated and unvaccinated individuals during the COVID-19 pandemic. In all six studies included from

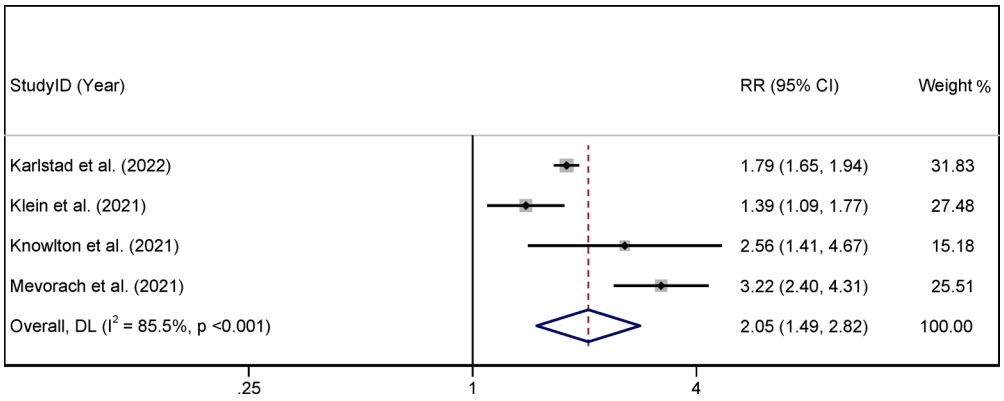

Figure 4 Rate ratio (RR) of myo/pericarditis in vaccinated relative to unvaccinated individuals within 30 days after vaccination and among concurrently unvaccinated comparators. DL, DerSimonian-Laird.

different countries, the risk of myo/pericarditis is consistent and elevated among those who received the mRNA COVID-19 vaccine compared with those who did not, in the absence of COVID-19 infection, with an overall RR of 2.06 (95% CI 1.60 to 2.67). Multiple sensitivity analyses did not have an appreciable impact on our overall results and conclusion. Even though restricting our analysis to shorter risk intervals by including only confirmed cases of myo/pericarditis that were reported within 30 days following an mRNA vaccination, and excluding the two studies that used historical comparator cohort group, the overall RR was still significant (RR=2.05, 95% CI 1.49 to 2.82). However, it is essential to consider the background incidence of myo/pericarditis when interpreting our results, which can vary widely depending on the region and population being studied.[63 64] For instance, a recent comprehensive study by the European Medicines Agency estimated the incidence rate to be in the range of 10–200 cases per 1 000 000 person-years of follow-up.[65] By incorporating these background incidence rates into our analysis, we can better contextualise the risk of myo/pericarditis following mRNA vaccination. To illustrate, consider two groups of 1 000 000 individuals each, with one group receiving an mRNA vaccine and the other remaining unvaccinated. Within a 30-day follow-up period, based on the background incidence rate, the unvaccinated group can expect approximately 0.8–16.7 cases of myo/pericarditis, derived from the background incidence rate calculations (10 and 200 cases per 1 000 000 person-years, respectively, multiplied by 30/365 for the 30-day follow-up period). In contrast, our study findings indicate an RR of about 2.05 for myo/pericarditis in the vaccinated group within the same time frame, which translates to 2.05×0.8=1.6 to 2.05×16.7=34.2 cases within 30 days following vaccination. Thus, while the risk of myo/pericarditis is higher in the vaccinated group than in the unvaccinated group, the absolute risk of myo/pericarditis is small in both groups.

Our findings are in line with multiple meta-analyses[66–69] that have evaluated the complex relationship between mRNA vaccinations and the rare risk of cardiac injury, indicating that vaccination with mRNA COVID-19 vaccines is associated with a short-term greater risk of myocarditis, however, the absolute risk appears to be low. This association has been demonstrated through different types of epidemiological studies, including national spontaneous reporting system studies,[70–73] comparisons of observed-to-expected rate studies,[74 75] case–control studies,[54 76] self-controlled cases series[35 77–79] and cohort studies.[48 77 80–82] To better understand whether these findings reflect an actual increase in incidence or simply improved reporting and carditis diagnosis, a recent meta-analysis aimed to evaluate and compare the incidence of myopericarditis following COVID-19 vaccinations to that of all other non-COVID-19 vaccines.[83] This meta-analysis included data from 22 studies (including 260 million individuals and more than 400 million vaccine doses), and reported an overall incidence of 33.3 cases per million vaccine doses, which did not differ significantly between people who received COVID-19 vaccines and those who received non-COVID-19 vaccines. Nonetheless, the rate of myopericarditis in young males after mRNA COVID-19 vaccines was still higher than expected. Interestingly, another study sought to compare the incidence of myocarditis in COVID-19 vaccinees compared with SARS-CoV-2-infected individuals: findings revealed that the risk of myocarditis is more than seven times higher in individuals infected with the SARS-CoV-2 versus those who received the vaccine[84]; however, there is currently no evidence demonstrating that existing COVID-19 vaccines are protective against myocarditis associated with SARS-CoV-2 infection.[85]

Two crucial research questions remain unanswered. First, what are the exact mechanisms linking COVID-19 mRNA inoculation to these rare incidences of myocarditis?[86] Second, are there any long-term effects of vaccine-associated myocarditis?[86] Although the biological mechanisms underlying COVID-19 vaccine-induced myocarditis are still unclear, hypotheses include molecular mimicry between the spike protein and cardiac self-antigens, mRNA immune reactivity and activation of the host immunological system.[9 87 88] Whereas the long-term effects of vaccine-associated myocarditis are still not fully understood, existing evidence on short-term clinical outcomes is favourable, with most cases being mild and

only a few patients requiring intensive therapy.[9 89] To better understand the potential long-term outcomes of myocarditis, a recent follow-up surveillance study funded by the CDC followed adolescents and young adults for at least 90 days after the onset of vaccine-induced myocarditis.[90] While 81% of patients were considered recovered by healthcare personnel and 68% were cleared for all physical activities, 54% of those who received follow-up cardiac MRIs still exhibited cardiac abnormalities, primarily late gadolinium enhancement, which signifies muscle injury or inflammation, and 26% also were still prescribed daily medications related to myocarditis.

Although our meta-analysis indicated that vaccinated individuals were twice as likely as unvaccinated individuals to develop myo/pericarditis in the absence of SARS-CoV-2 infection, this increased risk must be weighed against the overall benefits of vaccination. In public health practice, risk management decisions require consideration of various complex and sometimes conflicting factors.[91] When seeking to balance risks and benefits, it is important to consider the type of benefits and the individuals who will receive them, particularly when risks cannot be effectively eliminated or there are offsetting benefits. Given that mRNA COVID-19 vaccines have already been shown to effectively prevent severe illness, hospitalisation and death from COVID-19 at the individual level, and also help to reduce community spread and protect immunocompromised individuals while maintaining the operation of the healthcare system at the community level,[92] future research should focus on accurately determining the incidence rates of myo/pericarditis linked to mRNA COVID-19 vaccines, understanding the mechanisms behind these rare cardiac events and identifying those most at risk in order to create reliable benefit-risk profiles for specific age groups.

Our study has many strengths. First, data included in our quantitative synthesis came from several very well-conducted observational studies, and mostly from population-based cohort studies. Second, all myo/pericarditis cases in the six included studies were adjudicated by at least two methods, minimising the risk of misclassification that can arise from relying on diagnosis codes alone. Third, while the rates in our study are similar to those reported in other studies that examined only the incidence rate of myo/pericarditis following mRNA COVID-19 vaccination among the vaccinated individuals,[13 81 93–95] we attempted to overcome some of their limitations by also including the rate of myo/pericarditis in the unvaccinated individuals and calculating the overall RR. We also conducted an analysis restricted to shorter risk intervals by including only confirmed cases of myo/pericarditis that were reported within 30 days following vaccination, and excluding the two studies that used historical comparator cohort group; such that we had only concurrent comparators which comprised unvaccinated individuals rather than prepandemic historical records due to concerns about how the COVID-19 pandemic has affected the rate of patients seeking medical care.[96] Finally, since COVID-19 infection can have a lasting impact including symptoms of myo/pericarditis after the initial acute infection, we excluded all cases with a prior occurrence of COVID-19 infection. Additionally, the studies included in our analysis are population-based cohorts, demonstrating racial and ethnic diversity with the majority spanning similar time frames.

Our study has potential limitations that should be considered when interpreting our findings. First, due to insufficient data, we could not evaluate the possibility of sex differences, or variations in the risk according to the number of doses received (first, second or even booster doses). Second, the data did not allow to evaluate how COVID-19 infection can modify the association between mRNA COVID-19 vaccination and the risk of myo/pericarditis when compared with infected unvaccinated individuals. Third, despite the large number of individuals included in the review, the total number of identified myocarditis and pericarditis cases remained relatively small. Fourth, even though each study has adjudicated all identified cases by at least two different methods, there have been no cardiac biopsies for definitive diagnosis of all cases of myocarditis or pericarditis. Since COVID-19 infection can be asymptomatic in some individuals, there is a potential for overestimation or underestimation of the risk of myo/pericarditis among vaccinated and unvaccinated individuals since these cases would not have been excluded from the analysis. Moreover, due to the generally milder subclinical symptoms of myo/pericarditis and the possibility of undiagnosed cases, the actual incidence of both cardiac illnesses may be greater than reported. Lastly, all observational study designs may be subject to bias given the lack of randomisation of vaccination in real-world settings.[97] Vaccinated and unvaccinated groups might very well differ in major aspects, such as the risk of disease and access to screening and healthcare, and these factors were not considered in the present analysis. Additionally, confounding by indication and healthy vaccinee bias may be present in the studies included in our analysis.[98] Confounding by indication, individuals with comorbidities are more likely than healthy people to get vaccinated against COVID-19; healthy vaccinee bias can also occur when healthier people are more likely to follow COVID-19 vaccine recommendations. We would expect that shortly after the introduction of COVID-19 vaccines, the unvaccinated group would have comprised a large group of individuals awaiting vaccination as well as those individuals who were vaccine adverse, with the relative size of these two groups shifting with time and the availability of new information on vaccine safety. Although both sources of bias are almost certainly present, it is difficult to determine to what extent these biases may have influenced our risk estimates. Furthermore, as with all observational studies, the possibility of residual or unmeasured confounding bias remains a limitation.

CONCLUSION

The present systematic review and meta-analysis indicates that the risk of myocarditis and/or pericarditis was elevated among individuals who received the mRNA COVID-19 vaccine compared with those who did not, in the absence of COVID-19 infection. This association has been demonstrated in various types of epidemiological studies, including national spontaneous reporting systems, comparisons of observed-to-expected rates, case–control studies, self-controlled case series and cohort studies. As we were unable to reduce or account for the appreciable heterogeneity among studies that were considered, our findings should be interpreted with caution. The biological mechanisms behind the link between mRNA COVID-19 vaccines and myo/pericarditis, and the potential long-term effects of vaccine-associated myo/pericarditis, are currently not well understood. Nonetheless, given the proven effectiveness of mRNA COVID-19 vaccines in preventing severe illnesses, hospitalisations and deaths from COVID-19, future research should focus on accurately determining the rates of occurrence of myo/pericarditis linked to mRNA COVID-19 vaccines, understanding the biological mechanisms behind these rare cardiac events and identifying those most at risk.

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