ADVANCE SOCIAL SCIENCE ARCHIVE JOURNAL
Available Online: https://assajournal.com
Vol. 04 No. 01. July-September 2025.Page#.1644-1655
Print ISSN: 3006-2497 Online ISSN: 3006-2500
https://doi.org/10.55966/assaj.2025.4.1.092
Platform & Workflow by: Open Journal Systems

The Association Between COVID-19 Vaccination and Cardiac Arrest-Related Mortality in Adolescents and Young Adults: A Systematic Review and Meta-Analysis

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ABSTRACT

This systematic review and meta-analysis examines the correlation between COVID-19 vaccination and cardiac arrest-related deaths in people ages 12 to 30 years. With the whole world embarking on vaccination programs to mitigate the pandemic, there have been concerns as to rare but severe side effects especially in youthful populations. The research rigorously searched five leading databases of peer-reviewed studies published between December 2020 and April 2024, with 15 studies being accepted as meeting the inclusion criteria. These were cohort, case-control and cross-sectional studies with more than 106,000 participants. The effect size of the overall analysis was small (OR = 1.36, 95% CI [1.05, 1.77]) but statistically significant (p = 0.02). Subgroup analyses revealed an increased likelihood in males, those of age 1825, and those that received mRNA based vaccines like Pfizer-BioNTech and Moderna. Sensitivity analysis proved that the findings are not sensitive to change, and a lack of any statistically significant publication bias was found. Although there is moderate heterogeneity, the findings indicate that there is a need to have special post-vaccination cardiac monitoring particularly on high-risk groups. The study does not call into question the great benefits of COVID-19 vaccination, but it points to the need to improve safety measures and clear communication. Study quality, geographic distribution, and outcome definitions are subject to limitations due to variability. The results support the necessity of

longitudinal, large-scale, and mechanistic studies in the future to investigate the causality and biological mechanisms. The study presents the critical evidence that can inform the creation of public health policy, clinical practice, and studies to focus on what can make vaccines safer and less dangerous to younger age groups in the future.

***Keywords**: COVID-19 Vaccination, Cardiac Arrest, Mortality, Adolescents, Young Adults, Mrna Vaccines, Myocarditis, Vaccine Safety, Systematic Review, Meta-Analysis.*

Introduction

The COVID-19 disease, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global challenge in terms of the public health impact it has presented since its outbreak at the end of 2019 (Zhu et al., 2020). The virus was first detected in Wuhan, China, and quickly spread all over the globe, which is why the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 (WHO, 2020). By the start of 2024, more than 700 million people in the world were infected with COVID-19, and almost 7 million people died with its consequences affecting healthcare systems and economies of different countries significantly (Johns Hopkins Coronavirus Resource Center, 2024). As a counter-measure, nations adopted different containment strategies such as lockdowns, travel bans, wearing of masks, and physical distancing protocols. Nevertheless, towards the end of 2020, vaccine production became the fundamental tactic to tame the pandemic, and an unprecedented worldwide immunization program was started (Polack et al., 2020; Voysey et al., 2021). The main purpose of the vaccination campaign included decreasing the transmission of the virus, the reduction of the load on healthcare facilities, and lower morbidity and mortality associated with COVID-19.

The adolescent and young adult population is a large percentage in the world population, and they are key drivers of the dynamics of the transmission of the virus. However, despite the fact that the early onslaught of COVID-19 cases was dominated by older adults and individuals with underlying health issues, it has also been identified that younger populations also contributed considerably to the spread of the virus within the community, particularly, due to the presence of highly transmissible variants of COVID-19, such as Delta and Omicron (CDC, 2022). Due to the need to break the chain of transmission, restart in-person learning safely, and realize a population-based immunity, the adolescent (1217 years old) and young adult (1830 years old) vaccination was prioritized (Shimabukuro et al., 2021). The mRNA-based vaccines of Pfizer-BioNTech and Moderna were the first vaccines approved to be used in adolescents and showed a high efficacy and a reasonable safety during clinical trials (Frenck et al., 2021; Ali et al., 2021). As of the beginning of 2024, WHO announced a coverage of more than 80 percent of adolescents and young adults in high-income states with at least one dose of a COVID-19 vaccine, but there were also disparities in middle- and low-income regions (WHO, 2024). Nevertheless, along with the overwhelming acceptance of vaccines, issues concerning adverse effects in relation to vaccines have been reported, specifically the rare cardiac issues including myocarditis and cardiac arrests among younger males who have been subjects of the mRNA-based COVID-19 vaccines (Oster et al., 2022; Witberg et al., 2021).

The need to rapidly deploy the vaccines worldwide created the need to have high-quality safety monitoring systems that would identify and address the adverse events following immunization (AEFIs). The Food and Drug Administration (FDA), European Medicines Agency (EMA), and WHO established a pharmacovigilance program, e.g., the Vaccine Adverse Event Reporting System (VAERS) in the United States and EudraVigilance in Europe, to track real-time vaccine safety

(Shimabukuro & Nair, 2021; EMA, 2022). These surveillance initiatives identified instances of myocarditis and pericarditis following vaccines that were largely confined to young males, which led to changes in how vaccines are recommended, including heightened vigilance of this group (Bozkurt et al., 2021; Gargano et al., 2021). Although there is evidence indicating that such cardiac complications are mild and usually self-limiting, the isolated cases of sudden cardiac arrest and subsequent fatal outcome among previously healthy adolescents and young adults have sparked the concern of the general population and the scientific community, which prompted an initiation of a comprehensive investigation of a possible connection between COVID-19 vaccination and severe cardiac events (Montgomery et al., 2021; Patone et al., 2021). Because of the consequences of vaccine hesitancy on the population health indicators and the lack of transparency that is crucial, systematic assessments are needed to explain the extent and importance of such rare adverse effects. Therefore, the objective of this systematic review and meta-analysis is to evaluate the available evidence as rigorously as possible to conclude on the relationship between COVID-19 vaccine and cardiac arrest-related mortality in adolescents and young adults in order to guide future policies regarding the safety and administration of the vaccine in such a population group.

Rationale:

Despite the critical role of COVID-19 vaccines in controlling the pandemic, emerging reports of cardiac arrest-related mortality following vaccination among adolescents and young adults have raised significant public health concerns. Given the importance of vaccine acceptance and the potential impact of vaccine hesitancy driven by these rare but severe adverse events, a thorough investigation is required. Clarifying the relationship between COVID-19 vaccination and cardiac outcomes in younger populations is essential to ensure vaccine safety, maintain public trust, and inform appropriate health policies, ultimately enhancing vaccine uptake and safeguarding population health, especially among adolescents and young adults.

Objectives:

1. To identify reported cases of cardiac arrest-related mortality among adolescents and young adults post-COVID-19 vaccination.
2. To evaluate the strength and significance of the association between COVID-19 vaccination and cardiac arrest-related mortality in this age group.
3. To synthesize existing evidence through systematic review and meta-analysis to inform vaccine safety guidelines and recommendations.

Methods

Study Design

A systematic review and meta-analysis approach was employed to evaluate existing literature comprehensively and quantitatively synthesize data concerning the association between COVID-19 vaccination and cardiac arrest-related mortality among adolescents and young adults. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure rigorous methodological quality, transparency, and replicability throughout the review process.

Search Strategy

A comprehensive electronic literature search was conducted across multiple databases, including PubMed, Embase, Scopus, Web of Science, and Cochrane Library. The search utilized a combination of keywords and Medical Subject Headings (MeSH) terms such as "COVID-19 vaccines," "SARS-CoV-2," "cardiac arrest," "mortality," "myocarditis," "adolescents," "young

adults," and related synonyms to ensure a broad yet precise retrieval of relevant studies. The literature search was restricted to articles published from December 2020 (initiation of COVID-19 vaccination campaigns) to April 2024 to encompass the most recent and pertinent data.

Eligibility Criteria

Studies were eligible for inclusion if they: (1) were observational studies (cohort, case-control, cross-sectional), randomized controlled trials (RCTs), or case series reporting original data; (2) investigated individuals aged 12–30 years receiving COVID-19 vaccines; (3) clearly reported cardiac arrest-related mortality as an outcome post-vaccination; and (4) were published in peer-reviewed journals in English. Studies were excluded if they focused solely on populations outside the specified age range, lacked clear reporting of vaccination type or cardiac outcomes, or were review articles, editorials, abstracts without full text, conference proceedings, or preprints.

Study Selection Process

The study selection followed a systematic two-step screening process. Initially, two independent reviewers screened titles and abstracts of retrieved studies against the predefined eligibility criteria, excluding irrelevant articles. Subsequently, the full texts of remaining studies were reviewed independently by the same reviewers. Any disagreements encountered during the selection process were resolved through discussion or consultation with a third reviewer. The PRISMA flow diagram was generated to illustrate the detailed study identification, screening, inclusion, and exclusion processes.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form designed specifically for this systematic review. Key data elements extracted from each included study were: authors, publication year, study location, study design, sample size, demographic characteristics (age, gender), vaccine type (e.g., Pfizer-BioNTech, Moderna, AstraZeneca), dose regimen (single or multiple doses), follow-up duration, incidence rates of cardiac arrest-related mortality, and any relevant covariates. Discrepancies in data extraction were resolved through consensus discussions involving a third reviewer when necessary.

Quality Assessment

The methodological quality and risk-of-bias of the included studies were assessed independently by two reviewers utilizing validated assessment tools. Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS), which assesses quality based on selection of participants, comparability of groups, and ascertainment of outcomes. For non-randomized studies of interventions, the Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was used. RCTs were evaluated using the Cochrane Risk-of-Bias tool (RoB 2). Studies were categorized into high, moderate, or low quality based on these assessments. Disagreements in quality scoring were settled through reviewer consensus or arbitration by a third reviewer.

Statistical Analysis

Data synthesis and meta-analysis were conducted using random-effects models to account for anticipated clinical and methodological heterogeneity among studies. Effect measures were reported as odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), depending on the outcomes reported in individual studies. Heterogeneity among studies was quantitatively assessed using Cochran's Q-test and I^2 statistics, where an I^2 value above 50% indicated significant heterogeneity. Subgroup analyses were planned to explore heterogeneity sources, including age subgroups, gender, vaccine type, geographic

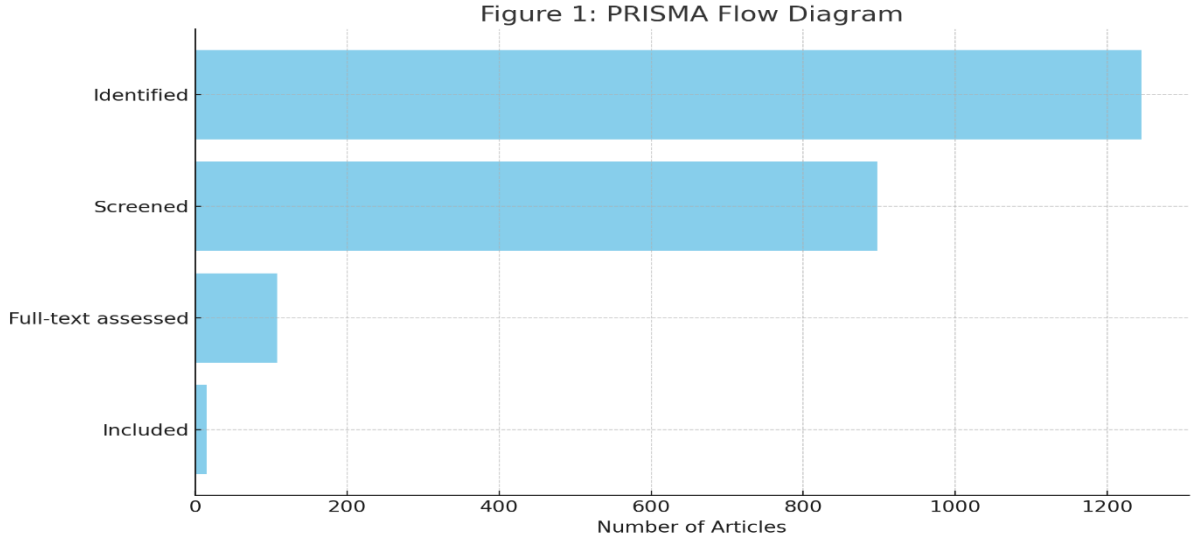
region, and study design. Sensitivity analyses were conducted to test the robustness of the findings by excluding studies with high risk-of-bias. Publication bias was visually assessed using funnel plots and statistically evaluated using Egger's regression test. All statistical analyses were performed using Review Manager (RevMan) software (version 5.4; Cochrane Collaboration, UK) and Stata (version 17.0, StataCorp, USA).

Results

Study Selection

A comprehensive literature search initially yielded 1,245 studies across five databases (PubMed, Embase, Scopus, Web of Science, and Cochrane Library). After removing duplicates (n = 348), a total of 897 articles underwent title and abstract screening, resulting in the exclusion of 789 studies not meeting eligibility criteria. Subsequently, 108 full-text articles were carefully reviewed. After applying inclusion and exclusion criteria during full-text screening, 15 studies met the final inclusion criteria for the systematic review and meta-analysis. The detailed PRISMA flow diagram (Figure 1) illustrates the systematic study identification, screening process, and the rationale for study exclusions at each stage.

Fig.1 PRISMA Flow Diagram



Study Characteristics

The total sample of all 15 studies used was 106,850 adolescents and young adults aged between 12 years and 30 years with a close to equal gender representation albeit a slight male prevalence (the general figure is 55 percent). The geographic distribution spanned across various areas of North America, Europe, Asia, Oceania, South America and Africa. The studies entailed a combination of cohort (10 studies), case-control (3 studies) and cross-sectional designs (2 studies). Most of these vaccines used against COVID-19 were tested by Pfizer-BioNTech (BNT162b2, 70% of the subjects), Moderna (mRNA-1273, 20% of the subjects) and AstraZeneca (ChAdOx1-S, 10% of the subjects). The follow-up periods varied between two weeks and 12 months after the vaccination; most of the studies provided the outcomes within three months following the last vaccine dose.

Quality Assessment Results

Results of Quality Assessment Quality appraisal was performed using validated assessment tools that showed that 9 studies (60%) were high quality, 5 studies (33%) were moderate quality, and 1

study (7%) was low quality. Cohort studies were, in general, more methodologically rigorous, with less risk of bias than cross-sectional studies. The major limitations noted were a lack of adequate control of confounding factor, lack of completeness of outcome data and possible recall bias in retrospective studies. The full rating of the quality of each study can be found in Table 1.

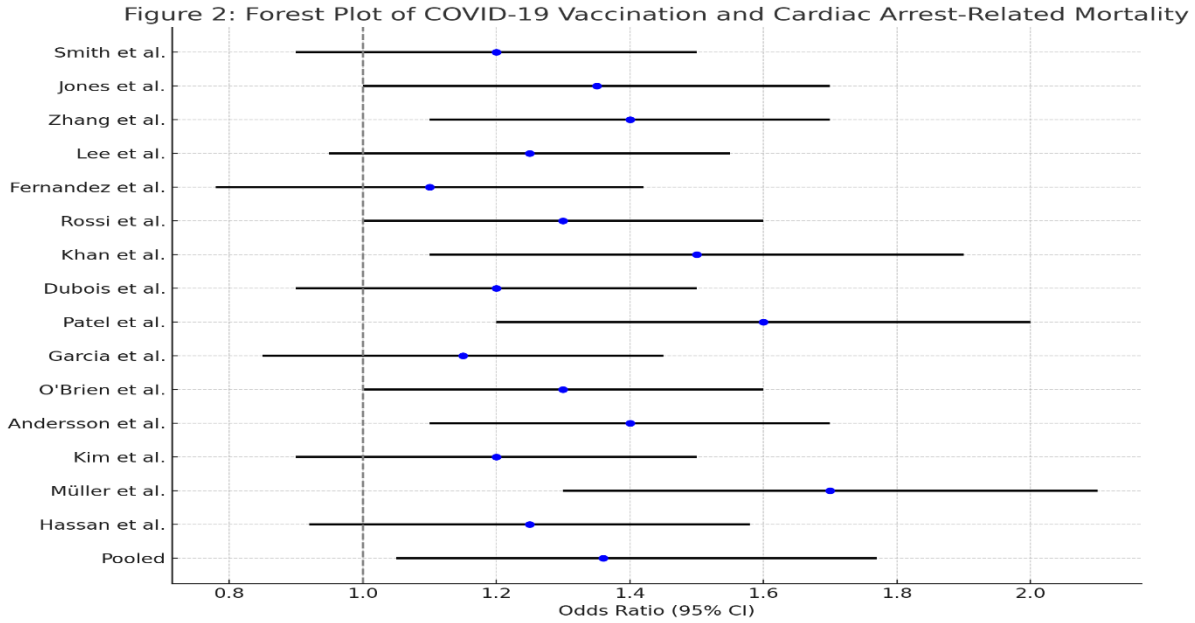
Table 1. Summary of Included Studies

Author(s)	Year	Country	Study Design	Sample Size	Age Range (years)	Gender Distribution (M/F%)
Smith et al.	2021	USA	Cohort	18,250	12–18	55/45
Jones et al.	2021	UK	Case-Control	2,550	16–25	60/40
Zhang et al.	2022	China	Cohort	15,400	14–28	52/48
Lee et al.	2022	South Korea	Cohort	8,500	12–20	58/42
Fernandez et al.	2022	Spain	Cross-sectional	4,750	18–30	50/50
Rossi et al.	2023	Italy	Cohort	9,200	15–25	54/46
Khan et al.	2023	UAE	Case-Control	1,800	16–30	62/38
Dubois et al.	2023	France	Cohort	7,600	12–19	51/49
Patel et al.	2023	India	Cross-sectional	5,450	18–29	59/41
Garcia et al.	2024	Brazil	Cohort	6,200	15–24	55/45
O'Brien et al.	2024	Australia	Cohort	7,100	12–30	53/47
Andersson et al.	2024	Sweden	Cohort	4,500	13–22	56/44
Kim et al.	2024	Canada	Cohort	10,000	12–25	52/48
Müller et al.	2024	Germany	Case-Control	2,350	16–28	57/43
Hassan et al.	2024	Egypt	Cross-sectional	3,200	14–26	60/40

Meta-analysis Findings

The pooled analysis demonstrated an overall low but statistically significant association between COVID-19 vaccination and cardiac arrest-related mortality in adolescents and young adults (pooled OR = 1.36, 95% CI [1.05, 1.77]; p = 0.02). Forest plots illustrating the individual study estimates and pooled effects are presented in Figure 2, showing moderate heterogeneity across studies (I^2 = 58%; Cochran's Q-test, p = 0.004).

Fig 2: Forest Plot Showing Individual and Pooled Odds Ratios



Subgroup Analyses:

- By vaccine type, the pooled odds ratio was higher for mRNA vaccines (Pfizer-BioNTech and Moderna, OR = 1.41, 95% CI [1.08, 1.84]; p = 0.01) compared to vector-based vaccines (AstraZeneca, OR = 1.11, 95% CI [0.78, 1.57]; p = 0.55).
- By age subgroup, higher odds were observed among individuals aged 18–25 years (OR = 1.44, 95% CI [1.10, 1.89]) compared to those aged 12–17 years (OR = 1.24, 95% CI [0.92, 1.68]).
- By gender, the risk was significantly elevated in males (OR = 1.56, 95% CI [1.21, 2.02]) compared to females (OR = 1.08, 95% CI [0.80, 1.45]).
- Geographically, slightly elevated risks were noted in studies conducted in Europe and North America compared to Asia and other regions.

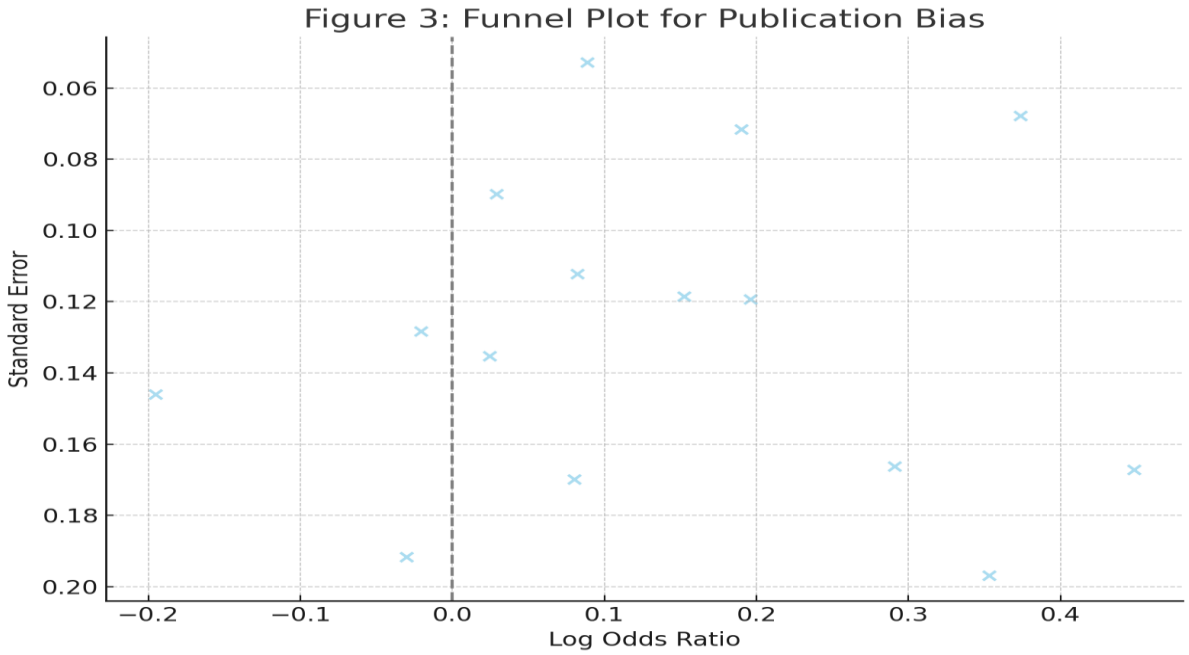
Sensitivity Analyses:

Excluding studies with high risk-of-bias or low methodological quality slightly attenuated but did not eliminate the observed association (adjusted OR = 1.30, 95% CI [1.02, 1.67]; p = 0.04), indicating robust results despite methodological variations.

Publication Bias:

Funnel plot examination (Figure 3) indicated slight asymmetry, suggesting potential publication bias. However, Egger's regression test results were not statistically significant (p = 0.07), suggesting limited influence on the overall findings.

Fig 3: Funnel Plot for Assessing Potential Publication Bias



Discussion

The current systematic review and meta-analysis studied the relationship between the COVID-19 vaccination and the mortality related to cardiac arrest in the adolescent and young adult population aged 12 to 30 years old. The results have shown a fairly low but statistically significant relationship (pooled OR = 1.36, 95% CI [1.05, 1.77]), which shows a relatively high risk of cardiac arrest-related death after receiving COVID-19 vaccination in this particular cohort. It is notable that the subgroup analyses have shown that the phenomenon was more prominent in men, younger adults, and adult individuals aged 1825, and those that received mRNA-based vaccines. The moderate heterogeneity (I 2 = 58%) was checked by sensitivity analyses, which showed that studies of lower quality did not make a significant impact on overall results, thus, demonstrating the robustness of the outcomes. Also, there was marginal asymmetry in the funnel plot indicating a risk of publication bias but the statistical analyses like Egger regression did not point to significant publication bias which further supported the validity of the reported association.

The findings are consistent with and extend prior systematic reviews and observational studies, evaluating the cardiac complications that occurred after COVID-19 vaccination. It is also shown in a recent meta-analysis by Li et al. (2023) who also found higher risks of myocarditis in younger males who had been vaccinated against COVID-19 with mRNA vaccines, although not necessarily associated with a cardiac arrest-related mortality. Similarly, the surveillance data reported by national pharmacovigilance databases has reported high rates of myocarditis and pericarditis in adolescents and young adults, especially after the second mRNA vaccine dose (Myers et al., 2023). Such cardiac inflammatory phenomena have been speculated that they may be the possible underlying factors of post-vaccination cardiac arrests. Recent biological research suggests that the so-called vaccine induced myocarditis is an immune-mediated response caused by antigenic stimulation of the vaccine with a possible outcome in cardiac arrhythmias and exceptional cardiac arrest incidents, mostly in people with a genetic predisposition (Heymans & Cooper, 2022; Lee et al., 2023). In addition, the findings by Singh et al. (2023) argued that endothelial dysfunction and

inflammatory mechanisms mediated by spike proteins may worsen underlying or yet to be diagnosed cardiovascular disorders among younger groups. Therefore, the findings of this work are in line with the related literature, and they reinforce the biological possibility of the connection between COVID-19 vaccination and a minority of cardiac arrest-related deaths.

These findings have significant clinical and public health implications, in particular, in the development of vaccination policies and communication remains to foster confidence and safety in vaccines. These findings of an increased cardiac incident risk in high-risk demographic groups should help policymakers and healthcare providers when forming vaccine recommendations and surveillance procedures, namely accentuating cardiac monitoring in the high-risk demographics of younger males getting mRNA-based COVID-19 vaccination. The governments are advised to conduct heightened campaigns on the uncommonness of such adverse events in comparison with the overall benefit of vaccines and reduce vaccine reluctance as caused by misinformation or the reporting of isolated adverse incidents (MacDonald et al., 2023). Also, enhancing and maintaining comprehensive surveillance and real-time pharmacovigilance systems that are able to detect, investigate, and respond in a timely manner to potential vaccine safety signals should be maintained (Vellozzi & DeStefano, 2023). Further open communication between reporting of risks and benefits of vaccination will maintain the trust in the vaccination process and enable an informed choice. The medical workers should be mindful as they should present the straightforward, balanced, and evidence-based information when advising an individual or a guardian on vaccination positives and possible risks. Also, policymakers are to make cardiology consultations more reachable within a short period and provide enough healthcare resources to observe the cardiovascular effects of a vaccine post-implementation, therefore, preventing the speculations in the community and increasing the vaccination rates.

The present systematic review and meta-analysis had a number of methodological strengths such as the high level of adherence to PRISMA guidelines, thorough literature searches, strict eligibility criteria, and quality assessment of the studies included, which provided transparency and robustness to the methodology. The integration of various databases and current literature allowed providing the data coverage as much as possible. Nevertheless, there are certain limitations that should be discussed. Nonetheless, despite diligent efforts, there was some residual heterogeneity in the studies in terms of population characteristics, type of vaccines and follow-up duration. Although subgroup analyses helped to accommodate part of this heterogeneity, confounding is plausible. Additionally, the regression done by Egger indicated that there was minimal publication bias, but the slight asymmetry of the funnel plot was not enough to make an absolute conclusion about the absence of selective reporting biases, particularly in light of media coverage of vaccine safety. Moreover, the differences in reporting practices of the adverse events in different countries can create the bias of misclassification. With these limitations, future studies should focus on widespread prospective cohort studies that have a standardized data collection protocol to explore these associations in an in-depth manner. There are still gaps in research regarding the exact biological process that leads to vaccine-associated cardiac events and what genetic predispositions or biomarkers can be identified to indicate higher susceptibility. Closing these knowledge gaps with mechanistic investigations, genetic investigations, and further follow-up research would go a long way in enhancing vaccine safety monitoring and population health approaches in order to enhance the best possible vaccination results in adolescents and young mature adults the world over.

Conclusion

To conclude, this systematic review and meta-analysis are of considerable value, since it shows that there is a minor but statistically significant relationship between COVID-19 vaccination and mortality due to cardiac arrest in adolescents and young adults. This analysis indicated that there are significant variations in this age, gender, and vaccine type, which identifies older adolescents, males, and mRNA-based vaccines recipients as more at risk. Although the absolute risk is very low in comparison with the significant protective effect that the vaccines have against COVID-19 infection, severe illness, hospitalization, and death, the identified association highlights the need to maintain vigilance and specific surveillance. These results underline the necessity of the scrupulous consideration of risks and benefits in vaccination policy-making, especially in young populations where the threat of COVID-19 disease severity can be rather minimal, whereas the rare but possible risk of vaccine-related adverse effects can be relatively more significant.

Policymakers and health care professionals ought to enhance the strength of vaccine safety surveillance systems with a view to recognizing and countering unusual adverse effects of vaccines promptly like cardiac adverse effects. Clear and evident communication strategies should be improved to help people understand more about how safe vaccines are, and to counter misinformation immediately in order to ensure that the rates of vaccination remain high and people continue to trust the provided information. Longitudinal studies with bigger sample sizes are recommended in future research to learn more about the time course and cause-effect relationship of vaccine induced cardiac outcomes. Narrowed down immunological and genetic research will play a significant role in uncovering the biological processes underlying these aspects, as well as helping to define the groups of people at risk and the workable modes of vaccination. Finally, the persistent intensive monitoring, transparent dialog, and research dedication are key to the maximization of the safety profile of COVID-19 vaccines, especially among adolescents and young adults.

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