
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

## Incidence of Myocarditis after Messenger RNA Vaccine for COVID-19 in Young Male Recipients

We have read with great interest the study by Wang et al.[1] They performed a meta-analysis including 5 studies and have shown that incidence of myocarditis was 0.0011% (95% confidence interval [CI] 0.0005 to 0.0025) in subjects vaccinated with the Messenger RNA (mRNA) COVID-19 vaccine.[1] Another meta-analysis including 7 studies done by Cordero et al[2] demonstrated the incidence of myocarditis was 0.0035% (95% CI 0.0034 to 0.0035). These studies have shown a very low incidence of myocarditis after the COVID-19 mRNA vaccine. However, we still have some other concerns that were not analyzed in these systematic reviews: the risk difference between BNT162b2 and mRNA-1273 and the increased risk of acute myocarditis in the young population, especially after the second dose in male teenagers.[1,2] However, several articles regarding this topic have been published since the database search of these systematic reviews. Therefore, we have increased the number of studies and added a subanalysis of the incidence of acute myocarditis by the types of vaccine administered and in young males who received the second dose of the mRNA vaccine.

On February 1, 2022, a literature search was performed using PubMed, Web of Science, the Cochrane library, and medRxiv by the search terms "COVID-19", "SARS-CoV-2", "vaccine", "myocarditis", and so on. We selected 13 eligible reports,[3−15] including 3 reports demonstrating incidence of myocarditis after the second dose of mRNA vaccine in young males (16 to 19 years old).[4,9,11] A total of 8 reports were from the United States,[4−6,10−14] 3 from Israel,[3,9,15] 1 from Denmark,[7] and 1 from Hong Kong.[8] Data of BNT162b2 or mRNA-1273 were assessed. The incidence of myocarditis was calculated using a random-model meta-analysis using the generic inverse variance method (RevMan version 5.4; Cochrane Collaboration, London, United Kingdom) Figure 1. demonstrated the results of a pooled meta-analysis. The incidence of myocarditis was 2.66 (95% CI 2.26 to 3.07) per 100,000 doses in an analysis regardless of age and gender (Figure 1); only 9.45 (95% CI: 5.35 to 13.55) among young males who received the second dose (Figure 1). Subgroup analyses suggested a trend toward higher event risk among those inoculated with mRNA-1273 (2.62, 95% CI, 0 to 6.23) than those with BNT162b2 (1.67, 95% CI, 0.59 to 2.75) (Figure 2). The heterogeneity of included data was substantial in these analyses ($I^2$ >60%).

We have demonstrated that the incidence of acute myocarditis after the second dose of mRNA vaccine in

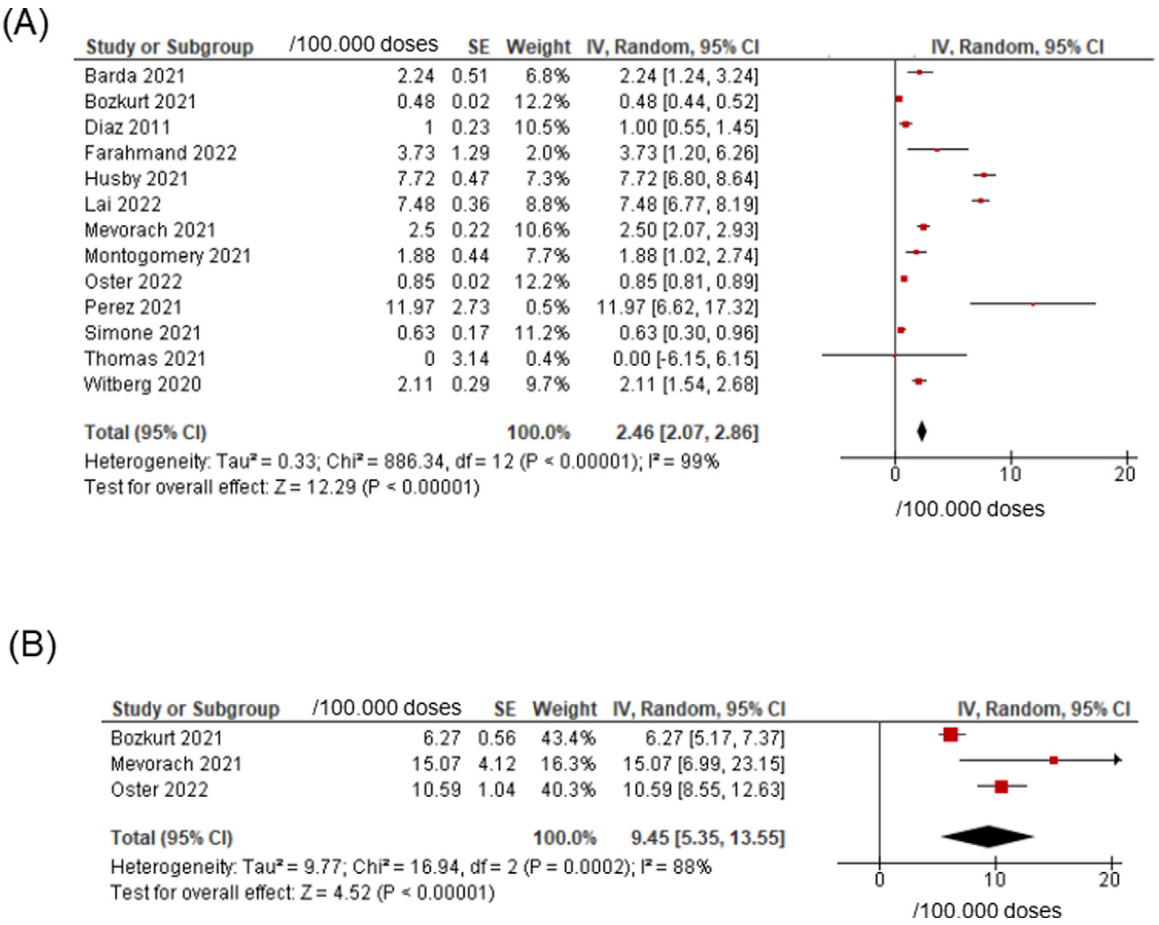


Figure 1. Incidence of acute myocarditis/pericarditis after COVID-19 mRNA vaccination *(A)* Incidence of myocarditis was 2.66 (95% CI: 2.26 to 3.07) per 100,000 doses.*(B)* Incidence of myocarditis and 9.45 (95% CI: 5.35 to 13.55) per 100,000 doses after second dose in a young male.

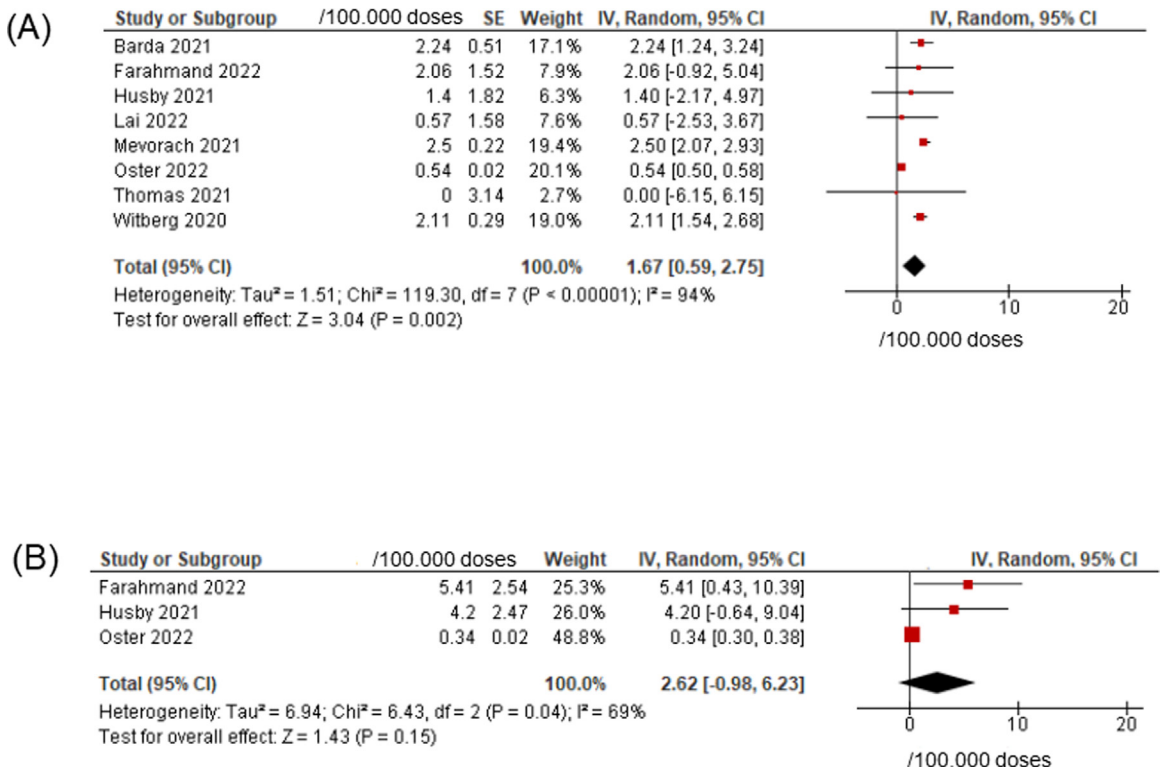


Figure 2. Incidence of acute myocarditis/pericarditis by the types of COVID-19 mRNA vaccination *(A)* Incidence of myocarditis was 1.67 (95% CI: 0.59 to 2.68) per 100,000 doses in BNT162b2. *(B)* Incidence of myocarditis and 2.62 (95% CI: 0 to 6.23) per 100.000 doses in mRNA-1273.

adolescent males is higher than that of the general population but substantially lower than the incidence of myocardial injury or myocarditis caused by COVID-19 infection (1.000 to 1.400 per 100.000 patients with COVID-19).[16] Typically, myocarditis can be diagnosed within days of mRNA vaccination. Symptoms are self-limiting and improve rapidly in almost all patients. The risk of occurrence of myocarditis is low and the short-term outcome is favorable. A recent study has shown that 76.3% of patients had an abnormal myocardial enhancement detectable on magnetic resonance imaging, indicating myocardial fibrosis/necrosis.[17] The long-term effect of myocardial fibrosis/necrosis on the heart is unknown; therefore, monitoring of these populations is desirable. In addition, the risk of myocarditis after the booster shot is unknown, data accumulation is also desirable. In this situation, elevated risk of myocarditis after mRNA vaccine should be known to recipients, but it should be also noted that the benefit-risk analysis performed by the Centers for Disease Control and Prevention has shown a positive balance of vaccination for all age groups of both genders. Further studies that focus on evaluating risk factors and mechanisms of developing acute myocarditis are needed, especially among young male recipients, as mRNA vaccine will become more widely available in young children.

## Disclosures

The authors have no conflicts of interest to declare.

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## Secular Trends in Prevalence of Heart Failure Diagnosis over 20 Years (from the US NHANES)

Heart failure (HF) is a well-recognized global public health problem with a diverse natural history and negative quality-of-life effects.[1] The definition of HF has also changed, covering an increasingly broad clinical condition and phenotypic spectrum of patients.[2] Previous projections suggested a substantial increase in HF prevalence by the year 2030 for patients of all ages[3] and increasing trends of predicted risk for HF development.[4] However, it is unknown to what extent the evolution of definition criteria, availability of effective prevention strategies, improved survival rates, aging of populations, and changes in epidemiology of cardiovascular risk factors and coronary heart disease (CHD) over the last 20 years have affected HF prevalence in the United States. We examined secular trends in a serial cross-sectional study cohort of the US National Health and Nutrition Examination Survey (NHANES).[5]

We considered adults in NHANES between 1999 and 2018 with available information on HF diagnosis and the relevant medical conditions of CHD and myocardial infarction at each 2-year survey cycle. The information of interest was self-reported according to predefined questionnaires.[3] We gathered information on age and sex and investigated the secular change in HF prevalence by calculating age- and sex-adjusted prevalence rates of HF for each 2-year survey cycle. We calculated the prevalence of HF for each NHANES cycle using survey-weighted methods.[6] Linear and restricted cubic spline meta-regression models were used to examine the secular trends over time (using survey cycles) while controlling for CHD prevalence as the main cause of HF in adults. Myocardial infarction was not considered in the models because of multicollinearity with the CHD variable. All analyses were conducted with R, version 4.0.2 (R Foundation, Vienna, Austria).

An unweighted total of 53,409 subjects (27,802 women, 25,607 men) over 10 survey cycles with available information on previously medically diagnosed HF were included in our analysis. Overall, 1,834 NHANES participants across all survey cycles reported HF (832 women, 1,002 men) Table 1. displays the range of prevalence estimates in subgroups. The HF prevalence remained relatively stable over the 20-year period and ranged from 1.9% to 2.6%, 1.6% to 2.9%, and 2.0% to 2.9% for all subjects, women, and men, respectively, without evident secular trend (Table 1, Figure 1). In ≥65-year-old subjects, the HF prevalence was considerably higher, with a wider range of estimates of 5.5% to 10.4%, 4.7% to 10.8%, and 6.2% to 12.2% for all subjects, women, and men, respectively. The HF prevalence increased sharply during the survey cycles from 1999 to 2004 in all subjects (5.5% to 9.8%), women (4.9% to 8.0%), and men (6.2% to 12.2%), with $p < 0.05$ for all changes in the slope (Table 1). After 2004, the same subgroups followed a similar pattern without pronounced variation in prevalence estimates, but with a trend toward lower values. By 2017 to 2018, the prevalence decreased to 6.4%, 5.7%, and 7.3%, respectively (Figure 1). The meta-regression model indicated stable HF prevalence over 20 years for younger subjects (<65-years-old). The sample sizes in each cycle were different, and the precision of HF prevalence estimates was not homogeneously distributed along the entire range of subgroup sizes (Figure 1). The higher prevalence estimate variability per cycle pertained to the older subjects for whom small-sized subgroups and less precise estimates were available.

Overall, despite population aging and increasing broadness of HF definition over time, we found a relatively stable HF prevalence in NHANES over the 20-year period (1999 to 2018), with a change of <5% in prevalence across all cycles and subgroups. A sharp increase in HF prevalence was observed in older subjects in between 1999-2004, which was diminished in the subsequent years. This analysis is limited to self-reported medical conditions, which