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.

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Letters

Impact of Vaccination on Major Adverse Cardiovascular Events in Patients With COVID-19 Infection

SARS-CoV-2 infection increases the risk of major adverse cardiac events (MACE) and long-term cardiovascular sequelae after recovery.[1] However, the association of vaccination on cardiovascular outcomes following infection has not been elucidated in the United States. We investigate association between vaccination and MACE among patients with prior SARS-CoV-2 infection.

Using data from the National COVID Cohort Collaborative (N3C), we included patients aged 18 to 90 years who were initially infected with SARS-CoV-2 between March 1, 2020, and February 1, 2022.[2] Starting from the first day following initial infection, the follow-up time was 180 days. We considered mRNA vaccines by Pfizer-BioNTech and Moderna and viral vector vaccines by Johnson and Johnson. Individuals were classified as fully vaccinated if they received ≥2 mRNA vaccines or 1 Johnson and Johnson vaccine ≥14 days before SARS-CoV-2 infection and as partially vaccinated if they received only 1 mRNA vaccine or their second mRNA or 1 Johnson and Johnson vaccine within 14 days of infection. Previous work suggests that COVID-19 vaccination may be associated with cardiovascular events within a few days.[3] Although causality is unclear,[4] we assess risk of MACE 14 days following last recorded vaccination to address this possibility and mitigate survivor bias. We excluded patients with ≥5 vaccine doses. We defined MACE by a composite set of diagnostic codes (OMOP codeset ID: 516422864). This study was approved by the Institutional Review Board at Mount Sinai.

What is the clinical question being addressed?
How does vaccination impact the occurrence of MACE in patients developing SARS-CoV-2 infection?

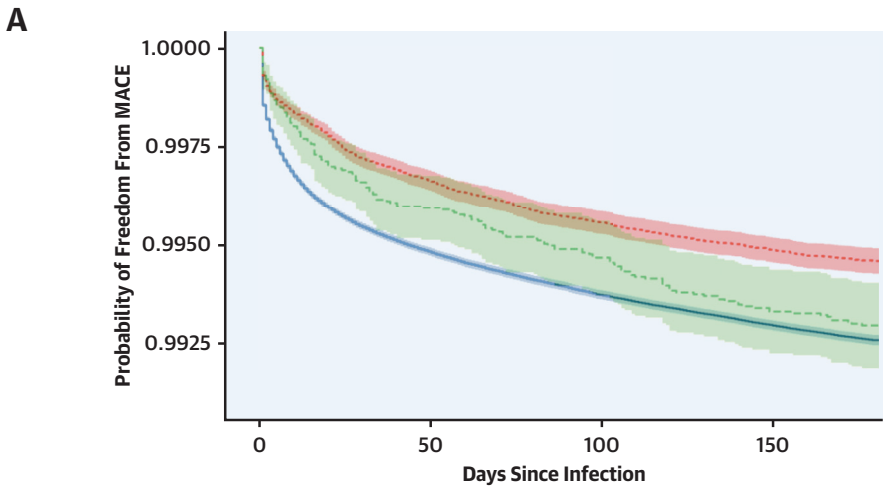
What is the main finding?
Either partial or complete vaccination is associated with a lower risk of MACE after SARS-CoV-2 infection.

We compared characteristics between individuals with and without MACE through the chi-square test. We used Cox proportional hazards to assess vaccination association with MACE. We adjusted for demographic characteristics, months since January 20, 2020 (first U.S. COVID-19 case), and comorbidities, classified by ≥2 entries on separate calendar days in patients' electronic health record, that were significant in univariate analyses to calculate adjusted HRs (aHR) and 95% CIs.

Among 1,934,294 patients, mean age was 45.2 years, and 55.9% were women. In total, 1,573,036 (81.3%) were White, 45,723 (2.4%) were Asian, 300,031 (15.5%) were Black, 12,324 (0.6%) were "other," and 3,180 (0.2%) were Native Hawaiian or Pacific Islander. A total of 195,136 (10.1%) patients were fully vaccinated, 22,707 (1.2%) were partially vaccinated, and 1,716,451 (88.7%) were not vaccinated. Overall, MACE was observed among 13,948 patients (0.7%): 12,733 cases occurred among non-vaccinated patients (0.7% of these patients), 160 in partially vaccinated patients (0.7%), and 1,055 in fully vaccinated patients (0.5%).

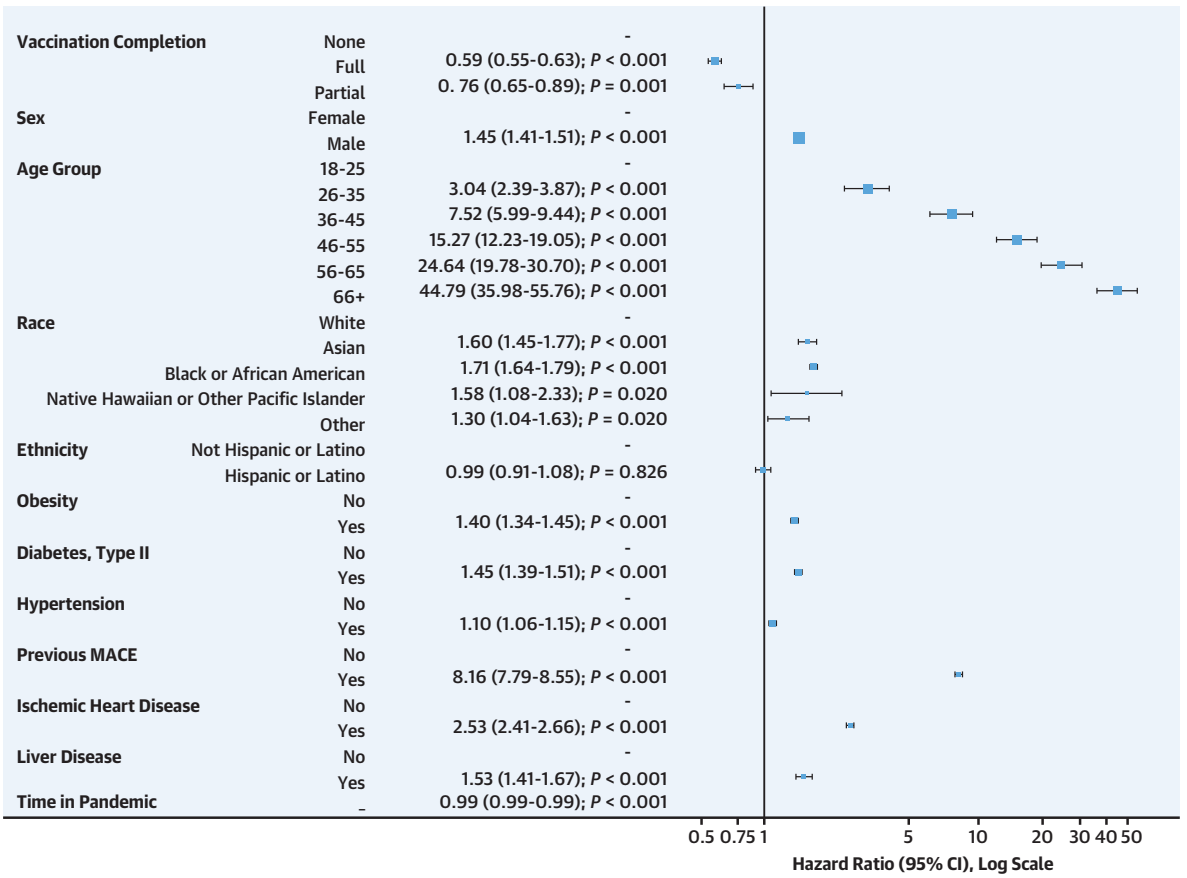
From index infection, median time to MACE was 17 days (IQR: 3-67 days) (**Figure 1A**). In total, 3,175 patients died following MACE. Patients with and without MACE had significant differences in comorbidities including previous MACE (29.1% vs 0.9%; $P < 0.001$), type II diabetes (33.9% vs 7.5%; $P < 0.001$), hyperlipidemia (50.7% vs 14.4%; $P < 0.001$), ischemic heart disease (40.6% vs 3.9%; $P < 0.001$), liver disease (4.0% vs 0.8%; $P < 0.001$), and obesity (29.4% vs 16.4%; $P < 0.001$). Cox proportional hazards model showed full (aHR of 0.59; 95% CI: 0.55-0.63) and partial (aHR of 0.76; 95% CI: 0.65-0.89) vaccination were associated with reduced risk of MACE (**Figure 1B**). Median time from last vaccination to MACE is 212 days (IQR: 133-293 days). Risk of MACE significantly increased with male sex; age, notably among patients ≥66 years of age; and comorbidities, especially previous MACE.

FIGURE 1 Kaplan-Meier Curve and HRs for Subgroups Stratified by Vaccination Status



Number at risk

No Vaccination	716,451	1,707,577	1,705,689	1,704,379
Full Vaccination	195,136	194,484	194,272	194,136
Partial Vaccination	22,707	22,615	22,586	22,555



(A) Kaplan-Meier curve for patients with COVID-19, stratified by full **(red)**, partial **(green)**, and no **(blue)** vaccination. **(B)** Forest plot with subgroup analysis. MACE = major adverse cardiac events.

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Our results are concordant with Kim et al,[5] who analyzed data from the Korean registry and found full vaccination was associated with decreased risk of myocardial infarction and ischemic stroke after COVID-19. However, the distinguishing strength of our work is that it draws from the largest open U.S. database of COVID-19-positive cases and control subjects, with greater size and racial diversity. We also investigated partial vaccination and included Johnson and Johnson vaccines, whereas previous work considered mRNA only.

Limitations include unmeasured confounding variables and inability to factor in vaccines beyond those distributed in the United States. However, although this would increase the number of vaccinated individuals, included vaccines comprise most U.S. vaccinations. We also did not consider SARS-CoV-2 reinfections following index illness, because patients may present with positive tests for varying periods. Finally, we could not account for different SARS-CoV-2 variants underlying infection.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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