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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Conflicts of interest
The authors disclose no conflicts.

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Reply. We thank Drs Tanaka and Vander Weg for their interest in our research exploring COVID-19 vaccination in liver transplant recipients.[1] They discuss several excellent points and clarifications on the methodology, and we appreciate the opportunity to respond.

We chose not to adjust for the etiology of the liver disease that led to transplantation. The most common indication for liver transplantation in the VA during the study period were alcohol and chronic hepatitis C–related cirrhosis, both of which are uncommon causes of significant liver disease after transplantation.[2,3] Therefore, we thought that unlike studies of participants with cirrhosis, the condition that led to cirrhosis was not a potential confounder in a study of transplant recipients.[4] The variables we chose to adjust for in our multivariable analysis included those that were used in early studies published on the topic.[5,6] However, we agree that diabetes mellitus, race/ethnicity, and geographic location within the US are important risk factors for COVID-19.[7] We therefore repeated our analysis by controlling for the suggested variables, including location within the US (northeast, southeast, midwest, south, northwest, and southwest), race/ethnicity, and diabetes mellitus, in estimating the propensity scores. We also controlled for diabetes mellitus and race in the Cox hazard model. Our revised analysis shows that the observed associations are similar to those from the original analysis, with full COVID-19 vaccination being associated with a significant reduction in COVID-19 (adjusted hazard ratio [aHR] 0.33, 95% confidence interval [CI] 0.23–0.49; $P < 0.0001$), symptomatic COVID-19 (aHR 0.32, 95% CI 0.19°0.55; $P < 0.0001$), and COVID-19 related death (aHR 0.11, 95% CI 0.03–0.37; $P = 0.0001$).

Regarding outcomes, we reported the time to a positive PCR test, time to symptomatic COVID-19, and the time to COVID-19–related death. By definition, participants with a positive SARS-CoV-2 PCR test (defined as COVID-19) are either symptomatic or asymptomatic, and COVID-19–related death occurs only after being infected with COVID-19. Therefore, we do not consider these as competing events.

We did set different "time zeros" for the fully vaccinated and control subjects to match for the time of exposure to COVID-19. We agree that an alternative would be to designate time zero as when vaccines first become available for both groups and treat vaccination status as a time-dependent covariate. However, the number of partially vaccinated participants in our study sample was low, and evaluating the effect of partial vaccination was outside the aims of the study.

We confirm that we applied Cox proportional hazard regression to the pseudo-population generated through IPTW, as adjusted for variables that were thought to be associated with outcomes. As Tanaka and Vander Weg pointed out, we did not attempt a doubly robust procedure owing to the possibility of significant unobserved confounding.

We agree on the importance of addressing confounding and selection bias in observational studies. Propensity score weighting and matching are widely accepted to account for observed characteristics in observational studies.[8,9] In our study, we tried to control for observed covariates that might confound the relation between COVID-19 vaccination and outcomes. Sensitivity analysis is a great tool to evaluate the size of confounding and bias of some potential confounders that were not observed, and we performed an analysis to estimate the E-value as suggested.

Our results estimated the aHR of COVID-19 infection at 0.36 (95% CI 0.26–0.51). The E-value for this was 5.0, with the upper confidence limit of 3.33, meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association at least as large as 5.0 with both COVID-19 infection and vaccination. Similarly, the E-values and the upper confidence limits were large: respectively, 4.19 and 2.45 for symptomatic COVID-19 and 14.87 and 4.85 for COVID-19–related death. Compared with the observed risk factors (ranges from 0.93 to 1.29), the unmeasured confounding would need to have a much stronger effect to explain away the reported vaccination association.

We think that the observed variables we used cover most potential confounders. Although, factors such as psychosocial factors, political beliefs, and vaccine hesitancy related to these beliefs may represent unmeasured confounding, it is unlikely that these confounders would significantly change the associations observed, based on the calculated E-values.

All of the above analyses revealed consistent associations as described in our original estimates, indicating that our analyses are consistent and the findings robust.

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Early Life: An Important Window of Susceptibility for Colorectal Cancer

Dear Editors:

Incidence rates of colorectal cancer have increased in young adults (age <50 years) in the US since the early 1990s, and more recently, incidence rates have increased in adults in their early 50s.[1] The shifting epidemiology of colorectal cancer has forced researchers to reconsider what we know about the causes of this disease. Importantly, incidence rates of colorectal cancer have increased across generations or birth cohorts, starting with those born in the 1960s.[2] This so-called "birth cohort effect" implicates exposures in early life as risk factors, consistently with a large literature demonstrating the importance of gestation, infancy, and childhood for several adult cancers.[3] Early life, beginning in utero, represents a critical window of susceptibility, and exposures during this time can translate into large effects on risk of cancer in adulthood.

In a recent issue of *Gastroenterology*, Gausman et al[4] explore the early life hypothesis in the UK Biobank, a large-scale biomedical database that provides medical and genetic information of more than 500,000 volunteer participants. Participants also completed a baseline questionnaire on health history, including early life factors. Gausman et al examined the associations of breastfeeding in infancy (yes vs no), maternal smoking (yes vs no), comparative body size (thinner vs average vs plumper) and height (shorter vs average vs taller) at age 10 years, age at menarche (women only, <11 vs 11–13 vs ≥14 years), and age at first facial hair (men only, younger vs average vs older) and colorectal cancer in young adults (diagnosed at age <50 years). There was no association with any of these 6 early life factors, and the authors conclude that early life factors do not play a meaningful role in colorectal carcinogenesis.

These null results, however, must be interpreted within the context of the study design and several limitations. First, case-control studies of early life factors require now-adult children to recall events and exposures that occurred decades earlier, and this often leads to measurement error. About 75% of study participants completed the baseline questionnaire more than 50 years after birth, and many of the early life factors, such as breastfeeding and maternal smoking, may have been nearly impossible to remember. Although the authors conducted a sensitivity analysis excluding prevalent cases (ie, those diagnosed before completing the baseline questionnaire), this does not address measurement error or improve the accuracy of information recalled from so long ago. Second, breastfeeding and maternal smoking were operationalized simply as yes vs no, and the timing and duration may matter most. Third, body size and puberty may be consequences of earlier or in utero exposures that were not measured. It is possible that these childhood and adolescent factors may not directly increase risk of colorectal cancer even if in utero exposures do. Finally, the participants comprise a mix of persons from higher- and lower-risk generations, an important consideration when studying early life factors.

In contrast to the findings of Gausman et al, a growing literature supports the importance of in utero exposures for colorectal cancer. Swedish and Norwegian studies report an association between birth size and colorectal cancer,[5] and a Finnish study identified placental shape and size as a risk factor.[6] In the US, in utero exposure to synthetic hormones, antinauseants, and sulfonamides—medications frequently prescribed to pregnant women in the 1960s—increases risk of colorectal cancer by 3- to 5-fold.[7] Maternal obesity, pregnancy weight gain, and fetal growth also appear to play a role.[8] Importantly, these studies have linked prospectively collected information on early life with cancer diagnoses ascertained from population-based registries over 60 or more years; they do not rely on participant-reported information and are not subject to the same methodologic challenges of case-control studies. The US study includes persons born from 1959 to 1967, the generation to first experience increasing incidence rates of colorectal cancer.