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CORRESPONDENCE

Analyzing Uncontrolled Confounding of the Perinatal Health Effects of Severe Acute Respiratory Syndrome Coronavirus 2 Infection During Pregnancy

To the Editor—We thank Pei-Yun et al [1] for their interest in our article [2]. They raised some issues with our study not controlling for some potential confounders and not addressing unmeasured effect modifiers that could also be "residual confounders" and claimed that matching on time-dependent propensity score would reduce such residual confounding.

First, like all observational studies, we could not adjust for all plausible confounders, including parity, previous cesarean delivery, and maternal obesity, with the data accessible to us. However, we could have quantified how sensitive our results were to uncontrolled confounding using existing quantitative bias analysis methods [3–6] or the recently introduced E-value [7–9]. For the potential variables—such as parity, previous cesarean delivery, and maternal obesity—suggested by Pei-Yun et al to be confounders of the perinatal health effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pregnancy, each unmeasured variable would need to cause both infection and each poor perinatal health outcome or cause infection (or outcomes) while being associated with outcomes (or infection) over and above the effects of the other unmeasured and measured confounders [3–5]. Lacking data on these unmeasured confounders, we conducted a simple quantitative bias analysis for some of the main results in Table 3 of our article [2]. Specifically, we posited strong or extreme relative risks or hazard ratios (HR of 2 or 3 for each unmeasured confounder) linking the 3 unmeasured confounders to SARS-CoV-2 infection and each outcome (an improbable, hence extreme scenario). We then simulated the amount of uncontrolled confounding (called bias factor) that they would generate together had they been omitted from the analysis and under the assumption that SARS-CoV-2 infection might have had no effect on outcomes [5]. We adjusted our study's HR estimates, dividing them by the bias factor generated from the previous step. We found that our findings mostly held up and were only sensitive to extreme confounding for reported HRs of ≤ 2 (Table 1).

We also calculated the E-value for each reported HR. The E-value has been defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and outcome, conditional on the measured confounders, to fully explain away a specific exposure–outcome association [7]. Given the observed HR reported for each outcome (eg, HR of 2.38 for the effect of SARS-CoV-2 infection on preterm birth), an unmeasured confounder that was associated with both the perinatal health outcome and SARS-CoV-2 infection by a relative risk or HR equal to

Table 1. Risks of Pregnancy Outcomes Following Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the Third Trimester, With Corresponding E-Values and Bias Adjustments for Strong or Extreme Uncontrolled Confounding

Pregnancy Outcome	Adjusted HR (95% CI)[a]	Point Estimate Adjusted for Spurious Association due to 3 Strong Unmeasured Confounders[b]	Point Estimate Adjusted for Spurious Association due to 3 Extremely Strong Unmeasured Confounders[c]	E-Value (for the Point Estimate)[d]
Prelabor rupture of membranes	1.59 (1.25–2.04)	1	0.80	2.56
Induction of labor	2.05 (1.74–2.42)	1.28	1.02	3.52
Cesarean delivery	2.09 (1.74–2.50)	1.30	1.05	3.60
Preterm birth	2.38 (1.78–3.19)	1.49	1.19	4.19
Clinician-induced	3.38 (1.93–5.90)	2.11	1.69	6.22
Spontaneous	2.16 (1.54–3.02)	1.35	1.08	3.74
Fetal growth restriction	2.09 (1.71–2.57)	1.30	1.05	3.60
Postpartum hemorrhage	2.08 (1.52–2.84)	1.30	1.04	3.60

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted HRs obtained from Cox proportional hazard models comparing the risks of outcomes among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–infected pregnancies vs uninfected pregnancies, treating SARS-CoV-2 infection as a time-varying exposure, and adjusting for maternal age, race/ethnicity, household income, presence of a preexisting medical condition, and week of pregnancy conception. Adapted from [2].

[b]Each HR point estimate in the second column was divided by the simulated bias factor due to not adjusting for 3 binary unmeasured confounders, each of which could have been associated with SARS-CoV-2 infection with a relative risk or HR of 2 and with each perinatal health outcome with an HR of 3; the resulting bias factor was approximately 1.6. See [5] and [10] for more details on the method of simulating the amount bias due to unmeasured confounders.

[c]Same as in footnote b above but with each unmeasured confounder being associated with both the exposure and each outcome with relative risk or HR of 3; the resulting bias factor was approximately 2; this extreme scenario was chosen as an implausible example of uncontrolled confounding since we are not aware of confounders in this topic with such extremely large effects or associations.

[d]E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and outcome, conditional on the measured confounders, to fully explain away a specific exposure–outcome association. See [7–97–9] for details and discussions.

each corresponding E-value (eg, 4.19 for preterm birth), conditional on the measured confounders, could explain away our HR estimate of the effect of SARS-CoV-2 infection on the outcome (eg, preterm birth), but weaker joint unmeasured confounder associations could not [9]. Again, we conclude that it would take very strong or extreme confounders acting in concert to explain away all our findings. We are not aware of the proposed unmeasured confounders having such strong links to our study exposure and outcomes. For example, the association between obesity and SARS-CoV-2 infection has been estimated to range from 1.15 to 1.39 [10], and similar ranges of association estimates have been observed for obesity and preterm birth. The existence of such strong confounding therefore seems incompatible with the relatively low incidence of adverse outcomes reported in our study.

Second, Pei-Yun et al are concerned that we neglected effect modifiers that may or may not cause residual confounding. Unmeasured effect(-measure) modifiers should not alter our study conclusions provided they are not confounders. Unmeasured effect modifiers can be confounders, in which case we would conduct quantitative bias analysis as we did in this correspondence. Our reported estimates simply average over unmeasured effect modifiers without bias.

Finally, Pei-Yun et al claim that matching on time-dependent propensity score [1] would have minimized the impact of residual confounding. We respectfully disagree, because there is no known statistical method that can eliminate confounding by unmeasured variables without using external information or using an alternative causal effect identification strategy (such as the instrumental variable or the front-door formula approach) that is not based on the typical exposure–outcome confounding adjustment. Thoughtful quantitative analysis is therefore indispensable when uncontrolled confounding is of concern [3–9].

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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