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CORRESPONDENCE

Unlinking time zero from test-negative controls exaggerates risk from COVID-19

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DEAR EDITOR,

The inclusion of test-negative controls allows for the comparison to the same illness and health care seeking behavior, but different diagnosis.[1] One key aspect of test-negative study designs is to ensure an equivalent time zero between groups. Lim et al sought to examine the long-term cardiovascular and thrombotic complications specific to a COVID-19 illness by including a control group of individuals with an acute respiratory illness (ARI) and tested negative for SARS-CoV-2.[2] Cases were identified based on the date of the positive test during the delta variant surge, whereas controls were artificially assigned an index date of infection (T_0) to match the distribution of cases between September and November 2021. This is problematic. If non-COVID ARI also increases the short-term risk of heart attacks, strokes, and thromboembolic events, as shown in previous studies, [3–5] then authors introduce two major biases by misclassifying time zero—ascertainment and immortal time bias (**Figure**).[6]

Delaying time zero in the control group *after* the date of the ARI will overestimate the association of COVID-19 on these complications by differential ascertainment of short-term events in COVID-19 group but not for all the control participants. In fact, the authors excluded individuals with an outcome of interest during the 5 years prior to the artificially assigned time zero. Thus,

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participants with an ARI that occurred between April 2020 and August 2021 who experienced an outcome will have been excluded from the analysis.

Conversely, defining an earlier time zero in the control group *before* the date of the ARI introduces immortal time bias because these individuals have survived at least until the date of their ARI. Furthermore, the additional time added is unlikely to carry the same risk of complications as does the time-period immediately after the ARI, thus likely further overestimating the adverse risks after COVID-19.

To overcome these biases, the authors should repeat their analyses, but only include test-negative control participants who had an ARI during the delta surge.

Conflicts of Interest: none

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FIGURE LEGEND:

Figure 1. Biases Introduced by Unlinking Time Zero from Test-Negative Controls

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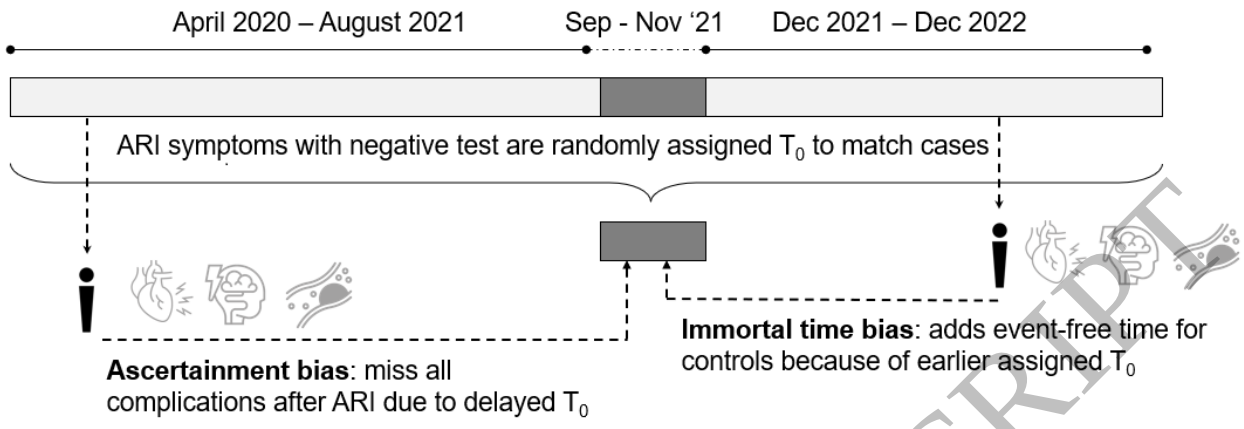

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