DAG (5). In Figure 2 (again, representing an association that may be studied in a hypothetical study), hypertension is a collider on the path from OSA to PO. Variable *U* in Figure 2 is an unmeasured variable, such as a medication or illness, that affects the risk of both hypertension and PO. If the data analyst controls for hypertension but does not control for *U* in this situation, then collider stratification bias will occur (3, 6). Controlling for a collider can result in a bias that is strong enough to move the observed association in a direction that is opposite of the true effect (3). Interestingly, in the analysis by Cade and colleagues, the odds ratio for the outcome of inpatient admission moved from 1.55 in the unadjusted model to 0.91 in model 4 (1). Without additional information, we cannot offer a reason why the odds ratio shifted to the other side of the null value of 1 in Cade's study.

DAGs are useful tools for identifying the minimally sufficient set of variables to control for to reduce confounding bias (3). Investigators may disagree over which DAG is correct for any given possible association. The DAGs presented here are overly simplistic. A freely available tool for creating DAGs is DAGitty (available at www.dagitty.net). ■

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Reply to Mulla and Pathak

From the Authors:

We thank Dr. Mulla and Dr. Pathak for their interest in our study (1) and their important discussion on causal modeling approaches. We agree that directed acyclic graphs are useful visual tools for representing assumptions used in causal modeling; that is, directed acyclic graphs illustrate the assumed relationships of candidate covariates (i.e., antecedents, confounders, mediators, and consequences) with the primary exposure and outcome of interest and thus can aid in selecting covariates in regression models, as was recently highlighted in a guideline on causal inference (2). Mulla and Pathak argue that hypertension is in the intermediate pathway linking obstructive sleep apnea (OSA) to poor coronavirus disease (COVID-19) outcomes, and by adjusting for hypertension the true causal effect of OSA will be underestimated. We agree with this concern, and because of that, we showed a range of models but emphasized the results of the simpler models to support the importance of further consideration of OSA as an unrecognized COVID-19 morbidity risk factor. The inclusion of a range of statistical models with successively more covariates reflected our uncertainty over the biological bases of COVID-19–related morbidity and how OSA may influence mechanistic pathways (3). In particular, hypertension is a complex condition with multifactorial etiologies, and it may be overly simplistic to assume that all potential subtypes of hypertension that may increase risk for COVID-19 are consequences of OSA (thus, "hypertension" as identified in the electronic medical record may include subtypes that operate as confounders as well as mediators). Assessing temporality of diagnoses is challenging at a referral hospital where patients with COVID-19 may have been transferred from outside hospitals and do not have prior electronic health records in our system. Mulla and Pathak correctly point out that inappropriate inclusion of covariates may also introduce collider bias (i.e., opening a "back door" by adjusting for factors that are causally influenced by both the exposure and outcome), and that adjusting for colliders may even reverse the directionality of the observed associations. Although they point to the results of the model 4 odds ratio (0.92) to support that contention, in fact, the 95% confidence interval for this estimate was

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wide, indicating low precision. Nonetheless, recent work has highlighted the many ways that observational studies of COVID-19 risk factors are susceptible to collider bias, including nonrandom sampling (4). Therefore, we wholeheartedly endorse the need for careful consideration of covariates, especially with COVID-19 research, in which so many risk factors are highly correlated and samples often derive from nonrandom ascertainment. However, we also feel it is important to acknowledge the limitations of our understanding of underlying causal mechanisms, and the value in comparing estimates across models. Moreover, given the strength of our minimally adjusted models as well as subsequent papers that support OSA as a COVID-19 morbidity risk factor (5, 6), further research is warranted to understand whether sleep apnea–related hypoxemia, endothelial dysfunction, coagulopathy, inflammation, cardiac dysfunction, and other related pathologies contribute to the excessive COVID-19 morbidity and mortality. In parallel, there is need to develop improved prediction equations (where assumptions made for causal modeling generally do not apply but issues such as external validation are critical) to better identify individuals to prioritize for early vaccination, aggressive early treatment, and more intensive monitoring (2). ■

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Subclinical Tuberculosis: Some Flies in the Ointment

To the Editor:

Clinical, epidemiological, and biological evidence convincingly supports the existence of subclinical tuberculosis (TB), as argued by Kendall and colleagues (1). However, a certain imprecision of definition, compounded by varying usages in research literature, hampers conceptual clarity. Following Drain and colleagues, the authors define subclinical TB as "disease due to viable *M. tuberculosis* bacteria that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays" (2). This definition is intended to capture two salient features: first, that active TB can be asymptomatic and will therefore go largely undetected by current means (self-presentation

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