

For the SMART Investigators and the Pragmatic Critical Care Research Group

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Ⓞ Sleep Apnea and Poor COVID-19 Outcomes: Beware of Causal Intermediates and Colliders

To the Editor:

We read with interest the report by Cade and colleagues on the association between obstructive sleep apnea (OSA) and adverse outcomes such as hospitalization and death among adults with coronavirus disease (COVID-19) (1). We commend the authors for asking this important research question and their thorough analysis. However, for each of the three outcomes that they investigated, the

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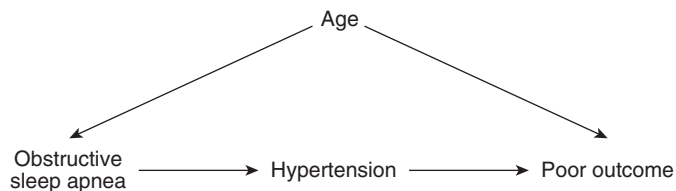


Figure 1. Directed acyclic graph for the effect of obstructive sleep apnea on poor outcome among patients with coronavirus disease (COVID-19). Age is a confounder of the association, whereas hypertension is a causal intermediate.

effect of OSA as measured by the odds ratio was progressively attenuated as additional variables were adjusted for. It is possible that a portion of this attenuation may be due to overadjustment bias (2).

Overadjustment bias occurs when a data analyst controls for an intermediate variable on the causal path from the exposure variable (e.g., OSA) to the outcome (e.g., hospitalization due to COVID-19) (2). Causal diagrams may be used to identify causal intermediates and hence avoid overadjustment bias (2, 3).

Figure 1 is a causal diagram known as a directed acyclic graph (DAG). In this simplified DAG from a hypothetical study, OSA is the exposure and the endpoint is poor outcome (PO), which represents the composite endpoint of inpatient admission, receipt of mechanical ventilation, or death. OSA may lead to hypertension, which in turn is a risk factor for a PO. Hypertension is a causal intermediate on the path between OSA and PO. According to this DAG, hypertension should not be adjusted for using stratification or other techniques such as multiple regression modeling. Controlling for (adjusting for) an intermediate will prevent the estimation of the total causal effect of OSA on PO (3).

In Figure 1, the data analyst believes the patient's age is a confounder of the association between OSA and PO. A confounder is a variable that is related to both the exposure and the outcome yet is not an effect of the exposure (4). When inspecting a DAG, a variable can be identified as a confounder of the association between the exposure and the outcome if it is a common cause of the exposure variable and the outcome (3). Confounders should be adjusted for.

An additional benefit of DAGs is the ability to identify colliders. A collider is a variable where two arrowheads meet (3). In other words, a collider is a variable that is in the middle of an inverted fork in a

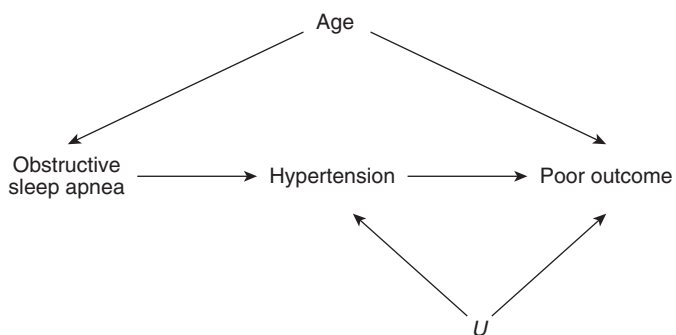


Figure 2. Directed acyclic graph for the effect of obstructive sleep apnea on poor outcome among patients with coronavirus disease (COVID-19). Hypertension is a collider on the path from obstructive sleep apnea to poor outcome. *U* is an unmeasured variable such as a medication or illness.

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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