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LETTER TO THE EDITOR

The total effect of ethnicity on COVID-19 outcomes is underestimated when conditioning for comorbidities: response to Learoyd et al.

In a recent study, A.E. Learoyd et al. examined the relationship between ethnicity and COVID-19 outcomes while considering the collider bias due to conditioning for hospitalization [1]. The risk of this bias could be inherent in hospital-based research since hospitalization is usually driven by prognosis determinants. Therefore, if the exposure was also associated with the medical decision to admission, hospitalization would become a collider (Fig. 1A). Consequently, besides adjustment for potential confounders, the authors illustrated the usefulness of weighting by the inverse of the probability of hospitalization as a strategy to correct or mitigate collider bias. However, we believe that certain factors may have adversely affected the purpose of estimating the effect of ethnicity on COVID-19 outcomes in the illustrative example.

Firstly, the use of a composite outcome can introduce bias in estimating effects. Such outcomes often encompass diverse and occasionally counter-directional mechanisms [4]. In the illustrative case, the composite outcome comprised intensive care unit admission and death, which revealed frequency disparities across ethnic groups but in opposing directions. Therefore, the association between the exposure variable and the prognosis can have been attenuated by using a composite outcome [5].

Nevertheless, we considered that the main concern is the adjustment for comorbidities performed in the multiple models (3 and 4). Studies addressing the relationship between ethnicity and clinical outcomes should consider comorbidities as mediators in the causal pathway [6,7]. Thus, adjusting for comorbidities can lead to overadjustment when assessing the total effect of ethnicity. Such adjustment would only be justifiable if the authors' goal was to quantify the direct effect of ethnicity, but not the total effect. In this case, we believe that adjusting only for sex, age, and probably for contextual factors that have a common determinant preceding the individual (eg, due to ancestry) would be appropriate and enough (as suggested in our directed acyclic graphs, Fig. 1B) [2,3,8].

In conclusion, the total effect of ethnicity on COVID-19 outcomes can be underestimated when conditioning from comorbidities. This is because comorbidities are on the causal path from ethnicity to death (and not on a backdoor path). The mentioned issues do not affect the conclusions related to the importance of correcting for collider bias using weighting. However, the differentiation between mediators and confounders is essential to estimate the total effect of distal determinants (such as ethnicity) on health outcomes.

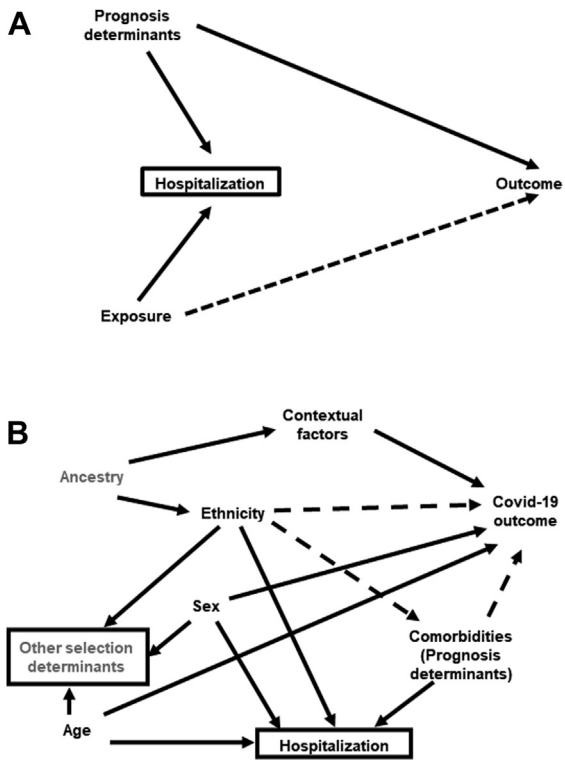

Fig. 1. Illustrative directed acyclic graphs (DAG). A box around indicates the conditioning of the factor; unmeasured factors were written with gray letters; and, the dashed lines refer to the causal paths of interest. In A, the structure of a collider bias is due to conditioning for hospitalization, which is motivated by both prognosis determinants and the evaluated exposure. In B, a suggested causal structure for evaluating the effect of ethnicity on COVID-19 outcomes. The weighting is justified to reverse the conditioning due to restricting the study to hospitalized patients. Furthermore, adjustment for age and sex is justified because, along with ethnicity, they may be associated with unmeasured selection determinants (other than hospitalization) [2]. Contextual factors would be another confounder for being in an alternative pathway involving a common cause related to ancestry [2,3]. In this DAG, comorbidity is a mediator, meaning it lies on the causal path between ethnicity and Covid-19 outcomes.

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What is new?

Key findings

- Collider bias is a concern inherent to studies restricted to hospitalized patients, which can be prevented or mitigated by weighting.
- Additionally, other adjustments may be justified in the evaluation of determinants of clinical outcomes.

What this adds to what was known?

- When evaluating the effect of a distal determinant, such as ethnicity, comorbidities could be mediators and their conditioning could lead to over-adjustment.

What is the implication and what should change now?

- We highlighted the importance of distinguishing between mediators and confounders for a valid estimation of the total effect of distal determinants, like ethnicity, on health outcomes.

CRediT authorship contribution statement

Fredi Alexander Diaz-Quijano: Conceptualization, Writing − original draft. **Luís Ricardo Santos de Melo:** Conceptualization, Writing − original draft.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

None.

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