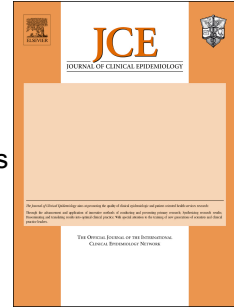


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The complexity of the relationship between ethnicity and Covid-19 outcomes: author's reply

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The complexity of the relationship between ethnicity and Covid-19 outcomes: author's reply

Response to letter to the editor: The total effect of ethnicity on Covid-19 outcomes is underestimated when conditioning for comorbidities

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We thank Dr Diaz-Quijano and Mr Melo for their knowledgeable input into the topic of how bias and adjustment can influence causal relationships. We agree there are inherent biases, some unobserved, in hospital-based research and that even our illustrative example(1) is unlikely to account for every factor. This is partly due to, as raised by our colleagues, the complexity of the relationship between ethnicity as exposure of interest, Covid-19 severity as the outcome and other influencing factors (colliders, mediators, and confounders).

Regarding use of the composite outcome: ICU admission/death within 30 days. This outcome was chosen to reflect suggestions by WHO and others(2–4) that composite outcomes be utilised in Covid-19 research. This literature emphasises that outcomes should reflect the study objective and the stakeholders of interest. We focused on patient-centric measures of disease severity. This included both the composite outcome in question and a non-composite outcome time to death. Our colleagues correctly point out that the estimated effects of ethnic group on our composite outcome do seem to be attenuated compared to the estimated effects when examining time to death. In addition, both the descriptive univariate statistics and other studies(5–7) examining both ICU admission and mortality suggest differing relationships between ethnicity and each endpoint.

Previously, we have highlighted(8) the potential exposure gap in healthcare including ethnic adjustments to risk scores and innate biases of physiological measures which could contribute to the disparate relationships. Additionally, the relationship between ICU admission and comorbidities more or less prevalent in different ethnic groups should be considered.

Regarding the adjustment for comorbidities in models 3 and 4 of our study: We agree comorbidities are probably mediators in the relationship between ethnicity and Covid-19 severity as indicated by our extended DAG(1). This means we have estimated the direct effect of ethnicity on Covid-19 severity rather than the total effect. To emphasise, Table 1 provides the estimated total effect of ethnicity on time to death alongside the direct effect estimated in model 4. The total effect of ethnicity includes a significant association between Black ethnicity and Covid-19 mortality which is attenuated when accounting for comorbidities. The adjustment for comorbidities as mediators is intentional. Most studies(5,9–11) exploring ethnic discrepancies in Covid-19 adjust for comorbidities and make definitive statements about the association without considering unaccounted-for bias. The aim of our illustrative example was to highlight this issue focusing on collider bias due to the evidence for a relationship between ethnicity and Covid-19 hospitalisation(5,11,12) and the clear example in our hospitalised cohort (unadjusted model 1: reduced risk of mortality in Black individuals).

In conclusion, the relationship between ethnicity and Covid-19 is complicated and multi-faceted. We hoped to demonstrate the impact of collider bias on this relationship. Meanwhile our colleagues have highlighted other issues that must be considered. Combined, this discussion emphasises the importance of considering the causal relationships between exposures and outcomes of interest and any colliders, mediators, or confounders that may influence either the association between exposure and outcome or the selection of a cohort.

Death	Direct effect of ethnicity		Total effect of ethnicity	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
White (ref)	1	-	1	-
Black	1.29 (0.87, 1.93)	0.211	1.47 (1.07, 2.02)	0.017
Asian	2.06 (1.15, 3.67)	0.014	2.29 (1.41, 3.71)	0.001
Mixed/Other	0.79 (0.39, 1.64)	0.533	0.85 (0.48, 1.51)	0.583
Unknown	0.96 (0.64, 1.44)	0.838	1.01 (0.72, 1.42)	0.953

Table 1: Association of ethnicity with the risk of death if infected with Covid-19 between Feb-2020-May 2021 (Wave 1 and 2 in the UK) in two models accounting for collider bias. Direct effect of ethnicity is model 4 in Learoyd et al. (2023)(1) – this model adjusts for age, sex, medical history (cardiovascular, kidney and liver conditions, COPD/emphysema, diabetes, and the application of DNAR CPR orders), and IMD quintile. Total effect of ethnicity is the model suggested by Dr Diaz-Quijano and Mr Melo – adjusting for sex and age only. Both models are competing risk regression models with discharge as a competing event using inverse probability weights derived from Mathur et al. (2021)(5) to account for conditioning on hospitalisation. P-values are derived from univariate Wald tests of the relevant hazard ratio. CI=Confidence Interval.

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Declarations of interest

None

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What is new?

Key findings

- Choices of outcomes in clinical research is an important consideration that can influence the conclusions made.
- Adjustments for comorbidities in Covid-19 research is common, despite the influence this has on the effect being measured.

What this adds to what was known?

- We have provided an example of how estimation of the total and direct effect of an exposure on an outcome such as the effect of ethnicity on Covid-19 mortality can produce different results.

What is the implication and what should change now?

- Careful consideration of causal relationships and the estimand of interest is needed when designing studies to ensure the results obtained matched the objectives of the study.