Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Misclassification bias in estimating clinical severity of SARS-CoV-2 variants

Tommy Nyberg and colleagues[1] use an unvaccinated cohort to show differences between the intrinsic severity of the omicron (B.1.1.529) and delta (B.1.617.2) variants of SARS-CoV-2 without confounding by pre-existing immunity. They report an 80% reduction in the severity of the omicron compared with the delta variant, suggesting the possibility of living through the COVID-19 pandemic without social and economic disruptions. However, reliance on SARS-CoV-2 test positivity to identify cases of COVID-19 and on all-cause hospitalisations and deaths as outcomes could have introduced misclassification bias and residual confounding.

Up to one in three SARS-CoV-2 infections are asymptomatic,[2] and this proportion was even greater during the omicron wave.[3] Studies that exclusively use test positivity as the case definition might report inflated hospitalisation and case-fatality rates. Misclassification is exacerbated by the higher prevalence of infection due to more transmissible variants and by the increased ratios of non-severe to severe cases, potentially attenuating the differences in severity between variants. In the appendix, we show the potential effects of three SARS-CoV-2 case phenotypes on apparent hospitalisation and case-fatality rates of SARS-CoV-2 infection with the delta and omicron variants. Misclassification could also differ by age, vaccination status, and comorbidities that influence susceptibility to infection and disease.[4,5]

The use of other data streams might help to populate large datasets when clinical data are scarce or absent. For example, administrative coding could be used to identify reasons for hospital admission that are likely to be related (eg, pneumonia) or unrelated (eg, trauma) to COVID-19,[4] and to identify comorbid conditions for inclusion as covariates in comparative analyses.[4,5] The delivery of therapeutics used specifically or most commonly for COVID-19 (eg, remdesivir and dexamethasone) could enrich for those hospitalised with the disease. Ultimately, applying a probabilistic approach to case definition might allow for estimates of confidence when identifying cases and associating outcomes.

After correcting for misclassification bias, the intrinsic severity of the omicron variant of SARS-CoV-2 might be even lower than that suggested by Nyberg and colleagues.

We declare no competing interests.

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See **Online** for appendix

Authors' reply

We thank Christina Yek and colleagues for their Correspondence regarding our Article.[1] They note that people who test positive for SARS-CoV-2 generally have more severe disease than those who are infected but not tested. This finding could lead to the overestimation of absolute risks, but relative risks are not necessarily biased unless the