

The missing link in ethnicity and covid-19 research – time to separate the risk of infection from the risk of severe disease

Daniel Pan^{1,2}, Shirley Sze³, Christopher A Martin^{1,2}, Clareece R Nevill⁴, Jatinder S Minhas³, Pip Divall⁵, Joshua Nazareth^{1,2}, Laura J Gray⁴, Kamlesh Khunti^{6,7}, Keith R Abrams⁴, Laura B Nellums⁷, Manish Pareek^{1,2}

¹Department of Respiratory Sciences, University of Leicester, United Kingdom

²Department of Infection and HIV Medicine, University Hospitals Leicester NHS Trust, United Kingdom

²Department of Cardiovascular Sciences, University of Leicester, United Kingdom

⁴Department of Health Sciences, University of Leicester, United Kingdom

⁵University Hospitals of Leicester, Education Centre Library, Glenfield Hospital and Leicester Royal Infirmary, United Kingdom

⁶Diabetes Research Centre, University of Leicester, United Kingdom

⁷Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, United Kingdom

Correspondence to:

Dr Manish Pareek

Associate Clinical Professor in Infectious Diseases

Department of Respiratory Sciences

University of Leicester

Email: mp426@le.ac.uk

Word Count: 799

Ethnic minority groups, such as those of Black and Asian backgrounds, continue to be disproportionately affected by covid-19.[1] A large number of studies have emerged investigating the relationship between covid-19 and clinical outcomes, often with conflicting results, especially as to whether those of ethnic minority groups are at increased risk of infection, intensive therapy unit (ITU) admission, and death.[2] These studies usually follow one of three approaches. The first kind of study investigates patients with confirmed or clinically suspected covid-19 in a hospital setting and assesses whether ethnicity is a predictor of severe disease, by looking at rates of ITU admission or mortality. The second are transmission studies which use a community dataset to investigate the role of ethnicity and infection from covid-19. The third involve large datasets representative of a population linked to national databases of death from covid-19. All three studies can be extremely large (ranging from 5 million to over 13 million) and therefore thought to be robust, especially when multiple key confounders, such as age, comorbidity, socioeconomic status and deprivation are adjusted for.[3–5]

Although all of these studies ask relevant research questions, none so far make the distinction between the risk of infection and the risk of severe disease once infected. Variables relating to both outcomes are often grouped together and consequently, the ability to delineate differences in risk by ethnic background continues to be severely inhibited. For example, whilst studies of hospitalized cohorts can adjust for differences between ethnic groups at admission, they miss the crucial information of those who were infected but did not present or get admitted to hospital – which can only be adjusted for in studies which encompass both community and hospitalized patients. However, no transmission studies present the proportion of patients hospitalized, or had died from covid-19, and no population studies investigating the role of

ethnicity have yet adjusted for the simple risk of testing positive for covid-19 when examining mortality.

Compared to non-communicable diseases, where predictors for the development and progression of cardiovascular, chronic lung disease, or chronic kidney disease are similar (eg, smoking, lifestyle habits and the presence of other comorbidities), the risk of getting covid-19 is more related to settings where high intensity, long-duration interactions occur, such as within households or workplaces with poor ventilation, with no definitive evidence yet of an association between environmental virus exposure and subsequent disease severity.[6,7] The risk of severe covid-19 on the other hand is related to obesity, older age, and cardiometabolic comorbidities.[8] In other words, factors relating to increased risk of infection are more likely to be in the public health domain, compared to factors relating to increased risk of disease severity, which are more biological. Ethnicity, being a social construct is intrinsically related to all these variables—but it remains uncertain whether the risk is mainly weighted towards risk of infection or severity of disease.

The simplest method of addressing this problem is for large population studies to acquire data on the number of participants that have been infected with SARS-CoV-2, and adjust for this in subsequent analysis on hospitalization or death. In the UK, this can be done by linking with Pillar 1 and Pillar 2 data from Public Health England, which include community and hospital test results.[9] Transmission studies investigating factors relating to the risk of SARS-CoV-2 infection in the community should also expand to explore how the risk of infection contributes to ITU admission and mortality as secondary outcomes. Finally, prospective biomarker, therapeutic, and vaccine trials must also investigate markers of disease severity or therapeutic efficacy in relation to ethnic group. Recently, the Pfizer BioNTech vaccine appears to be equally

effective across multiple ethnic groups, suggesting that the disproportionate risk of covid-19 on clinical outcomes in these groups may be more likely to be related to increased exposure to the virus rather than severe disease.[10]

If ethnicity is more strongly associated with an increased risk of infection, it would be important to communicate to the general population that for most, simply belonging to an ethnic minority group does not mean they are more likely to die if they get covid-19. A targeted public health approach, focused on risk factors relating to increased risk of infection in ethnic minority groups would also prevent disproportionate death. This will be of particular importance given the emergence of two new variants of SARS-CoV-2 in the UK, both of which appear to have increased infectivity.[11,12] However, should ethnic minorities be found to mainly have a higher risk of disease severity once infected, this provides a powerful argument for the early initiation of effective therapeutics, including prioritising vaccination to these cohorts. To move forward with covid-19 public health policies involving ethnic groups, it is time we acknowledge that the risks of infection are very different to those for severe disease.

References

- 1 Pareek M, Bangash M, Pareek N, *et al.* Ethnicity and COVID-19: an urgent public health research priority. *Lancet* 2020.
- 2 Sze S, D P, Nevill C, *et al.* Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine* Published Online First: 2020.
doi:10.1016/j.eclinm.2020.100630
- 3 Holman N, Knighton P, Kar P, *et al.* Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020;**8**:823–33. doi:10.1016/S2213-8587(20)30271-0
- 4 Barron E, Bakhai C, Kar P, *et al.* Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020;**8**:813–22. doi:10.1016/S2213-8587(20)30272-2
- 5 Williamson EJ, Walker AJ, Bhaskaran K, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–6. doi:10.1038/s41586-020-2521-4
- 6 Cevik M, Marcus J, Buckee C, *et al.* SARS-CoV-2 transmission dynamics should inform policy. *Clin Infect Dis* 2020.
- 7 Meyerowitz E, Richterman A, Gandhi R, *et al.* Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. *Ann Intern Med* Published Online First: 2020.
doi:<https://doi.org/10.7326/M20-5008>
- 8 Wolff D, Nee S, Hickey NS, *et al.* Risk factors for Covid-19 severity and fatality: a structured literature review. *Infection* Published Online First: 2020. doi:10.1007/s15010-

020-01509-1

- 9 Office for National Statistics United Kingdom Government. COVID-19 testing data: methodology note. 2020.<https://www.gov.uk/government/publications/coronavirus-covid-19-testing-data-methodology/covid-19-testing-data-methodology-note> (accessed 10 Nov 2020).
- 10 Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;:1–13. doi:10.1056/NEJMoa2034577
- 11 UK Government. Confirmed cases of COVID-19 variant from South Africa identified in UK. 2020.<https://www.gov.uk/government/news/confirmed-cases-of-covid-19-variant-from-south-africa-identified-in-uk>
- 12 COG-UK. COG-UK update on SARS-CoV-2 Spike mutations of special interest Report 1 Summary Limitations. 2020.

Funding

DP, SS and CAM are supported by NIHR Academic Clinical Fellowships. JSM is funded by an NIHR Clinical Lectureship in Older People and Complex Health Needs. CRN works for the Complex Reviews Support Unit which is funded by the NIHR (project number 14/178/29). KRA is supported by Health Data Research (HDR) UK, the UK National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM), and as a NIHR Senior Investigator Emeritus (NF-SI-0512-10159). LBN receives funding from the Academy of Medical Sciences (SBF005\1047), the Medical Research Council/Economic and Social Research Council/Arts and Humanities Research Council (MR/T046732/1), and UKRI/MRC (MR/V027549/1). LJG receives funding from UK National Institute for Health Research (NIHR) and UKRI. KK, KM, MP and LG are supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM). KK and MP are supported by the NIHR Leicester Biomedical Research Centre (BRC). MP and KRA are members of the Health Data Research (HDR) UK COVID-19 Taskforce. MP is supported by a NIHR Development and Skills Enhancement Award and UKRI/MRC/NIHR (MR/V027549/1). KK and MP are supported by NIHR Leicester Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NIHR, NHS or the Department of Health and Social Care.

Declaration of interests

KRA has served as a paid consultant, providing unrelated methodological advice, to; Abbvie, Amaris, Allergan, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Creativ-

Ceutical, GSK, ICON/Oxford Outcomes, Ipsen, Janssen, Eli Lilly, Merck, NICE, Novartis, NovoNordisk, Pfizer, PRMA, Roche and Takeda, and has received research funding from Association of the British Pharmaceutical Industry (ABPI), European Federation of Pharmaceutical Industries & Associations (EFPIA), Pfizer, Sanofi and Swiss Precision Diagnostics. He is a Partner and Director of Visible Analytics Limited, a healthcare consultancy company. KK has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda, Servier and Pfizer, and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Pfizer. KK is Director for the University of Leicester Centre for BME Health, Trustee of the South Asian Health Foundation, national NIHR ARC lead for Ethnicity and Diversity, Chair of the SAGE subgroup on Ethnicity and COVID and a member of Independent SAGE. MP reports grants and personal fees from Gilead Sciences and personal fees from QIAGEN, outside the submitted work.