OPEN ACCESS

Unequal impact of the COVID-19 crisis on minority ethnic groups: a framework for understanding and addressing inequalities

Srinivasa Vittal Katikireddi ,[1] Sham Lal ,[2] Enitan D Carrol,[3] Claire L Niedzwiedz ,[4] Kamlesh Khunti,[5] Ruth Dundas ,[1] Finn Diderichsen ,[6] Ben Barr[7]

[1]MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK
[2]Department of Disease Control, London School of Hygiene and Tropical Medicine, London, UK
[3]Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK
[4]Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK
[5]Primary Care and Public Health, Imperial College London, London, UK
[6]Department of Public Health, University of Copenhagen Faculty of Health and Medical Sciences, Copenhagen K, Denmark
[7]Public Health and Policy, University of Liverpool, Liverpool, UK

Correspondence to
Professor Srinivasa Vittal Katikireddi, University of Glasgow MRC/CSO Social and Public Health Sciences Unit, Glasgow G3 7HR, UK; vittal.katikireddi@glasgow.ac.uk

Received 16 November 2020
Revised 20 February 2021
Accepted 8 April 2021

To cite: Katikireddi SV, Lal S, Carrol ED, *et al*. *J Epidemiol Community Health* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jech-2020-216061

ABSTRACT

Minority ethnic groups have been disproportionately affected by the COVID-19 pandemic. While the exact reasons for this remain unclear, they are likely due to a complex interplay of factors rather than a single cause. Reducing these inequalities requires a greater understanding of the causes. Research to date, however, has been hampered by a lack of theoretical understanding of the meaning of 'ethnicity' (or race) and the potential pathways leading to inequalities. In particular, quantitative analyses have often adjusted away the pathways through which inequalities actually arise (ie, mediators for the effect of interest), leading to the effects of social processes, and particularly structural racism, becoming hidden. In this paper, we describe a framework for understanding the pathways that have generated ethnic (and racial) inequalities in COVID-19. We suggest that differences in health outcomes due to the pandemic could arise through six pathways: (1) differential exposure to the virus; (2) differential vulnerability to infection/disease; (3) differential health consequences of the disease; (4) differential social consequences of the disease; (5) differential effectiveness of pandemic control measures and (6) differential adverse consequences of control measures. Current research provides only a partial understanding of some of these pathways. Future research and action will require a clearer understanding of the multiple dimensions of ethnicity and an appreciation of the complex interplay of social and biological pathways through which ethnic inequalities arise. Our framework highlights the gaps in the current evidence and pathways that need further investigation in research that aims to address these inequalities.

INTRODUCTION

Minority ethnic groups have been disproportionately affected by the COVID-19 pandemic, with the clearest evidence from the UK and the USA.[1–4] While the exact reasons for this remain unclear, they are likely due to a complex interplay of a number of factors rather than a single cause. Reducing these inequalities requires a greater understanding of the causes. Research to date, however, has been hampered by a lack of theoretical understanding of the meaning of 'ethnicity' or the potential pathways leading to ethnic inequalities.

In this paper, we describe a framework for understanding the pathways that have generated ethnic inequalities in COVID-19—to our knowledge, the first of its kind. Current research provides only a partial understanding of some of these pathways. Future research and action will require a clearer understanding of the complex dimensions of ethnicity and an appreciation of the complex interplay of social and biological pathways through which ethnic inequalities arise. Our framework highlights the gaps in the current evidence and pathways that need further investigation in research that aims to address these inequalities.

UNDERSTANDING ETHNICITY

Ethnicity is socially constructed.[5] It can be defined as a 'social group a person belongs to, and either identifies with or is identified with by others, as a result of a mix of cultural and other factors including language, diet, religion, ancestry, and physical features traditionally associated with race'.[6] Ethnicity is therefore a complex concept which includes multiple dimensions including country of birth, language, religion and culture. Although it is socially constructed, it may be associated with biological attributes such as skin colour, that influence the unequal treatment of people within racist societies. The act of categorising people into ethnic groups is a social process, influenced by particular social, cultural and historical contexts. For this reason, ethnic categories differ across the world, with the same term often referring to different groups of people—for example, the term 'Asian' is often understood as referring mainly to East Asian people in the USA whereas in the UK the same term is typically interpreted as including people from the Indian subcontinent.[5]

In this paper, we therefore use the term ethnicity throughout but include the concept of race within this term (as defined above) and consider racial inequalities as core to ethnic inequalities. This reflects a tradition in the UK of focusing on ethnic inequalities in health, but we acknowledge inter-related dimensions on inequality are often given greater emphasis in different countries. For example, in the USA the term race is more widely used, with the socially constructed nature of racial categories also explicitly acknowledged by public health researchers.[7] Similarly, in many European countries outside of the UK the health of migrants

(classified on the basis of country of birth) has often been the focus of research, rather than minority ethnic groups—at least in part due to a lack of data collection on ethnicity. While we use terminology related to ethnicity throughout the remainder of the paper, we believe our framework and the arguments expressed broadly apply to inequalities related to migrant status and similar related inequalities. The use of ethnicity also allows us to include inequalities experienced within broader racial groups—for example, by white traveller and gypsy communities across Europe.[8] We also note that ethnic groups that experience disadvantage can be numerical majorities in some countries and our use of the term minority ethnic also refers to relative power within society.[9]

While not all minority ethnic groups in all countries experience worse health than the majority ethnic group,[10] differences in health across ethnic groups, in terms of both morbidity and mortality, have been repeatedly documented in the UK and other countries.[11] It is important to note that the health and related experiences of minority ethnic groups are not homogenous, with different patterns seen depending on which health outcomes are studied.[5] While understanding by current researchers has largely moved on from racist scientific thinking of the 19th century that narrowly viewed these differences through a biological lens,[7] this is not universally the case.[12] The multiple dimensions of ethnicity influence health through their interaction with wider social processes. In the past, social disadvantage, and particularly experiences of racism, have been downplayed as explanations for these differences. However, there is now increasing recognition of the role of structural racism. Processes of racialisation are contingent on socio-historical context, such that some groups may be more or less racialised at different times. For example, white Irish people living in the UK were subject to substantial and overt racism in the early 20th century, with other racial groups (such as white Eastern European and travelling community groups) being more targeted at the end of the century.[13]

Structural racism has been defined as 'the macrolevel systems, social forces, institutions, ideologies, and processes that interact with one another to generate and reinforce inequities among racial and ethnic groups'.[14] The term draws attention to the way these ethnic inequalities arise not only from the intended actions of individuals, but rather from broader societal mechanisms. For example, historical experiences of minority ethnic groups and long-term discrimination may lead to a higher proportion working in lower paid jobs on insecure contracts without sickness benefits and in public-facing occupations, living in crowded housing conditions, and having fewer resources for health (eg, education, income).[15] These factors are likely to increase psychosocial stress, mental health problems and harmful health behaviours (eg, smoking, poor diet and physical inactivity). There is also a wealth of evidence documenting inequalities faced by minority ethnic groups in accessing quality healthcare.[5] Healthcare planning may not take into account different experiences, perceptions and expectations of ethnic minorities, and therefore health services may not meet the needs of some ethnic groups—further widening inequalities.[5] Reported experiences of racial discrimination are also associated with poorer health.[16] This includes both interpersonal racism (which refers to discriminatory actions between individuals) and institutional racism (when discriminatory policies and practices are embedded in organisations). While ethnic inequalities in health are often linked to socioeconomic differences, they are not entirely explained by these factors due to the experiences of discrimination and intersecting inequalities within and across social groups.

Studies of ethnic differences in health have not paid sufficient attention to the social processes that give rise to these inequalities. Often studies include 'ethnic group' as one of many variables in regression models 'controlling or adjusting' for clinical, social and economic factors that are in fact important explanations of ethnic inequalities. This process has resulted in researchers sometimes erroneously concluding that ethnic inequalities do not exist (eg, see Yehia and colleagues[17]). Adjusting away the pathways through which inequalities actually arise (ie, mediators) can lead to the effects of social processes, and particularly structural racism, becoming hidden. This 'black box epidemiology', which has been often used in recent studies of ethnic inequalities in COVID-19,[18] has been rightly criticised for ignoring the theory underpinning analyses.[19] More theory-informed analyses can help yield more informative insights.

FRAMEWORK TO UNDERSTAND ETHNIC INEQUALITIES IN THE HEALTH IMPACTS OF THE PANDEMIC

To inform analyses of ethnic inequalities in the health impacts of the COVID-19 crisis, we present a framework of the potential mechanisms and pathways that could contribute to health differences between ethnic groups (figure 1). We build on a well-established framework for studying health inequalities[20 21] which distinguished the individual proximate causes of disease from their societal causes and highlighted the potential importance of differential exposure to causes of disease, differential vulnerability to their effects and differential consequences of disease. In our model, we suggest that differences in health outcomes due to COVID-19 could occur at multiple stages: from exposure to the virus, development of disease, and through the indirect impacts of control measures and management of an individual with COVID-19. At each step, ethnic inequalities could develop through social and economic mechanisms which have biological effects. A comprehensive understanding of these pathways will help identify targets for policy interventions, as well as future research. We provide a brief introduction to each element of the framework, drawing on relevant studies to illustrate how it might be relevant to ethnic inequalities in health arising from the pandemic. We note that we have not conducted a systematic assessment of the evidence base in relation to each of these pathways and we therefore provide these studies for illustrative purposes only.

Differential exposure

Minority ethnic groups could experience greater exposure to the virus and therefore higher risk of infection, which could relate to the frequency of contact or the potential infective dose of each contact. For example, working in specific occupations (eg, health and social care workers, transport workers) or living in overcrowded housing could lead to being in contact with potentially infected persons more frequently and for a longer duration potentially leading to a higher viral load.[22 23] Recent findings from a representative English infection survey found evidence that all minority ethnic groups studied were more likely to have serological evidence of previous SARS-CoV-2 infection compared with the majority white British population.[24]

Differential vulnerability to infection/disease

Minority ethnic groups could be more likely to develop disease once exposed. This could result from differences in nutritional status, comorbidities and immune response, which themselves could be driven by stress or environmental conditions, such as air pollution. There is considerable evidence that incidence of

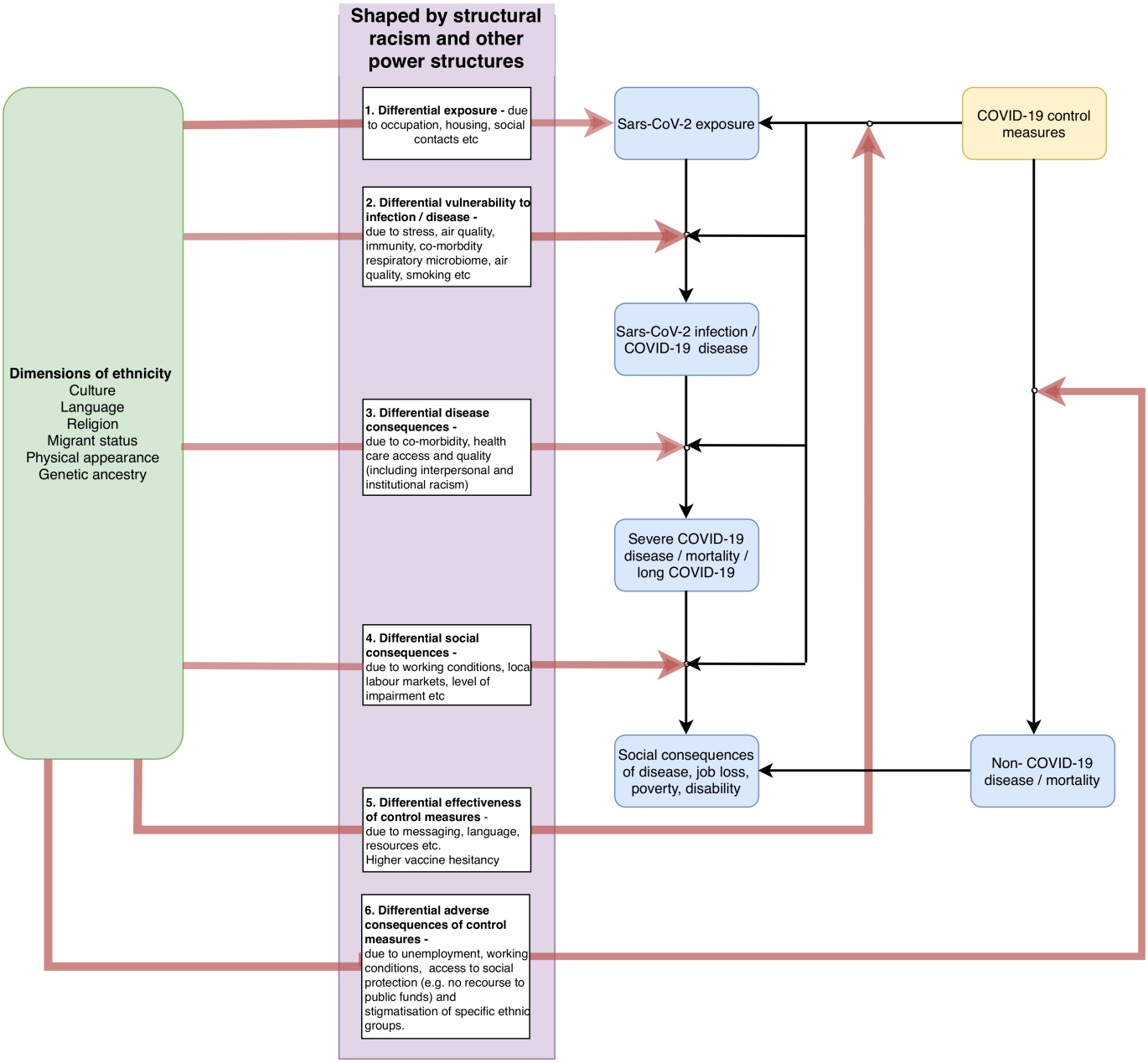


Figure 1 A framework for understanding pathways underpinning ethnic inequalities in COVID-19 and potential targets for policy.

clinically important disease (reflected by positive symptomatic tests or hospitalisations) are higher in many minority ethnic groups.[2 18] However, it is not clear if this merely reflects greater exposure or differences in vulnerability to developing disease. To differentiate vulnerability to the disease from greater exposure, analysis would need to compare ethnic differences in the risk of reporting symptomatic disease among both symptomatic and asymptomatically infected people.

Differential disease consequences

Of those with disease, some minority ethnic groups may be more likely to develop severe disease, require mechanical ventilation, experience complications and potentially die. This could, for example, be due to differences in underlying comorbidities or differential access to healthcare between ethnic groups.[23] A large cohort study of nearly 35 000 UK hospitalisations found a 30% increased relative risk of critical care admission and mechanical ventilation among people from South Asian, black or minority ethnic groups and this relationship was still present after adjusting for age and sex.[25] After accounting for some potential explanations of this increased risk (such as comorbidities like diabetes), minority ethnic groups were still more likely to require critical care and mechanical ventilation than white groups. Different ethnic groups may be at risk of longer term health consequences, such as greater risks of 'long COVID-19' (also referred to as post-COVID-19 syndrome),[26] but evidence is currently limited.

Differential social consequences

Minority ethnic groups may also experience differential social consequences following recovery from COVID-19 disease. COVID-19 disease may lead to long-lasting disability that results in job loss and future loss of earnings due to poor health. One important reason for a potential disproportionate impact

on minority ethnic groups is the often higher levels of insecure employment (such as self-employment or being on 'zero hours' contracts) that were already experienced prepandemic. Contracting COVID-19 disease, and especially 'long COVID-19', could lead to minority ethnic people being more likely to experience job loss and poverty. However, empirical data remain relatively scarce on the social consequences of the disease[26] and further research is required to address this gap.

Differential effectiveness of control measures

Public health interventions designed to control the pandemic may also, in themselves generate ethnic health inequalities, as their impact on risk of exposure, vulnerability and consequences (pathways 1–4) may be different for some ethnic groups, sometimes also referred to as intervention-generated inequalities.[27] We believe conceptualising of the differential effectiveness of control measures as a distinct pathway is important given the necessity of understanding the impacts of public health actions. These unintended intervention-generated inequalities may operate through changing the risk across the other four pathways. For example, health communications which have not been culturally adapted to their target audiences may be less effective in some groups.[28] Control measures that are inequitably implemented could mean that people in the same occupation experience different exposure risks. There is evidence to suggest that minority ethnic healthcare workers were less likely to be able to access personal protective equipment.[29] In contrast, lockdown measures appeared to reduce COVID-19 mortality more among some minority ethnic groups than the majority population.[30] The availability of effective vaccines is hugely welcome but could further exacerbate ethnic inequalities. For example, some minority ethnic groups (such as black and Pakistani/Bangladeshi ethnic groups) have higher levels of vaccine hesitancy in the UK.[31] Importantly, differences in vaccine hesitancy reflect broader societal processes, such as the dominant communication strategies used in vaccination programmes and understandable concerns arising from longstanding experiences of discrimination (such as the Windrush scandal which led to the illegal deportation of black British citizens).

Differential adverse consequences of control measures

Social and economic impacts of pandemic control measures (such as loss of income) may also disproportionately affect disadvantaged groups more and these impacts may affect non-COVID-19 health outcomes.[32] Evidence already suggests that some minority ethnic groups have disproportionately experienced unemployment during the initial lockdown period and a greater increase in psychological distress, exacerbating existing ethnic inequalities in mental health.[33 34]

All of these six pathways arise from the wider social and political context that drive ethnic and other social inequalities, including structural racism and other power imbalances across society. Furthermore, multiple risks can affect multiple pathways—for example, poor working conditions might affect both the potential for differential exposure and experiencing differential consequences of control measures. Despite this, an understanding of the pathways driving ethnic inequalities can help identify policy targets.

CONCLUSIONS

The COVID-19 pandemic has highlighted existing health inequalities among ethnic minority groups and exacerbated them. This has led to an increase in research studies to understand ethnic inequalities in health, but many research studies are based on a constrained and limited understanding of ethnicity and the potential pathways generating differences in health between ethnic groups. Ethnicity is a complex, multidimensional social construct and health differences between some ethnic groups largely reflect social pathways, embedded within the unequal power relationships that propagate inequalities. It is inappropriate for researchers to investigate ethnic groupings like biomarker or biomedical variables in naïve multivariable analysis that is not theoretically informed. In particular, overadjustment for mediating variables can lead to misleading interpretations, provide little insight to inform policy and practice and may ultimately have harmful real-world consequences.[35] The unequal impacts of the pandemic can be mitigated, through more comprehensive and evidence informed action at each of the pathways we outlined above. This requires research that elucidates how specific dimensions of ethnicity differentially affect the mechanisms of differential exposure, vulnerability and consequences, identifying the most effective policy entry points to reduce ethnic inequalities in health. Our framework is a first step towards encouraging clearer thinking on ethnic inequalities in COVID-19 and we welcome feedback, anticipating that refinements will be needed over time.

What is already known on this topic

- Minority ethnic populations have experienced disproportionate harms during the COVID-19 pandemic.
- Considerable research is ongoing to understand the reasons for the greater risks being experienced, but a lack of theoretical underpinning for epidemiological analyses is often leading researchers to make erroneous conclusions.

What this study adds

- We present a framework for understanding the drivers of ethnic inequalities in COVID-19 harms, highlighting the multitude of mechanisms through which structural racism and power imbalances operate.
- Applying a theoretical framework can help policymakers and researchers develop more valid conclusions and ultimately better inform public health policies to mitigate adverse consequences of the pandemic on ethnic inequalities in health.

Twitter Srinivasa Vittal Katikireddi @vkatikireddi and Ben Barr @benj_barr

Contributors SVK and BB conceived the idea for the paper. SVK wrote the first draft. All authors contributed to the ideas expressed, critically revised the manuscript and agreed to the final version.

Funding SVK and RD acknowledge funding from the Medical Research Council (MC_UU_00022/2). SVK additionally acknowledges funding from the Scottish Government Chief Scientist Office (SPHSU17) and an NRS Senior Clinical Fellowship (SCAF/15/02). SL is supported by grants from the Wellcome Trust. EDC acknowledges funding from the NIHR i4i Programme (II-LA-0216-20002), HTA Programme (15/188/42, 17/136/13), EME Programme (NIHR129960) and H2020 (Project No. 848196). CLN is funded by a Medical Research Council Fellowship (MR/R024774/1). KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). BB, is supported by National Institute for Health Research (NIHR) Applied Research Collaboration North West Coast (ARC NWC, NIHR200182) and NIHR School for Public Health Research (PD-SPH-2015-10062). The funders had no involvement in the writing or decision to submit the manuscript. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests SVK, SL, EDC, KK and BB are members of the UK Government's Scientific Advisory Group on Emergencies (SAGE) subgroup on ethnicity and COVID-19. SVK is co-chair of the Scottish Government's Expert Reference Group on ethnicity and COVID-19. SL is currently seconded to the UK's Government Office of Science. 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 and a member of Independent SAGE. All authors write in an independent capacity and the views expressed do not necessarily represent any government or funding organisation.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

ORCID iDs
Srinivasa Vittal Katikireddi http://orcid.org/0000-0001-6593-9092
Sham Lal http://orcid.org/0000-0002-3650-1398
Claire L Niedzwiedz http://orcid.org/0000-0001-6133-4168
Ruth Dundas http://orcid.org/0000-0002-3836-4286
Finn Diderichsen http://orcid.org/0000-0002-9998-4972

REFERENCES

1 England PH. *COVID-19: review of disparities in risks and outcomes*. London: Public Health England, 2020.
2 Niedzwiedz CL, O'Donnell CA, Jani BD, *et al*. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. *BMC Med* 2020;18:160.
3 Raharja A, Tamara A, Kok LT. Association between ethnicity and severe COVID-19 disease: a systematic review and meta-analysis. *J Racial Ethn Health Disparities* 2020. doi:10.1007/s40615-020-00921-5. [Epub ahead of print: 12 Nov 2020].
4 Sze S, Pan D, Nevill CR, *et al*. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 2020;29:100630.
5 Bhopal RS. *Migration, ethnicity, race, and health in multicultural societies*. Oxford University Press: Oxford, 2014.
6 Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. *J Epidemiol Community Health* 2004;58:441–5.
7 Krieger N. Refiguring "race": epidemiology, racialized biology, and biological expressions of race relations. *Int J Health Serv* 2000;30:211–6.
8 McFadden A, Siebelt L, Gavine A, *et al*. Gypsy, Roma and traveller access to and engagement with health services: a systematic review. *Eur J Public Health* 2018;28:74–81.
9 Johnson MRD, Bhopal RS, Ingleby JD, *et al*. A glossary for the first world Congress on migration, ethnicity, race and health. *Public Health* 2019;172:85–8.
10 Bhopal RS, Gruer L, Cezard G, *et al*. Mortality, ethnicity, and country of birth on a national scale, 2001-2013: a retrospective cohort (Scottish health and ethnicity linkage study). *PLoS Med* 2018;15:e1002515.
11 Nazroo JY. The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. *Am J Public Health* 2003;93:277–84.
12 Yudell M, Roberts D, DeSalle R, *et al*. Taking race out of human genetics. *Science* 2016;351:564–5.
13 Rzepnikowska A. Racism and xenophobia experienced by Polish migrants in the UK before and after Brexit vote. *J Ethn Migr Stud* 2019;45:61–77.
14 Gee GC, Ford CL. Structural racism and health inequities: old issues, new directions. *Du Bois Rev* 2011;8:115.
15 Karlsen S, Nazroo JY, Smith NR. Ethnic, religious and gender differences in Intragenerational economic mobility in England and Wales. *Sociology* 2020;54:883–903.
16 Priest N, Paradies Y, Trenerry B, *et al*. A systematic review of studies examining the relationship between reported racism and health and wellbeing for children and young people. *Soc Sci Med* 2013;95:115–27.
17 Yehia BR, Winegar A, Fogel R, *et al*. Association of race with mortality among patients hospitalized with coronavirus disease 2019 (COVID-19) at 92 US hospitals. *JAMA Netw Open* 2020;3:e2018039-e:e2018039.
18 Williamson EJ, Walker AJ, Bhaskaran K, *et al*. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430–6.
19 Tennant PWG, Murray EJ. The quest for timely insights into COVID-19 should not come at the cost of scientific rigor. *Epidemiology* 2021;32:e2.
20 Diderichsen F, Andersen I, Manuel C, *et al*. Health inequality--determinants and policies. *Scand J Public Health* 2012;40:12–105.
21 Diderichsen F, Augusto LGdaS, Perez B. Understanding social inequalities in Zika infection and its consequences: a model of pathways and policy entry-points. *Glob Public Health* 2019;14:675–83.
22 Mutambudzi M, Niedwiedz C, Macdonald EB, *et al*. Occupation and risk of severe COVID-19: prospective cohort study of 120 075 UK Biobank participants. *Occup Environ Med* 2021;78:307–14.
23 Daras K, Alexiou A, Rose TC, *et al*. How does vulnerability to COVID-19 vary between communities in England? developing a small area vulnerability index (SAVI). *J Epidemiol Community Health* 2021. doi:10.1136/jech-2020-215227. [Epub ahead of print: 04 Feb 2021].
24 Office for National Statistics. *Coronavirus (COVID-19) infection survey: characteristics of people testing positive for COVID-19 in England, August 2020*. London, 2020.
25 Harrison EM, Docherty AB, Barr B. Ethnicity and outcomes from COVID-19: the ISARIC CCP-UK prospective observational cohort study of hospitalised patients. *SSRN preprint* 2020.
26 Yelin D, Wirtheim E, Vetter P, *et al*. Long-Term consequences of COVID-19: research needs. *Lancet Infect Dis* 2020;20:1115–7.
27 Lorenc T, Petticrew M, Welch V, *et al*. What types of interventions generate inequalities? Evidence from systematic reviews. *J Epidemiol Community Health* 2013;67:190–3.
28 Davidson EM, Liu JJ, Bhopal R, *et al*. Behavior change interventions to improve the health of racial and ethnic minority populations: a tool kit of adaptation approaches. *Milbank Q* 2013;91:811–51.
29 Nguyen LH, Drew DA, Graham MS, *et al*. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health* 2020;5:e475–83.
30 Ayoubkhani D, Nafilyan V, White C. Ethnic minority groups in England and Wales - factors affecting the size and timing of elevated COVID-19 mortality: a retrospective cohort study linking Census and death records. *medRxiv* 2020.
31 Robertson E, Reeve KS, Niedzwiedz CL, *et al*. Predictors of COVID-19 vaccine hesitancy in the UK household longitudinal study. *Brain Behav Immun* 2021. doi:10.1016/j.bbi.2021.03.008. [Epub ahead of print: 11 Mar 2021].
32 Douglas M, Katikireddi SV, Taulbut M, *et al*. Mitigating the wider health effects of covid-19 pandemic response. *BMJ* 2020;369:m1557.
33 Hu Y. Intersecting ethnic and native-migrant inequalities in the economic impact of the COVID-19 pandemic in the UK. *Res Soc Stratif Mobil* 2020;68:100528.
34 Niedzwiedz CL, Green MJ, Benzeval M, *et al*. Mental health and health behaviours before and during the initial phase of the COVID-19 lockdown: longitudinal analyses of the UK household longitudinal study. *J Epidemiol Community Health* 2021;75:224-231.
35 Katikireddi SV, Valles SA. Coupled Ethical-Epistemic analysis of public health research and practice: categorizing variables to improve population health and equity. *Am J Public Health* 2015;105:e36–42.

BMJ Open

Quantifying the association between ethnicity and COVID-19 mortality: a national cohort study protocol

Hajira Dambha-Miller ,[1,2] Pui San Tan,[3] Defne Saatci,[3] Ashley Kieran Clift ,[3] Francesco Zaccardi,[4] Carol Coupland,[5] Patrick Locufier,[6] Firoza Davies,[6] Kamlesh Khunti ,[7] Simon J Griffin,[8] Julia Hippisley-Cox [9]

To cite: Dambha-Miller H, Tan PS, Saatci D, *et al*. Quantifying the association between ethnicity and COVID-19 mortality: a national cohort study protocol. *BMJ Open* 2021;**11**:e045286. doi:10.1136/bmjopen-2020-045286

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-045286).

Received 30 September 2020
Revised 07 March 2021
Accepted 16 March 2021

For numbered affiliations see end of article.

Correspondence to
Dr Hajira Dambha-Miller; hajiradambha@doctors.org.uk

ABSTRACT

Introduction Recent evidence suggests that ethnic minority groups are disproportionately at increased risk of hospitalisation and death from SARS-CoV-2 infection. Population-based evidence on potential explanatory factors across minority groups and within subgroups is lacking. This study aims to quantify the association between ethnicity and the risk of hospitalisation and mortality due to COVID-19.

Methods and analysis This is a retrospective cohort study of adults registered across a representative and anonymised national primary care database (QResearch) that includes data on 10 million people in England. Sociodemographic, deprivation, clinical and domicile characteristics will be summarised and compared across ethnic subgroups (categorised as per 2011 census). Cox models will be used to calculate HR for hospitalisation and COVID-19 mortality associated with ethnic group. Potential confounding and explanatory factors (such as demographic, socioeconomic and clinical) will be adjusted for within regression models. The percentage contribution of distinct risk factor classes to the excess risks seen in ethnic groups/subgroups will be calculated.

Ethics and dissemination The study has undergone ethics review in accordance with the QResearch agreement (reference OX102). Findings will be disseminated through peer-reviewed manuscripts, presentations at scientific meetings and conferences with national and international stakeholders.

Strengths and limitations of this study

- The QResearch database includes a large sample that represents 18% of the English population.
- As data are based on primary care clinical entries, recording of exposures and outcomes may vary in completeness.
- Total COVID-19 cases in the cohort will be underestimated as national systematic testing is still being established in the UK.

INTRODUCTION

Recent reports and early observational data suggest that the prevalence of COVID-19, hospitalisation and deaths are disproportionately higher among ethnic minority populations.[1–3] Potential speculative mechanisms include genetic variations, comorbidities, cultural or behavioural patterns, occupational factors, social constructs and inequalities. In the UK, people with ethnic minority backgrounds constitute 16% of the population, but the Intensive Care National Audit and Research Centre reports that over 30% of people admitted to intensive care with COVID-19 were from these backgrounds.[4 5] Furthermore, 64% of 119 National Health Service (NHS) staff who died from COVID-19 as of 30 April 2020 were from ethnic minority backgrounds.[6] A rapid review on the subject led by Khunti *et al* suggests that there are also variations in mortality within broad ethnic minority groups.[3] Most national and international data on COVID-19 are aggregated and have not reported outcome by ethnic group sufficiently to permit examination of within-group differences.

At the time of submitting this manuscript, a limited number of population-based cohort studies regarding COVID-19 have been undertaken worldwide. In the USA, a study within the largest healthcare system, the Veterans Health Administration, reports excess mortality among ethnic minorities.[7] In the UK, the availability of high-quality, large (multimillion) databases that have linkage across varying information sources are starting to examine this association further. Large primary care databases have been used, for example, to develop risk prediction models for adverse COVID-19 outcomes in the general population and to undertake large-scale epidemiological evaluations of COVID-19 risk factors and drug safety.[8] In the UK, two large cohorts have reported to date on the association between ethnicity and COVID-19-related mortality outcomes: the OpenSAFELY Collaborative of

23 million UK records and the NHS England cohort study of over 61 million people. The OpenSAFELY consortium reported that people with black or Asian backgrounds have a higher risk of death from COVID-19 compared with people who are white.[9] Data from NHS England also showed a greater mortality risk for Asian (HR 1.3) and black (HR 1.7) backgrounds. Further analysis of these data, carried out by the Office for National Statistics (ONS), showed that the mortality risk in black men and women was 1.9 times higher than in white individuals. Contradictory to a previous study in a smaller, single-state US health system database, both studies identify a persisting excess risk of COVID-19-specific mortality after accounting for known risk factors, including age, sex, deprivation and comorbidities such as obesity, diabetes and cardiovascular disease. The causes of these excess risks are poorly understood, incompletely quantified and may vary within and between ethnic minority groups.

Previous studies have been limited by the lack of consideration of additional potential explanatory variables, such as specific medications, rarer comorbidities,[10] social differences such as household structure, or vaccination status.[9] A recent population-based study, for example, identified a significant interaction between ethnicity and ACE inhibitors/angiotensin receptor blockers for COVID-19.[11] Several smaller studies have also suggested a role of glucose-lowering medications in the ethnicity-dependent variations observed in COVID-19 outcomes.[12 13] Single-centre studies and case series are providing additional insights into the potential interaction between ethnicity and haematological disorders, such as sickle cell disease,[10] in relation to COVID-19. Population-based studies with adequate number of people from different ethnic groups that consider these wider variables are necessary to evaluate the explanatory factors surrounding this risk. Moreover, earlier studies have been limited, and larger cohorts that extend to the wider English population are needed for validation and to allow generalisability of findings. Accordingly, in this study we aim to quantify ethnic group-specific risk of SARS-CoV-2 infection, COVID-19 mortality and COVID-19 hospital admission, and examine the effect of non-modifiable (eg, age and sex) and explanatory factors on the associations between ethnicity and mortality/hospitalisation risk.

METHODS

Study design

This is a retrospective cohort study from electronic general practice (GP) records linked at the individual level to hospital admissions, SARS-CoV-2 testing and death registry databases.

Data sources

We will use the QResearch national primary care database, which includes 1205 GPs with 10 million records. The sample represents 18% of the English population. QResearch holds data on a heterogeneous and representative ethnic minority population, with comprehensive information on a range of clinical and socioeconomic factors. Further details on the population included within the QResearch database and representative are updated regularly on the database website.[14] Additional databases may be included as these become available.

Study period

We will include the period from the date of the first case of COVID-19 in the UK (24 January 2020) until death, deregistration or 30 October 2020.

Inclusion criteria

We will include all adults aged over 18 years registered with a GP practice during the study period and for at least 12 months prior to inclusion. The GP practice registration needs to be linked to a relevant clinical system (ie, EMIS).

Primary outcome

The primary outcome will be COVID-19-related mortality as recorded in the primary care records and linked to ONS data. Details on the extent of linkage available within the database have been reported previously and can be found in full on the QResearch website.[15] COVID-19-related mortality will be defined as the presence of U07.1 or U07.2 on death certificates or death from any cause in a patient with a confirmed positive SARS-CoV-2 test in the immediately preceding 28 days.

Secondary outcomes

COVID-19 hospitalisation was defined as hospitalisation with confirmed or suspected COVID-19 (as per International Classification of Diseases-10 codes), or new hospitalisation in a patient with a positive SARS-CoV-2 test in the immediately preceding 14 days.

Ethnicity definition

A self-reported ethnic group is recorded in medical records. QResearch has ethnicity records in 80% of all patients. Ethnicity will be considered in two ways: first in 9 high-level categories: white, Indian, Bangladeshi, Pakistani, other Asian, black African, black Caribbean, Chinese and 'Other'; and then, if numbers allow, further subdivided into the standard 17 categories used by ONS and include the following: English/Welsh/Scottish/Northern Irish/British, Irish, Gypsy or Irish Traveller, any other white background, white and black Caribbean, white and black African, white and Asian, any other mixed/multiple ethnic backgrounds, Indian, Pakistani, Bangladeshi, Chinese, any other Asian background, African, Caribbean, any other black/African/Caribbean background, Arab or any other ethnic group.

Explanatory variables

We will extract data (where available) corresponding to the following potential exposure and confounding variables. The following list is indicative and correct as of 29

August 2020, but will be kept under review as new information arises in the literature:

Demographic variables

- Ethnicity (9 categories, and numbers permitting, subdivision into 17 ONS groups).
- Sex.
- Age (continuous variable).
- Geographical region.

Concurrent medication

- Glucose-lowering medications (metformin, sulfonylureas, thiazolidinedione, SGLT-2 inhibitors, DPP-4 inhibitors, GLP-1R agonists) and insulin therapy.
- Hormone therapy (in women).

Clinical/blood test assessments

- Body mass index.
- Blood pressure (systolic and diastolic).
- Haemoglobin A1c.
- Total cholesterol and low-density lipoprotein.
- Liver function tests, including alanine aminotransferase.
- Estimated glomerular filtration rate.

Comorbidities

- Sickle cell status.[10]
  - Sickle trait.
  - Sickle cell disease.
- Diabetes (type 1 and type 2 separately).[13 16]
  - Diabetes duration.
- Chronic kidney disease (CKD).
  - CKD stage 3.
  - CKD stage 4.
  - CKD stage 5 (including those requiring dialysis or ever receiving a transplant).
- Cancer.
  - Active or past haematological or solid cancer.
- Transplant (solid organ or bone marrow).
- Vaccination status.

Key confounding variables

Demographic variables

- Quintile of Townsend Deprivation Score: this is an area-level quintile score based on the patient's postcode. Originally developed by Townsend, it includes unemployment (as a percentage of those aged 16 and over who are economically active); non-car ownership (as a percentage of all households); non-home ownership (as a percentage of all households); and household overcrowding. These variables are measured for a given area of approximately 120 households, via the 2011 census, and combined to give a 'Townsend score' for that area. A higher Townsend score implies a greater level of deprivation.
- Residence type.
  - Lives in a care home (nursing home or residential care).
  - Homelessness.
  - Lives in own home.
- Household characteristics.
  - Age of household members.
  - Number of household inhabitants.

Lifestyle factors

- Smoking status coded as non-smoker, ex-smoker, light (<10 cigarettes/day), moderate (10–19) and heavy (20+).

Comorbidities

- Cardiovascular disease.
- Hypertension.
- Chronic respiratory disease.
- Liver cirrhosis.
- Depression.
- Dementia.
- Other chronic neurological diseases.
- Severe mental health illness.
- Learning disability.

Concurrent medication

- Lipid-lowering medications.
- Antihypertensive medications.

All predictor variables will be based on the latest coded information recorded in the GP record prior to entry to the cohort.

Sample size calculation

As of 9 August 2020, there had been 41 686 COVID-19 deaths in England out of a total population of 56 million. Assuming a 0.074% mortality rate in the general population, to detect a conservative estimate of an HR of 1.2 for COVID-19 mortality in the ethnic minority population that represents 18.6% of the study population (based on recent QResearch studies) with 90% power and a significance level of 0.01, we would need a sample size of 3 995 350 individuals with 2957 COVID-19 deaths. As recent studies of COVID-19 using QResearch have included cohorts of over 8 million adults with over 5000 COVID-19 deaths, even with 40% missing data, our study is sufficiently powered.

Statistical methods

Participant characteristics will be summarised by ethnicity, age, sex, comorbidities and outcome with appropriate summary statistics. We will describe SARS-CoV-2 infection, COVID-19 hospitalisation and COVID-19 mortality rates in the general population and stratify this by ethnicity. Plots of survival curves stratified by ethnic group will be generated using the Kaplan-Meier method and compared with the log-rank test. We will use Cox proportional hazards models to estimate unadjusted and adjusted HRs for the associations between ethnicity and the outcomes of interest. When proportional hazards assumptions are not met, we will consider using more flexible models which do not assume proportionality of hazards, for example, flexible parametric survival models. Subsequently, we will seek to quantify the contribution of risk factor groups to

any observed increased mortality or hospitalisation risks in people of non-white ethnicity. For all analyses, we will conduct complete case analyses, and then separately impute for missing values, for example, ethnic group, body mass index, deprivation quintile and smoking status, using five imputations incorporating all model outcomes and predictors with model coefficients and SEs pooled in accordance with Rubin's rules. Data will be analysed using STATA V.16. Our study will be conducted and findings reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology[17] and RECORD guidelines for observational studies using routinely collected health data.[18]

Patient and public involvement

Patient representatives have been involved in the development of the study aims and design. We sought feedback from study inception and design from patients and the public within the Centre for BME Health, Leicester. We additionally have two public representatives as part of the study team whose contributions have been acknowledged in the authorship list of this manuscript. They will continue to be involved in all stages of the study, with additional public and patient views sought for dissemination strategies.

Ethics and dissemination

The project has been independently peer-reviewed and received ethics approval from the QResearch Scientific Board (reference OX102). Findings will be disseminated through peer-reviewed manuscripts, presentations at scientific meetings and conferences with national and international stakeholders.

DISCUSSION

Our findings aim to provide rapid evidence on the patterns of COVID-19 and associated mortality across and within ethnic groups in England. This study will be one of the largest COVID-19 cohorts, with a representative population across both rural and urban areas. Our cohort size will enable us to detect national-level variations within ethnic minority subgroups across a large geographical area and thus, to some extent, overcome selection bias limitations of previous cohort studies. Our findings have the potential to inform targeted mitigation public health strategies and could alter clinical thresholds for at-risk patients presenting with the infection.

As we are using routinely recorded clinical data from primary care records rather than prospectively collecting the data, we anticipate that our study will be subject to limitations. First, the precision and completeness of routine NHS patient records will vary, although previous work from QResearch suggests that key variables have high levels of accuracy and completeness. Second, our sample is likely to underestimate the total number of people in the population with COVID-19 due to the lack of systematic national testing programmes, which are still being rolled out, and also due to false-negative test results. There is also some evidence that testing rates are lower among ethnic minority groups. Our confirmed SARS-CoV-2 infection cases will additionally over-represent people with more severe disease who died or were hospitalised. During the earlier part of the pandemic, testing in the UK was limited to the hospital setting and people with COVID-19 who were not admitted or recovered (who may be from ethnic minority groups) are less likely to be captured in the data. Further, the admission criteria for Intensive Care Units varied during the course of the pandemic, with particular characteristics such as older age resulting in a lower chance of admission at a time when high admission rates were anticipated, which may introduce a selection bias.

Author affiliations
[1]Primary Care Research Centre, University of Southampton, Southampton, UK
[2]MRC Epidemiology Unit, University of Cambridge, Cambridge, UK
[3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[4]Diabetes Research Centre, University of Leicester, Leicester, UK
[5]Division of Primary Care, University of Nottingham, Nottingham, UK
[6]PPI Representative, Leicester, UK
[7]Department of Health Sciences, University of Leicester, Leicester, UK
[8]Institute of Public Health, The Primary Care Unit, Cambridge, UK
[9]Nuffield Department of Primary Care Sciences, University of Oxford, Oxford, UK

Twitter Hajira Dambha-Miller @HDambhaMiller

Contributors HD-M led the study conceptualisation, wrote the first draft and revised the protocol. PST, DS and AKC critically revised the manuscript. FZ and CC critically revised the manuscript and contributed to the statistical methods. PL and FD critically revised the manuscript as PPI contributors. KK, SJG and JH-C contributed to study conceptualisation, study design and revised the protocol. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. HD-M is the guarantor.

Funding This work is funded by an MRC grant (MR/V027778/1). SJG is supported by an MRC Epidemiology Unit programme (MC_UU_12015/4). The University of Cambridge has received salary support in respect of SJG from the NHS in the East of England through the Clinical Academic Reserve. HD-M is a National Institute for Health Research (NIHR)-funded Academic Clinical Lecturer. JH-C receives support from the NHS and the NIHR and various research councils. KK and FZ are supported by the NIHR Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the UK NIHR or the Department of Health and Social Care.

Competing interests JH-C is founder and director of QResearch database, which is a not-for-profit organisation with EMIS (leading commercial supplier of IT for 55% of general practices in the UK). JH-C is co-owner of ClinRisk and was a paid director until June 2019. ClinRisk develops open and closed source software to ensure the reliable and updatable implementation of clinical risk equations within clinical computer systems to help improve patient care, outside the submitted work. KK is national lead for NIHR ARC ethnicity and diversity, Director for the University of Leicester Centre for BME Health, Trustee of the South Asian Health Foundation and member of the Independent SAGE. The authors declare that no support from any organisation and no financial relationships have influenced the submitted work.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Hajira Dambha-Miller http://orcid.org/0000-0003-0175-443X
Ashley Kieran Clift http://orcid.org/0000-0002-0061-979X
Kamlesh Khunti http://orcid.org/0000-0003-2343-7099
Julia Hippisley-Cox http://orcid.org/0000-0002-2479-7283

REFERENCES

1 Pareek M, Bangash MN, Pareek N, *et al*. Ethnicity and COVID-19: an urgent public health research priority. *Lancet* 2020;395:1421–2.
2 Laurencin CT, McClinton A. The COVID-19 pandemic: a call to action to identify and address racial and ethnic disparities. *J Rac Ethnic Health Disparit* 2020;7:398–402.
3 CEBM. Bame COVID-19 Deaths - What do we know? Rapid data & evidence review. Available: https://www.cebm.net/covid-19/bame-covid-19-deaths-what-do-we-know-rapid-data-evidence-review/ [Accessed 6 May 2020].
4 ICNARC – reports. Available: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports [Accessed 4 May 2020].
5 The King's Fund. Ethnic minority deaths and Covid-19. Available: https://www.kingsfund.org.uk/blog/2020/04/ethnic-minority-deaths-covid-19 [Accessed 4 May 2020].
6 Rimmer A. Covid-19: two thirds of healthcare workers who have died were from ethnic minorities. *BMJ* 2020;369:m1621.
7 Rentsch ID CT, Kidwai-Khan F, Tate JP. Patterns of COVID-19 testing and mortality by race and ethnicity among United States veterans: a nationwide cohort study.
8 Clift AK, Coupland CAC, Keogh RH, *et al*. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* 2020;371:m3731.
9 Mathur R, Rentsch CT, OpenSAFELY Collaborative. Ethnic differences in COVID-19 infection, hospitalisation, and mortality: an OpenSAFELY analysis of 17 million adults in England. *medRxiv* 2020.
10 Arlet J-B, de Luna G, Khimoud D, *et al*. Prognosis of patients with sickle cell disease and COVID-19: a French experience. *Lancet Haematol* 2020;7:e632–4.
11 Hippisley-Cox J, Young D, Coupland C, *et al*. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* 2020;106:1503–11.
12 Zhu L, She Z-G, Cheng X, *et al*. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab* 2020;31:1068–77.
13 Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. *Diabetes Metab* 2020;46:265–71.
14 Summary of GP population characteristics - QResearch. Available: https://www.qresearch.org/data/summary-of-gp-population-characteristics/#h-H2_0 [Accessed 24 Jan 2021].
15 Summary Analysis of Linked Mortality Data - QResearch. Available: https://www.qresearch.org/data/summary-analysis-of-linked-mortality-data/ [Accessed 24 Jan 2021].
16 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.
17 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
18 Benchimol EI, Smeeth L, Guttmann A, *et al*. The REporting of studies conducted using observational Routinely-collected health data (record) statement. *PLoS Med* 2015;12:e1001885.

European Journal of Public Health, 1–5

doi:10.1093/eurpub/ckab041

Ethnic minorities and COVID-19: examining whether excess risk is mediated through deprivation

Cameron Razieh [1,2], Francesco Zaccardi[1,3], Nazrul Islam [4,5], Clare L. Gillies[1,3], Yogini V. Chudasama[3], Alex Rowlands[1,2], David E. Kloecker[3], Melanie J. Davies[1,2], Kamlesh Khunti[1,3,6]*, Thomas Yates[1,2]*,

1 Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester LE5 4PW, UK
2 National Institute for Health Research (NIHR) Leicester Biomedical Research Centre (BRC), Leicester General Hospital, Leicester LE5 4PW, UK
3 Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK
4 Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK
5 Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK
6 NIHR Applied Research Collaboration—East Midlands (ARC-EM), Leicester General Hospital, Leicester, UK

Correspondence: Tom Yates, Diabetes Research Centre, Leicester Diabetes Centre, Leicester General Hospital, Leicester, Leicestershire LE5 4PW, UK, Tel: +44 0116 258 6481, Fax: +44 0116 258 4499, e-mail: ty20@le.ac.uk
*Joint senior authors.

Background: People from South Asian and black minority ethnic groups are disproportionately affected by the COVID-19 pandemic. It is unknown whether deprivation mediates this excess ethnic risk. **Methods:** We used UK Biobank with linked COVID-19 outcomes occurring between 16th March 2020 and 24th August 2020. A four-way decomposition mediation analysis was used to model the extent to which the excess risk of testing positive, severe disease and mortality for COVID-19 in South Asian and black individuals, relative to white individuals, would be eliminated if levels of high material deprivation were reduced within the population. **Results:** We included 15 044 (53.0% women) South Asian and black and 392 786 (55.2% women) white individuals. There were 151 (1.0%) positive tests, 91 (0.6%) severe cases and 31 (0.2%) deaths due to COVID-19 in South Asian and black individuals compared with 1471 (0.4%), 895 (0.2%) and 313 (0.1%), respectively, in white individuals. Compared with white individuals, the relative risk of testing positive for COVID-19, developing severe disease and COVID-19 mortality in South Asian and black individuals were 2.73 (95% CI: 2.26, 3.19), 2.96 (2.31, 3.61) and 4.04 (2.54, 5.55), respectively. A hypothetical intervention moving the 25% most deprived in the population out of deprivation was modelled to eliminate between 40 and 50% of the excess risk of all COVID-19 outcomes in South Asian and black populations, whereas moving the 50% most deprived out of deprivation would eliminate over 80% of the excess risk of COVID-19 outcomes. **Conclusions:** The excess risk of COVID-19 outcomes in South Asian and black communities could be substantially reduced with population level policies targeting material deprivation.

Introduction

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Mounting evidence suggests that people from minority ethnic groups in the UK (predominantly South Asian and black African or Caribbean populations) and elsewhere are disproportionately affected by COVID-19 with a higher risk of infection, hospitalization and mortality.[1–5] The reasons for these ethnic disparities are unclear.

Material deprivation is a universal underpinning determinant of health inequalities within and between populations.[6,7] It has further been suggested that factors linked to material deprivation may also be important in understanding the excess risk of COVID-19 observed in minority ethnic communities.[4] This hypothesis has not been rigorously investigated. Several studies have reported that the risk of COVID-19 outcomes in ethnic minorities is independent of potential confounders including deprivation,[8,9] while other studies have reported the opposite finding.[10] A recent analysis of population level data from the UK concluded that the elevated risk of COVID-19 mortality in South Asian and black populations was largely explained by demographic and socio-economic factors closely linked to deprivation,[3] with conclusions based on the degree of attenuation with adjustment. However, these findings only provide estimates of risk when markers of deprivation are held at a fixed value; they do not quantify the degree to which the excess risk in ethnic minority groups could be eliminated by reducing material deprivation using formal mediation analysis frameworks.

We conducted a mediation analysis to model how much of the excess risk in testing positive for COVID-19, developing severe disease or COVID-19 mortality in South Asian or black individuals compared with white individuals would be eliminated if levels of material deprivation were reduced.

Methods

We used UK Biobank, a large prospective cohort of middle-aged adults designed to support health research focused on improving the prevention, diagnosis and treatment of chronic diseases. Between March 2006 and July 2010, individuals living within 25 miles of one of the 22 study assessment centres located throughout UK, Scotland and Wales were recruited and attended data collection.[11] Ethical approval was obtained from the North West Centre for Research Ethics Committee (Ref: 11/NW/0382); all participants provided informed consent.

Outcomes

UK Biobank data are linked to Public Health England's Second Generation Surveillance System for SARS-CoV-2 laboratory test data collected throughout UK.[12] Data were available for the period

16th March 2020 to 24th August 2020 and included the outcome (positive, negative) of the test, as well as whether the specimen was collected within a hospital testing. For the purposes of this analysis, we classified a positive test result from an in-hospital setting as defining severe COVID-19 cases, as proposed through the linkage method.[12] Furthermore, we additionally investigated COVID-19 mortality and defined a COVID-19-related death as any death with ICD-10 code U07.1 or U07.2 as the primary cause of death on the death certificate using national mortality records through NHS Digital. Death data were available up to 24 August 2020. As linked testing data are only available for participants based in UK, those from Wales and Scotland were not included in this analysis. Those who died before the first COVID-19 testing sample date (16 March 2020) were also excluded. Supplementary figure S1 shows the selection of participants.

Exposure

Ethnicity was self-reported using a touch screen questionnaire. For this analysis, those classifying themselves as white (British, Irish, white or any other white background), South Asian (Asian or Asian British: Indian, Pakistani or Bangladeshi) or black (black or black British: Caribbean, African or any other black background) were included. South Asian and black individuals (SAB) were analysed as a single ethnic minority group. This approach was subject to a sensitivity analysis (details are reported in the statistical methods). Other minority ethnic groups, including those reporting a mixed ethnicity, were not included due to low numbers and evidence that the risk of COVID-19 outcomes is highest for SAB individuals.[2–4]

Mediator

The mediator in this analysis was considered as material deprivation status, measured by the Townsend score,[13] a composite of four domains: unemployment, non-car ownership, non-home ownership and household overcrowding. Within UK Biobank, data for each domain are taken from the UK Census (2001) that preceded the start of recruitment (2006) with output at the postcode area level. Each domain is given equal weighting. The resulting total score is log transformed and standardized to the UK population. A higher score represents greater deprivation. It has previously been shown that the Townsend score at the area level correlates strongly with measures of deprivation at the individual level.[14]

Selected confounders

Age, measured at 16 March 2020, and sex were included as covariates in this analysis due to lower age and proportion of women in the SAB population within UK Biobank. Additional confounders were not considered due to the mediation model and pathway specified.

Specifically, mediation analyses assume that: (i) there is no exposure-outcome confounding; (ii) there is no mediator-outcome confounding; (iii) there is no exposure-mediator confounding and (iv) no mediator-outcome confounder is itself affected by the exposure. When ethnicity is set as the exposure, assumptions (i) and (iii) hold *a priori* as only unmeasured historical or genetic factors are true potential confounds of the construct of ethnicity. For assumption (ii), traditional confounders such as health behaviour or chronic disease are implausible confounders of deprivation and may further violate assumption (iv) as both can be argued to be influenced by ethnicity.[15,16] Implausibility of confounders for deprivation within the model follows from a hypothesis supported by the literature that inequalities in health or health behaviours in people living with high deprivation are, in the most part, the result of high deprivation itself.[17,18] The DAG shown in Supplementary figure S2 illustrates this concept in detail.

Statistical analysis

Analysed outcomes were testing positive for COVID-19, developing severe (inpatient) disease or COVID-19 mortality. The population with each confirmed outcome was compared with the overall linked population without the outcome, as previously described.[19]

To test the mediating effect of deprivation in the association of ethnicity with COVID-19 outcomes, we used the four-way counterfactual approach proposed by Vanderweele,[20] applied using regression models through the user-written *med4way* command in Stata,[21] adjusted for age and sex. The counterfactual approach provides a framework for determining the strength of the direct and indirect pathways and their possible interactions through decomposing the excess relative risk into four components, described as the controlled direct effect (CDE), reference interaction (INT_{ref}), mediated interaction (INT_{med}) and the pure indirect effect (PIE). The counterfactual notation for each output is displayed in Supplementary table S1, with the underpinning mathematical formulae presented elsewhere.[20]

From a public health perspective, the INT_{ref}, INT_{med} and the PIE can be summed to model the proportion of the excess risk in the exposure that would be eliminated at a fixed level of the mediator.[20,22] For this analysis, the mediator–material deprivation, was included as a binary variable, categorised at the 75th percentile of the Townsend score (value = 0.4) defining the most deprived quarter of population. The outputs from the model can therefore be interpreted as the degree to which the excess risk in SAB, compared with white populations, would be eliminated following a hypothetical intervention where the most deprived within the UK Biobank population were moved to below the 75th percentile of the Townsend score.[20,22] We repeated the analysis when defining deprivation status at the median value (Townsend Score = −2.2).

A sensitivity analysis was also conducted for testing positively for COVID-19 and severe disease when South Asian and black populations were considered separately; mortality analysis was not stratified due to the limited number of events. Results are reported with 95% CI unless reported otherwise.

The code for the analysis and to identify the population, main exposure, mediator, covariates and outcomes are available on GitHub (razieh93).

Results

Supplementary figure S1 shows the flow diagram of individuals included for this analysis while table 1 reports the study characteristics. The analysis included 15 044 SAB ethnic minority and 392 786 white individuals. Subjects of SAB ethnic minorities had a median (IQR) age of 62.1 (56.3, 69.5) years and were younger than white individuals [68.8 (61.2, 74.0) years]. In total, there were 151 (1.0%) positive tests, 91 (0.6%) severe cases and 31 (0.2%) deaths due to COVID-19 cases in SAB individuals compared with 1471 (0.4%), 895 (0.2%) and 313 (0.1%), respectively, in white individuals. Deprivation scores were higher in SAB individuals, with a median (IQR) score of 1.4 (−1.2, 4.1) compared with −2.3 (−3.7, −0.2) for white individuals. The distribution of deprivation within each ethnic group is displayed in Supplementary figure S3.

Compared with white individuals, the age and sex-adjusted relative risk of testing positive for COVID-19, developing severe disease and COVID-19 mortality in SAB individuals were 2.73 (95% CI: 2.26, 3.19), 2.96 (2.31, 3.61) and 4.04 (2.54, 5.55), respectively. The results from the mediation analysis are displayed in Supplementary table S2. The combined PIE, INT_{med} and INT_{ref} suggest that moving the 25% most deprived in the population out of deprivation would substantially reduce the relative risk in SAB compared with white populations, eliminating between 40 and 50% of the excess risk for all COVID-19 outcomes (figure 1; data in Supplementary table S2). When modelling the impact of moving the 50% most deprived in the population out of deprivation, over 80% of the excess risk in all COVID-19 outcomes were eliminated, with SAB individuals no longer

Table 1 Cohort characteristics

	White ($n = 392\,786$)	South Asian and Black ($n = 15\,044$)	Total ($n = 407\,830$)
Age (years)	68.8 (61.2, 74.0)	62.1 (56.3, 69.5)	68.6 (60.9, 73.9)
Women	216 874 (55.2%)	7978 (53.0%)	224 852 (55.1%)
Men	175 912 (44.8%)	7066 (47.0%)	182 978 (44.9%)
Deprivation (Townsend score)	−2.3 (−3.7, 0.2)	1.4 (−1.2, 4.1)	−2.2 (−3.7, 0.4)
Positive cases	1471 (0.4%)	151 (1.0%)	1622 (0.4%)
Severe disease	895 (0.2%)	91 (0.6%)	986 (0.2%)
COVID-19 mortality	313 (0.1%)	31 (0.2%)	344 (0.1%)

Data as number (%) or median (IQR).

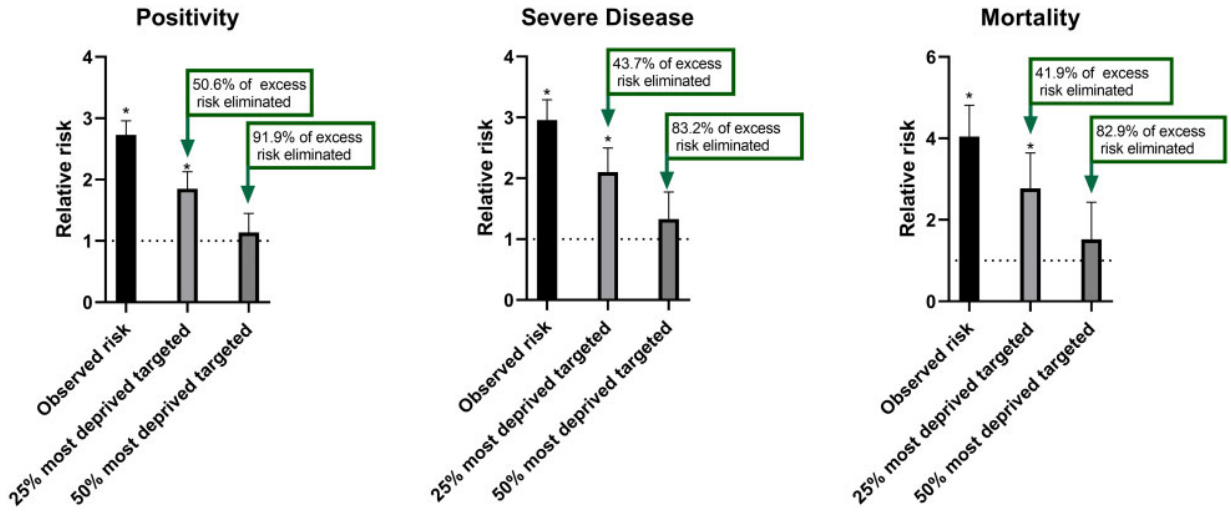


Figure 1 Modelling showing the relative risk of COVID-19 outcomes in black and South Asian relative to white ethnicities and the degree to which the risk is eliminated if the most deprived 25% or 50% in the population were moved out of deprivation. Data represent relative risk compared with white ethnicities. Error bars represent the standard error. Dotted line represents the reference (white ethnicities) $*P < 0.05$

having a meaningfully higher risk (figure 1; data in Supplementary table S2).

The proportion of the excess relative risk eliminated through targeting deprivation was similar when South Asian and black populations were analysed separately (Supplementary figure S4).

Discussion

This analysis provides novel evidence suggesting that interventions aimed at reducing material deprivation within the whole population could act to substantially reduce ethnic inequalities in the risk of COVID-19 outcomes. Specifically, a hypothetical intervention to move the 25% most deprived out of material deprivation would eliminate 40–50% of the relative excess risk for developing COVID-19 outcomes in SAB populations compared with white populations. A more extreme intervention to move the 50% most deprived out of material deprivation would eliminate over 80% of the excess risk. These findings suggest the central importance of material deprivation in driving ethnic inequalities for COVID-19 outcomes.

To our knowledge, this is the first analysis to apply a counterfactual mediation model to the role that deprivation plays in the risk of COVID-19 outcomes in SAB communities. Previously, studies have used deprivation as a covariate in logistic regression models with some concluding that the risk of COVID-19 outcomes are independent of deprivation.[8,9] A larger population level analysis of UK data suggested the opposite,[3] concluding that adjusting for factors linked to deprivation attenuated much of elevated risk of COVID-19 mortality in SAB individuals. These studies cannot be used to quantify the portion mediated by material deprivation or eliminated if material deprivation was reduced.

Key strengths of this study are the application of Vanderweele's four-way decomposition model to a large contemporary population linked to COVID-19 outcomes, with the outputs designed to allow public health inferences around mediation and elimination of risk in the exposure by changing the mediator.[20,22] There are also potential limitations that should be highlighted. Although well defined, the Townsend score assesses material deprivation across four narrow domains at the postcode area level. Material deprivation is a complex construct that is likely to be influenced at the individual level by a wide range of factors beyond those assessed. Therefore, the analysis will not capture the impact of material deprivation in its entirety. The mediation analysis is also contingent on the model assumptions, including the lack of adjustment for mediator-outcome confounders given that deprivation was postulated to be a stronger driver of health and health behaviours than the other way around. It is also acknowledged that rather being confounders, factors like chronic disease and health behaviours could potentially act as additional mediators between ethnicity and COVID-19 outcomes, and thus more complex models may be needed to examine whether a greater proportion of the excess risk in SAB individuals could be explained through additional mediation pathways compared with that explained by material deprivation alone. The observational design of this study means the findings from the mediation analysis are subject to the usual caveats around causality; results should therefore be interpreted as modelled values based on observational data rather than supporting definite direct causal inferences. The UK Biobank cohort has been noted to be healthier and more affluent than the national average, with a lower proportion of SAB individuals[23]; however, relative comparisons of associations within the cohort are still informative.[24] Indeed, the relative risk in the ethnic minorities included in this analysis were consistent with recently reported estimates from a larger population level study,[3] suggesting the excess relative risk examined as part of the

mediation analysis is consistent with the excess risk observed in the general population.

The comparator population used in the analysis also has strengths and limitations.[17] While cases of severe disease or COVID-19 mortality should have been picked up through the linkage system, the comparator population would nevertheless have contained those with undiagnosed mild or asymptomatic disease. In particular, during the first wave of the pandemic in UK, it is estimated that the majority of cases remained undetected,[24] with early testing policies limited to clinical need or health care professionals. This can lead to collider bias, particularly when a positive test is used as the outcome.[19] However, this cause of bias will be less relevant to the harder outcomes of severe (in-hospital) disease or mortality when the whole cohort without these outcomes is used as the comparator.[19] It is also possible that some reported cases may have resulted from a false-positive, although false-positive rates in UK are estimated to be low at between 0.8% and 4.0%.[25] The findings should therefore be interpreted as the UK Biobank population level risk of testing positive for COVID-19 within the national testing frameworks, developing severe disease or COVID-19 mortality, but not as the risk of overall infection or exposure. As this is an evolving pandemic, data should be interpreted as relating to the first wave of the pandemic in UK only. It is also acknowledged that the terms 'black African or Caribbean' and 'South Asian' cover a wide range of different cultures, languages and religions and possess fundamental differences in their physiological makeup. Consequently, our results may not apply to all black African or Caribbean and South Asian populations. However, comparisons using these ethnic groupings are still informative for understanding initial ethnic differences that can then be further investigated and stratified.

In conclusion, these results suggest reducing levels of material deprivation within the whole population could potentially play a pivotal role in reducing ethnic inequalities in COVID-19 outcomes observed South Asian and black communities. This further highlights the central role that deprivation is likely to play in driving ethnic health inequalities and the importance of policies working to reduce levels of deprivation within the whole population.

Supplementary data

Supplementary data are available at *EURPUB* online.

Acknowledgements

We would like to thank the Reviewers of this manuscript who provided considerable support to the authors in refining the usage and interpretation of the mediation model used.

Funding

This work was supported by the National Institute of Health Research (NIHR) Leicester Biomedical Research Centre (BRC), NIHR Applied Research Collaboration-East Midlands (ARC-EM) and a grant from the UKRI-DHSC COVID-19 Rapid Response Rolling Call (MR/V020536/1). The funder/sponsor had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication.

Conflicts of interest: K.K. is supported by the National Institute for Health Research Applied Research Collaboration East Midlands (ARC-EM) and T.Y. by the NIHR Leicester Biomedical Research Centre. K.K. 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 and a member of Independent SAGE and Chair of the SAGE subgroup on ethnicity and COVID-19. Other authors declare no conflicts of interests.

Data availability

We use data from UK Biobank application number 36371 to support the case being made. All bona fide researchers can apply to use UK Biobank for health-related research that is in the public interest. Further information on the application process is available from UK Biobank https://www.ukbiobank.ac.uk/register-apply/

Key points

- People from minority ethnic groups are at higher risk of COVID-19 hospitalization and death, compared with white individuals.
- It is currently unclear why these ethnic inequalities are present.
- Deprivation has been suggested as a possible factor that may explain this increased risk.
- Reducing deprivation would eliminate much of the excess risk of COVID-19 outcomes in minority ethnic groups.
- Policies to reduce social inequality and deprivation are required to reduce COVID-19 disparities.

References

1 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430–6.

2 Office for National Statistics (ONS). Coronavirus (COVID-19) Related Deaths by Ethnic Group, England and Wales, 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelateddeathsbyethnicgroupenglandandwales/2march2020to10april2020 (28 July 2020, date last accessed).

3 Office for National Statistics (ONS). Updating Ethnic Contrasts in Deaths Involving the Coronavirus (COVID-19), England and Wales, Deaths Occurring 2 March to 28 July 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/updatingethniccontrastsindeathsinvolvingthecoronaviruscovid19englandandwales/deathsoccurring2marchto28july2020 (26 October 2020, date last accessed).

4 Pan D, Sze S, Minhas JS, et al. The impact of ethnicity on clinical outcomes in COVID-19: a systematic review. *EClinicalMedicine* 2020;23:100404.

5 The South Asian Health Foundation. COVID-19 in Black, Asian and Minority Ethnic populations: An Evidence Review and Recommendations From the South Asian Health Foundation, 2020. Available at: https://www.sahf.org.uk/covid19 (28 July 2020, date last accessed).

6 Marmot M. Health equity in England: the marmot review 10 years on. *BMJ* 2020;368:m693.

7 Marmot M. Social determinants of health inequalities. *Lancet* 2005;365:1099–104.

8 Raisi-Estabragh Z, McCracken C, Bethell MS, et al. Greater risk of severe COVID-19 in black, Asian and minority ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25 (OH)-vitamin D status: study of 1326 cases from the UK Biobank. *J Public Health* 2020;42:451–60.

9 Sapey E, Gallier S, Mainey C, et al. Ethnicity and risk of death in patients hospitalised for COVID-19 infection in the UK: an observational cohort study in an urban catchment area. *BMJ Open Resp Res* 2020;7:e000644.

10 Yehia BR, Winegar A, Fogel R, et al. Association of race with mortality among patients hospitalized with coronavirus disease 2019 (COVID-19) at 92 US hospitals. *JAMA Netw Open* 2020;3:e2018039.

11 Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12:e1001779.

12 Armstrong J, Rudkin JK, Allen N, et al. Dynamic linkage of COVID-19 test results between Public Health England's second generation surveillance system and UK biobank. *Microb Genom* 2020;6.

13 Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. London, UK: Croom Helm, 1988.

14 Adams J, Ryan V, White M. How accurate are Townsend deprivation scores as predictors of self-reported health? A comparison with individual level data. *J Public Health* 2005;27:101–6.

15 Misra A, Ramchandran A, Jayawardena R, et al. Diabetes in South Asians. *Diabet Med* 2014;31:1153–62.

16 Barnett AH, Dixon AN, Bellary S, et al. Type 2 diabetes and cardiovascular risk in the UK South Asian community. *Diabetologia* 2006;49:2234–46.

17 Marmot M. Fair society, healthy lives: the Marmot review; strategic review of health inequalities in England post-2010. The Marmot Review, Institute for Health Equity, 2010. Available at: http://www.instituteofhealthequity.org/resources-reports/fair-society-healthy-lives-the-marmot-review (10 March 2021, date last accessed).

18 Marmot M, Allen J, Boyce T, et al. The Marmot Review 10 Years On. Institute for Health Equity. Available at: http://www.instituteofhealthequity.org/resources-reports/marmot-review-10-years-on (10 March 2021, date last accessed).

19 Yates T, Zaccardi F, Razieh C, et al. Framework to aid analysis and interpretation of ongoing COVID-19 research. *Wellcome Open Res* 2020;5:208.

20 Vanderweele TJ. A unification of mediation and interaction: a four-way decomposition. *Epidemiology* 2014;25:749–61.

21 Discacciati A, Bellavia A, Lee JJ, et al. Med4way: a Stata command to investigate mediating and interactive mechanisms using the four-way effect decomposition. *Int J Epidemiol* 2019;48:15–20.

22 VanderWeele TJ. Policy-relevant proportions for direct effects. *Epidemiology* 2013;24:175–6.

23 Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026–34.

24 Batty GD, Gale CR, Kivimäki M, et al. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ* 2020;12:368.

25 Surkova E, Nikolayevskyy V, Drobniewski F. False-positive COVID-19 results: hidden problems and costs. *Lancet Respir Med* 2020;8:1167–8.

Rowlands et al. BMC Public Health (2021) 21:773
https://doi.org/10.1186/s12889-021-10839-0

BMC Public Health

RESEARCH Open Access

Association of working shifts, inside and outside of healthcare, with severe COVID–19: an observational study

A. V. Rowlands[1,2*], C. Gillies[3], Y. Chudasama[3], M. J. Davies[1,2], N. Islam[4], D. E. Kloecker[1,3,5], C. Lawson[3], M. Pareek[6], C. Razieh[1,2], F. Zaccardi[1,3], T. Yates[1,2†] and K. Khunti[1,3,7†]

Abstract

Background: Health and key workers have elevated odds of developing severe COVID-19; it is not known, however, if this is exacerbated in those with irregular work patterns. We aimed to investigate the odds of developing severe COVID-19 in health and shift workers.

Methods: We included UK Biobank participants in employment or self-employed at baseline (2006–2010) and with linked COVID-19 data to 31st August 2020. Participants were grouped as neither a health worker nor shift worker (reference category) at baseline, health worker only, shift worker only, or both, and associations with severe COVID-19 investigated in logistic regressions.

Results: Of 235,685 participants (81·5% neither health nor shift worker, 1·4% health worker only, 16·9% shift worker only, and 0·3% both), there were 580 (0·25%) cases of severe COVID-19. The odds of severe COVID-19 was higher in health workers (adjusted odds ratio: 2·32 [95% CI: 1·33, 4·05]; shift workers (2·06 [1·72, 2·47]); and in health workers who worked shifts (7·56 [3·86, 14·79]). Being both a health worker and a shift worker had a possible greater impact on the odds of severe COVID-19 in South Asian and Black and African Caribbean ethnicities compared to White individuals.

Conclusions: Both health and shift work (measured at baseline, 2006–2010) were independently associated with over twice the odds of severe COVID-19 in 2020; the odds were over seven times higher in health workers who work shifts. Vaccinations, therapeutic and preventative options should take into consideration not only health and key worker status but also shift worker status.

Keywords: Coronavirus, SARS-CoV-2, Employment, Ethnicity, UK Biobank

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease-2019 (COVID-19), is a global health threat [1]. It has led to an unprecedented co-ordinated global research effort to develop and evaluate a range of vaccines. To date, preliminary results are in for candidate vaccines and vaccination of priority groups has commenced. The provisional priority list in the UK focuses on care home residents and their carers', front-line health and social care workers, and older adults [2]. The high priority for health workers and care workers is due to the established elevated odds of infection, development of severe infection, and spreading infection in these groups [3–8]. This is further increased for health workers from ethnic minorities [6]. There has been less attention on whether the odds are exacerbated in

* Correspondence: alex.rowlands@le.ac.uk
†T. Yates and K. Khunti are joint senior authors
[1]Diabetes Research Centre, Leicester General Hospital, University of Leicester, Gwendolen Rd, Leicester LE5 4PW, UK
[2]National Institute for Health Research (NIHR) Leicester Biomedical Research Centre (BRC), Leicester General Hospital, Leicester LE5 4PW, UK
Full list of author information is available at the end of the article

those with irregular work patterns, i.e. shift work, which is common in health and care.

Working shifts is associated with an increased risk for cardiovascular disease [9–12] which appears to persist following retirement, although attenuated [12]. Research suggests risk factors for cardiometabolic diseases [12] are also risk factors for COVID-19 [13–15]. Further, shift work is associated with alterations in the immune system and an increased risk for viral infections [16]. In this view, it is not surprising that recent evidence suggests that shift work is associated with elevated odds of severe COVID-19 [5, 17], and that health care workers on night shifts have higher odds of in-hospital SARS-CoV-2 infection than those on day shifts [18]. However, it is not known whether working shifts interacts with health worker status or ethnicity, both of which are independently associated with elevated odds of COVID-19 [6, 19, 20].

Shift workers are more likely to have disturbed sleep and variable sleep patterns [21] leading to disruption of the circadian rhythm. This has been hypothesised to increase the odds of COVID-19 in night shift workers [22], but is evident even if the shift pattern does not include night work, likely due to sleep disruption in relation to circadian rhythms [21], which may persist in the years following cessation of shift work [23]. Recent data have suggested that sleep disruption and high variability in sleep timing are associated with the odds of testing positive for COVID-19 and development of severe infection [15]. Exacerbating this, shift work is common in health workers where exposure to infection with SARS-CoV-2 and odds of developing severe COVID-19 are already relatively high [6, 7]. Therefore, we hypothesise both health workers and shift workers will independently be at increased odds of developing severe COVID-19, but the odds will be further increased in health workers who are also shift workers. Further, we hypothesise that increased odds of developing severe COVID-19 will be evident across ethnic groups and for males and females.

Methods

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary material: Checklist S1) and following a pre-specified protocol (Application Number 36371) [24].

Study population

For this analysis, we used data from UK Biobank (application 36,371), a prospective cohort of > 500,000 adults aged 40–69 years [25]. UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). All methods were carried out in accordance with relevant guidelines and regulations and all participants gave written informed consent prior data collection. All baseline assessments were conducted between March 2006 and July 2010. UK Biobank data are linked to national SARS-CoV-2 laboratory test data through Public Health England's Second Generation Surveillance System [26]. This secure, pseudonymized, individual-level rapid dynamic linkage is described in detail elsewhere [26]. Data provided by the system is incorporated into the UK Biobank (UKB) database and released through the usual governance processes (http://www.ukbiobank.ac.uk/register-apply). The data were available from 16th March 2020 to 31st August 2020 and included outcome of the test (positive/negative) and specimen origin (hospital inpatient vs other). Analyses were restricted to those who were alive on 16th March 2020 (the first COVID-19 testing sample date) and to English centres as testing data were initially only for those based in England.

Exposure

Participants' occupation was categorised according to whether or not they were health workers and/or shift workers based on the occupation information reported at baseline (2006–2010). Health care workers were classified based on UK Biobank occupational codes 2,211,001–2,216,012. Participants who reported that their work involved shift work "sometimes", "usually" or "always" were classified as shift workers, while participants who reported that their work "never/rarely" involved shift work were classified as non-shift workers. Shift or health worker status was defined as four mutually exclusive categories: neither (reference category), health worker only, shift worker only, or both health and shift worker. Only participants who reported being in paid employment or self-employed at baseline were asked about shift work. Those without data for shift work and health work status were excluded. A flow chart detailing all participant exclusions is provided in Figure S1 in Supplementary material.

Outcome

Severe COVID-19 was defined as a composite of a positive test result for SARS-CoV-2 from a hospital setting in line with guidance for this dataset [26], or death related to the disease (i.e. any death with an ICD-10 code of U07.1 or U07.2 as the primary cause of death on the death certificate). Positive tests in an outpatient setting were removed from this analysis as we were unable to determine whether these ultimately resulted in hospitalisation. Results can thus be interpreted as the overall population level risk of being admitted to hospital with or dying from COVID-19 during the linkage period within UK Biobank. This population level method of assessing risk has been commonly reported within COVID-19 risk factor research, enabling comparison to the literature in terms of how the risk

factors assessed compare to other commonly reported risk factors [13–15, 27].

Co-variates/confounders

Participant characteristics, including body mass index (BMI), sex, ethnicity (White, South Asian, Black and African Caribbean), deprivation (Townsend score, a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding; negative values represent less deprivation), cancer (self-reported), co-morbidities (yes/no; one or more medical condition(s): i.e. cardiovascular, respiratory, renal, neurology, musculoskeletal, haematology, gynaecology, immunology, infections), and smoking status (never, previous current) were collected at the baseline assessment. Age on 16th March 2020 was calculated. Confounders were selected based on current clinical knowledge showing the risk of COVID-19 is elevated in men, ethnic minorities [6], people who are older [2], obese [14], deprived [2], have co-morbidities [2], or who smoke [28].

Statistical analysis

Logistic regression was used to identify the odds associated with developing severe COVID-19 in participants who were shift workers only, health workers only, or were both health and shift workers. The reference category for comparison was workers who did not work shifts, or work in healthcare. These four categories are mutually exclusive to facilitate interpretation of the independent effects of shift and health worker status, and whether their combination provides an additive or multiplicative association. Analyses were carried out for the whole cohort, and also stratified by ethnicity, and sex. All analyses were adjusted for the aforementioned potential confounders.

Two sensitivity analyses were carried out: 1) with self-reported sleep duration at baseline included as a further co-variate; 2) stratified by retirement age (currently 66 years of age in the UK). People below retirement age at the beginning of the pandemic were assumed most likely to still be working and thus at higher exposure to the virus. People above retirement age were assumed to be less likely to be working and thus at lower exposure to the virus. Individuals with an age at time of COVID-19 test equal to or below 65 years were classed as below retirement age, those with an age at time of COVID-19 above 65 years as above retirement age. Age was measured as an integer in years.

All analyses were carried out in Stata version 16.0 (StataCorp LLC, TX, USA). The code used to run the analysis is available on github (https://github.com/clg13/Employment-analysis-code/blob/main/employment%20analysis%20code%20for%20github.do). Statistical significance was set at the alpha level of .05.

Results

There were 235,685 participants eligible for inclusion in this analysis (i.e. with information on outcome of severe COVID-19, shift or health worker status, and full co-variate profile), of which 580 (0·25%) had severe COVID-19. Mean participant age was 63·8 years (SD 7·1), BMI 27·2 $kg{\cdot}m^{-2}$ (SD 4·7), 52·2% were female, and 96·1% were White (Table 1); 81·5% (n = 193,135) were neither a shift nor health worker, 16·9% (n = 38,738) were a shift worker only, 1·4% (n = 3193) a health worker only, and 0·3% (n = 620) both.

After adjustment for potential confounders, a significant association was found between shift worker only (adjusted odds ratios (aOR): 2·06 [95% CI: 1·72, 2·47]) or health worker only (2·32 [1·33, 4·05]) status and odds of

Table 1 Participant characteristics

Characteristic	All (n = 235,685)	Severe covid-19 (hospitalisation or death)	
		Yes (n = 580)	No (n = 235,105)
Age at test (years)	63·8 (7·11)	63·6 (7·70)	63·8 (7·10)
Body mass index (kg/m^2)	27·2 (4·68)	28·7 (5·34)	27·2 (4·68)
Townsend score	-1·39 (2·96)	-0·47 (3·39)	-1·39 (2·96)
Sex			
Female	123,127 (52·2)	275 (47·4)	122,852 (52·3)
Ethnicity			
White	226,436 (96·1)	518 (89·3)	225,918 (96·1)
South Asian	4345 (1·8)	30 (5·2)	4315 (1·8)
Black	4904 (2·1)	32 (5·5)	4872 (2·1)
Smoking status			
Never	135,710 (57·6)	300 (51·7)	135,410 (57·6)
Previous	75,767 (32·2)	221 (38·1)	75,546 (32·1)
Current	24,208 (10·3)	59 (10·1)	24,149 (10·3)
Past or current cancer			
Yes	13,957 (5·9)	39 (6·7)	13,918 (5·9)
Co-morbidities			
Yes	162,290 (68·9)	438 (75·5)	161,852 (68·9)
Shift or health worker			
Neither	193,134 (81·5)	375 (64·7)	192,759 (82.0)
Shift worker	38,738 (16·9)	183 (31.6)	38,555 (16·4)
Health worker	3193 (1·4)	13 (2·2)	3180 (1·4)
Both	620 (0·3)	9 (1·6)	611 (0·3)

Values reported are mean (SD) or N (%)
Co-morbidities: yes/no; one or more medical condition(s): i.e. cardiovascular, respiratory, renal, neurology, musculoskeletal, haematology, gynaecology, immunology, infection
Townsend score: a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding; negative values represent less deprivation

severe COVID-19 (Fig. 1a). The estimated odds were greatest for individuals who were both a shift and health worker (aOR: 7·56 [3·86, 14·79]). A similar pattern was found when the analysis was stratified by sex (Fig. 1a), with a higher estimated association for both shift and health worker status in men (aOR: 10·70 [4·92, 23·28]) than women (aOR: 3·58 [0·88, 14·54]). When the analysis was stratified by ethnicity (Fig. 1b), there was a tendency for a greater impact of being both a health worker and a shift worker in South Asian and Black and African Caribbean ethnicities when compared to White, but confidence intervals were large.

Results of unadjusted models were consistent with the adjusted models and are given in Supplementary Table S1.

Sensitivity analyses

In the first sensitivity analysis, controlling for sleep duration did not change the results (Supplementary Figure S2).

The second sensitivity analysis, stratified by retirement age, was conducted for the whole sample only, due to small numbers in the sex and ethnicity sub-groups. There were 125,118 eligible individuals below retirement age (54·2% female, 94·8% White) and assumed to be working, of which 312 (0·25%) had severe COVID-19. Of these 80·1% (n = 100,170) were neither a shift nor health worker, 18·2% (n = 22,819) were a shift worker only, 1·4% (n = 1708) a health worker only, and 0·3% (n = 421) both. There was a similar pattern of results, with estimated odds ratios generally larger than when the whole cohort was considered (Fig. 2).

Eligible people above retirement age and assumed to be retired were 110,567 (50·0% female, 97·6% White), of which 268 (0·24%) had severe COVID-19. Of these, 84·1% (n = 92,964) had been neither a shift nor health worker, 14·4% (n = 15,919) a shift worker only, 1·3% (n = 1485) a health worker only, and none who had been both. Elevated odds associated with prior shift worker status persisted, albeit lower (aOR: 1·45 [1·08, 1·95]); conversely, no association with prior health worker status was evident (Fig. 2).

Discussion

Both being a health worker, or working shifts, were independently associated with over twice the population level odds of severe COVID-19; notably, the odds were more than seven times higher in health workers who work shifts. The impact of health and shift work tends to be higher in males and in minority ethnic groups, who are already at increased risk of severe COVID-19 [19, 20].

The substantially higher odds of severe COVID-19 associated with health workers who work shifts may reflect a greater patient-facing role. This would lead to more viral exposure than non-shift health workers who may be more likely to be in managerial, supervisory or technician roles. The odds of severe COVID-19 were also stronger when considering only people below retirement age at the beginning of the pandemic, thus more likely to still be working and at increased viral exposure. When considering only people above retirement age at the beginning of the pandemic, the association with health

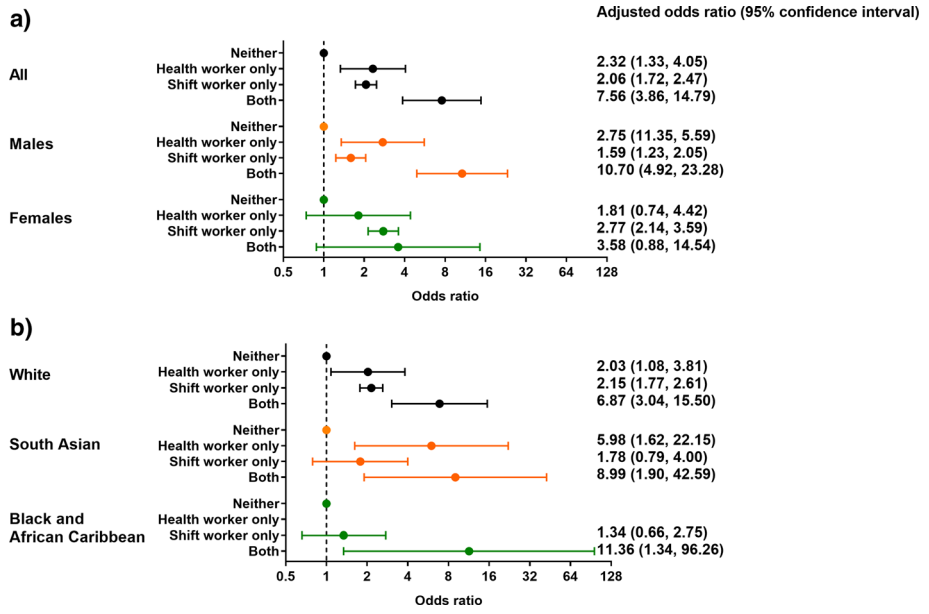


Fig. 1 Employment status and odds of severe COVID-19 stratified by **a**) sex, **b**) ethnicity. Model (**a**) adjusted for: age, sex (for all participants), Townsend score, BMI, cancer (self-reported, past or current at time of data collection), co-morbidities (yes/no), smoking status (never, previous current) and ethnicity. Model (**b**) same as model (**a**) except without ethnicity

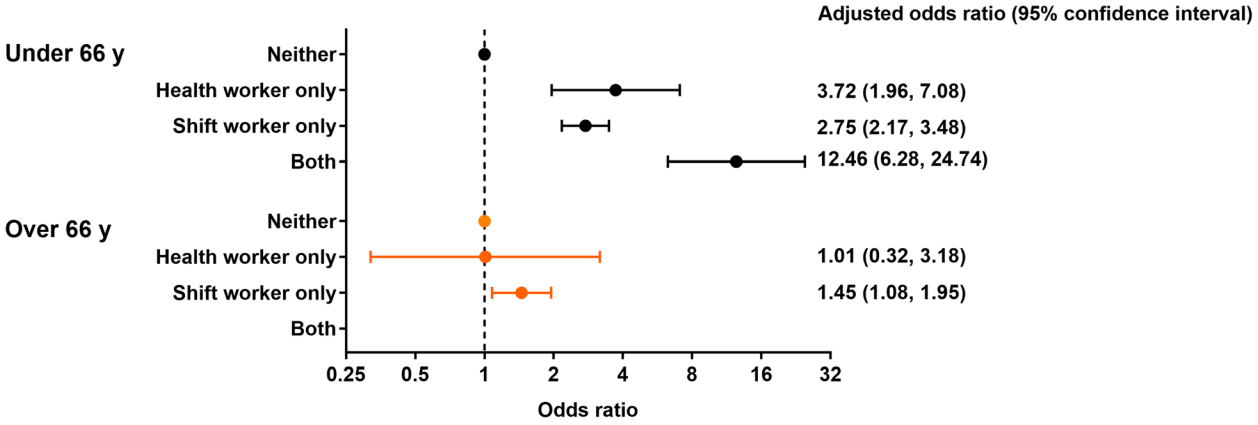


Fig. 2 Employment status and odds of severe COVID-19 stratified by UK retirement age (66y). Adjusted for age, sex (for all participants), Townsend score, BMI, cancer (self-reported, past or current at time of data collection), co-morbidities (yes/no), smoking status and ethnicity

worker status appears to dissipate. This potentially suggests that the elevated odds of severe COVID-19 in the whole population or those under retirement age is indeed explained by increased exposure to the virus. In contrast, an association of severe COVID-19 with prior shift-work status persists, although attenuated. Alongside the higher odds for health workers who work shifts, this suggests that the association between severe COVID-19 and shift work may not be fully explained by an increased viral exposure.

The persistence of elevated odds associated with shift work following retirement has previously been identified for cardiovascular disease [12]. Purported mechanisms include disruptions to the behavioural and circadian rhythm [9], which can lead to chronic inflammation [29], potentially contributing to the increased risk of cardiovascular disease observed in previous shift workers. As COVID-19 is an acute inflammatory disease [29], it may exacerbate any existing chronic inflammation. Alongside other risk factors (e.g. health-related behaviours [15], psychological stress and genetic predisposition), this may be associated with a 'cytokine storm' [22, 29, 30] contributing to the increased odds of severe COVID-19 we observed in shift-workers.

The demand for 24-h services has extended shift work beyond factories to more traditionally "white collar" occupations, e.g. retail and service [31], with approximately 15–25% of workers in Europe employed on shift schedules [11, 16]. Irrespective, shift workers still tend to be more deprived and subject to psychosocial stresses [10], which may contribute to increased risk for cardiovascular disease and COVID-19. While we controlled for a range of available co-variates, including age, sex, ethnicity, deprivation, co-morbidities and self-reported sleep (sensitivity analysis), other residual confounders, e.g. health-related behaviours, may be present that predispose the shift workers to greater odds of severe COVID-19. However, Maidstone et al. [17] recently showed that the incidence of COVID-19 in shift workers was still greater when compared to non-shift workers in the same job. Further, in a previous UK Biobank study, we showed that objectively measured sleep disruption and variability in sleep timing was associated with increased odds of severe COVID-19 [15]. While disturbed sleep is prevalent in shift workers,[21] the odds were similar when excluding shift workers from the cohort [15]. This observation would suggest that sleep disturbance and variability in sleep timing, even in the absence of shift work status, is associated with increased odds of severe COVID-19 [32]. Likewise, irregular sleep timing was associated with metabolic abnormalities in a prospective study on cardiovascular events in ~ 2000 participants [33], with similar results when shift workers were excluded.

Strengths of this study include the large population with linked COVID-19 data. In addition, the UK Biobank differs from many other datasets currently being analysed to better understand COVID-19, in that it is an extensively phenotyped population, allowing the impact of issues such as shift worker status to be assessed. However, the study also has several important limitations. Characteristics of participants, including health worker and shift work status, were measured between 2006 and 2010 and may have changed prior to the pandemic. Mutambudzi et al. [5] and Maidstone et al. [17] similarly used occupation at UK Biobank baseline to ascertain odds of severe COVID-19. In support of this assumption, Matambudzi et al. [5] determined a high correlation ($r = 0.71$, $p < 0.001$) between occupation at baseline and occupation between 2014 and 2019 in a sub-sample of > 12,000, participants indicating a high likelihood that participants had continued working in the same profession. Further, in our analyses stratified by retirement age, we assumed that those below retirement age at the date of their COVID-19 test were still working and at

relatively high exposure to COVID-19, while those above retirement age were not working and were at lower exposure. It is not possible to confirm this assumption with the available data. Additionally, the definition of severe COVID-19 was a positive test from a hospital inpatient; while this is consistent with the definition proposed by the researchers that developed the linkage method [25], actual disease severity cannot be confirmed from the linkage data available. Finally, participants in UK Biobank may not be representative of the wider population and testing in the UK has not been universal, making analyses vulnerable to bias.

Conclusions

In conclusion, both shift and health work status (measured in 2006–2010) were associated with increased odds of developing severe COVID-19 independent of age, sex, ethnicity, deprivation and co-morbidities. The odds were compounded more than three-fold further in health workers who work shifts, irrespective of sex or ethnicity, compared to neither health nor shift worker. The impact of health and shift work tended to be higher in minority ethnic groups, who are already at increased risk of severe COVID-19. The UK Reach study (https://uk-reach.org/main/) will investigate how, and why, ethnicity affects COVID-19 outcomes in healthcare workers. Notably, the elevated odds associated with health workers was no longer apparent in people over retirement age, suggesting that the increased odds are likely explained by the exposure to the virus inherent to the occupation. However, in shift workers, elevated albeit attenuated odds were still evident in people over retirement age, suggesting that the elevated odds associated with shift work may not be fully explained by increased exposure to the virus. This is consistent with previous reports of elevated risk of cardiovascular disease in former shift workers [12] and further supports that risk factors for cardiovascular and cardiometabolic disease are also risk factors for COVID-19 [13–15]. Vaccination, therapeutic and prevention programmes are being prioritised for health care workers. Our data suggest that shift workers should also be prioritised for these preventive measures.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-021-10839-0.

Additional file 1: Checklist S1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). **Figure S1**. Flow chart of participants included in main analysis. **Figure S2**. Association between employment status and odds of severe COVID-19, stratified by a) sex and b) ethnicity, additionally controlled for self-reported sleep duration. Model (a) adjusted for: age, sex (for all participants), Townsend score, BMI, cancer (self-reported, past or current at time of data collection), co-morbidities (yes/no), smoking status (never, previous current), ethnicity, and self-reported sleep duration. Model (b) same as model (a) except without ethnicity. **Table S1**. Unadjusted Associations between employment status and odds of severe COVID-19.

Acknowledgements

Data were analysed using UK Biobank application number 36371.

Authors' contributions

Concept and design: AR, CG, KK, TY; Acquisition, analysis or interpretation of the data: All authors (AR, CG, YC, MD, NI, DK, CL, MP, CR, FZ, TY, KK); Statistical analysis and data verification: CG, AR; Drafting of the manuscript: AR, CG; Critical revision of the manuscript for important intellectual content: All authors (AR, CG, YC, MD, NI, DK, CL, MP, CR, FZ, TY, KK) had full access to the data, accept responsibility to submit for publication, and read and approved the final manuscript.

Funding

This research was supported by the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre, the NIHR Applied Research Collaborations – East Midlands, and a grant from the UKRI-DHSC COVID-19 Rapid Response Rolling Call (MR/V020536/1). MP is supported by a NIHR Development and Skills Enhancement Award and UKRI/MRC/NIHR (MR/V027549/1). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Availability of data and materials

This research has been conducted using the UK Biobank Resource under Application 36371. The database supporting the conclusions of this article is available from UK Biobank project site, subject to registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

Declarations

Ethics approval and consent to participate

All participants gave written informed consent prior data collection. UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

KK is chair for SAGE subgroup on ethnicity and COVID-19 and a member of independent SAGE. All other authors declare that they have no competing interests.

Author details

[1]Diabetes Research Centre, Leicester General Hospital, University of Leicester, Gwendolen Rd, Leicester LE5 4PW, UK. [2]National Institute for Health Research (NIHR) Leicester Biomedical Research Centre (BRC), Leicester General Hospital, Leicester LE5 4PW, UK. [3]Leicester Real World Evidence Unit, Diabetes Research Centre, Leicester General Hospital, University of Leicester, Gwendolen Rd, Leicester LE5 4PW, UK. [4]Nuffield Department of Population Health, University of Oxford, Oxford, UK. [5]St George's University of London, Tooting, London, UK. [6]Department of Respiratory Sciences, University of Leicester, Leicester, UK. [7]NIHR Applied Research Collaboration – East Midlands (ARC-EM), Leicester General Hospital, Leicester, UK.

Received: 22 December 2020 Accepted: 1 April 2021
Published online: 22 April 2021

References

1. Anderson RM, Heesterbeek H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet. 2020;395(10228):931–4. https://doi.org/10.1016/S0140-6736(20)30567-5.
2. Joint Committee on Vaccination and Immunisation. Independent report: Priority groups for COVID-19 vaccination: advice from the JCVI, 2020. https://

www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020. Accessed 6th December 2020.
3. Karlsson U, Fraenkel C-J. Covid-19: risks to healthcare workers and their families. Br Med J. 2020;371:m3944. https://doi.org/10.1136/bmj.m3944.
4. Marrinaccio A, Gueraa R, Iavicoli S. Work a key determinant in COVID-19 risk. Lancet. 2020;8:e1368. https://doi.org/10.1016/S2214-109X(20)30411–3.
5. Mutambudzi M, Niedzwiedz CL, Macdonald, et al. Occupation and risk of severe COVID-19: prospective cohort study of 120,075 UK Biobank participants. Occup Environ Med. 2020. https://doi.org/10.1136/oemed-2020-106731.
6. Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health. 2020;5(9):e475–83. https://doi.org/10.1016/S2468-2667(20)30164-X.
7. Shah ASV, Wood R, Gribben C, Caldwell D, Bishop J, Weir A, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: nationwide linkage cohort study. Br Med J. 2020;371:m3582. https://doi.org/10.1136/bmj.m3582.
8. Chirico F, Magnavita N. The crucial role of occupational health surveillance for health-care workers during the COVID-19 pandemic. Workplace Health Safety. 2021;69(1):5–6. https://doi.org/10.1177/2165079920950161.
9. Lajoie P, Aronson KJ, Day A, Tranmer J. A cross-sectional study of shift work, sleep quality and cardiometabolic risk in female hospital employees. BMJ Open. 2015;5(3):e007327. https://doi.org/10.1136/bmjopen-2014-007327.
10. Puttonen S, Härmä M, Hublin C. Shift work and cardiovascular disease – pathways from circadian stress to morbidity. Scand J Work Environ Health. 2010;36(2):96–108. https://doi.org/10.5271/sjweh.2894.
11. Tenkanen L, Sjöblom T, Kalimo R, Alikoski T, Härmä M. Shift work, occupation and coronary heart disease over 6 years of follow-up in the Helsinki heart study. Scan J Work Environ Health. 1997;23(4):257–65. https://doi.org/10.5271/sjweh.218.
12. Virkkunen H, Härmä M, Kauppinen T, Tenkanen L. The triad of shift work, occupational noise, and physical workload and risk of coronary heart disease. Occup Environ Med. 2006;63(6):378–86. https://doi.org/10.1136/oem.2005.022558.
13. Yates T, Razieh C, Zaccardi F, Rowlands AV, Seidu S, Davies MJ, et al. Obesity, walking pace and risk of severe COVID–19: analysis of UK Biobank. Int J Obes. 2021. https://doi.org/10.1101/2020.07.10.20150003.
14. Yates T, Razieh C, Zaccardi F, Davies MJ, Khunti K. Obesity and risk of COVID-19: analysis of UK Biobank. Prim Care Diabetes. 2020;14(5):566–7. https://doi.org/10.1016/j.pcd.2020.05.0117.
15. Rowlands AV, Kloecker DE, Chudasama Y, Davies MJ, Dawkins NP, Edwardson CL, et al. Association of balance and timing of physical activity and rest with risk of COVID-19 in UK Biobank. Mayo Clin Proc. 2020;96(1):156–64. https://doi.org/10.1016/j.mayocp.2020.10.032.
16. Almeida CMO, Malheiro A. Sleep, immunity and shift workers: a review. Sleep Sci. 2016;9(3):164–8. https://doi.org/10.1016/j.slsci.2016.10.007.
17. Maidstone R, Anderson SG, Ray DW, Rutter MK, Durrington HJ, Blaikley JF. Shift work is associated with positive COVID-19 status in hospitalised patients. medRxiv. 2020. https://doi.org/10.1101/2020.12.04.20244020.
18. Rizza S, Coppeta L, Grelli S, Ferrazza G, Chiocchi M, Vanni G, et al. High body mass index and night shift work are associated with COVID-19 in health care workers. J Endocrinol Investig. 2020;44(5):1097–101. https://doi.org/10.1007/s40618-020-01397-0.
19. Aldridge RW, Lewer D, Katikireddi SV, et al. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. [version 2; peer review: 3 approved]. Wellcome Open Res. 2020;5:88. https://doi.org/10.12688/wellcomeopenres.15922.2.
20. Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, et al. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. Eclinical Medicine. 2020;29-30:100630. https://doi.org/10.1016/j.eclinm.2020.100630.
21. Åkerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med. 2003;53(2):89–94. https://doi.org/10.1093/occmed/kqg046.
22. Lim RK, Wambier CG, Goren A. Are night shift workers at an increased risk for COVID-19? Med Hypotheses. 2020;144:110147. https://doi.org/10.1016/j.mehy.2020.110147.
23. Dumont M, Montplaisir J, Infante-Rivard C. Sleep quality of former night-shift workers. Int J Occup Environ Health. 1997;1997(suppl 2):S10–4.
24. UK Biobank: Protocol for a large-scale prospective epidemiological resource. Available at [https://www.maelstrom-research.org/mica/individual-study/ukb] Assessed 7th December 2020.
25. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779. https://doi.org/10.1371/journal.pmed.1001779.
26. Armstrong J, Rudkin JK, Allen N, Crook DW, Wilson DJ, Wyllie DH, et al. Dynamic linkage of COVID-19 test results between Public Health England's second generation surveillance system and UK Biobank. Microb Genom. 2020;6(7). https://doi.org/10.1099/mgen.0.000397.
27. Yates T, Zaccardi F, Razieh C, et al. Framework to aid analysis and interpretation of ongoing COVID-19 research [version 1; peer review: 1 approved with reservations]. Wellcome Open Res. 2020;5:208. https://doi.org/10.12688/wellcomeopenres.16227.1.
28. Hopkinson NS, Rossi N, El-Sayed Moustafa J, et al. Current smoking and COVID-19 risk: results from a population symptom app in over 2.4 million people. Thorax. 2021. https://doi.org/10.1136/thoraxjnl-2020-216422.
29. Vepa A, Bae JP, Ahmed F, Pareek M, Khunti K. COVID-19 and ethnicity: a novel pathophysiological role for inflammation. Diabetes Metab Syn. 2020;14(5):1043–51. https://doi.org/10.1016/j.dsx.2020.06.056.
30. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383(23):2255–73. https://doi.org/10.1056/NEJMra2026131.
31. Harrington JM. Health effects of shift work and extended hours of work. Occup Environ Med. 2001;28:68–72.
32. Garbarino S, Magnavita N. Sleep problems are a strong predictor of stress-related metabolic changes in police officers. A prospective study. PLoS One. 2019;14(10):e0224259. https://doi.org/10.1371/journal.pone.0224259.
33. Huang T, Redline S. Cross-sectional and prospective associations of actigraphy-assessed sleep regularity with metabolic abnormalities: the multi-ethnic study of atherosclerosis. Diabetes Care. 2019;42(8):1422–9. https://doi.org/10.2337/dc19-0596.

Publisher's Note

Research

The Royal Society of Medicine

Journal of the Royal Society of Medicine; 2021, Vol. 114(4) 182–211
DOI: 10.1177/0141076821999973

Ethnicity, household composition and COVID-19 mortality: a national linked data study

Vahé Nafilyan[1,2], Nazrul Islam[3], Daniel Ayoubkhani[1], Clare Gilles[4], Srinivasa Vittal Katikireddi[5], Rohini Mathur[6], Annabel Summerfield[1], Karen Tingay[1], Miqdad Asaria[7], Ann John[8], Peter Goldblatt[9], Amitava Banerjee[10], Myer Glickman[1] and Kamlesh Khunti[4]

[1]Office for National Statistics, Newport, UK
[2]Department of Public Health, Environments and Society, London School of Hygiene and Tropical Medicine, London, UK
[3]Nuffield Department of Population Health, Big Data Institute, University of Oxford, Oxford, UK
[4]Diabetes Research Centre, University of Leicester, Leicester, UK
[5]MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK
[6]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[7]LSE Health, London School of Economics and Political Sciences, London, UK
[8]Swansea University, Swansea, UK
[9]UCL Institute of Health Equity, University College London, London, UK
[10]Institute of Health Informatics, University College London, London, UK
Corresponding author: Vahé Nafilyan. Email: vahe.nafilyan@ons.gov.uk

Abstract

Objective: To estimate the proportion of ethnic inequalities explained by living in a multi-generational household.
Design: Causal mediation analysis.
Setting: Retrospective data from the 2011 Census linked to Hospital Episode Statistics (2017-2019) and death registration data (up to 30 November 2020).
Participants: Adults aged 65 years or over living in private households in England from 2 March 2020 until 30 November 2020 (n=10,078,568).
Main outcome measures: Hazard ratios were estimated for COVID-19 death for people living in a multi-generational household compared with people living with another older adult, adjusting for geographic factors, socioeconomic characteristics and pre-pandemic health.
Results: Living in a multi-generational household was associated with an increased risk of COVID-19 death. After adjusting for confounding factors, the hazard ratios for living in a multi-generational household with dependent children were 1.17 (95% confidence interval [CI] 1.06–1.30) and 1.21 (95% CI 1.06–1.38) for elderly men and women. The hazard ratios for living in a multi-generational household without dependent children were 1.07 (95% CI 1.01–1.13) for elderly men and 1.17 (95% CI 1.07–1.25) for elderly women. Living in a multi-generational household explained about 11% of the elevated risk of COVID-19 death among elderly women from South Asian background, but very little for South Asian men or people in other ethnic minority groups.
Conclusion: Elderly adults living with younger people are at increased risk of COVID-19 mortality, and this is a contributing factor to the excess risk experienced by older South Asian women compared to White women. Relevant public health interventions should be directed at communities where such multi-generational households are highly prevalent.

Keywords

Clinical, ethnic studies, housing and health, infectious diseases, public health

Received: 5th February 2021; accepted: 15th February 2021

Research in context

Evidence before this study

A systematic review by Sze and colleagues demonstrated that people of ethnic minority background in the UK and the USA have been disproportionately affected by the Coronavirus disease 2019 (COVID-19) compared to White populations. We reviewed all papers included within the above systematic review to identify studies which empirically explored potential mediating pathways underpinning ethnic inequalities in COVID-19. In addition, we searched PubMed for studies related to the association between household composition and COVID-19 risk, using the terms 'household', 'COVID-19' and 'mortality', 'death' or 'infection' on 1 December 2020. Previous research has demonstrated that household size is associated with COVID-19 risk, but there is a lack of studies based on nationally representative individual records that examine the links between household composition and COVID-19 risk. In addition, no study has focused on multigenerational

households. While several studies have examined whether socio-demographic and economic factors are driving ethnic inequalities in COVID-19, no study has sought to explicitly quantify the contribution of household composition to the elevated risk of COVID-19 mortality in ethnic minority groups.

Added value of this study

Using retrospective data from the 2011 Census linked to Hospital Episode Statistics and death registration data for England, we examined the relationship between household composition and COVID-19 mortality risk among elderly adults (≥65 years). Living in a multi-generational household was associated with an increased risk of COVID-19 death. The adjusted hazard ratios for living in a multi-generational household with dependent children were 1.17 (95% confidence interval [CI] 1.06–1.30) and 1.21 (95% CI 1.06–1.38) for elderly men and women. The hazard ratios for living in a multi-generational household without dependent children were 1.07 (1.01–1.13) for elderly men and 1.17 (95% CI 1.07–1.25) for elderly women. Using a causal mediation approach, we estimated whether the higher propensity to live in multi-generational households among ethnic minority groups contributed to their raised risk of COVID-19 death. We found that living in a multi-generational household explained around 11% of the elevated risk of COVID-19 death among elderly women from a South Asian background, but little for South Asian men or people in other ethnic minority groups.

Implications of all the available evidence

Living in a multi-generational household is associated with an increased risk of COVID-19 infection and death. The increase in risk appears greater for elderly women than men living in a multi-generational household, and this is particularly the case when living with dependent children. It explains some of the excess COVID-19 mortality risk for women of South Asian background, but very little for men of South Asian background or people from other ethnic groups. Differences in household composition are therefore unlikely to be the main explanation of ethnic inequalities in COVID-19 outcomes, but may make an important contribution for some specific population subgroups, and may therefore be taken into account when prioritising vaccination. Relevant public health interventions (such as the provision of free accommodation to assist with self-isolation) should be considered to mitigate risks of infection spread within a household. Ensuring such interventions are accessible to communities where multi-generational households are highly prevalent (such as South Asian women) may be warranted.

Introduction

People of ethnic minority background in the UK and the USA have been disproportionately affected by COVID-19[1–5] compared to the White population, particularly Black and South Asian groups. While several studies have investigated whether adjusting for socio demographic and economic factors and medical history reduces the estimated difference in risk of mortality and hospitalisation,[6–8] the reasons for the differences in the risk of experiencing harms from COVID-19 are still being explored.

One important driver of these ethnic inequalities may be differences in household structure between ethnic groups. Household composition varies substantially between ethnic groups, with some ethnic minority populations more likely to live in large, multi-generational households.[9] While living in multi-generational households is associated with increased social capital,[10] which could have beneficial health effects,[11] it may also increase the risk of potential viral transmission.[12,13] For older people, who are at greater risk of experiencing severe complications if infected, residing with younger people may represent an increase in exposure to infection, which could lead to an increased risk of hospitalisation and mortality from COVID-19. To the best of our knowledge, no study has yet examined whether the difference in household composition partly explains the elevated risk of COVID-19 mortality in ethnic minority groups.

In this study, we examined the relationship between household composition and COVID-19 mortality risk among elderly adults (≥65 years) in England, with a focus on multi-generational households (elderly adults living with younger adults or dependent children). We then investigated how the propensity to live in a multi-generation household varies across ethnic groups, and whether this heterogeneity contributes to the raised risk of COVID-19 mortality among ethnic minority groups compared to the White population.

Methods

Data

This retrospective cohort study was based on the 2011 Census of England linked to mortality registration data and Hospital Episodes Statistics (2017–2019). The study population included all usual residents of England aged 65 years or over in 2020, who

had been enumerated in private households at the time of the 2011 Census (27 March 2011), had not moved to a care home by 2019 (identified by linking to the NHS Patient Register) and were still alive on 2 March 2020. We further excluded individuals who entered the UK in the year before the Census due to their higher propensity to leave the UK prior to the study period, and those aged over 100 years at the time of the Census. Our study population consisted of 10,078,568 individuals aged 65 years or over at 2 March 2020 (see Table 3 in Appendix 1 for details on the number of participants at each stage of the sample selection).

To adjust for out-migration, we applied weights reflecting the probability of having remained in the country until March 2020 after being enumerated in March 2011, based on data from the NHS Patient Register and the International Passenger Survey (IPS). Further information on the data has already been published.[6] All the variables used in the analysis, including their definitions and sources, are detailed in Table 4 in Appendix 1.

Outcome and exposure

Deaths involving COVID-19 included those with an underlying cause, or any mention, of International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified). We analysed deaths that occurred between 2 March 2020 and 30 November 2020, which corresponds to the deaths that occurred during the first and second COVID-19 waves.

Household composition in 2020 was derived based the household composition at the time of the Census. We excluded people who died between 27 March 2011 and 1 March 2020 or had moved to a care home by 2019. To mitigate measurement error, we removed people aged 10 to 24 at the time of the Census because they were more likely to have moved out in 2020. We defined a multi-generational household to be a household in which someone aged 65 years or over on 2 March in 2020 co-resided with at least one other adult aged more than 20 years younger or with at least one child. Our household composition variable classified households in five categories: Single; Two elderly adults; Multi-generational household without dependent children; Multi-generational household with dependent children; three or more elderly adults. As sensitivity analyses, we removed people aged 10 to 19 instead of 10 to 24. We also defined a multi-generational household to be one in which someone aged 65 years or over in 2020 co-resided with at least one other adult aged more than 15 years (instead of 20 years) younger. We also used longitudinal data from the English Longitudinal Study of Ageing to estimate change in household composition among adults aged 65 or over between 2008–2009 and 2016–2017 (see Appendix for more details). We also compare estimates of the proportion of elderly adults living in multi-generational households by ethnic group in our linked data to estimates based on the 2019 Annual Population Survey.

In the mediation analysis, the exposure was self-reported ethnic affiliation based on a nine-group classification (Table 4 in Appendix 1). The two mediators were binary variables for living in a multi-generational household with or without children.

Covariates

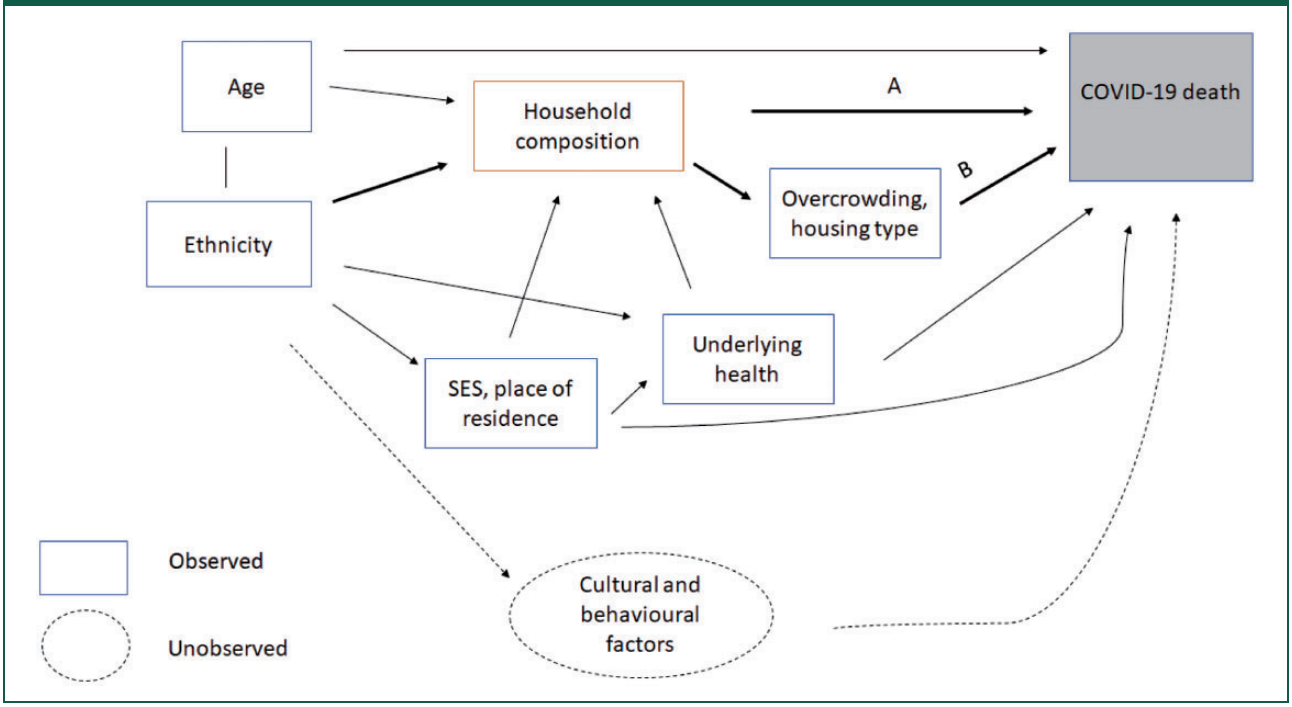
Demographic factors, geographical variables, socio-economic characteristics and measures of pre-pandemic health are listed in Table 4 in Appendix 1. These covariates were generally considered to be confounders of the relationship between household composition and COVID-19 mortality risk, and mediators of the ethnicity–mortality relationship (Figure 1).

Statistical analyses

We calculated age-standardised mortality rates (ASMRs) stratified by household composition and sex, separately for COVID-19-related deaths and other deaths. The ASMRs were standardised to the 2013 European Standard Population and can be interpreted as deaths per 100,000 of the population at risk during the analysis period.

We estimated Cox proportional hazard models to assess whether the risk of COVID-19-related death varies by household type (using living with one other older adult with as the reference category) after adjusting for the geographical factors, socio-economic characteristics and measures of health listed in Table 4 in Appendix 1. These factors could confound the relationship between household composition and COVID-19-related mortality, as shown in Figure 1. We estimated separate models for men and women, as the risk of death involving COVID-19 differs markedly by sex.[7] When fitting the Cox models, we included all individuals who died during the analysis period and a weighted random sample of those who did not (5% of White people, and 20% among ethnic minority groups), and applied case weights to reflect the original population totals. Standard errors were clustered at the household level. We assessed the proportional hazard

Figure 1. Directed Acyclic Graphs summarising the relationship between ethnicity, household composition and COVID-19 mortality. Note: When analysing whether household composition directly affects the risk of COVID-19 death, our effect of interest is A. In the mediation analysis, where we estimate the proportion of the ethnic disparity in COVID-19 that is explained by living in a multi-generational household, the effects of interest are A + B.



assumption by testing for the independence between the scaled Schoenfeld residuals and time-at-risk.

We conducted a causal mediation analysis[14] to estimate the proportion of excess risk in ethnic minority groups which is attributable to living in a multigenerational household. As a measure of inequality in COVID-19 mortality, ethnicity-specific odds ratios for COVID-19 mortality were estimated using logistic regression models, fitted to men and women separately and adjusting solely for age in the baseline model. The proportion of the difference in COVID-19 mortality rates between ethnic groups mediated by living in a multi-generational household was then estimated as the Average Causal Mediated Effect as a proportion of the age-adjusted difference in the probability of COVID-19 mortality, using a non-parametric approach[15] (see Appendix 1 for more details). The mediator models and the full outcome model were adjusted for geographical factors (region, population density, urban/rural classification), socio-economic characteristics (IMD decile, educational attainment, social grade, household tenancy) and health (self-reported health and disability from the Census, pre-existing conditions based on hospital contacts), We did not adjust for overcrowding or housing type, as these are likely to be consequences of living in a multi-generational household rather than confounding factors (Figure 1) In addition, among elderly adults, household size and overcrowding are strongly linked to multi-generational households, because most households with more than two people are multi-generational. Confidence intervals were obtained via bootstrapping, clustered at the household level, using 500 replications. All statistical analyses were performed using R version 3.5.

Results

Characteristics of the study population

Characteristics of the study population are reported in Table 1. In our study population of 10,078,568 individuals in England aged 65 years or over who were not in a care home in 2019 and were still alive on 2 March 2020, just over half (54.0%) were female, the mean age was 75.2 years, and 93.9% reported being from a White ethnic background (Table 2). Over the outcome period (2 March 2020 to 30 November 2020), 39,419 (0.39%) died of COVID-19, and 227,041 (2.3%) died of other causes.

Table 1. Distribution of study variables, stratified by household composition.

		All		Single	Two-adult households	MGH without young children	MGH with young children	3 + older adults
		Mean	SD	Mean	Mean	Mean	Mean	Mean
Mortality	COVID-19 death	0.0039	0.0624	0.0030	0.0055	0.0033	0.0045	0.0032
	Other death	0.0225	0.1484	0.0182	0.0323	0.0161	0.0146	0.0204
Household composition	Two older adults	0.5502	0.4975					
	Single	0.3260	0.4688					
	MGH without young children	0.0975	0.2967					
	MGH with young children	0.0197	0.1388					
	Other 3 + adults	0.0065	0.0806					
Age	Age in 2020	75.2	7.6	74.2	78.0	72.6	72.6	76.0
Sex	Female	0.5396	0.4984	0.4822	0.6561	0.4866	0.4889	0.5040
	Population density	3536.2	3818.7	3118.1	3915.0	4190.1	5449.0	4320.3
Ethnicity	Bangladeshi	0.0023	0.0483	0.0011	0.0011	0.0065	0.0381	0.0016
	Black African	0.0045	0.0670	0.0027	0.0046	0.0092	0.0276	0.0112
	Black Caribbean	0.0086	0.0926	0.0060	0.0114	0.0124	0.0181	0.0128
	Chinese	0.0035	0.0593	0.0030	0.0026	0.0085	0.0088	0.0059
	Indian	0.0181	0.1334	0.0121	0.0088	0.0640	0.1064	0.0387
	Mixed	0.0044	0.0665	0.0035	0.0055	0.0051	0.0074	0.0121
	Other	0.0119	0.1085	0.0089	0.0084	0.0297	0.0625	0.0261
	Pakistani	0.0077	0.0876	0.0039	0.0031	0.0251	0.1071	0.0070
	White	0.9388	0.2398	0.9588	0.9546	0.8396	0.6241	0.8847

(continued)

Table 1. Continued.

		All		Single	Two-adult households	MGH without young children	MGH with young children	3 + older adults
		Mean	SD	Mean	Mean	Mean	Mean	Mean
Region	East	0.1196	0.3245	0.1246	0.1155	0.1112	0.0929	0.1031
	East Midlands	0.0905	0.2869	0.0948	0.0878	0.0799	0.0725	0.0759
	London	0.1026	0.3035	0.0817	0.1094	0.1695	0.2243	0.1617
	North East	0.0519	0.2219	0.0523	0.0539	0.0465	0.0392	0.0436
	North West	0.1336	0.3402	0.1303	0.1400	0.1333	0.1239	0.1282
	South East	0.1726	0.3779	0.1776	0.1685	0.1646	0.1406	0.1729
	South West	0.1222	0.3275	0.1298	0.1194	0.0967	0.0844	0.1247
	West Midlands	0.1070	0.3091	0.1062	0.1047	0.1139	0.1328	0.1032
	Yorkshire and the Humbers	0.1000	0.3000	0.1028	0.1008	0.0845	0.0894	0.0866
Household deprivation	Not deprived	0.3525	0.4777	0.4198	0.2356	0.3832	0.3068	0.1958
	Deprived along 1 dimension	0.3840	0.4863	0.3712	0.4168	0.3525	0.3547	0.3738
	Deprived along 2 dimensions	0.2158	0.4114	0.1727	0.2911	0.1996	0.2302	0.2883
	Deprived along 3 dimensions	0.0447	0.2066	0.0346	0.0526	0.0597	0.0944	0.1246
	Deprived along 4 dimensions	0.0031	0.0556	0.0018	0.0038	0.0050	0.0139	0.0174
Urban/rural classification	Rural hamlets and isolated dwellings	0.0434	0.2038	0.0509	0.0317	0.0405	0.0395	0.0510
	Rural hamlets and isolated dwellings in a sparse setting	0.0042	0.0646	0.0048	0.0032	0.0036	0.0041	0.0057

(continued)

Table 1. Continued.

		All		Single	Two-adult households	MGH without young children	MGH with young children	3 + older adults
		Mean	SD	Mean	Mean	Mean	Mean	Mean
	Rural town and fringe	0.1055	0.3072	0.1143	0.1006	0.0835	0.0595	0.0792
	Rural town and fringeï¿½in a sparse setting	0.0050	0.0708	0.0052	0.0056	0.0029	0.0033	0.0035
	Rural village	0.0740	0.2618	0.0852	0.0617	0.0583	0.0481	0.0652
	Rural villageï¿½in a sparse setting	0.0052	0.0716	0.0057	0.0047	0.0035	0.0031	0.0100
	Urban city and town	0.4362	0.4959	0.4406	0.4473	0.3945	0.3440	0.4106
	Urban city and town in a sparse setting	0.0022	0.0465	0.0021	0.0024	0.0014	0.0016	0.0031
	Urban major conurbation	0.2905	0.4540	0.2578	0.3061	0.3828	0.4688	0.3459
	Urban minor conurbation	0.0338	0.1806	0.0332	0.0367	0.0288	0.0280	0.0259
Approximated social grade	AB	0.1972	0.3979	0.2267	0.1480	0.1951	0.2139	0.1519
	C1	0.2961	0.4565	0.2920	0.3135	0.2667	0.2757	0.2774
	C2	0.2006	0.4004	0.2207	0.1487	0.2536	0.2242	0.2323
	D	0.2675	0.4427	0.2405	0.3156	0.2618	0.2525	0.2798
	E	0.0386	0.1926	0.0201	0.0743	0.0227	0.0337	0.0586
Health	Very good	0.2209	0.4148	0.2460	0.1790	0.2242	0.1990	0.2071
	Good	0.4464	0.4971	0.4655	0.4168	0.4505	0.3951	0.4126
	Fair	0.2525	0.4344	0.2221	0.3044	0.2445	0.2740	0.2679
	Poor	0.0661	0.2484	0.0546	0.0825	0.0665	0.1069	0.0843

(continued)

Table 1. Continued.

		All		Single	Two-adult households	MGH without young children	MGH with young children	3 + older adults
		Mean	SD	Mean	Mean	Mean	Mean	Mean
	Very poor	0.0141	0.1180	0.0117	0.0172	0.0143	0.0251	0.0281
Long-term health problem or disability	Daily activities no limited	0.1234	0.3288	0.1002	0.1609	0.1150	0.1650	0.1956
	Daily activities limited a little	0.1937	0.3952	0.1717	0.2374	0.1714	0.1963	0.1853
	Daily activities limited a lot	0.6830	0.4653	0.7280	0.6017	0.7137	0.6387	0.6191
Hospital-based co-morbidities	Cancer	0.1009	0.3012	0.1059	0.0980	0.0896	0.0758	0.0738
	Cardiovascular disease	0.2829	0.4504	0.2703	0.3122	0.2612	0.2830	0.2029
	Digestive disorder	0.0193	0.1375	0.0190	0.0197	0.0197	0.0193	0.0165
	Mental health condition	0.0210	0.1435	0.0159	0.0319	0.0150	0.0153	0.0178
	Metabolic disorder	0.0854	0.2794	0.0784	0.0904	0.0983	0.1364	0.0738
	Musculoskeletal disorder	0.0989	0.2985	0.0883	0.1237	0.0810	0.0864	0.0598
	Neurological disorder	0.0178	0.1322	0.0173	0.0193	0.0163	0.0140	0.0145
	Renal disorder	0.0674	0.2508	0.0575	0.0885	0.0551	0.0614	0.0513
	Respiratory disorder	0.1375	0.3443	0.1259	0.1616	0.1241	0.1394	0.1049
Overcrowded		0.0313	0.1741	0.0141	0.0372	0.0630	0.2104	0.1682
IMD decile	1	0.0670	0.2501	0.0495	0.0902	0.0729	0.1343	0.0981
	2	0.0723	0.2590	0.0590	0.0883	0.0823	0.1235	0.0927
	3	0.0813	0.2733	0.0705	0.0950	0.0899	0.1102	0.0964

(continued)

Table 1. Continued.

		All		Single	Two-adult households	MGH without young children	MGH with young children	3 + older adults
		Mean	SD	Mean	Mean	Mean	Mean	Mean
	4	0.0911	0.2877	0.0842	0.0997	0.0975	0.1037	0.1053
	5	0.1021	0.3028	0.0999	0.1050	0.1050	0.1013	0.1038
	6	0.1106	0.3136	0.1138	0.1074	0.1058	0.0959	0.1150
	7	0.1170	0.3214	0.1243	0.1088	0.1094	0.0866	0.1155
	8	0.1188	0.3235	0.1288	0.1064	0.1112	0.0867	0.1008
	9	0.1205	0.3256	0.1335	0.1035	0.1140	0.0807	0.0951
	10	0.1193	0.3242	0.1366	0.0958	0.1120	0.0770	0.0773
Level of highest qualification	No qualification	0.3740	0.4839	0.3271	0.4570	0.3519	0.4099	0.3994
	Level 1: 1–4 GCSE/O-Level	0.0926	0.2898	0.0968	0.0840	0.0985	0.0854	0.0911
	Level 2: 5 + GCSE/O levels	0.1048	0.3063	0.1092	0.0992	0.1050	0.0790	0.0931
	Apprenticeship	0.0587	0.2351	0.0686	0.0424	0.0623	0.0381	0.0448
	Level 3: 2 + A Levels or equivalent	0.0663	0.2489	0.0731	0.0534	0.0713	0.0583	0.0874
	Level 4 +: degree or above	0.2381	0.4259	0.2608	0.2070	0.2243	0.1983	0.2064
	Other	0.0655	0.2474	0.0643	0.0569	0.0866	0.1310	0.0776
Tenure of household	Owned outright	0.6197	0.4855	0.6621	0.5912	0.5398	0.3326	0.5195
	Owned with a mortgage	0.1952	0.3964	0.2109	0.1169	0.3196	0.4272	0.2303

(continued)

Table 1. Continued.

	All		Single	Two-adult households	MGH without young children	MGH with young children	3 + older adults
	Mean	SD	Mean	Mean	Mean	Mean	Mean
Shared ownership	0.0041	0.0641	0.0033	0.0057	0.0032	0.0049	0.0056
Social rented from council	0.0659	0.2481	0.0437	0.1068	0.0512	0.0782	0.0828
Other social rented	0.0550	0.2279	0.0352	0.0933	0.0375	0.0564	0.0634
Private rented	0.0492	0.2162	0.0373	0.0682	0.0424	0.0912	0.0756
Living rent-free	0.0109	0.1040	0.0075	0.0179	0.0063	0.0094	0.0229

MGH: multi-generational household; IMD: Index of Multiple Deprivation; GCSE: General Certificate of Secondary Education.

Compared with elderly adults living with one other older adult ($n = 5{,}538{,}963$), people living by themselves ($n = 3{,}287{,}395$) had a higher mean age, were more likely to be female and tended to be more deprived. Older people living in a multi-generational household without dependent children ($n = 987{,}306$) and with dependent children (n = 199,112) were on average younger and were more likely to be from an ethnic minority group, live in London and large urban conurbations, and tended to be more deprived than older people living with another older adult. Summary statistics stratified by ethnic groups are reported in Table 5 in Appendix 1.

Figure 2 shows that household composition varied substantially between ethnic groups. Among older people, just over 10% of those of White background lived in a multi-generational household, compared to over half of Bangladeshi or Pakistani background (58.7% and 58.8%, respectively) and 45.8% of Indian background. The patterns were similar for men and women, although a larger proportion of women live by themselves (Figure 5 in Appendix 1). Similar proportions are obtained when using data from the 2019 Annual Population Survey and applying the same definition of multi-generational households (Table 6 in Appendix 1).

Household composition and death involving COVID-19

Elderly people living by themselves were more likely to have died from COVID-19 over the study period than those living with another adult. For men, the ASMRs were 632 (95% confidence interval [CI]: 618 – 646) and 465 (95% CI 456–473) per 100,000 of the population for those living by themselves and those living with another adult, respectively (Figure 3, Panel A). For women, the ASMRs were 309 (95% CI 302–316) and 236 (95% CI 230–243) per 100,000, respectively. A similar pattern is observed for deaths from other causes (Figure 3, Panel B).

There was a positive association between the risk of COVID-19 death and living a in multi-generational household. Both elderly men and women living a multi-generational household without school-age children were more likely to die from COVID-19 than elderly people living with another elderly adult (ASMR 563 [95% CI 538–589] per 100,000 for men, 307 [95% CI 288–327] for women), with the risk of death being greater still if there were children in the household (ASMR 773 [95% CI 704–843] per 100,000 for men, 415 [95% CI 369–461] per 100,000 for women). The risk of COVID-19 mortality was higher in men than that in women across all the household compositions

Figure 2. Household composition by ethnic group for people in England aged ≥ 65 years. Note: Linked 2011 Census and mortality registration data for people in England aged ≥ 65 years, excluding those living in a care home in 2019. The number of adults in the household was calculated as the number of people aged ≥ 25 years who lived in the household at the time of the Census, minus those who died between 27 March 2011 and 1 March 2020.

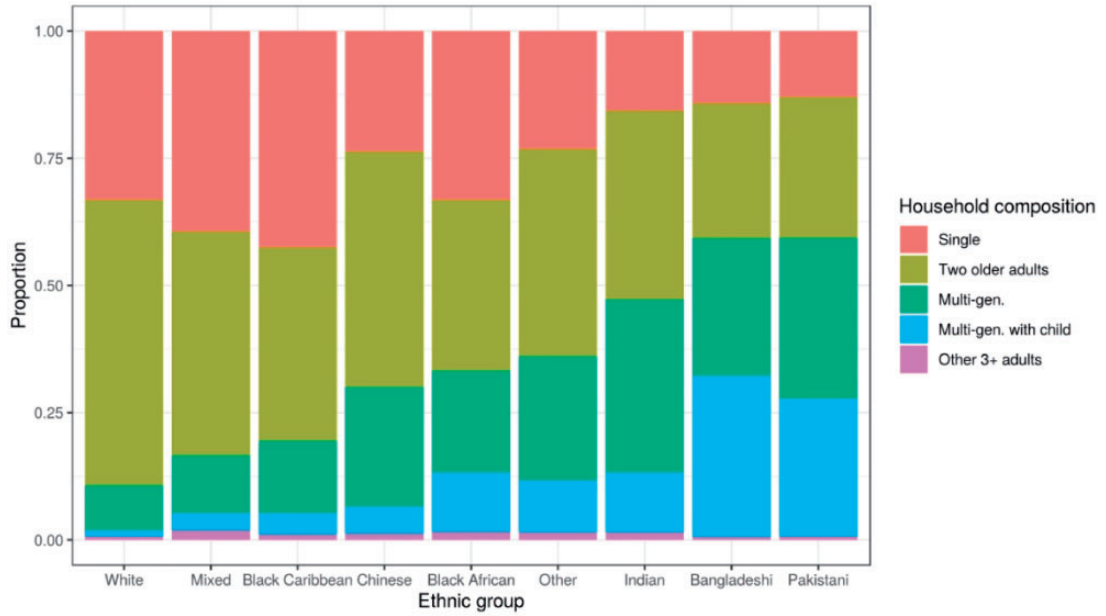


Figure 3. Age-standardised mortality rates per 100,000 adults aged 65 years or over, stratified by sex and household composition. Note: Deaths occurring between 2 March 2020 and 30 November 2020. 95% confidence intervals are reported. Mortality rates are standardised to the 2013 European Standard Population.

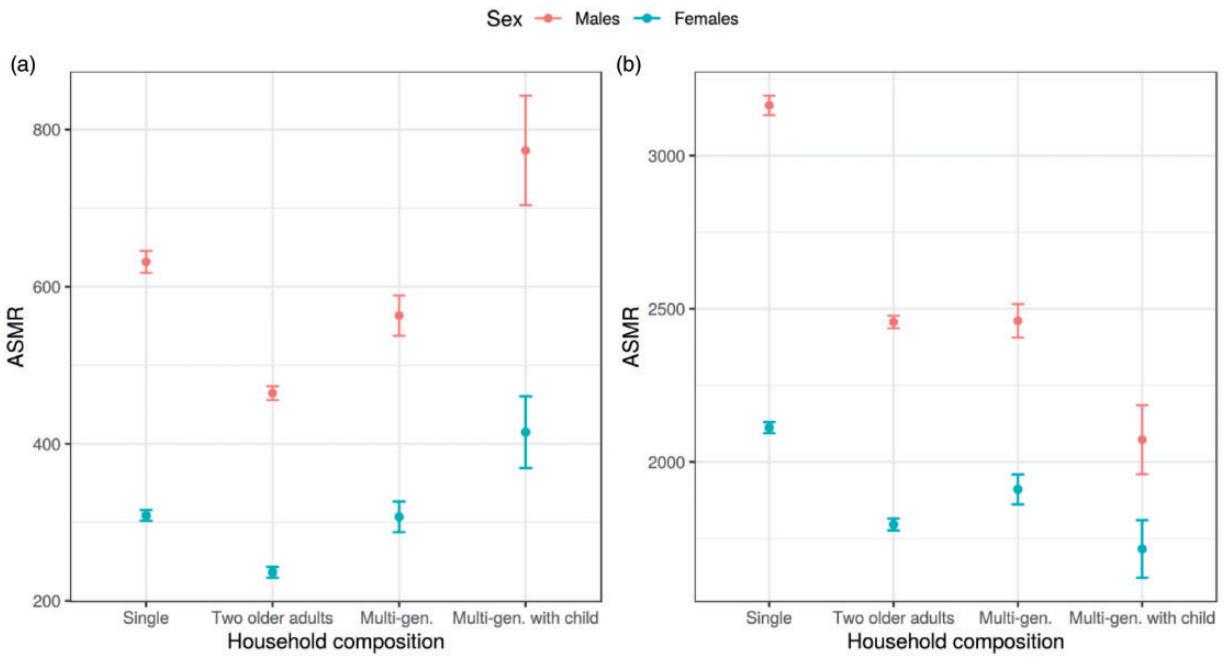


Table 2. Hazard ratios for COVID-19-related death for elderly adults (aged ≥65 years) in England, compared to living in a household with one other older adult, stratified by sex.

	Men		Women	
	Age-adjusted	Fully adjusted	Age-adjusted	Fully adjusted
Single	1.37	1.132	1.291	1.105
	[1.328–1.414]	[1.091–1.174]	[1.244–1.341]	[1.059–1.152]
Multi-generational household without children	1.304	1.065	1.322	1.156
	[1.242–1.369]	[1.009–1.125]	[1.234–1.417]	[1.073–1.246]
Multi-generational household with children	1.772	1.174	1.858	1.21
	[1.619–1.940]	[1.062–1.299]	[1.656–2.084]	[1.060–1.380]
3+ elderly adults	0.894	0.995	0.722	0.845
	[0.745–1.073]	[0.824–1.080]	[0.570–0.916]	[0.658–1.086]
Observations	405,182		443,650	
Concordance	0.740	0.826	0.755	0.852

Note: Hazard ratios compared to living in a household with one other older adult. Fully adjusted Cox regression models include geographical factors (region, population density, urban/rural classification), ethnicity, socioeconomic characteristics (IMD decile, household deprivation, educational attainment, social grade, household tenancy), health (self-reported health and disability from the Census, pre-existing conditions based on hospital contacts, number of hospital admissions, total days spent in hospital), a measure for overcrowding and property type.

(Figure 3). There was no clear relationship between living in a multi-generational household and mortality from other causes.

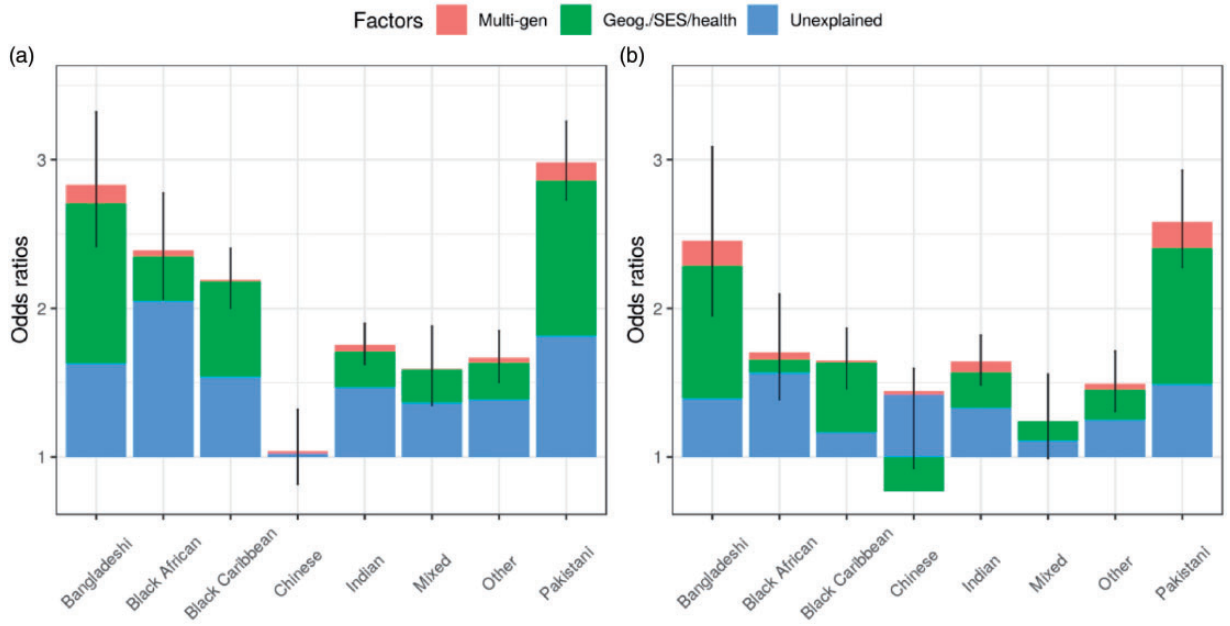
Adjusting for individual- and household-level characteristics (including age, geographical factors, socioeconomic characteristics and measures of pre-pandemic health) reduced the estimated differences in COVID-19 mortality rates between elderly adults living in different types households (Table 2). Adjusting for socioeconomic factors, such as IMD decile, household deprivation, educational attainment, social grade and household tenancy, had the strongest effect of the hazard ratio (Table 7 in Appendix 1). However, even after adjusting for these characteristics, living in a multi-generational household, especially with children, remained associated with an increased risk of COVID-19-related death. Compared to living with another elderly adult aged 65 years or above, the rate of COVID-19-related death was 1.16 (95% CI 1.07–1.25) and 1.21 (95% CI 1.06–1.38) times greater for elderly women living in a multi-generational household without and with children, respectively. For elderly men, after adjusting for individual and household characteristics, living in a multi-generational household without children was associated with a 1.07 (95% CI 1.01–1.13) times greater risk of COVID-19-related death and living in a multi-generational household with children with a 1.17 (95% CI 1.06–1.30) times greater risk.

Using the ASMRs for women living with another elderly adult as the baseline risk, these hazard ratios imply that living in a multi-generational household without children would increase the ASMRs from 236 to 274 death per 100,000 people, and living in a multi-generational household with children to 286 death per 100,000 people. For men, living in a multigenerational household without children is expected to increase the ASMRs from 465 to 498 death per 100,000 people, and living in a multi-generational household with children to 544 death per 100,000 people.

The rate of COVID-19-related death was also 1.13 (95% CI 1.09–1.17) times greater for elderly men living alone than for those living with another older adult, and 1.10 (95% CI 1.06–1.15) times greater for elderly women. The results were similar in the sensitivity analyses using different definitions of household composition (Table 8 in Appendix 1).

We tested the proportional hazard assumption by testing for the independence between the scaled Schoenfeld residuals and time-at-risk. For men, the test failed to reject the independence for the exposure ($p = 0.112$ for men), suggesting that the proportional hazard assumption was unlikely to be violated. However, for women, the test suggested that the proportional hazard assumption was likely to be violated

Figure 4. Decomposition of odds ratios for COVID-19 mortality among elderly adults (aged ≥ 65 years) across ethnic groups, stratified by sex. Note: The overall height of the bar corresponds to the odds ratio (OR), relative to the White population, based on a logistic regression model adjusted for age. Error bars are 95% confidence intervals. The proportion of the age-adjusted ORs explained by living in a multi-generational household were calculated through a mediation analysis. The unexplained part corresponds to the ORs from a model adjusted for age, geographical factors (region, population density, urban/rural classification), socioeconomic characteristics (IMD decile, household deprivation, educational attainment, social grade, household tenancy), and health (self-reported health and disability from the Census, pre-existing conditions based on hospital contacts, number of hospital admissions, total days spent in hospital).



(p = 0.002), However, as shown by the smoothed Schoenfeld residuals for each group (Figure 6 in Appendix 1), the deviation from the estimated log-hazard ratio is small, and the 95% confidence intervals around the smoothed Schoenfeld residuals always included the estimated log-hazard ratio, suggesting that violation of the proportional hazard assumption was unlikely to substantially affect our main results.

Living in a multi-generational household as a mediator for the disparity in COVID-19 death between ethnic groups

Figure 4 shows the decomposition of the age-adjusted odds ratios of COVID-19 death for ethnic minority groups compared to those of white ethnic group into and Three parts: (i) the part explained by living in a multi-generational household (in red); (ii) the part explained by other individual and household characteristics, such as geographical factors, socioeconomic factors and pre-pandemic health (in green); and (iii) a residual component that is not explained by our model (in blue).

Among people aged 65 years or over, those from all ethnic minority groups except Chinese were at greater risk of COVID-19-related death than those from the White population. Compared to men and women from White ethnic group, the odds of COVID-19 death were 2.98 (95% CI 2.73–3.26) and 2.58 (95% CI 2.28–2.93) times greater for men and women from Pakistani ethnic background. The odds of death were also notably greater for people of Bangladeshi, Black African, Black Caribbean or Indian ethnic background than the White population, with odds ratios of 2.83 (95% CI 2.42–3.32), 2.39 (95% CI 2.06–2.77), 2.19 (95% CI 2.00–2.40) and 1.75 (95% CI 1.26–1.90), respectively, for men and 2.45 (95% CI1.95–3.09), 1.71 (95% CI 1.39–2.09), 1.65 (95% CI 1.46–1.86) and 1.64 (95% CI 1.48–1.86), respectively, for women.

Living in a multi-generational household did not explain much of the difference in COVID-19 mortality rates among elderly men. It accounted for 6.9% (95% CI 2.7–11.3) of the excess risk of COVID-19 mortality for men of Pakistani background, 6.0% (95% CI 2.3–9.9) for men of Indian background and 6.3% (95% CI 2.6–10.2) for men of Pakistani

background. It did explain a larger proportion the difference in risk between elderly women of South Asian background and White elderly women Living in a multi-generational household accounted for 11.6% (95% CI 5.9–18.0) of the excess risk of COVID-19 mortality for women of Indian background, and 11.5% (95% CI 4.0–20.0) and 11.1% (95% CI 4.8–17.5) for women of Bangladeshi and Pakistani background (see Table 9 in Appendix 1 for full results). The results were similar in the sensitivity analyses using different definitions of household composition (Table 10 in Appendix 1).

Discussion

Principal findings

This paper makes two contributions to the research on COVID-19. First, we find that among elderly adults, household composition is associated with COVID-19 mortality, even after adjusting for a range of sociodemographic factors and measures of health. Our results indicate that compared to those living in a two older adult household, elderly adults, especially women, living in a multi-generational household are at greater risk of COVID-19 death. Living alone is also associated with elevated COVID-19 mortality. Second, we find that living in a multi-generational household explains around 11% of the excess COVID-19 mortality risk for women of South Asian background, but little for men or people from other ethnic groups.

Comparison with related studies

Our results are consistent with emerging evidence that household size is associated with the risk of infection,[16,17] and that elderly adults tend to be at greater risk of household transmission.[18,19] Older people living in large household tend to live in multi-generational households, co-habiting with younger adults and children. There is some evidence that, among elderly adults, living with dependent children is not strongly associated with the risk of COVID-19 infection or adverse outcomes.[20] While our results indicate that elderly adults living in a multi-generational household are at greater risk of COVID-19 death compared to those living with another older adult, we find little difference in risk between older people living in a multi-generational household with or without young children. Our results are consistent with a recent study using Swedish data, which show that for elderly adults, living with a working-age adult was associated with increased COVID-19 mortality.[21]

Several studies have analysed ethnic differences in COVID-19 infection and mortality.[3,4,6–8] Although we focus on elderly adults only, we find that almost all ethnic minority groups were at higher risk of COVID-19 deaths compared to the White population, and that the differences were attenuated once we adjusted for a range of geographical factors, sociodemographic characteristics and co-morbidities. We improve the existing evidence on ethnic inequalities in COVID-19 mortality by using a causal mediation approach to quantify the importance of living in a multi-generational household.

Mechanisms

Our results suggest that older people are placed at increased exposure to infection by living with younger adults rather than young children. After adjusting for confounding factors, we find that the risk of COVID-19 death is similar among elderly adults living in a household with young children and those living in a household with younger adults only. This could be due to schools having been closed for a substantial proportion of the period at risk. The increased risk is likely to be driven by co-residing with younger adults, who have a higher risk of infection than older people.[17] Younger adults are likely to be at increased risk of exposure because of work, as evidence suggests that in England people who are working were at greater risk of infection compared to people not in employment, especially if they were working in patient or client-facing occupations.[17,22,23] The interaction between job characteristics and household composition is likely to account for some of the elevated mortality among ethnic minority groups in the USA.[24]

Elderly adults living by themselves were also found to be at greater risk of COVID-19 death than those living with another older adult. During the COVID-19 pandemic, older people living alone were more likely to have received help from carers, including informal helpers, than people living with another older adult.[25] These frequent contacts with people from different households could increase the risk of being exposed to the virus.

We find that living in a multi-generational household explains around 11% of the excess COVID-19 mortality risk for women of South Asian background, but little for men, despite a similar proportion of them living in a multi-generational household. Women spend more time at home than men and still do the majority of unpaid housework,[26] which could increase the risk of household transmission. However, further research would be needed to understand the mechanisms driving our results.

Strengths and limitations

The primary strength of our study lies in the use of a unique linked population-level dataset which combine the 2011 Census with death registration data and hospital records. Unlike data based solely on health records, our study dataset contains a broad range of information on demographic, socio-economic, and household characteristics, including occupation. Unlike sample survey data, it contains millions of observations covering the entire population of interest, allowing us to examine both the association between household composition and COVID-19 mortality and also whether living in a multi-generational household explains some of the disparity in COVID-19 mortality between ethnic groups. We were able to examine differences between disaggregated ethnic minority groupings rather than high-level categories of South Asian, Black and Other.

The main limitation of our study is that household composition is likely to be imprecisely measured. While household composition is based on a detailed and accurate measurement taken in 2011, we could only identify changes since then due to death of household members or a move to a care home. While we took several steps to limit the measurement error, such as focusing on elderly adults, including only adults aged 25 or over and children aged 0 to 9 at the time of the census in our definition of household composition, our household composition measure may not reflect current living circumstances of everybody in our population of interest. To mitigate concerns about measurement error, we showed that our results are robust to using different definitions of household composition. Nonetheless, measurement error is likely to attenuate the explanatory power of household composition in our models. In addition, while we have used a causal mediation approach, our analysis remains based on observational data and therefore residual confounding is likely. Another limitation is that our statistical approach assumes that the effect of living in different types of household composition is the same across ethnic groups.

Conclusions

Elderly adults living in multi-generational households are at elevated risk of experiencing harms from COVID-19 compared to elderly adults living with people of the same age. However, there has been little focus on implementing effective interventions (such as creating plans to effectively isolate and improving ventilation within the home) to reduce transmission risk within the household.[27] Relevant public health interventions should be directed at communities where multi-generational households are highly prevalent. Living in a multi-generational household explains some of the excess COVID-19 mortality risk for women of South Asian background, but little for men or people from other ethnic groups. Further research is needed to explain the difference in COVID-19 mortality between ethnic groups.

Declarations

Competing Interests: Prof. Khunti is a member of the Independent Scientific Advisory Group for Emergencies (SAGE), a Trustee of the SAHF, Director of the NIHR Applied Research Collaboration (ARC) East Midlands, and Director of the Centre for Black and Minority Ethnic (BME) Health. The other authors declare no competing interests.

Funding: This research was funded by the Office for National Statistics. VN is also funded by Health Data Research UK (HDR-UK). HDR-UK is an initiative funded by the UK Research and Innovation, Department of Health and Social Care (England) and the devolved administrations, and leading medical research charities. SVK acknowledges funding from a NRS Senior Clinical Fellowship (SCAF/15/02), the Medical Research Council (MC_UU_12017/13) and the Scottish Government Chief Scientist Office (SPHSU13).

Ethics approval: Ethical approval was obtained from the National Statistician's Data Ethics Advisory Committee (NSDEC(20)12).

Guarantor: VN.

Contributorship: VN, NI, DA, CL and KK contributed to the study conceptualisation and design. VN lead the preparation of the study data and performed the statistical analyses. AS assisted with the preparation of the data. All authors contributed to interpretation of the results. VN drafted the manuscript. DA, NI, CG, VK, RM, MA, PG, AJ, AB, SG and KK contributed to the critical revision of the manuscript. All authors approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement: Under the provisions of the Statistics and Registration Service Act 2007, the linked 2011 Census data used in this study are not permitted to be shared.

Acknowledgments: None.

Provenance: Not commissioned; peer-reviewed by Azeem Majeed, Michael Liu, Julie Morris, Marc Farr.

ORCID iDs: Vahé Nafilyan https://orcid.org/0000-0003-0160-217X
Nazrul Islam https://orcid.org/0000-0003-3982-4325
Miqdad Asaria https://orcid.org/0000-0002-3538-4417
Amitava Banerjee https://orcid.org/0000-0001-8741-3411
Myer Glickman https://orcid.org/0000-0001-6067-3811

References

1. ONS. *Updating Ethnic Contrasts in Deaths Involving the Coronavirus (COVID-19), England and Wales: Deaths Occurring 2 March to 28 July 2020*. See https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/updatingethniccontrastsindeathsinvolvingthecoronaviruscovid19englandandwales/deathsoccurring2marchto28july2020 (last checked 18 February 2021).

2. Public Health England. *Disparities in the Risk and Outcomes of COVID-19*. See https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/892085/disparities_review.pdf (last checked 18 February 2021).
3. Aldridge RW, Lewer D, Katikireddi SV, Mathur R, Pathak N, Burns R, et al. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. *Wellcome Open Res* 2020; 5: 88.
4. Niedzwiedz CL, O'Donnell CA, Jani BD, Demou E, Ho FK, Celis-Morales C, et al. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. *BMC Med* 2020; 18: 5.
5. Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: a systematic review. *EClinicalMedicine* 2020; 23: 100404.
6. Ayoubkhani D, Nafilyan V, White C, Goldblatt P, Gaughan C, Blackwell L, et al. Ethnic minority groups in England and Wales – factors affecting the size and timing of elevated COVID-19 mortality: a retrospective cohort study linking Census and death records. *International Journal of Epidemiology* 2020; 49: 1951–1962.
7. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* 2020; 8: 7.
8. Mathur R, Rentsch CT, Morton CE, Hulme WJ, Schultze A, MacKenna B, et al. Ethnic differences in COVID-19 infection, hospitalisation, and mortality: an OpenSAFELY analysis of 17 million adults in England. *medRxiv* 2020; 2020.09.22.20198754.
9. ONS. *Ethnicity Facts and Figures: Families and households*. See https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/families-and-households/latest (accessed 18 February 2021).
10. Muennig P, Jiao B and Singer E. Living with parents or grandparents increases social capital and survival: 2014 General Social Survey-National Death Index. *SSM – Population Health* 2018; 4: 71–75.
11. Kawachi I and Berkman LF. Social capital, social cohesion, and health. In: Berkman LF,Kawachi I and Glymour MM (eds) *Social Epidemiology*. Oxford: Oxford University Press, 2015, pp.174–190.
12. Harlem G and Lynn M. Descriptive analysis of social determinant factors in urban communities affected by COVID-19. *J Public Health* 2020; 42: 466–469.
13. Haroon S, Chandan JS, Middleton J and Cheng KK. Covid-19: breaking the chain of household transmission. *BMJ* 2020; 370: m3181.
14. Imai K, Keele L and Tingley D. A general approach to causal mediation analysis. *Psychol Meth* 2010; 15: 309–334.
15. Imai K, Keele L and Yamamoto T. Identification, inference and sensitivity analysis for causal mediation effects. *Stat Sci* 2010; 25: 51–71.
16. Martin CA, Jenkins DR, Minhas JS, Gray LJ, Tang J, Williams C, et al. Socio-demographic heterogeneity in the prevalence of COVID-19 during lockdown is associated with ethnicity and household size: results from an observational cohort study. *EClinicalMedicine* 2020; 25: 8.
17. Ward H, Atchison CJ, Whitaker M, Ainslie KEC, Elliott J, Okell LC, et al. Antibody prevalence for SARS-CoV-2 in England following first peak of the pandemic: REACT2 study in 100,000 adults. *medRxiv* 2020; 2020.08.12.20173690.
18. Jing QL, Liu MJ, Zhang ZB, Fang LQ, Yuan J, Zhang AR, et al. Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. *Lancet Infect Dis* 2020; 20: 1141–1150.
19. Fung HF, Martinez L, Alarid-Escudero F, Salomon JA, Studdert DM, Andrews JR, et al. The household secondary attack rate of SARS-CoV-2: a rapid review. *Clin Infect Dis* 2020; 10.1093/cid/ciaa1558.
20. Forbes H, Morton CE, Bacon S, McDonald HI, Minassian C, Brown JP, et al. Association between living with children and outcomes from COVID-19: an OpenSAFELY cohort study of 12 million adults in England. *medRxiv* 2020; 2020.11.01.20222315.
21. Brandén M, Aradhya S, Kolk M, Härkönen J, Drefahl S, Malmberg B, et al. Residential context and COVID-19 mortality among adults aged 70 years and older in Stockholm: a population-based, observational study using individual-level data. *Lancet Healthy Longevity* 2020; 1: E80–E88.
22. Mutambudzi M, Niedzwiedz CL, Macdonald EB, Leyland AH, Mair FS, Anderson JJ, et al. Occupation and risk of severe COVID-19: prospective cohort study of 120,075 UK Biobank participants. *medRxiv* 2020; 2020.05.22.20109892.
23. Shah ASV, Wood R, Gribben C, Caldwell D, Bishop J, Weir A, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: nationwide linkage cohort study. *BMJ* 2020; 371: m3582.
24. Selden TM and Berdahl TA. COVID-19 and racial/ethnic disparities in health risk, employment, and household composition. *Health Affairs* 2020; 39: 1624–1632.
25. Evandrou M, Falkingham J, Qin M and Vlachantoni A. Older and 'staying at home'during lockdown: informal care receipt during the COVID-19 pandemic amongst people aged 70 and over in the UK. *SocArXiv* 2020.
26. McMunn A, Bird L, Webb E and Sacker A. Gender divisions of paid and unpaid work in contemporary UK couples. *Work Employ Soc* 2020; 34: 155–173.
27. Little P, Read RC, Amlôt R, Chadborn T, Rice C, Bostock J, et al. Reducing risks from coronavirus transmission in the home—the role of viral load. *BMJ* 2020; 369: m1728.
28. Department for Communities and Local Government. *The English Indices of Deprivation 2015*. Department for Communities and Local Government, UK, 2015.
29. Welsh Government. *Welsh Index of Multiple Deprivation (WIMD) 2014*. Welsh Government, UK, 2014.

MR. CAMERON RAZIEH (Orcid ID : 0000-0003-3597-2945)

PROF. MALCOLM GRACIE SEMPLE (Orcid ID : 0000-0001-9700-0418)

Article type : Original Article

OBESITY, ETHNICITY AND RISK OF CRITICAL CARE, MECHANICAL VENTILATION AND MORTALITY IN PATIENTS ADMITTED TO HOSPITAL WITH COVID-19: ANALYSIS OF THE ISARIC CCP-UK COHORT

Thomas Yates, PhD[1, 2] ty20@leicester.ac.uk

Francesco Zaccardi, PhD[1, 3] fz43@leicester.ac.uk

Nazrul Islam, PhD[4, 5] nazrul.Islam@ndph.ox.ac.uk

Cameron Razieh, MSc[1, 2] cr288@leicester.ac.uk

Clare L Gillies, PhD[1, 3] clg13@leicester.ac.uk

Claire A. Lawson, PhD[1] cl417@leicester.ac.uk

Yogini Chudasama, PhD[3] yc244@leicester.ac.uk

Alex Rowlands, PhD[1, 2] alex.rowlands@leicester.ac.uk

Melanie J Davies, MD[1, 2] melanie.davies@uhl-tr.nhs.uk

Annemarie B Docherty PhD[6, 7] annemarie.docherty@ed.ac.uk

Peter JM Openshaw, PhD[8] p.openshaw@imperial.ac.uk

J Kenneth Baillie, PhD[9] j.k.baillie@ed.ac.uk

Malcolm G Semple, PhD[10, 11] M.G.Semple@liverpool.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/oby.23178

ISARIC4C investigators*

Kamlesh Khunti, PhD[1, 3, 12] kk22@leicester.ac.uk

1. Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, LE5 4PW, UK.
2. National Institute for Health Research (NIHR) Leicester Biomedical Research Centre (BRC), Leicester General Hospital, Leicester, LE5 4PW, UK.
3. Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK.
4. Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK.
5. Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK.
6. Centre for Medical Informatics, Usher Institute, University of Edinburgh, Edinburgh, UK
7. Intensive Care Unit, Royal Infirmary Edinburgh, Edinburgh, UK
8. National Heart and Lung Institute, Imperial College London, London, UK
9. Roslin Institute, University of Edinburgh, Edinburgh, UK
10. NIHR Health Protection Research Unit in Emerging and Zoonotic Infections and Institute of Translational Medicine, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK
11. Respiratory Medicine, Alder Hey Children's Hospital, Institute in The Park, University of Liverpool, Alder Hey Children's Hospital, Liverpool L12 2AP, UK
12. NIHR Applied Research Collaboration – East Midlands (ARC-EM), Leicester General Hospital, Leicester, UK.

*ISARIC4C Investigators listed in end material

***Corresponding author*:** Prof Tom Yates; Tel: 0116 258 6481; Fax: 0116 258 4499; Email: ty20@le.ac.uk; Address: Diabetes Research Centre, Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW, UK.

Key words: ethnicity, ethnic differences, obesity, COVID-19, ISARIC

Short running title: Obesity, ethnicity and COVID-19

Abstract word count: 192

Word count (excluding abstract, acknowledgements and references): 2,914

Number of references: 33

Number of tables and figures: 3 tables and 2 figures.

Conflict of Interest Disclosures

KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and TY by the NIHR Leicester Biomedical Research Centre (BRC). 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 and a member of Independent SAGE and Chair of the SAGE subgroup on ethnicity and COVID-19. MGS is a member of HMG SAGE COVID-19. MGS reports grants from DHSC NIHR UK, grants from MRC UK, grants from HPRU in Emerging and Zoonotic Infections, University of Liverpool, during the conduct of the study, other from Integrum Scientific LLC, Greensboro, NC, USA, outside the submitted work. Other authors declare no conflicts of interests.

Three study importance questions

What is already known about this subject?

- People of South Asian or black ethnic origin have been shown to have a higher risk of infection, severe disease and COVID-19 mortality compared to those of white ethnicities.

- Obesity is an established risk factor for COVID-19 outcomes, but less in known about whether ethnicity acts to modify the strength of association observed with obesity or whether the risk remains consistent across ethnic groups.

What are the new findings in the manuscript?

- Compared to white subjects without obesity, all other combinations of obesity and ethnicity had a higher risk of admission to critical care, receiving mechanical ventilation or mortality in those admitted to hospital with COVID-19. However, the risk of all outcomes was greatest in those of black ethnicity with obesity.

How might your results change the direction of research or the focus of clinical practice?

- Black ethnic groups with obesity represent a particularly high-risk group of patients with implications for targeted public health and vaccination strategies and for identifying those most likely to suffer severe outcomes once admitted to hospital.

Objective: To investigate the association of obesity with in-hospital COVID-19 outcomes in different ethnic groups.

Methods: Patients admitted to hospital with COVID-19 in the United Kingdom through the Clinical Characterisation Protocol UK (CCP-UK) developed by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) were included from 6th February to 12th October 2020. Ethnicity was classified as: white, South Asian, black and other minority ethnic groups. Outcomes were admission to critical care, mechanical ventilation and in-hospital mortality, adjusted for age, sex and chronic diseases.

Results: 54,254 (age = 76 years; 45.0% women) white, 3,728 (57 years; 41.1%) South Asian, 2,523 (58 years; 44.9%) black and 5,427 (61 years; 40.8%) other ethnicities were included. Obesity was associated with all outcomes in all ethnic groups, with associations strongest for black ethnicities. When stratified by ethnicity and obesity status, the OR for admission to critical care, mechanical ventilation and mortality in black ethnicities with obesity were 3.91 (3.13, 4.88), 5.03 (3.94, 6.63), 1.93 (1.49, 2.51) respectively, compared to white ethnicities without obesity.

Conclusions: Obesity was associated with an elevated risk of in-hospital COVID-19 outcomes in all ethnic groups, with associations strongest in black ethnicities.

INTRODUCTION

Obesity and ethnicity are well described risk factors for COVID-19 outcomes (1-7). People of South Asian or black ethnic origin, in particular, have been shown to carry a higher risk of infection, severe disease and COVID-19 mortality compared to those of white backgrounds (1-5). In addition, subjects with obesity have around twice the risk of severe outcomes or mortality compared to normal weight individuals (6,7). However, whilst obesity and ethnicity have been shown to be independent of each other as risk factors for COVID-19 outcomes, less in known about whether ethnicity acts to modify the strength of association observed with obesity or whether the risk remains consistent across different ethnic groups.

The hypothesis that ethnicity may modify associations between obesity and COVID-19 outcomes is drawn from previous research, suggesting that the dose-repose relationship between levels of obesity and cardiometabolic health is steeper in minority ethnic communities compared to white populations: indeed, the higher the BMI, the greater the difference in health outcomes between minority ethnic groups and white Europeans (9-12). As cardiometabolic diseases are known risk factors for COVID-19 outcomes (13-16), it is possible that obesity may also act as a particularly important risk factor for severe COVID-19 outcomes in minority ethnic communities. Early research supported this hypothesis, where the risk of SARS-CoV-2 infection, severe disease and COVID-19 mortality in minority ethnic communities has been shown to be magnified in the presence of obesity (17,18), although this has not been confirmed in all studies (19). However, evidence to date is preliminary and based on small cohorts with a limited number of outcomes, with minority ethnic groups analysed as one category. As minority ethnic groups cover heterogeneous populations, it remains uncertain whether associations between obesity and COVID-19 outcomes differ in all minority ethnic groups or how they apply to national in-hospital settings.

Investigating whether obesity is a stronger risk factor for in-patient outcomes in specific minority ethnic groups will help inform public health and vaccination strategies aimed at identifying and targeting patients at greatest risk along with informing in-hospital clinical decision making. In this view, we investigated associations of obesity and ethnicity with in-hospital critical care and mortality outcomes in patients admitted with COVID-19 using data from the Clinical Characterisation Protocol UK (CCP-UK), a preparedness protocol for severe emerging diseases developed by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) cohort (20). Previous ISARIC CCP-UK publications have helped characterise in-hospital patients admitted with COVID-19 (21), and shown a greater risk of in-hospital outcomes with both obesity and ethnicity (21, 22) during early phases of the pandemic. Having previously established independent associations, this paper investigates their interaction.

5 Skajaa N, Horváth-Puhó E, Adelborg K, Prandoni P, Rothman KJ, Sørensen HT. Venous thromboembolism in Denmark: seasonality in occurrence and mortality. *TH Open* 2019; **3:** e171–79.

6 Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019; **11:** 563–91.

7 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7:** 449–90.

8 Søgaard KK, Adelborg K, Darvalics B, et al. Risk of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis in Denmark: a population-based cohort study. *Lancet Haematol* 2018; **5:** e441–49.

9 Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016; **61:** e012832.

10 BBC. Covid: France approves AstraZeneca vaccine for over-65s. March 2, 2021. https://www.bbc.com/news/world-europe-56242617 (accessed March 22, 2021).

11 BBC. Covid: Germany approves AstraZeneca vaccine for over-65s. March 4, 2021. https://www.bbc.com/news/world-europe-56275342 (accessed March 22, 2021).

12 Moustsen-Helms IR, Emborg H-D, Nielsen J, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 vaccine in long-term care facility residents and healthcare workers – a Danish cohort study. *MedRxiv* 2021; published online March 9. https://doi.org/10.1101/2021.03.08.21252200 (preprint).

13 Vogel G, Kupferschmidt K. 'It's a very special picture.' Why vaccine safety experts put the brakes on AstraZeneca's COVID-19 vaccine. March 17, 2021. https://www.sciencemag.org/news/2021/03/it-s-very-special-picture-why-vaccine-safety-experts-put-brakes-astrazeneca-s-covid-19 (accessed March 22, 2021).

14 Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med* 2013; **126:** 832.e13–21.

15 Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007; **5:** 692–99.

16 Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). *Am J Med* 2014; **127:** 829–39.e5.

17 European Medicines Agency. COVID-19 vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. March 18, 2021. https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots (accessed March 22, 2021).

Ramadan and COVID-19 vaccine hesitancy—a call for action

The Islamic month of fasting, Ramadan, begins around April 12, 2021. In 2020, Ramadan coincided with the beginning of the COVID-19 pandemic, moving what is a month of communal prayers and social gatherings into the era of virtual prayers. 2021 brings further challenges with ongoing virtual prayers and a global vaccination programme. For 1·9 billion Muslims worldwide, Ramadan coinciding with the vaccination programmes crucially means that their vaccinations might be offered during this time. With ongoing concerns of vaccine hesitancy among minority ethnic populations,[1] could Ramadan impede successful vaccination roll-out?

Ramadan fasts require Muslims to abstain from food and drink during daylight hours (exemptions include ill-health). Fasting during Ramadan also requires "refraining from anything entering the body cavities".[2] Although for most people, this term applies only to nutrition or medicine entering the gastrointestinal tract or brain, some reluctance to receiving vaccinations is anticipated during Ramadan.

To date, there is little global information surrounding vaccination hesitancy during this Islamic month of fasting; historically, vaccination programmes have not been rolled out with such urgency. During the west African Ebola epidemic, a study[3] in Guinea showed a high overall acceptability of vaccination during Ramadan by Muslim scholars (80%), but a significantly lower acceptance in the general Muslim population (40%). Furthermore, a boycott of the polio vaccination campaign in three states in Nigeria following misinformation was resolved when Nigerian religious leaders received assurance about vaccine safety, subsequently confirming its acceptability to the communities.[4]

Growing concerns around uptake of the COVID-19 vaccine during Ramadan are focused on whether the injection invalidates the fast, any possible side-effects, and whether people have to break the fast. Therefore, there is an urgent need for a global call for action to reduce vaccine hesitancy.

The public and health-care professionals need to be made aware of the announcements by Muslim scholars advising that the COVID-19 vaccine is permissible during Ramadan, without invalidating the fast. The statement, made in March, 2021, from the president of Two Holy Mosques in Saudi Arabia, should allay any religious concerns.[5]

Ebola and polio vaccination programmes highlight the key role that religious leaders play in promoting acceptability and education of their communities towards vaccination during Ramadan. Religious leaders should use Friday prayer sermons to promote the acceptance of vaccines, dispelling myths with worshippers.

Despite these efforts, some people still do not wish to be vaccinated during fasting hours. A solution to this problem would be to extend vaccination times outside of fasts, such as during special Ramadan nightly prayers, Taraweeh. Using mosques as vaccination sites would allow vaccinations to occur during Ramadan, including in non-fasting hours. Concerns about vaccine-related side-effects and requiring to break the fast should be addressed and weighed against the serious morbidity related to COVID-19. Vaccinations are the greatest tool to aid the world back to normality, and to the gradual return of celebrating festivals and future Ramadans.

Dan Kitwood/Getty Images

Published **Online**
April 7, 2021
https://doi.org/10.1016/S0140-6736(21)00779-0

KK is a director at the University of Leicester Centre for Black Minority Ethnic Health, chair of the Ethnicity Subgroup of the Scientific Advisory Group for Emergencies (SAGE), and a member of Independent SAGE. All other authors declare no competing interests.

*Sarah N Ali, Wasim Hanif, Kiran Patel, Kamlesh Khunti, on behalf of the South Asian Health Foundation, UK
sarah.ali6@nhs.net

Royal Free London NHS Foundation Trust, London NW3 2QG, UK (SNA); University Hospitals Birmingham, Birmingham, UK (WH); University Hospitals Coventry and Warwickshire NHS Trust, Warwick Medical School, University of Warwick, Coventry, UK (KP); Diabetes Research Centre (KK), and the Centre for Black Minority Ethnic Health (KK), University of Leicester, Leicester, UK

1 Scientific Advisory Group for Emergencies. Factors influencing COVID-19 vaccine uptake among minority ethnic groups, 17 December 2020. Jan 15, 2021. https://www.gov.uk/government/publications/factors-influencing-covid-19-vaccine-uptake-among-minority-ethnic-groups-17-december-2020 (accessed March 13, 2021).

2 Ihsan UU. The fiqh of fasting in the Hanafi madhhab. July 31, 2010. https://islamqa.org/hanafi/seekersguidance-hanafi/32700 (accessed March 13, 2021).

3 Peiffer-Smadja N, Ouedraogo R, D'Ortenzio E, et al. Vaccination and blood sampling acceptability during Ramadan fasting month: a cross-sectional study in Conakry, Guinea. *Vaccine* 2017; **35:** 2569–74.

4 Ghinai I, Willott C, Dadari I, Larson HJ. Listening to the rumours: what the northern Nigeria polio vaccine boycott can tell us ten years on. *Glob Public Health* 2013; **8:** 1138–50.

5 Sharifain H. COVID-19 vaccine does not invalid the fast during Ramadan: Abdul Rehman Al Sudais. March, 2021. https://www.haramainsharifain.com/2021/03/covid-19-vaccine-does-not-invalid-fast.html (accessed March 10, 2021).

For **UK Government updates on COVID-19 in the UK** see https://coronavirus.data.gov.uk/details/deaths

Institutional racism and national lockdowns

Soham Bandyopadhyay[1] claimed that the UK Government's national lockdown, announced in November, 2020, to control COVID-19, was an institutionally racist policy. Claims of institutional racism are serious allegations and thus warrant critical appraisal. I therefore raise three points.

First, Bandyopadhyay claims that, through these restrictions, the UK Government prevented a large proportion of minority ethnic university students from visiting home. This assessment is an incomplete and unfair representation of the policy, which prohibited all students living at universities, regardless of ethnicity, from travelling during lockdown.[2] This policy probably had deleterious effects on the mental health and wellbeing of all students, regardless of ethnicity, and irrespective of their reasons for travelling home. There is no evidence to suggest that students who specifically celebrate Diwali were intentionally targeted in a policy designed to contain an ongoing pandemic.

Second, Bandyopadhyay claims that limitations on the movements of minority ethnic students were imposed to protect the Christmas period. No evidence is provided to support this claim; yet malicious intent on the part of the UK Government is clearly implied. It is, however, more probable that the urgency and severity of lockdown restrictions were in response to an out-of-control pandemic that threatened to collapse the UK health system. Their relationship to university term times, and the proximity of Christmas, is irrelevant, coincidental, and void of discriminatory intent.

Finally, Christmas Day is one of numerous public holidays available to all UK citizens. It is not restricted to those affiliated with Christianity, and there is no requirement for religious observance. Instead, families and friends use the day to gather and celebrate their importance to one another. The inclusion of all people in this public holiday, without exception, and regardless of religious affiliation, strengthens its importance and deepens its meaning. Prime Minister Boris Johnson's statement that, "by taking tough action now, we can allow families across the country to be together [at Christmas],"[3] was in reference to all families. As such, this statement was intended to bolster public motivation for lockdown adherence and not to impose discriminatory policy.

It seems to me that Bandyopadhyay's argument is weak and unfounded. At best, it is simply an unhelpful opinion. At worst, it represents a dangerous trend towards locating institutional racism where it might not exist. Great solidarity is required during the COVID-19 pandemic; everyone must take responsibility.

I declare no competing interests.

Richard Armitage
msxra37@nottingham.ac.uk

Division of Epidemiology and Public Health, University of Nottingham, Nottingham NG5 1PB, UK

1 Bandyopadhyay S. An institutionally racist lockdown policy. *Lancet* 2020; **396:** 1802.

2 UK Government. Prime Minister announces new national restrictions. Oct 31, 2020. https://www.gov.uk/government/news/prime-minister-announces-new-national-restrictions (accessed Nov 17, 2020).

3 UK Government. Prime Minister's statement on coronavirus (COVID-19). Oct 31, 2020. https://www.gov.uk/government/speeches/prime-ministers-statement-on-coronavirus-covid-19-31-october-2020 (accessed Nov 17, 2020).

Reading Soham Bandyopadhyay's Correspondence,[1] we find it unfortunate that lockdown measures are viewed with religious and racist sentiments amid a pandemic. Bandyopadhyay seems to have unilaterally misinterpreted the UK Government's advice on returning home for Christmas, which to many people in the UK simply means a holiday period. It would be incorrect to drag minority ethnic and religious beliefs into this policy.

In 2020, spending Diwali in lockdown with restrictions could have saved hundreds, if not thousands, of lives, especially considering that Black, Asian, and minority ethnic people have a higher mortality rate following COVID-19 infection, as Bandyopadhyay rightly pointed out. In India, the vibrant festivities of Ganesha Chaturthi and Dussehra were celebrated in different phases of lockdown. Diwali was also celebrated under severe restrictions, with the fear it could turn into a superspreading event. Several Muslim countries, including the United Arab Emirates and Kuwait, introduced strict public policies for celebration of Eid-Al-Fitr to raise awareness and discourage irresponsible behaviour. In the UK, Christmas was celebrated with restrictions on families and other households mixing.[2] Festivities and markets across the UK, events families look forward to and cherish, were cancelled.

Approximately 60% of the UK population is Christian. Hindus, Sikhs,