

Drivers of the higher COVID-19 incidence, morbidity and mortality among minority ethnic groups

Executive summary

- **Ethnicity is a multi-dimensional concept which includes culture, language, religion, migrant status and physical appearance (race)**, with considerable diversity within and between ethnic minority groups (Page 4).
- In the first six months of the pandemic **ethnic minority groups have experienced:**
 - **a) higher prevalence of SARS-CoV-2 infection (high confidence)**
 - **b) higher incidence of COVID-19 disease (high confidence)**
 - **c) higher COVID-19 mortality than White ethnic groups (high confidence).**
 - These patterns may be different in coming months, highlighting the importance of ongoing investigations by ethnicity and social characteristics (Page 4).
- Different dimensions of ethnicity could each affect COVID-19 risks through a variety of mechanisms, leading to risks potentially being different along different stages of the disease: from exposure, developing symptomatic disease, disease severity and to long term consequences of the disease (Page 6).
- **Some ethnic minorities who are admitted to hospital may also experience poorer outcomes, like death and critical care admissions, compared to White ethnic groups (medium confidence)** (Page 8).
- Modifiable social factors such as poverty and occupation make a large contribution to the greater burden of COVID-19 in ethnic minorities (high confidence) (Page 9).
- **Some evidence suggests ethnic minorities working in the same occupation as White ethnic groups experience greater COVID-19 risk. Difficulty in accessing personal protective equipment is a suggested and potentially modifiable reason for this in healthcare workers (low confidence).** These social determinants of health are likely to be driven by broader issues of structural racism (the social forces which lead to inequalities between ethnic and racial groups) (Page 10).
- **Some comorbidities associated with severe COVID-19 are more common in some ethnic minority groups which may contribute to the ethnic inequalities seen.** Evidence on obesity, diabetes and cardiovascular disease to suggest they contribute to the differences in COVID-19 risk between South Asian ethnic groups and White ethnic groups (medium confidence). **Obesity is an important comorbidity that is potentially modifiable in the medium-term** (Page 12).
- **Other factors, including the appropriateness of public health messages for reaching all communities and the accessibility of health services, are likely to explain some of the greater burden among ethnic minorities** (Page 12).
- The evidence suggests genetics alone cannot explain the higher number of severe cases and deaths since ethnic minorities are very genetically diverse (high confidence) (Page 14).
- Greater exposure (infective dose or contact frequency) to the virus contributes to higher levels of clinical disease (as reflected by hospital admissions, for example). It is unclear if this fully accounts for the higher levels of clinical disease in ethnic minority groups.
- The relative importance of different pathways that cause ethnic inequalities in COVID-19 is not well understood. **Focusing on understanding the immediately modifiable pathways (such as occupation and healthcare access) should be an urgent priority** (Page 14).
- **Datasets do not currently include adequate information on both the different stages of the disease, detailed clinical information and the social determinants of health**, limiting insights that can be gained from detailed quantitative analysis (Page 14).

This paper summarises the available evidence on the epidemiology of ethnic inequalities in COVID-19 and potential explanations for differences observed. We use a conceptual model that highlights potential

pathways at each of the steps from exposure to the virus, through infection to the development of severe disease.

Background

There is now substantial evidence from the first six months of the pandemic in the UK that people from minority ethnic backgrounds have been disproportionately affected. Data from the Office for National Statistics (ONS) found a higher risk of death from minority ethnic groups when compared to the White group and data from Public Health England (PHE) has shown higher risks of COVID-19 death amongst minority ethnic groups during the pandemic, after accounting for age and sex differences (1,2). An analysis of 17 million primary care and death records found people from Black and South Asian ethnicities had an approximate 2-fold increased risk of death compared with White ethnicities, after taking into account differences in age and sex (3).

The causes of ethnic inequalities in COVID-19 are unclear. **There is likely to be an interplay of social, economic, biological and pre-pandemic health risks that vary across ethnic groups. This is because ethnicity is a multi-dimensional concept.** Ethnicity can be defined as the “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” (4). Ethnicity is therefore a complex concept which includes country of birth, language, religion, culture and physical appearance, and these characteristics are themselves influenced by where an individual lives, their ancestry and, to a limited extent, their genetic background (5). These dimensions of ethnicity are an important consideration when considering research findings. This paper aims to explain the role of sociological, behavioural, and biological factors driving the unequal impacts among minority ethnic groups in the UK.

Conceptual model to understand COVID-19 ethnic inequalities

Many studies to date have focused on highlighting the unequal impact of COVID-19 on minority ethnic groups, with limited understanding of the mechanisms and pathways that have led to these differences. We outline below potential mechanisms and pathways and then highlight the current evidence of how these may lead to the observed differences in health outcomes from COVID-19 between ethnic groups. A comprehensive understanding of the role of each of these factors and the relationships between them can inform targeting and developing policy interventions, as well as future research.

The differences in health outcomes from COVID-19 between ethnic groups could occur at multiple points from exposure to the virus, through infection to the development of severe disease. *Diderichsen et al* propose a framework widely used in studying health inequalities that highlights potential pathways at each of these steps (See Figure 1) (6, 7). At each step, ethnic inequalities could develop through social, economic and biological mechanisms. A framework to understand ethnic inequalities in COVID-19 is first described, with the evidence related to each stage and potential explanations provided later in the document.

Firstly, minority ethnic groups could experience greater exposure to the virus (differential exposure – pathway 1), for example due to the working in occupations with high contact with potentially infected persons or living in overcrowded housing. Secondly minority ethnic groups may be at greater risk of infection after having come in contact with the virus, for example due to differences in immune response and nutritional status, which in itself could be related to stress or environmental conditions such as air pollution (differential susceptibility to infection - pathway 2). Some minority ethnic groups may be more likely to develop disease once infected (differential vulnerability to disease- pathway 3) and of those with disease, some minority ethnic groups may be more likely to develop severe disease, complications and potentially die (differential disease consequences – pathway - 4). This could for example be due to differences in underlying co-morbidities or differences in access to health care between ethnic groups.

Ethnic inequalities may also arise due to other pathways during the pandemic, however these are out of scope for this paper. These include:

- Pathway 5: differential effectiveness of COVID-19 control measures i.e. the public health responses taken to control the pandemic could be less effective amongst some ethnic groups compared to others. However, existing evidence suggests lockdown measures may have been more effective in reducing COVID-19 mortality for some ethnic minority groups (8).
- Pathway 6: differential social consequences of COVID-19 disease (pathway 6) – for example COVID-19 disease may lead to chronic impairments that result in job loss and future loss of earning due to poor health.
- Pathway 7: differential consequences of pandemic control measures, for example lockdown leading to unemployment and health service disruption that disproportionately effects some ethnic groups.

All of these mechanisms arise from the wider social context that drive ethnic and other social inequalities, such as power relations and structural racism. 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” (9). **The term draws attention to the way inequalities may arise not 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 high risk occupations, living in crowded higher risk housing conditions, and having fewer resources for health (e.g. education, income) (10, 11). These factors are likely to increase mental health problems such as psychosocial stress and harmful health behaviours (e.g. smoking, diet, lack of exercise), increasing co-morbidities that put people are greater risk of COVID-19 disease (see Figure 1) (12,13). These social processes largely underpin biological risks that are correlated with some ethnic groups (14). Due to structural racism, health care planning may not take into account different experiences, perceptions and expectations of ethnic minorities, and therefore health services may poorly meet the needs of some ethnic groups – further widening inequalities (15-17). **These are the factors that mediate the relationship between ethnicity and health outcomes and whilst they are often statistically “controlled or adjusted” for in epidemiological studies, they are in fact important explanations of ethnic inequalities and not ‘confounding factors’ (18).** Interventions to address the excess risk of poor outcomes from COVID-19 in ethnic minorities therefore likely requires a multi-faceted approach to address the mechanisms working across the pathways identified in Figure 1. The current evidence indicating which of these pathways are important in driving ethnic inequalities in COVID-19 is outlined below.

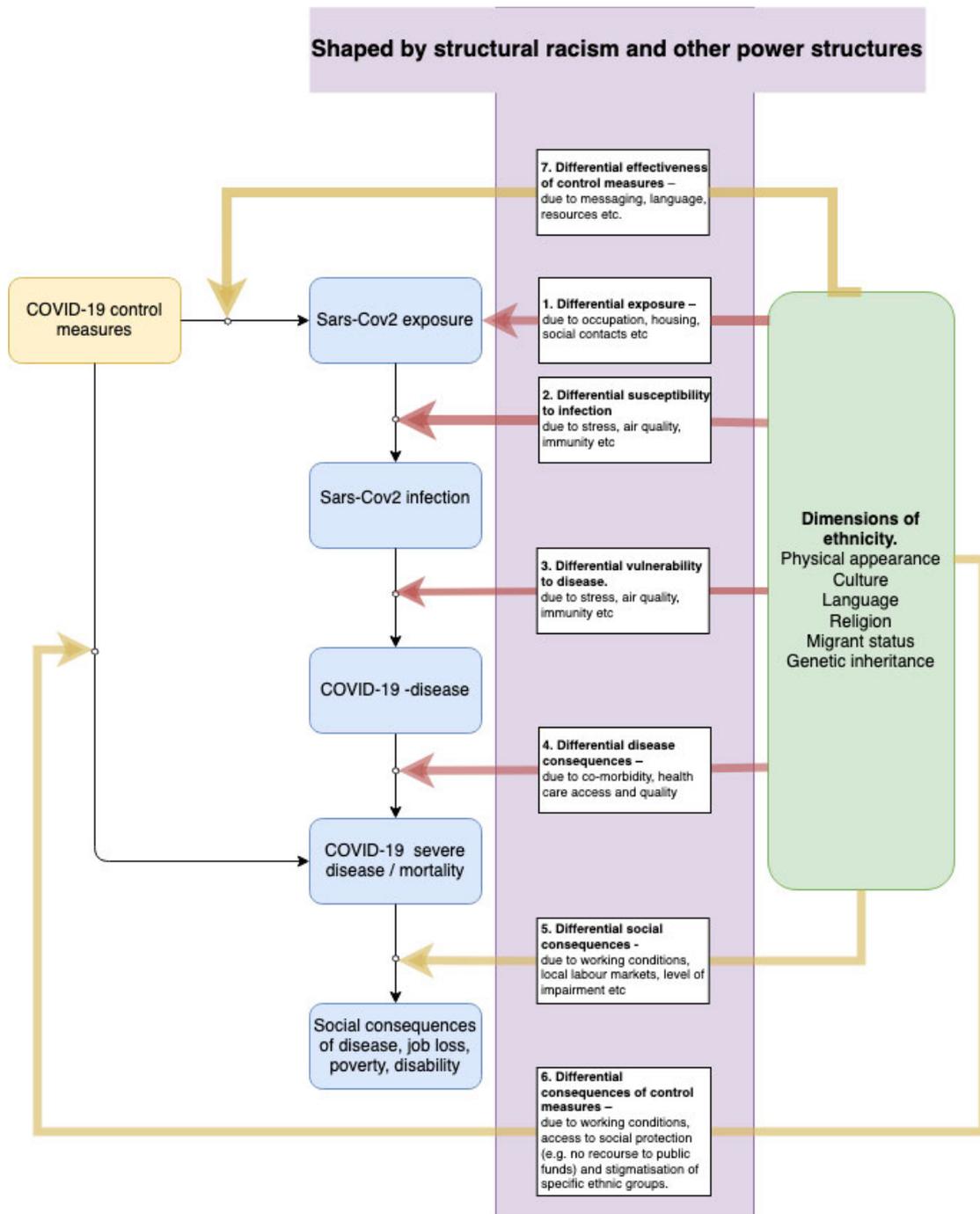


Figure 1: A framework for understanding ethnic inequalities in COVID-19, adapted from Diderichsen et al (6).

Ethnic inequalities can arise through seven different pathways, with pathways 1-4 impact on the direct health impacts of COVID-19 disease. Differential effectiveness of COVID-19 control measures (7) is the focus of another SAGE subgroup paper; Differential social consequences of experiencing disease (5) and Differential consequences of pandemic control measures (6) are outside the scope of this paper but are under-researched areas. The main text summarises epidemiological evidence related to pathways 1-4. Note that the total burden of ethnic inequalities in COVID-19 harms (e.g. deaths) is likely to reflect causes that occur along pathways 1-4 plus 7 cumulatively. COVID-19 control measures (7) include all government, public health and health system responses taken to control the pandemic. Each of the pathways reflects potential targets for intervention to reduce ethnic inequalities in health.

Differential exposure to the virus and susceptibility to infection (Pathways 1 & 2)

Exposure to SARS-CoV-2 amongst some minority ethnic groups is likely to be higher, but direct data – for example, on social contacts between individuals who are infected and non-infected, by ethnicity, are lacking. Furthermore, it is possible that differences in exposure could be due to differences in the frequency of exposure or differences in the dose of virus that occurs at exposure (or both). As noted in the section on potential explanations later, we highlight potential reasons such as occupational and housing-related exposures. Having been exposed to the virus, individuals may develop infection, which could be asymptomatic or symptomatic (Pathway 2). If the infected individual develops symptoms, then this is called disease (Pathway 3), which may be mild or severe or fatal (Pathway 4).

Overall, there are few data available on SARS-CoV-2 infection across ethnic groups. However, the recent representative ONS national infection survey found evidence that ethnic minorities were more likely to have experienced the infection at some point in the past (19). Those from ethnic minorities had a higher proportion of positive serology (antibody) tests compared to White groups (Figure 2). This suggests that these minority ethnic groups have experienced greater contact with the virus (pathway 1), however it could also indicate that they were more susceptible to infection when exposed (differential susceptibility – pathway 2). A study of over 100 thousand people in the UK (the REACT2 study), again designed to be representative, found higher antibody prevalence amongst all ethnic minorities studied (20). Similar patterns of findings have also been found within the UK Biobank study, with statistical adjustment for age, sex, deprivation, region and urban-rural status leading to the associations remaining largely unchanged (21).

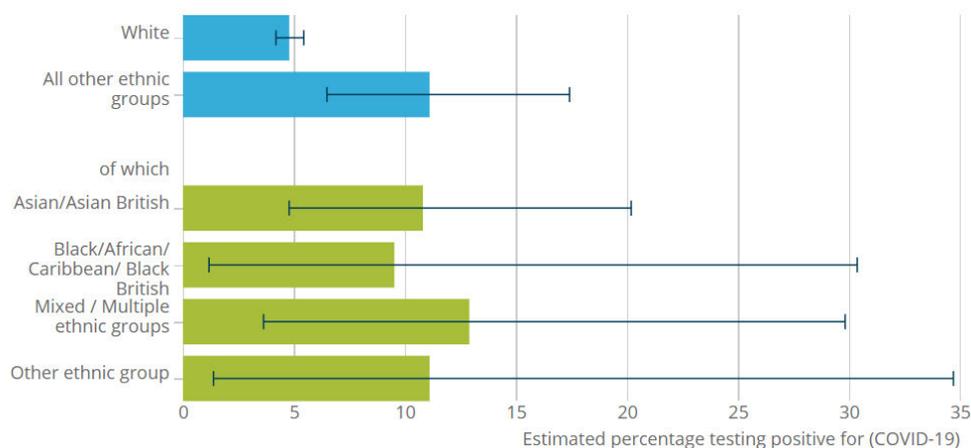


Figure 2: Serology (antibody) test results by ethnicity in a representative population. Source: ONS infection survey (7).

Differential vulnerability to disease (Pathway 3)

We can be confident that there are inequalities among ethnic groups in the chance of experiencing COVID-19 disease, as evidenced by test results and hospitalisations data from several studies (high confidence). These studies however are not able determine whether these differences have arisen due to differences in exposure to the virus (pathway 1), differences in susceptibility to infection (pathway 2) or differences in the risk of developing symptomatic disease amongst those infected (pathway 3). It is therefore unclear if the findings summarised below reflect pathway 3 or actually pathways 1-2 earlier in the transmission process, with the ONS infection survey suggesting that at least part of the differences arising in these earlier pathways.

An early study from primary care settings in Oxford found patients from a Black background had a 4-fold increased risk of getting the disease (test positive compared to patients from a White background, once accounting for differences in comorbidities such as hypertension and diabetes (22). Similar findings are found in national studies; for example, findings from a UK Biobank cohort of nearly 400,000 people, found people from a Black and South Asian background, in particular those from a Pakistani background, had a 3-fold increased risk of testing positive compared to those from a White background (23). The chance of being tested did not substantially differ across ethnic groups, suggesting bias due to differential counting of cases did not explain the findings. A second systematic review and meta-analysis of 60 published studies examined the relationship between ethnicity and clinical outcomes, such as hospitalisation, finding people from some minority ethnic backgrounds experienced disease more commonly than White ethnic groups, after accounting for other explanations such as age and sex differences (24).

The recently available OPENSANELY study extended an analysis of COVID-19 mortality outcomes to study other outcomes along the disease pathway. They found important ethnic inequalities in testing positive, being admitted to intensive care and dying while the chance of actually being tested showed minimal ethnic differences among ethnic groups (suggesting results are unlikely to be due to differential testing).

To differentiate vulnerability to the disease from greater exposure, **data should be analysed to consider how risk changes across different stages of the disease process – for example, comparing the risk of reporting symptomatic disease amongst those with evidence of infection.**

Differential disease consequences (Pathway 4)

Evidence of ethnicity as the sole cause of poorer clinical outcomes when compared to people of White background is limited. A systematic review examining hospitalisation and/or need to be put on a ventilator in intensive care found little evidence of a relationship between ethnicity and poorer clinical outcomes (25). However, a large cohort study of nearly 35,000 UK hospitalisations found a 30% increased relative risk of critical care admission and ventilation among people from South Asian, Black or Minority ethnic groups and this relationship was still present after accounting for age and sex (26). After accounting for some potential explanations of this increased risk (such as co-morbidities like diabetes), these minority ethnic groups were still more likely to require critical care and ventilation than White groups (medium confidence). However, it is possible that some differences in presentation could not be fully accounted for that could arise from **modifiable factors such as awareness of optimal healthcare seeking behaviours.**

Explanation and mechanisms

The evidence presented thus far suggests that there are a range of individual-level and societal-level mechanisms, working across the pathways outlined above that may be responsible for driving ethnic inequalities in COVID-19 outcomes. However, there is limited evidence that robustly studies the mechanisms through which such disproportionate outcomes arise among minority ethnic groups.

Socioeconomic position

Socioeconomic circumstances are known to strongly shape health in general and to be important contributors to ethnic inequalities in health. The ONS investigated ethnic differences in COVID-19 mortality using linked data bringing together information from the census (which provided ethnicity and socioeconomic variables) and deaths (2, 8). It showed that several minority ethnic groups were at more risk of COVID-19 death than those from White backgrounds – for example, Black males had a 3.3 times greater risk than the White ethnic group. **Males from a Black background had a 2-fold increased risk of death after taking into account age, sex, geography, socioeconomic position (assessed using the Index of Multiple Deprivation, highest educational attainment, occupation and tenure status), multigenerational household and household characteristics.** Similar patterns were seen for Bangladeshi, Pakistani and Indian ethnic groups (Figure 3). Risks were lower once socioeconomic position was included together with other factors (2). **This suggests that socioeconomic position is a very important contributor to the risk of death.** Studies have not looked specifically at causality, but these factors related to socioeconomic position could act on any of the pathways 1-4 outlined above. It is worth noting that these socioeconomic measures may not be up to date as they were from the 2011 census. Changes in circumstances since this time could not therefore be incorporated and this is likely to lead to an under-estimation of the explanatory power of these factors (27).

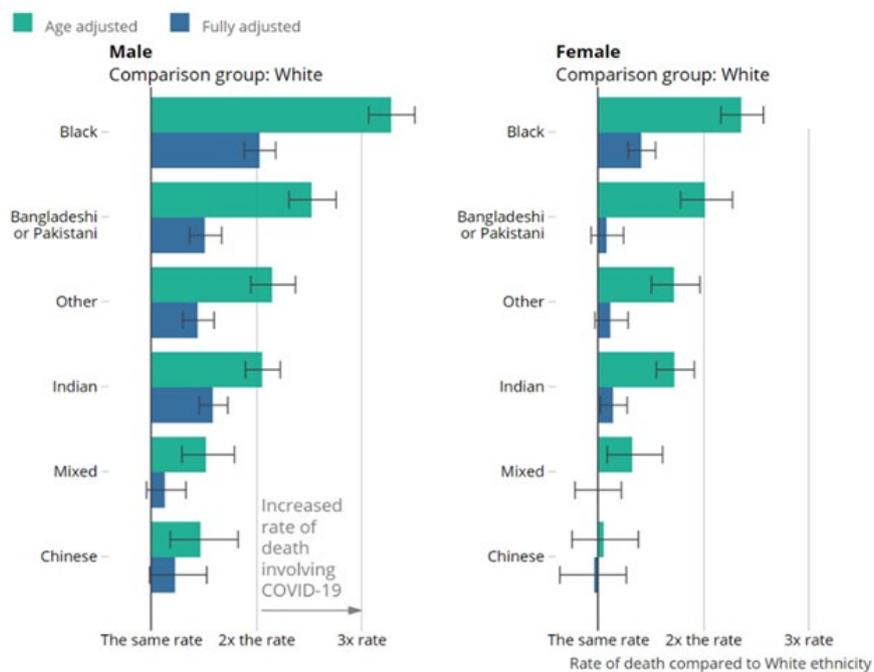


Figure 3: Rate of COVID-19 death by ethnic group and sex relative to the White group in England and Wales between 2 March to 15 May 2020. Source ONS. Fully adjusted factors include region, population density, area deprivation, household composition, socioeconomic position, highest qualification held, household tenure, multigenerational household flags and occupation indicators (including key workers).

Occupation

The risk of exposure to the virus (as well as viral dose) is likely to vary according to occupation, **modifiable risk factor**; for example, those working in public-facing roles are likely to have a greater potential for viral contacts due to increased social mixing. **Some minority ethnic groups are overrepresented in health and social care and other key public sectors (Figure 4).**

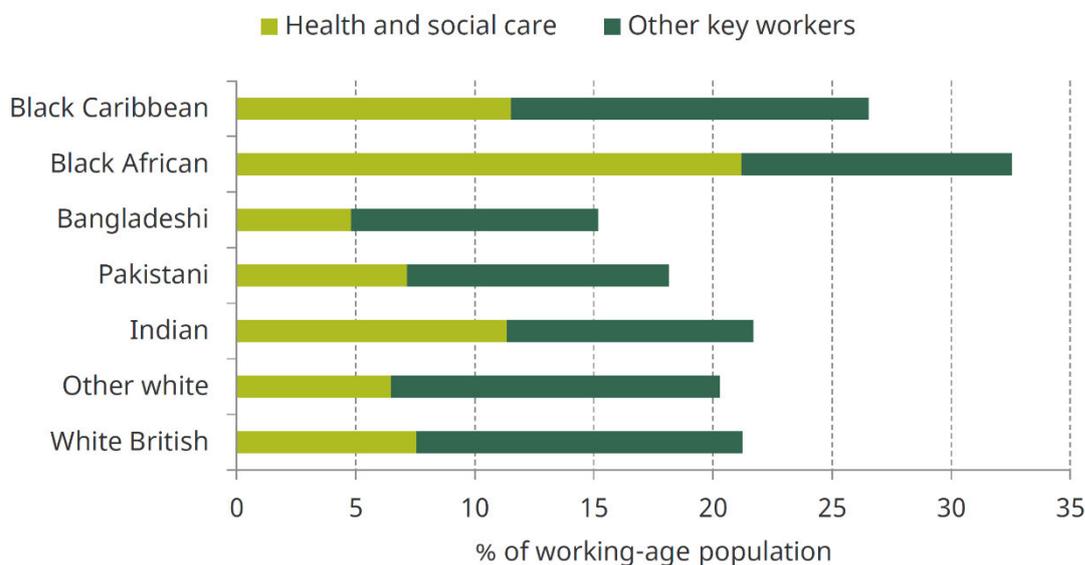


Figure 4: Percentage of the working-age population in key worker roles (light green health and social care roles, dark green other key workers) broken down by ethnic group. Source: Institute for Fiscal Studies May 2020 (27).

This is particularly evident for people from a Black ethnic minority, where more than a quarter are employed in key worker positions. Differences also emerge within groups, for example, people from a Black African background make-up less than 3% of the employed population but account for 7% of nurses and contributed to the largest proportion of deaths among NHS staff (28).

It is also possible that the impact of working in a specific occupation may differ for minority ethnic groups compared to the White British majority. **In frontline healthcare workers in the UK and USA, ethnic minorities experienced a greater risk of a positive test and reporting inadequate access to effective personal protective equipment (29).** Similarly, an analysis of UK Biobank data suggested an increased risk of being a positive hospitalised COVID-19 case among non-White frontline essential workers compared to White essential workers (30).

In addition to higher levels of unemployment which affects socioeconomic conditions, some minority ethnic groups experience higher risks of under-employment and insecure employment (e.g. the 'gig economy', self-employment, zero hours contract care workers) (31). **There is therefore a risk that loss of earnings resulting in financial hardship is more likely among some minority ethnic groups which could act as a barrier to self-isolation when individuals experience COVID-19 symptoms or are asked to quarantine.** This may in turn lead to secondary spread from individuals not self-isolating due to financial concerns. **The higher representation of some minority ethnic groups in at-risk occupations and insecure employment is likely to increase their risk of exposure to the virus compared to the White British majority (pathway 1 above).**

Household circumstances

There is good evidence that both aerosol and droplet transmission of the virus occurs more frequently indoors than outdoors (32, 33), in particular from confirmed cases to household members who might be

mixing when sharing bathrooms, bedrooms and other household living spaces (34). It is likely that during the peak viral shedding period, people living in overcrowded housing (more than one person per bedroom) are at greater risk of infection. **Data from the ONS English Housing Survey shows overcrowding is higher among minority ethnic groups compared with the white group: 24% and 16% people of a Bangladeshi and Black African background live in overcrowded housing, compared with 2% of those from a White British background (Figure 5) (35).**

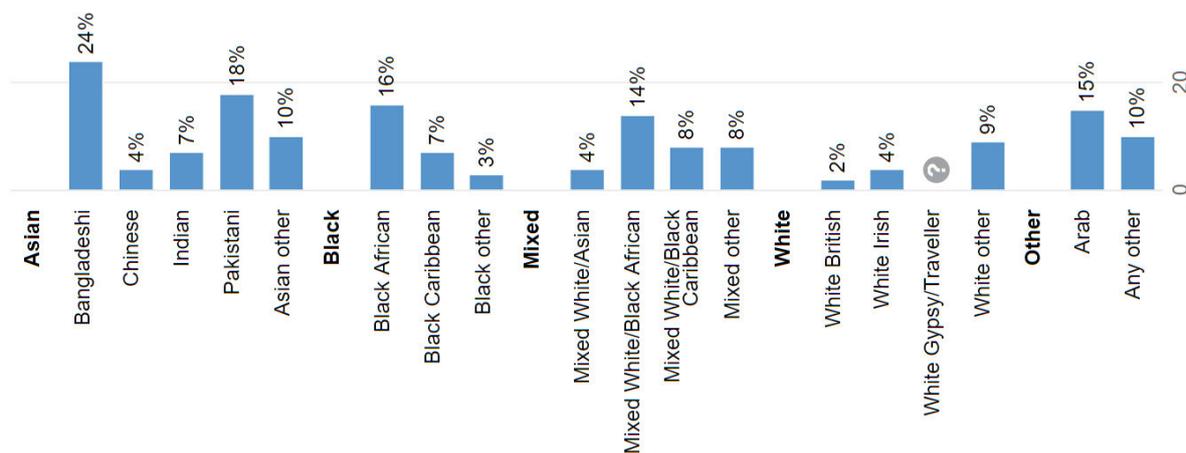


Figure 5: Percentage (%) of households that were overcrowded between April 2016 to March 2019.
Source: ONS Housing Survey July 2020

Older people living in multi-generational housing may be at risk of contracting potentially severe disease from household members (36). **ONS Census data shows that Asian and Black ethnic minority populations are more frequently living in households with multiple generations**, for example people with children living with grandparents, compared to White groups. Approximately 21.7% of Asian ethnic minorities and 14.1% of Black minorities live in multi-generational households compared to only 6.8% from a White group (37). There was little difference among the Asian ethnic minority groups, whilst within the Black ethnic groups, Black African groups more often lived in multi-generational households compared with Caribbean. **The combination of overcrowded housing and multi-generational households among minority ethnic groups could lead to greater exposure to infection (pathway 1 above), particularly amongst the older generations, when compared to White groups (36).** However, the most recent OPENSsafely study found statistical adjustment for a proxy measure of household size led to very small changes in the observed relationships between ethnicity and COVID-19 outcomes, suggesting (but not confirming) that this is unlikely to be an important mechanism.

Neighbourhood circumstances

Ethnic minorities tend to live within urban areas and more densely populated areas where viral transmission may be greater due to more contacts with infected persons. Using census data for England alongside information on COVID-19 deaths, a study found that differences in population density and local authority of residence made an important contribution to ethnic inequalities (2), which likely due to the increased risk of exposure (pathway 1). It is also possible that the frequency of social contacts between households could differ across ethnic groups, even after accounting for population density, but studies directly assessing this during the pandemic have not been conducted to our knowledge.

Modifiable factors such as air pollution which differs across neighbourhoods has been linked to increased risks of COVID-19, probably due to increased susceptibility (pathway 2) and it is known that some ethnic minorities often live in areas with higher levels of air pollution within the UK (38-40). However, evidence is currently contradictory about its importance, with some studies finding that air pollution does not appear important when population density is accounted for (41). **Other modifiable factors such as stress, including racism, has also been linked to the impacts of air pollution on lung health being exacerbated (42).** It is therefore possible that air pollution could lead to even greater susceptibility in minority ethnic groups, than might be expected on the basis of solely the levels of air pollution observed.

Comorbidities and health-related behaviours

Chronic health conditions from before the pandemic might contribute to ethnic inequalities in COVID-19. Comorbidities which impair a person's immune system (such as autoimmune conditions, cancers and diabetes) could influence the chance of developing COVID-19 disease following SARS-CoV-2 exposure (differential susceptibility – pathway 2) and some **comorbidities (such as respiratory conditions) have been shown to affect COVID-19 disease prognosis** (differential disease consequences – pathway 3). **Similarly, modifiable health-related behaviours (such as smoking and diet) are associated with increased COVID-19 risks, with evidence that these relationships are causal (43).**

Unfortunately, there are few studies which have investigated the complex relationships between comorbidities and COVID-19. **In the OPENSANELY study, the risk for ethnic differences in COVID-19 death slightly changed after accounting for a large number of comorbidities and some behaviour-related risk factors, suggesting they only explain a small part of these inequalities.** In the UK Biobank study, even after accounting for comorbidities at baseline, South Asians were still more than twice as likely to be hospitalised compared to the White British group. When investigating disease outcomes amongst people admitted to hospital, **the ISARIC-CCP study identified diabetes as a potentially important factor for the poorer outcomes of South Asians, accounting for 18% of the greater risk of death.** Many of the studies to date have assumed similar effects of comorbidities and health-related behaviours across ethnic groups. However, it is possible that the same comorbidity may result in differing impacts – for example, obesity could lead to greater COVID-19 risk in some ethnic groups (44).

Unequal health care access

Before the pandemic, evidence suggests modifiable barriers to healthcare are experienced by many ethnic minorities, but they vary across different parts of the health system and impact different ethnic groups in different ways. For example, Scottish data suggested that while secondary care was largely equitable, primary health care met the needs of the Pakistani ethnic group less well (45). Differences in healthcare access and quality between ethnic groups, will potentially lead to differences in the severity of COVID-19 outcomes (pathway 3 - differential disease consequences). Modifiable barriers to healthcare can arise across different settings, with potential for the impact of differential care to accumulate. These are illustrated in Figure 6. It is important to note that differential healthcare reflects not only the actions of the individual person but also the design of the health system, which may not be meeting the needs of ethnically diverse communities. **There are limited data on access to healthcare during COVID-19.** However, the ISARIC-CCP study found amongst people who had been admitted to hospital, ethnic minorities had a similar delay between the onset of symptoms and their hospital admission (26). Published studies have been limited on the accessibility of primary care, testing settings and those who were not admitted to hospital. Migrants (including those with 'no recourse to public funds') may be a specific group at risk of experiencing barriers to healthcare.

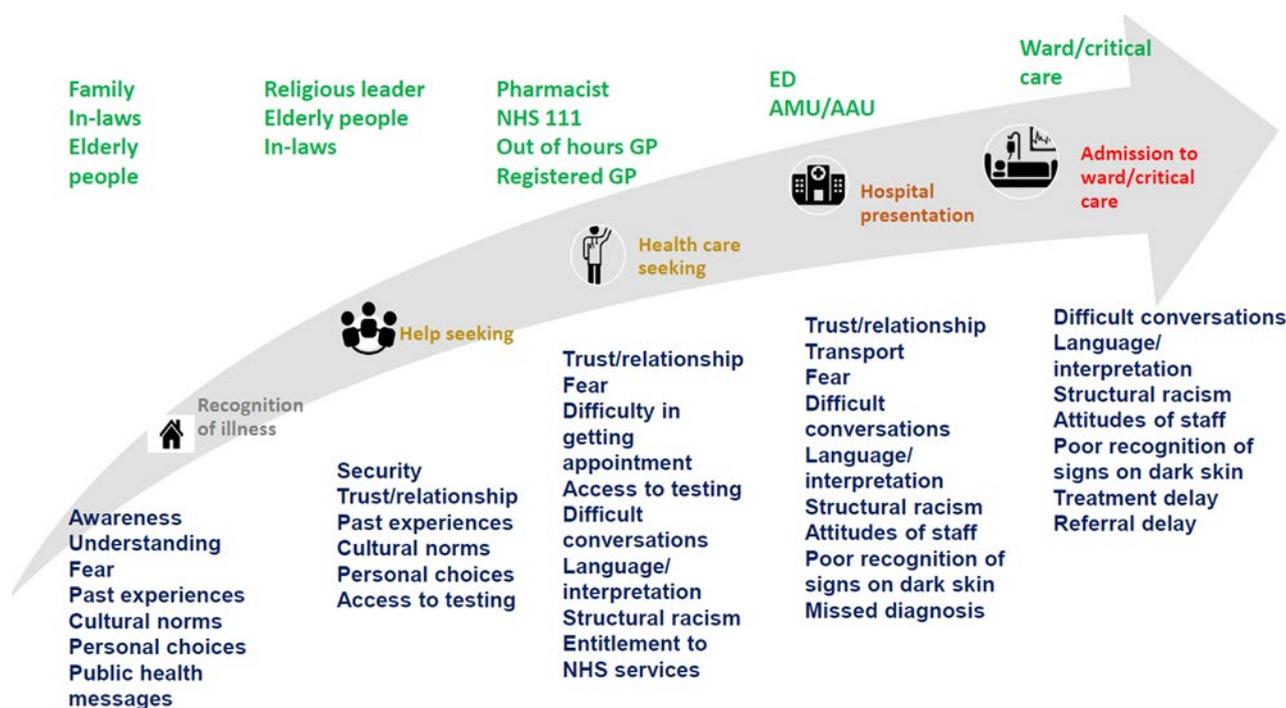


Figure 6: Trajectory of health seeking and health care, and factors which may influence delays in presenting to healthcare or receiving appropriate care, or in having care escalated due to progressive disease (ED=Emergency Department, AMU= Acute Medical Unit, AAU= Acute Admissions Unit).

Individual or family lack of awareness or understanding of COVID-19 symptoms, cultural norms, or mistrust in health care professionals, may lead to delays in seeking health advice. Other factors such as fear, mistrust, language barriers, difficulty in getting an appointment, and lack of entitlement to NHS services, might lead to further delays in seeking medical help. Once the individual arrives at the hospital, language barriers, miscommunication, fear, and mistrust, might contribute to the individual not conveying relevant information to the health care professional or the health care professional not receiving the relevant information. In addition, structural racism, and poor recognition of signs in dark skin (such as cyanosis due to low oxygen in the blood), could lead to further delays in admission or escalation of care.

Psychosocial stress

Social threats in day-to-day life due to individuals' experiences of racism (either structural or as a result of another's actions) can lead to psychosocial stress which has direct biological effects (33). Stress has been associated with less effective immune functioning, with evidence that this impact might differ across ethnic groups (46). **It is therefore possible that stress-related pathways could increase susceptibility to the virus** but direct evidence in relation to COVID-19 remains limited though is developing (47).

There are early indications that the adverse mental health consequences of the pandemic might also be disproportionately affecting ethnic minorities (Figure 7). However, evidence on ethnic inequalities in the indirect health consequences of the pandemic on non-COVID-19 health outcomes remain limited.

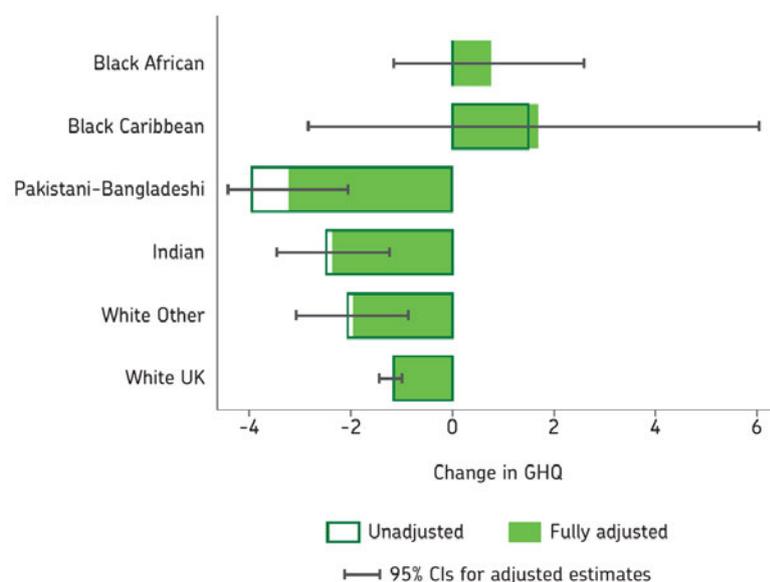


Figure 7: Change in mental health status as measured by the General Health Questionnaire (GHQ), between two surveys conducted pre-pandemic (2017/2018) and during the pandemic (April/May 2020) shown by ethnicity. Negative change indicates worsening in mental health. Source: Understanding Society Working Paper August 2020.

Biological factors

The role of biological factors such as genetics has drawn considerable attention, however these are unlikely to explain the ethnic inequalities. The ACE receptor is a binding site for SARS-CoV-2 to the human cell, and genetic variations which alter how the virus binds to the cell, may confer resistance against or susceptibility to SARS-CoV-2 infection (48, 49). Most ACE2 gene variants are rare, but three variants which affect how the virus binds to human cells are more common in African populations. A second genetic study spanning the whole human genome, highlighted some genes which confer susceptibility and confirmed that blood group A was associated with a higher risk than non-A blood groups (49). Other genetic variations which are specific to certain races, called human leukocyte antigens, could also act as key determinants of susceptibility to, or protection from SARS-CoV-2 infection (50). Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory syndrome associated with SARS-CoV-2, affecting heart, skin, mucous membranes, and guts (51). Most studies report that children from minority ethnic backgrounds were over-represented, but reasons for this are unclear (52).

Predisposing genetic factors may influence infection susceptibility, regulate a person's immune response against SARS-CoV-2 (Pathway 2) and influence disease severity (pathway 3) (53). Genetic variations such as those that provide protection against malaria, tuberculosis and pneumococcal infection due to an enhanced host immune response, may be harmful for other conditions such as sepsis (54). Tal et al. demonstrated that, compared to White Americans, people from a Black background, were more likely to develop a more vigorous inflammatory host response. This raises the possibility that when confronted with SARS-CoV-2, people from a Black minority ethnic group could be more prone to develop a damaging overreaction of the body's immune system, the so called "cytokine storm" (53). However, whether this actually reflects genetic differences is unclear. **For most other conditions where such ethnic differences in health are observed, they reflect underlying social differences which have been affected by ethnicity rather than genetic differences (55-57).**

Vitamin D levels have been suggested as potentially contributing to ethnic differences in COVID-19 risk, given absorption could potentially differ by skin colour. However, both observational analysis and more causal

genetic studies have not found a relationship between Vitamin D and COVID-19 disease, suggesting this is unlikely to be an important explanation (58).

In summary, the overall evidence suggests genetic factors are not major contributors to ethnic inequalities but there are some specific genetic factors which may have a small influence on COVID-19 risk. More definitive genetic studies could subsequently determine variants which make individuals more vulnerable to infection and progression towards unfavourable outcomes or make them more or less likely to respond to different drugs (59).

Current evidence gaps

Since the start of the pandemic evidence indicates marked ethnic inequalities in COVID-19, with risks arising through several mechanisms. The most important factors are likely to be related to the social determinants of health, including socioeconomic position, occupation and housing circumstances, which are modifiable. These are in turn likely to impact on comorbidities and health-related behaviours. **It is important to stress that not all these factors are modifiable; for example, we can't change an individual's ancestry, culture, religion or country of birth, but we can change their occupational risks, employment contracts, housing circumstances, health-related behaviours and differential healthcare experiences.** In summary, the risks of getting the infection primarily relate to more systemic and structural issues (such as exposure at work or in the home, social contacts, stress, immunity, pollution etc), and risks of developing more severe infection relate to pre-existing co-morbidities, and access to health care (including optimisation of control of co-morbidities).

Direct evidence about exposure to the virus is currently limited, but indirect evidence about likely exposure suggests this may be important. Improving our understanding of if and how behaviours differ by ethnicity (such as following public health recommendations) may be warranted. A major gap is a lack of understanding on what actually causes the inequality, and the relative importance of different pathways to each other. For example, is occupation twice as important as health behaviours, or differential healthcare five times more important as housing? Addressing these questions therefore requires more causal approaches to analysing data, such as G-methods (e.g. marginal structural models, g-formula and structural nested models) (60, 61). Similarly, nearly all analyses to date have assumed that these factors have the same effect across all ethnic groups, but this is at best simplistic, as our conceptual model illustrates, and issues of structural racism may mean this is not the case (62, 63). The accessibility and adequacy of healthcare across ethnic groups, including for testing and health protection services, remains unclear. Uncertainty also remains about the extent to which different ethnic groups experience adverse consequences of the disease too. Lastly, **some genetic influences on COVID-19 risks are emerging, but these are very unlikely to be important explanations of the differences between ethnic groups.**

The conceptual model (Figure 1) provides a starting point for guiding future analyses, highlighting the data requirements needed to investigate different causal pathways. If the causal mechanisms are to be unravelled successfully, more granular data are needed to capture the complexities of ethnicity and socioeconomic position. It is unlikely that any single dataset will be able to provide a comprehensive understanding of this issue, so coordinated analyses across datasets are likely to be necessary. This may involve focusing on different pathways within different analyses. Further research involving specific occupational risks, in-depth ethnographic study of previous life events (in first generation immigrants versus later generation immigrants), and ethnographic studies of the patient healthcare journey with COVID-19, may provide valuable insights. **In addition, interventions to address the excess risk of poor outcomes from COVID-19 in ethnic minorities therefore likely requires a multi-faceted approach to address the mechanisms working across the pathways identified in Figure 1.**

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