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Clinical outcomes following COVID-19 infection in ethnic minority groups in the UK: a systematic review and meta-analysis

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A systematic review and meta-analysis of clinical outcomes following COVID-19 infection in ethnic minority groups in the UK.
Abstract:

Objectives:

This systematic review and meta-analysis evaluated the clinical outcomes of COVID-19 disease in the ethnic minorities of the UK in comparison to the White ethnic group.

Methods:

The study included adult residents of the UK with confirmed COVID-19. Outcomes evaluated were mortality, ICU admission, and invasive mechanical ventilation need in ethnic minorities compared to people from a White background. Medline, Embase, Cochrane, MedRxiv, and Prospero were searched for articles published between May 2020 to April 2021. Risk of bias was evaluated using the Newcastle-Ottawa Scale checklist. PROSPERO ID: CRD42021248117.

Results:

Fourteen studies (767177 participants) were included in the review. In the adjusted analysis, the pooled Odds Ratio (OR) for the mortality outcome was higher for the Black (1.83, 95% CI: 1.21-2.76, number of studies: k=6), Asian (1.16, 95% CI: 0.85-1.57, k=6), and Mixed and Other (MO) groups (1.12, 95% CI: 1.04-1.20, k=5) in comparison to the White group. The adjusted and unadjusted ORs of intensive care admission were more than double for many of the ethnic minorities (OR Black 2.32, 95% CI: 1.73-3.11, k=5, Asian 2.34, 95% CI: 1.89-2.90, k=5, MO group 2.26, 95% CI: 1.64-3.11, k=4). In the adjusted analysis of mechanical ventilation need, the ORs were similarly significantly raised (Black group 2.03, 95% CI: 1.80-2.29, k=3, Asian group 1.84, 95% CI: 1.20-2.80, k=3, MO 2.09, 95% CI: 1.35-3.22, k=3).
Conclusion:

This review found that in the UK, Black, Asian, and MO groups suffered from increased COVID-19 related disease severity and mortality compared to the White majority.

Keywords:

COVID-19, UK, ethnic minorities, mortality, ethnic
1 Introduction

In the UK, there were 152490 deaths (192 deaths/100000 population), 471045 hospital admissions, and 4717811 confirmed cases (7062 cases per 100000 population) due to the COVID-19 pandemic between March 2020 to June 2021.\footnote{1} There are growing concerns in the UK that people belonging to many, if not all ethnic minorities, have been disproportionately impacted by COVID-19.\footnote{2-4}

A systematic review study conducted between December 2019-August 2020 found that Asian people had a higher risk of intensive care admissions and death.\footnote{5} However, another review of COVID-19 patients did not find that ethnicity was associated with the worst outcomes.\footnote{6} This present study was adapted from the systematic reviews by Sze et al., 2020\footnote{5} and Raharja et al., 2020.\footnote{6} Hence, it builds on the work of these two earlier reviews.\footnote{5,6} Since the demographics, socioeconomic issues, healthcare policies and systems of each country are unique, a UK-centric review was needed to understand if her ethnic minority groups faced a greater risk of adverse outcomes from COVID-19 or not.

In order to reduce the impact of COVID-19 on the population, pandemic related research was prioritized and classified as urgent public health research by the National Institute for Health Research (NIHR).\footnote{7} Following the government’s call and support for research in this area, numerous studies were conducted. However, even after this call, there were no published systematic review and meta-analysis studies on the impact of COVID-19 on the ethnic minorities in the UK. Therefore, an up-to-date systematic review of UK-based studies was urgently needed to quantify the health inequalities faced by ethnic minority groups concerning COVID-19. This research aims to assess the clinical outcomes of COVID-19 amongst ethnic minorities in the UK.
2 Methods

The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The PRISMA checklist is available in the supplementary material (S1 Appendix). The protocol was registered with PROSPERO international prospective register of systematic reviews with the ID. CRD42021248117.

2.1 Information Sources

The reference lists of previous reviews were searched for relevant studies published from January 2020 to August 2020. The database searches (Ovid Medline, Ovid Embase, Ovid Cochrane, MedRxiv, and Prospero) were restricted to one year from May 2020 to April 2021.

2.2 Search Strategy

The Population, Exposure, Comparator, and Outcomes (PECO) framework was used to formulate the criteria for study selection. The target sample included adult population aged 18 years and above in the UK with a confirmed positive COVID-19 result using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) tests. The ethnic categorization into ‘White’, ‘Black’, ‘Asian’, ‘Mixed’, and other groups was based on the UK Census categories 2001. The Census 2001 categorisation was used because it is used by the National Health Service (NHS). However, there is no group for the Chinese in the Asian category. South Asians and East Asians differ in terms of mortality, so combining these two ethnic groups is not useful.
All-cause mortality and Intensive Care Unit (ICU) admission rates were assessed as the primary outcomes, with Invasive Mechanical Ventilation (IMV) as a secondary outcome. The measures of effect for the outcomes were Hazard Ratio (HR), Risk Ratio (RR), Odds Ratio (OR), or Standardised Mortality Ratio (SMR).

Interventional studies, systematic reviews, observational studies including case-control studies, and cohort studies were included, along with non-peer-reviewed studies as this is a rapidly evolving field.

Conference abstracts, commentaries, cross-sectional studies, reports, editorials, non-systematic review articles, case reports, late-breaking abstracts, studies without a comparator group, and papers whose full text was unavailable, were excluded. Risk of infection only studies were excluded. Studies were restricted to those in the English language. Studies from the same population, with similar outcomes, were reviewed and one relevant study was included; whilst the rest were excluded, as this may have created a duplication of data. Studies that grouped all ethnic minorities as one were excluded. Specialist librarians were asked to review the search strategy with the keywords COVID-19, ethnic minority, and the UK. The search strategy was based on the search originally conducted by Sze et al., 2020 and Public Health England (PHE), 2020 and was adapted for this review by the addition of ‘UK’ as a key term during the searches. The detailed search strategy for each database was provided in the research proposal. The search terms were tailored for each database and the searches were run separately for each database to enhance sensitivity. The search period defined was between May 2020 to April 2021.

2.3 Selection Process
Two reviewers independently screened the titles and the abstracts of the studies; and excluded non-relevant studies. Full texts of the remaining studies were retrieved and reviewed for inclusion in the study against the selection criteria defined earlier. Any disagreements between the researchers were resolved through discussion.

2.4 Data Collection Process

One researcher (SS) extracted data from the eligible studies and assessed the risk of bias. Data extraction was checked by a second reviewer (IA). Authors of relevant studies were also contacted for clarity on missing data.

2.5 Quality Assessment

The Newcastle-Ottawa Scale (NOS) (S2 Appendix) was employed to assess the risk of bias in the included studies.¹² A NOS score of 7-9 is classed as low risk of bias, a score of less than 5 as high risk of bias; and a score of 5-6 as moderate risk of bias.¹³ One researcher (SS) carried out the quality assessment at the study and outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.¹⁴ Publication bias was not assessed as there were fewer studies in the adjusted analysis. The funnel plot may not detect publication bias when the number of studies is small.¹⁵

2.6 Data Synthesis

The raw counts for the various outcome variables were used to calculate the RR and 95% Confidence Intervals (CIs). Studies that did not use the White group as a comparator group were excluded from the meta-analysis. As all the studies were observational designs, a Der Simonian-Laird Random-Effects Meta-analysis (REM) was conducted for all outcomes. For rare outcomes, OR was assumed to be equal to
RR, and RR was assumed to be equal to HR. Mortality in hospital-based studies was not a rare outcome. However, in population-based studies it was rare. The studies which provided Adjusted Odds Ratio (AOR) were pooled together in one group and those which provided Adjusted Hazard Ratio (AHR) were separately pooled together in another group (if the outcomes were not rare). Thus, adjustments were made, whilst extracting, for study characteristics of each included study. In studies where raw data was missing; the authors were contacted to obtain this. In order to include studies with missing data in the meta-analysis, the unadjusted HR/RR were combined using the inverse variance method. Using this method, the pooled risk estimates were calculated separately for each ethnic group and a summary statistic was provided. The results were written in tabulated form and as forest plots. Excel and RevMan were used to analyse and tabulate the data. Origin 2021b was used to convert graphical data into tabulated form. The statistical heterogeneity was explored by calculating the $I^2$ statistic using RevMan and by looking at the overlap of CIs in the forest plots. A subgroup analysis was conducted to explore differences in risk estimates across the subgroups.

Studies based only on ICU patients, general hospital patients, and the general population were analysed separately. A sensitivity analysis was conducted based on only peer-reviewed studies and a separate analysis was conducted based on studies with low risk of bias.

### 3 Results

The search on Medline, Embase, MedRxiv, Cochrane, and Prospero yielded 939 studies on 14-15 April 2021. Fourteen studies were selected to be included in the systematic review as shown in S1 Fig and S1 Table.
3.1 Study Characteristics

The 14 studies included a total of 767177 participants. The study characteristics are given in Table 1. As all the studies were observational, so no adjustment was needed.
Table 1: Study characteristics of included studies

| Study ID | Study Design | Population | Setting | Sample Size | Outcomes | Confounders adjusted for | Comorbidities |
|----------|--------------|------------|---------|-------------|----------|--------------------------|---------------|
| Alaa17   | cohort       | Data from ‘COVID-19 Hospitalisation in England Surveillance System’ (CHESS) database, which included COVID-19 cases admitted to hospitals | Hospital | 6068        | mortality | none | Asthma, diabetes mellitus (DM), Hypertension (HTN), kidney and liver diseases, cardiovascular disease (CVD), respiratory illness, immunosuppressive states |
| **Apea**<sup>18</sup> cohort | COVID-19 positive cases admitted to East London hospitals | hospital | 1737 | Mortality, IMV age, sex, deprivation, Body Mass Index (BMI), DM, HTN, Chronic Kidney Disease (CKD) | DM, CKD, HTN, Ischemic Heart Disease (IHD), CVD, Cerebrovascular Accident (CVA), Chronic Obstructive Lung Disease (COPD), liver disease, cancer, Acquired Immunodeficiency Syndrome (AIDS), Charlson Comorbidity index |
| Batty¹⁹ cohort | Participants of the UK Biobank cohort study | community | 4486 | mortality | age, sex, socioeconomic status, lifestyle factors, co-morbidities | CVD, DM, chronic bronchitis, HTN, mental illnesses |
| Ferrando-Vivas²⁰ cohort | COVID-19 cases from the Intensive Care National Audit & Research Centre (ICNARC) database, of ICU admitted cases | ICU | 9990 | mortality | age, sex, deprivation, BMI, prior dependency, immunocompromised state, sedated for first 24 hours, various clinical variables | Immunocompromised state |
| Field²⁹ cohort | COVID-19 positive hospital | hospital | 500 | mortality | none | none |
| Study | Cohort | Cases | Admitted | Mortality | Deprivation | Area of Residence | Comorbidities |
|-------|--------|-------|----------|-----------|--------------|-------------------|---------------|
| Gopal Rao<sup>21</sup> | Cohort | COVID-19 cases tested in London hospitals | Hospital | 1901 | Age, sex, deprivation | Area of residence | None |
| Mahida<sup>27</sup> | Case-control | Patients admitted to an ICU of a Birmingham hospital | ICU | 140 | ICU admission | None | HTN, obesity, IHD, DM, asthma, COPD, CVA, CKD, cancer |
| Perez-Guzman<sup>22</sup> | Cohort | COVID-19 positive cases admitted to a hospital | Hospital | 559 | Mortality, ICU admission | NEWS-2 score | HTN, DM, IHD, heart failure, stroke, CKD, dementia, previous deep venous |
| Study | Design | Population | Controls | Number | Mortality | Age | Causes |
|-------|--------|------------|----------|--------|-----------|-----|--------|
| Perkin | Case-control | COVID-19 and non-COVID-19 cases admitted to a London hospital | | 573 | Mortality | Age | DM, HTN, IHD |
| Russell | Cohort | COVID-19 positive cancer patients from a hospital | | 156 | Mortality | None | Cancer, HTN, chronic steroid use, DM, lung disease, liver disease, CVD, frailty |
| **Sapey**<sup>23</sup> cohort | London hospital COVID-19 cases admitted to Birmingham hospital Trust | 2169 | Mortality, ICU admission | Age, sex, deprivation, co-morbidities | Count of morbidities used; HTN, CVA, AF, IHD, DM, asthma, COPD, interstitial lung disease, CKD, malignancy, dementia, obesity |
|---|---|---|---|---|---|
| **Singh**<sup>4</sup> cohort | Living population of Wolverhampton Community and hospital | 2286 | Mortality | Sex, age, deprivation, smoking, BMI, co-morbidities, previous hospital admissions | DM, HTN, chronic heart, lung, kidney, joint diseases, cancer, dementia, mental illnesses, |
| Study   | Cohort | Setting                                                                 | Cases | Endpoints                              | Variables                                                                 |
|---------|--------|--------------------------------------------------------------------------|-------|----------------------------------------|---------------------------------------------------------------------------|
| Thomas  | cohort | COVID-19 cases admitted to an ICU in London                              | 156   | Mortality                              | Age, BMI, lowest PaO₂/FiO₂ ratio (P/F) on first day of ICU, pH and PaCO₂ at time of lowest P/F ratio |
|         |        |                                                                         |       |                                        | HTN, DM, hyperlipidaemia, IHD, chronic respiratory illnesses, CKD         |
| Yates   | cohort | COVID-19 cases admitted to hospitals in the UK, International Severe    | 6593  | Mortality, ICU admission, IMV          | age, sex, obesity, DM, chronic heart disease, CKD, chronic pulmonary disease, cancer |
|         |        |                                                                         |       |                                        | Chronic heart, kidney and lung diseases, DM, cancer                       |
Acute Respiratory and emerging Infections Consortium (ISARIC) dataset

1This is a surveillance system set up by PHE to obtain data regarding COVID-19 cases. 17

Fourteen studies were included in the systematic review and 12 in the meta-analysis. Thirteen studies provided data on risks of mortality due to COVID-19 in the various ethnic groups, six on ICU admission, and four on IMV need.

3.2 Quality of Studies

The risk of bias (ROB) was low, average NOS score was 7.7 (ranging from 4-9). Nine studies had a low risk of bias score on the NOS, four studies had a moderate risk of bias score on the NOS and one study had a high risk of bias as shown in S2 Table. The low scores were largely due to studies that failed to adjust for confounding factors. Most studies were hospital-based, and such populations are somewhat representative...
of the average COVID-19 patient in the community and did not necessarily reflect the wider community. Also, there might be bias introduced in such hospital-based studies as people in some ethnic groups might be reluctant to seek medical advice.

### 3.3 Mortality

The unadjusted OR, RR, AOR, and AHR are shown in S2 Fig, Figs 1,2, and S3 Fig. As seen in S2 Fig, 20,800/206,562 White individuals died due to COVID-19 compared to 1,254/22,232 Black cases, 1986/51,179 Asian cases and 1648/30,430 MO cases.

In the unadjusted analysis, the risk of death was similar in Blacks and Asians (Black OR: 0.89, 95% CI: 0.71-1.12, I²=83%, number of studies k=9) (Asian OR: 0.83, 95% CI: 0.68-1.02, I²=85%, k=9), but significantly reduced in Mixed and Others group (OR: 0.64, 95% CI: 0.55-0.74, I²= 42%, k=9) as shown in Fig 1. The adjusted mortality risk was significantly raised for the Asian group (1.32, 95% CI: 1.22-1.42, I²= 0%, k=3) but not for the Black and Mixed and Others groups. The odds of dying were significantly increased for the Blacks, Mixed, and Other ethnicities compared to the White group in the adjusted analysis (Black AOR: 1.83, 95% CI: 1.21-2.76, I²= 87%, k=6, MO AOR: 1.12, 95% CI: 1.04-1.20, I²= 0%, k=5) groups, but not for the Asian ethnic group. All the studies in the adjusted analysis were low risk of bias studies. In the sensitivity analysis, with only published studies, the increased odds of mortality in the Black and Mixed and Others groups were maintained (Black AOR 1.48, 95% CI: 1.10- 1.99, and MO AOR 1.12, 95% CI: 1.04-1.20) as shown in S3 Table. The odds of increased mortality for Black, Asian, and MO ethnicities were stronger in subgroup analysis with only hospital-based studies (AOR= 1.22, 95%CI 1.07-1.38, I²=6%, k=4 for Blacks, AOR= 1.28, 95%CI 1.04-1.57, I²=40%, k=4 for Asians, AOR= 1.12, 95%CI 1.04-1.20,
I²=0%, k=4 for MO). This subgroup had low heterogeneity and showed statistically significant results as shown in S4 Table. In the adjusted analysis, of only population-based studies, the odds of dying for the Black ethnic group were almost three times that of the White ethnic group (AOR=2.94, 95% CI: 1.46-5.90), but with a larger CI. However, the odds were not raised for the Asian group. Perkin et al., 2020 \textsuperscript{28} found that adjusted odds of mortality due to COVID-19 were increased for all ethnicities (Asian AOR 3.62, 95% CI=1.84–7.11, Black AOR 2.91, 95% CI= 1.43–5.91, and Other AOR 3.01, 95% CI=1.61–5.64) compared with hospital deaths in 2019.
Fig 1: Forest plot of unadjusted RR for the mortality outcome (REM, Inverse variance method)
Fig 2: Forest plot of AOR, REM, for the mortality outcome
3.4 Intensive Care Admission

Six studies provided data about ICU admissions for the various ethnic groups. Five of these studies were suitable for aggregating the raw outcomes and for pooling the unadjusted risk estimates. These studies included a total of 71791 participants who were admitted to critical care units in the UK. Eighty percent of them were White, 5% were Black, 9.5% were Asians and 8% were MO. The unadjusted and adjusted analyses for ICU admission are shown in Fig 3 and S4 Fig. From S4 Fig., it is seen that 11% White individuals were admitted to ICU with COVID-19 compared to 21% Black, 20% Asian, and 21% MO individuals. In the adjusted and unadjusted analysis, the odds of ICU admissions were more than double for patients of the Black, Asian, and MO ethnicities as compared to the White ethnic group. The unadjusted OR for the Black group was 2.32 (95% CI: 1.73-3.11, I^2 = 66%, k=5), for the Asian group 2.34 (95% CI: 1.89-2.90, I^2 = 58%, k=5), and for the MO group 2.26 (95% CI: 1.64-3.11, I^2 = 45%, k=4). In the pooled AOR, the results were not statistically significant for the ethnic minorities as the lower CI crossed the line of no effect as shown in Fig 3. However, the results indicated a strong association (OR twice as high) between ethnicity and ICU admission outcome. The pooled AOR for the Black group was 2.61 (95% CI: 0.89-7.68, I^2 = 91%, k=2), for the Asian group it was 2.05 (95% CI: 0.85-4.94, I^2 = 89%, k=2), and for the MO group 2.12 (95% CI: 0.94-4.78, I^2 = 80%, k=2). One study which was not included in the meta-analysis compared patients admitted to ICU with COVID-19, and patients admitted to ICU with community-acquired pneumonia (non-COVID controls). The study found that the cases with COVID-19 had statistically significantly fewer White (p= 0.012) and more Asian cases (p= 0.002).
Fig 3: Forest plot of ICU admission outcome, pooled AOR, REM
3.5 Mechanical Ventilation

Four cohort studies reported ethnicity data about the need for IMV for hospitalised patients in the UK. Amongst a total of 69707 patients, 80% were White, 5% were Black, 7% were Asian and 8% were from MO ethnic group. In the unadjusted analysis, the odds for the Black, Asian, and MO groups were twice as high, compared to the White group (Black OR: 2.44, 95% CI: 1.67-3.57, $I^2=67\%$, k=4, Asian OR: 2.29, 95% CI: 1.69-3.11, $I^2=58\%$, k=4, and the MO groups OR: 2.67, 95% CI: 1.77-4.01, $I^2=53\%$, k=4) as shown in S5 Fig. From S5 Fig. it is seen that 6% White cases were put on IMV, compared to 15% Black cases, 12% Asian cases, and 15% MO cases. After adjusting for confounders, the odds of needing ventilation were still high for the Black, Asian, and MO groups, indicating that other factors may have been putting them at increased risk. The AOR for the Black group was 2.03 (95% CI: 1.80-2.29, $I^2=1\%$, k=3), for the Asian group 1.84 (95% CI: 1.20-2.80, $I^2=74\%$, k=3) and for the MO group 2.09 (95% CI: 1.35-3.22, $I^2=60\%$, k=3) as shown in Fig 4.
Fig 4: Forest plot of the IMV outcome, pooled adjusted OR, REM
The studies which were included in the IMV need and ICU admission analysis are all low risk of bias studies, published, and hospital-based studies and so further sensitivity analyses were not conducted. The heterogeneity was high for most of the outcomes.

### 3.6 Quality of Evidence Assessment

As best evidence regarding risk factors is usually obtained from observational studies, so the evidence in this review was started with high ratings as advised by Foroutan et al., 2020 (for prognostic studies). The overall GRADE assessment indicated a high level of confidence for all outcomes, except for the mortality outcomes for the Asian group which was moderate and was downrated due to inconsistency, as shown in the summary of findings in S5 Table.

### 4 Discussion

There was heterogeneity in the populations, settings, methodology, and statistical analysis. The meta-analysis was still conducted since this degree of heterogeneity had been reported by other reviews and conducting the latter was beneficial.

The results indicate greater disease severity in the Black, Asian, and MO groups necessitating ICU admission and IMV provision. Overall, it can be said that ethnicity is a risk factor for worse prognosis in ethnic minorities and they do suffer from increased disease severity. Several studies and data from Office for National Statistics (ONS) and Intensive Care National Audit and Research Centre (ICNARC) also validate this finding of the worst outcomes or ethnic minorities in the UK.

In the UK, in the national publications, all ethnic groups apart from the White British are considered as ethnic minorities including white minorities like Irish traveller groups, Gypsy, Roma, any other white background.
Some reviews on this topic have combined data from all over the world.\textsuperscript{5,6} The results from these cannot be extrapolated to the UK, as the healthcare systems, health inequalities issues, and ethnic make-up vary from country to country. A more recent review has attempted to address this issue by analysing the COVID data regionally, but they did not include any data on ICU admissions nor conduct any adjusted analysis on mortality in Europe.\textsuperscript{38} Agyemang et al. concluded that hospitalised ethnic minorities did not suffer from worse COVID-19 outcomes except for increased mortality among ethnic minorities in Brazil.\textsuperscript{38}

The odds of mortality for hospitalised COVID cases were raised for the Black, Asian, and MO groups in the adjusted analysis. The result from this review is significant as it shows that after hospital admission, there are additional factors in play, which increase the risk of mortality. So, the difference in mortality cannot be attributed to differential access to healthcare facilities or increased risk of infection alone. The odds of mortality due to COVID for the general population were raised for the Black ethnic group similar to findings by ONS and Mathur.\textsuperscript{32,34} Increased prevalence of comorbidities and raised C-Reactive Protein (CRP) levels, a non-specific marker of inflammation, maybe the cause of the greater severity of COVID-19 in Black and Asian communities. Obesity has been identified as an important risk factor associated with morbidity and mortality due to COVID-19.\textsuperscript{25,45,46} It has been proven that Black people with obesity suffer the worst outcomes and the effect of this association is attenuated in them.\textsuperscript{25} Another study reported that the association between obesity and mortality was stronger for non-Whites (especially Black and South Asian people) compared to White people (p-value= 0.002).\textsuperscript{46} The highest obesity rates have been observed in Black people (68%) compared to the other groups (White 64%, Asian 60%, average 63% adults in the
DM and HTN were three times more common in cases who died due to COVID-19. HTN is three to four times more prevalent in Black people in the UK compared to the rest of the population. DM is more prevalent in South Asian (six times more) and Black people (three times more) compared to White people in the UK. Genetic predisposition, urbanization, migration to Western countries, and reduced physical activity are important causative factors of DM in South Asians.

Black and Asian people have raised CRP compared to White people, putting them at an increased risk of severe COVID-19 infection. Raised CRP levels are an important predictor of the severe form of COVID-19 disease and are also a risk factor for DM and cardiovascular disease. It has been observed in one study that the median CRP levels in Black (181.5 mg/L) and Asian (146 mg/L) people were higher than in White people (136 mg/L) on presentation to the hospital for COVID-19 related symptoms. Lower socioeconomic status is a risk factor for raised CRP levels and it has been hypothesized that stress may be a mediator in this. It has also been hypothesized that chronic inflammation linked to insulin resistance, obesity, cardiovascular disease, stress, and chronic infections in the Black and other ethnic minority groups can trigger a cytokine storm which is associated with the severe form of COVID-19 disease. A cytokine storm is an abnormal dysregulated inflammatory response diagnosed by the presence of respiratory distress, and hyper inflammation (raised CRP levels more than 100mg/L or raised ferritin levels) in COVID-19 cases.

This is the first meta-analysis that analyses IMV data, and ICU data from the UK. The odds of ICU admission in hospitalised patients are similar to findings by ICNARC and
the study by Mathur which also found that the adjusted risk of ICU admission was raised 2-3 times for Blacks, Asians, Mixed, and Other ethnic groups (in the general population). Sze et al. only found raised odds of ICU admission for Asians. However, their analysis was limited by very small numbers (only 4439) compared to this review which included ICU data on 67,833 COVID cases. Several studies have pointed out that the COVID-19 cases presenting to UK hospitals, tend to be people who are White, elderly, and have more comorbidities (like dementia and COPD). In contrast, Black and Asian people tend to be younger and have fewer comorbidities but have a higher prevalence of DM. Elderly White people are not good candidates for ICU admission and IMV. However, the Black and Asian cases are more suitable for ICU admission, and this may be a reason why they have higher rates of ICU admission and IMV.

### 4.1 Strengths

This is the first systematic review and meta-analysis conducted to assess the burden of disease faced by ethnic minorities in the UK. The strength of the research lies in its comprehensive analysis of relevant databases for published and pre-print articles. Although the heterogeneity was quite high, this was to be expected with observational studies that had a very large number of participants. The heterogeneity was explored by conducting a subgroup and sensitivity analysis.

### 4.2 Limitations

A broad ethnic classification was used in this review. The Asian group included very diverse subgroups, each of which has now been shown to have different risk profiles.
This review was limited to adults so the results could not be generalised to children. The PCR test for COVID-19 has a high false-negative rate, which led to some cases being wrongly classified as non-COVID. As this review concentrated on UK-based studies, the results were less generalisable to other countries. It has been noted that many participants' ethnicities have been put down as ‘Other’, and this may have created erroneous results for the MO group. The representativeness of study populations would be a limitation of the review. The variables used for the adjustment differed greatly from one paper to another. This is a possible limitation as the amount and nature of adjustment could affect the results.

4.3 Policy Implications

These results have urgent implications for formulating a COVID-19 response strategy (including vaccination provision) that protects ethnic minorities who are at most risk from the worst outcomes related to COVID-19, and addressing long-standing health inequalities. Recommendations made by Marmot et al. (2020a) to address the health inequalities should be adopted in full. He recommended increased public health funding, investment in key areas like housing and employment, development of a national strategy to reduce health inequalities, and setting targets to monitor government interventions. Measures to reduce the effects of COVID-19, like health promotion efforts, should be targeted at high-risk communities. Clinical guidelines should be adapted to keep in mind the health inequalities faced by ethnic minorities. The NICE guidance on possibly excluding cases with cardiovascular disease especially angina patients from critical care; disproportionately influences ethnic minorities as Asian and Black people are more prone to heart disease. The risk assessment of being employed in healthcare does not allow for the redeployment
of staff based on ethnicity alone. As ethnicity has been proven now to be associated with increased mortality, these workers should be given the choice of being redeployed in non-patient-facing roles.

4.4 Implications of Research

This review needs to be upgraded to a living systematic review so that the changing pandemic risks can be identified in the various ethnicities as the pandemic progresses. There is a need for more epidemiological population-based studies to assess the true risk experienced by various ethnic groups with regards to the worst clinical outcomes. The dataset needs to be large enough to appreciate the risk in the various sub-groups. Ethnic minority focused healthcare research concerning COVID-19 treatments can help to reduce the health inequalities. Research should be conducted to assess why COVID-19 related health inequalities exist for some ethnic minorities.

4.5 Conclusion

It can be concluded that the Black, Asian, and MO groups faced the worst outcomes with regards to COVID-19 in the UK. These findings are of immense public health importance and should be used to help formulate policy concerning COVID-19 and reducing socioeconomic disparities.

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Table 1: Study characteristics of included studies

| Study ID | Study Design | Population | Setting | Sample Size | Outcomes | Confounder(s) adjusted for | Co-morbidities |
|----------|--------------|------------|---------|-------------|----------|--------------------------|---------------|
| **Alaa**¹⁷ | cohort       | Data from ‘COVID-19 Hospitalisation in England Surveillance System’ (CHESS)¹ database, which included COVID-19 cases admitted to hospitals | hospital | 6068 | mortality | none | asthma, diabetes mellitus (DM), Hypertension (HTN), kidney and liver diseases, cardiovascular disease (CVD), respiratory illness, immunosuppressive states |
| **Apea**¹⁸ | cohort       | COVID-19 positive cases admitted to East London hospitals | hospital | 1737 | mortality, IMV | age, sex, deprivation, Body Mass Index (BMI), DM, HTN, Chronic Kidney Disease (CKD) | DM, CKD, HTN, Ischemic Heart Disease (IHD), CVD, Cerebrovascular Accident (CVA), Chronic Obstructive Lung Disease |
| Study | Cohort | Study Population | Number | Cause of Death | Other Variables | Comorbidities |
|-------|--------|------------------|--------|----------------|----------------|--------------|
| Batty\(^{19}\) | Cohort | Participants of the UK Biobank cohort study | 4486 64 | Mortality | Age, sex, socioeconomic status, lifestyle factors, co-morbidities | COPD, liver disease, cancer, Acquired Immunodeficiency Syndrome (AIDS), Charlson Comorbidity index |
| Ferrando-Vivas\(^{20}\) | Cohort | COVID-19 cases from the Intensive Care National Audit & Research Centre (ICNARC) database, of ICU admitted cases | 9990 | Mortality | Age, sex, deprivation, BMI, prior dependency, immunocompromised state, sedated for first 24 hours, various clinical variables | Immunocompromised state |
| Field\(^{29}\) | Cohort | COVID-19 positive cases admitted to a London hospital | 500 | Mortality | None | None |
| Gopal Rao\(^{21}\) | Cohort | COVID-19 cases tested in hospital | 1901 | Mortality, ICU admission | Age, sex, deprivation | None |
| Study            | Design                  | Setting                                                                 | Hospital | ICU admission | Area of residence                                                                 |
|------------------|-------------------------|-------------------------------------------------------------------------|----------|---------------|-----------------------------------------------------------------------------------|
| Mahida et al.    | Case-control            | London hospitals                                                        | ICU      | 140           | ICU admission, IMV, area of residence, HTN, obesity, IHD, DM, asthma, COPD, CVA, CKD, cancer |
| Perez-Guzman et al. | Cohort                  | COVID-19 positive cases admitted to London hospital                     | Hospital | 559           | Mortality, ICU admission, IMV, age, sex, comorbidity, deprivation, admission NEWS-2 score, HTN, DM, IHD, heart failure, stroke, CKD, dementia, previous deep venous thrombosis/pulmonary embolism, atrial fibrillation (AF), COPD, liver disease, cancer, AIDS |
| Perkin et al.    | Case-control            | COVID-19 and non-COVID-19 cases admitted to London hospital             | Hospital | 573           | Mortality, age                                                                     | DM, HTN, IHD |
| Russell et al.   | Cohort                  | COVID-19 positive cancer patients from London hospital                  | Hospital | 156           | Mortality, none                                                                    | Cancer, HTN, chronic steroid use, DM, lung disease, liver disease, CVD, frailty |
| Sapey           | Cohort                  | COVID-19 cases                                                          | Hospital | 2169          | Mortality, ICU, age, sex, deprivation, count of morbidities                        |
| Study | Cohort | Population | Admission | Mortality Factors | Outcomes |
|-------|--------|------------|------------|-------------------|-----------|
| Singh² | cohort | Living population of Wolverhampton | admission | comorbidities | DM, HTN, chronic heart, lung, kidney, joint diseases, cancer, dementia, mental illnesses, learning difficulties, immunosuppressive states, palliative care |
| Thomson²⁶ | cohort | COVID-19 cases admitted to an ICU in London | ICU | lowest PaO₂/FiO₂ ratio (P/F) on first day of ICU, pH and PaCO₂ at time of lowest P/F ratio | HTN, DM, hyperlipidaemia, IHD, chronic respiratory illnesses, CKD |
| Yates²⁵ | cohort | COVID-19 cases admitted to hospitals in the UK, hospitals | ICU admission, IMV | age, sex, obesity, DM, chronic heart disease, CKD, chronic pulmonary | chronic heart, kidney and lung diseases, DM, cancer |
| Internatio
nal
Severe
Acute
Respirato
ry and
emerging
Infections
Consortiu
m (ISARIC)
dataset | disease, cancer |

¹This is a surveillance system set up by PHE to obtain data regarding COVID-19 cases. ¹⁷
### S1 Table: Excluded studies

| Study                                         | Reason for Exclusion                                      |
|-----------------------------------------------|----------------------------------------------------------|
| Aldridge et al., 2020                        | Wrong study type... cross-sectional study                 |
| Atkins et al., 2020                         | Same database... UK Biobank                               |
| Ayoubkhani et al., 2021                     | Includes suspected COVID-19 cases                         |
| Bannaga et al., 2020                        | Full text not available                                  |
| Boddington et al., 2021                     | Risk of infection study                                  |
| Baumer et al., 2020                         | No relevant outcomes, OR/RR/HR not given                  |
| Brendish et al., 2020                       | Risk of infection study                                  |
| Brill et al., 2020                          | No relevant outcomes, OR/RR/HR not given                  |
| Cheng et al., 2021                          | Includes suspected COVID-19 cases                         |
| Cheng et al., 2020                          | Full text not available                                  |
| Clough et al., 2021                         | Includes suspected COVID-19 cases                         |
| Corcillo et al., 2021                       | Limited ethnic data                                      |
| Davies et al., 2021                         | No relevant outcomes, OR/RR/HR not given                  |
| De Lusignan, Joy M. et al., 2020            | Includes suspected COVID-19 cases                         |
| De Lusignan, Dorward J. et al., 2020        | Risk of infection study                                  |
| Dennis et al., 2021                         | Includes suspected COVID-19 cases                         |
| Desai et al., 2020                          | Full text not available                                  |
| Drozd et al., 2021                          | No relevant outcomes, OR/RR/HR not given                  |
| Elliot et al., 2021                         | Includes suspected COVID-19 cases                         |
| Gates et al., 2020                          | Full text not available                                  |
| Galloway et al., 2020                       | Limited ethnic data                                      |
| Goodacre et al., 2020                       | No relevant outcomes, OR/RR/HR not given                  |
| Ho et al., 2020                              | Risk of infection study                                  |
| Hull et al., 2020                           | Includes suspected COVID-19 cases                         |
| Joy et al., 2020                            | No relevant outcomes, OR/RR/HR not given                  |
| Ken-Dror et al., 2020                       | Limited ethnic data                                      |
| Khalil et al., 2020                         | No relevant outcomes, OR/RR/HR not given                  |
| Knight et al., 2020                         | Includes suspected COVID-19 cases                         |
| Lassale et al., 2020                        | Same database... UK Biobank                               |
| Martin et al., 2020                         | Risk of infection study                                  |
| Study                          | Findings                                                                 |
|-------------------------------|--------------------------------------------------------------------------|
| Miles et al., 2020            | Includes suspected COVID-19 cases                                        |
| Milln et al., 2021            | Includes suspected COVID-19 cases                                        |
| Moret et al., 2021            | Full text not available                                                  |
| Nafilyan et al., 2021         | Includes suspected COVID-19 cases                                        |
| Navaratnam et al., 2021       | Includes suspected COVID-19 cases                                        |
| Niedzwiedz et al., 2020       | Same database… UK Biobank                                               |
| Patel et al., 2021            | Includes suspected COVID-19 cases                                        |
| Raharja et al., 2020          | Not UK based, global study                                              |
| Raisi-Estabragh et al., 2020  | Includes suspected COVID-19 cases                                        |
| Razieh et al., 2021           | Same database… UK Biobank                                               |
| Richards-Belle et al., 2020   | Includes suspected COVID-19 cases                                        |
| Sattar et al., 2020           | Includes suspected COVID-19 cases                                        |
| Shah et al., 2020             | No relevant outcomes, OR/RR/HR not given                                 |
| Soltan et al., 2021           | Full text not available                                                  |
| Sze et al., 2020              | Not UK based, global study                                              |
| Tay et al., 2020              | Full text not available                                                  |
| Thompson et al., 2020         | Included Chinese in Asian group                                         |
| Williamson et al., 2020       | Includes suspected COVID-19 cases                                        |
| Zakeri et al., 2020           | Included Chinese in Asian group                                         |
S2 Table: Quality assessment of studies using a modified NOS for assessing studies

| Study ID   | Selection Representativeness of exposed cohort (*) | Selection Selection of non-exposed cohort (*) | Selection Ascertainment of exposure (*) | Selection Outcome not present at start (*) | Outcome Assesment of outcome (*) | Outcome Follow-up long enough (*) | Outcome Adequacy of follow-up (*) | Total (*9) |
|------------|--------------------------------------------------|---------------------------------------------|----------------------------------------|------------------------------------------|---------------------------------|-------------------------------|---------------------------------|-----------|
| Alaa 17    | *                                                 | *                                           | *                                      | *                                        | *                               | *                             | *                               | 6         |
| Apea 18    | *                                                 | *                                           |                                        | *                                        | *                               | *                             | *                               | 8         |
| Batt y 19  | *                                                 | *                                           |                                        | *                                        | *                               | *                             | *                               | 7         |
| Ferr ando - Vivas 20 | *                                      |                                               |                                        |                                           | *                               | *                             | *                               | 8         |
| Field 29   | *                                                 | *                                           |                                        |                                           | *                               | *                             | *                               | 6         |
| Gopal Rao 21 |                                               |                                               |                                        |                                           | *                               | *                             | *                               | 8         |
| Mahida 27  | *                                                 | *                                           | *                                      |                                           | *                               | *                             | *                               | 4         |
| Perez-Guzman 22 |                                               |                                               |                                        |                                           | *                               | *                             | *                               | 9         |
| Perkin 28  | *                                                 |                                             |                                        |                                           | *                               | *                             | *                               | 6         |
| Author      | Reference  | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value |
|------------|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Russell    | 30         | *     | *     | *     | *     | *     | *     | *     | *     | *     | *     | *     | *     |
| Sapey      | 23         | *     | *     | *     | **    | *     | *     | *     | *     | *     | *     | *     | *     | 9     |
| Singh      | 24         | *     | *     | *     | **    | *     | *     | *     | *     | *     | *     | *     | *     | 9     |
| Thomson    | 26         | *     | *     | *     | *     | *     | *     | *     | *     | *     | *     | *     | *     | 7     |
| Yates       | 25         | *     | *     | *     | **    | *     | *     | *     | *     | *     | *     | *     | *     | 9     |
S3 Table: Sensitivity analysis for the mortality outcome

|                              | Studies | Pooled unadjusted OR (95% CI) | $I^2$ | Studies | Pooled unadjusted RR (95% CI) | $I^2$ | Studies | Pooled AOR (95% CI) | $I^2$ |
|------------------------------|---------|-------------------------------|-------|---------|-------------------------------|-------|---------|-------------------|-------|
| All studies with raw mortality data |         |                               |       |         |                               |       |         |                   |       |
| Black                        | 9       | 0.89, (0.71-1.12)             | 83    | 11      | 0.98, (0.86-1.12)             | 88    | 6       | 1.83, (1.21-2.76) | 87    |
| Asian                        | 9       | 0.83, (0.68-1.02)             | 85    | 11      | 0.97, (0.84-1.12)             | 91    | 6       | 1.16, (0.85-1.57) | 71    |
| Mixed and Other              | 9       | 0.64, (0.55-0.74)             | 42    | 10      | 0.74, (0.64-0.85)             | 74    | 5       | 1.12, (1.04-1.20) | 0     |
| Only published, peer-reviewed studies |         |                               |       |         |                               |       |         |                   |       |
| Black                        | 9       | 0.89, (0.71-1.12)             | 83    | 10      | 0.98, (0.83-1.15)             | 84    | 5       | 1.48, (1.10-1.99) | 69    |
| Asian                        | 9       | 0.83, (0.68-1.02)             | 85    | 10      | 0.96, (0.82-1.14)             | 90    | 5       | 1.14, (0.80-1.60) | 77    |
| Mixed and Other              | 9       | 0.64, (0.55-0.74)             | 80    | 10      | 0.74, (0.64-0.85)             | 45    | 4       | 1.12, (1.04-1.20) | 0     |
| Only studies with low ROB |   |   |   |   |   |
|--------------------------|---|---|---|---|---|
| Black                    | 8 | 0.92, (0.73-1.15) | 84% | 8 | 0.94, (0.80-1.11) | 85% | 6 | 1.83, (1.21-2.76) | 87% |
| Asian                    | 8 | 0.81, (0.66-0.99) | 86% | 8 | 0.86, (0.74-1.00) | 88% | 6 | 1.16, (0.85-1.57) | 71% |
| Mixed and Other          | 8 | 0.63, (0.54-0.74) | 48% | 8 | 0.72, (0.64-0.82) | 58% | 6 | 1.12, (1.04-1.20) | 0% |
## S4 Table: Subset analysis for the mortality outcome

|                      | Studies | Pooled unadjusted OR (95%) | I²  | Studies | Pooled unadjusted RR (95%) | 1²  | Studies | Pool ed AOR (95%) | 1²  |
|----------------------|---------|---------------------------|-----|---------|---------------------------|-----|---------|-------------------|-----|
| **All studies with raw mortality data** |         |                           |     |         |                           |     |         |                   |     |
| Black                | 9       | 0.89 (0.71-1.12)          | 83 %| 11      | 0.98 (0.86-1.12)          | 88 %| 6       | 1.83 (1.21-2.76)  | 87 %|
| Asian                | 9       | 0.83 (0.68-1.02)          | 85 %| 11      | 0.97 (0.84-1.12)          | 91 %| 6       | 1.16 (0.85-1.57)  | 71 %|
| Mixed and Other      | 9       | 0.64 (0.55-0.74)          | 42 %| 10      | 0.74 (0.64-0.85)          | 74 %| 5       | 1.12 (1.04-1.20)  | 0%  |
| **Hospital based**   |         |                           |     |         |                           |     |         |                   |     |
| Black                | 8       | 0.82 (0.67-1.00)          | 75 %| 8       | 0.87 (0.75-1.01)          | 79 %| 4       | 1.22 (1.07-1.38)  | 6%  |
| Asian                | 8       | 0.87 (0.70-1.09)          | 86 %| 8       | 0.94 (0.80-1.11)          | 89 %| 4       | 1.28 (1.04-1.57)  | 40 %|
| Mixed and Other      | 8       | 0.68 (0.60-0.76)          | 23 %| 8       | 0.76 (0.69-0.84)          | 33 %| 4       | 1.12 (1.04-1.20)  | 0%  |
| **Population based** |         |                           |     |         |                           |     |         |                   |     |
| Black                |         |                           |     |         |                           |     |         | 2.94 (1.46-5.90)  | 83 %|
| Asian                |         |                           |     |         |                           |     |         | 0.80 (0.30-2.15)  | 81 %|
| Mixed and Other      |         |                           |     |         |                           |     |         |                   |     |
| Intensive care based |       |       |       |       |
|---------------------|-------|-------|-------|-------|
| Black               | 2     | 1.00, (0.87-1.15) | 0%    | 2     | 1.00, (0.92-1.09) | 0%    |
| Asian               | 2     | 1.36, (0.65-2.80) | 67%   | 2     | 1.24, (0.74-2.08) | 69%   |
| Mixed and Other     | 2     | 0.74, (0.51-1.08) | 5%    | 2     | 0.82, (0.57-1.17) | 6%    |
## S5 Table: GRADE, a summary of findings table

### MORTALITY

|         | AOR   | Number of participants (studies) | ROB | Inconsistency | Imprecision | Indirectness | Publication bias | Strong association | GRAD E |
|---------|-------|----------------------------------|-----|---------------|-------------|--------------|-----------------|-------------------|--------|
| Black  | 1.83  | 74584 4 (6)                      | no  | no            | no          | no           | -               | potential risk factor, OR between 1-2 | high   |
| Asian  | 1.16  | 74584 4 (6)                      | no  | yes           | no          | no           | -               | neutral           | moderate, due to inconsistency |
| MO     | 1.12  | 74584 4 (6)                      | no  | no            | no          | no           | -               | potential risk factor, OR between 1-2 | high   |

### ICU ADMISSION

|         | AOR   | Number of participants (studies) | ROB | Inconsistency | Imprecision | Indirectness | Publication bias | Strong association | GRAD E |
|---------|-------|----------------------------------|-----|---------------|-------------|--------------|-----------------|-------------------|--------|
| Black  | 2.61  | 67833 (2)                         | no  | no            | no          | no           | -               | yes               | high, due to strong association |
|   | $I^2$=91% |                |                |                |                |                |                |
|---|---------|----------------|----------------|----------------|----------------|----------------|----------------|
| Arabian | 2.05 (0.85-4.94) | P=0.003, $I^2$=89% | 67833 (2) | no | no | no | no | - | yes | high, due to strong association |
| M | 2.12 (0.94-4.78) | P=0.03, $I^2$=80% | 67833 (2) | no | no | no | no | - | yes | high, due to strong association |

### IMV

|   | AOR | Number of participants (studies) | R O B | Inconsistency | Imprecision | Indirectness | Publication bias | Strong association | GRAD E |
|---|-----|----------------------------------|-------|---------------|-------------|--------------|------------------|----------------------|--------|
| Black | 2.03 (1.8-2.29) | P=0.36, $I^2$=1% | 69570 (3) | no | no | no | no | - | yes | high, due to strong association |
| Arabian | 1.84 (1.2-2.8) | P=0.02, $I^2$=74% | 69570 (3) | no | no | no | no | - | no | high, due to strong association |
| M | 2.09 (1.35-3.22) | P=0.08, $I^2$=60% | 69570 (3) | no | no | no | no | - | yes | high, due to strong association |
| Study or Subgroup | BAME | White | Odds Ratio | M-H, Random, 95% CI |
|-------------------|------|-------|------------|---------------------|
|                   | Events | Total | Events | Total | Weight |                         |
| 10.7.1 Black      |       |       |        |       |        |                         |
| Apea 2021         | 97    | 340   | 210    | 703   | 4.9%   | 0.94 [0.70, 1.25]        |
| Ferrando-Vivas 2020 | 373  | 940   | 2530   | 6384  | 6.6%   | 1.00 [0.87, 1.15]        |
| Gopal Rao 2021    | 61    | 237   | 166    | 514   | 4.2%   | 0.73 [0.51, 1.03]        |
| Perez Guzman 2020 | 41    | 133   | 67     | 236   | 3.1%   | 1.12 [0.70, 1.78]        |
| Russell 2020      | 5     | 35    | 21     | 78    | 0.9%   | 0.45 [0.16, 1.32]        |
| Sapely 2020       | 40    | 134   | 502    | 1540  | 3.8%   | 0.70 [0.48, 1.03]        |
| Singh 2021        | 39    | 17858 | 190    | 142781| 4.2%   | 1.64 [1.16, 2.32]        |
| Thomson 2020      | 7     | 32    | 16     | 73    | 1.0%   | 1.00 [0.37, 2.72]        |
| Yales 2021        | 591   | 2523  | 17018  | 54254 | 7.0%   | 0.67 [0.61, 0.74]        |
| Subtotal (95% CI) | 22232 | 206562| 35.6%  | 0.89 [0.71, 1.12] |
| Total events      | 1254  | 20800 |        |        |        |                         |
|                   |       |       |        |       |        | Heterogeneity: Tau² = 0.08, Chi² = 45.82, df = 8 (P < 0.00001), I² = 83% |
|                   |       |       |        |       |        | Test for overall effect: Z = 0.98 (P = 0.33) |

10.7.2 Asian

| Study or Subgroup | BAME | White | Odds Ratio | M-H, Random, 95% CI |
|-------------------|------|-------|------------|---------------------|
|                   | Events | Total | Events | Total | Weight |                         |
| Apea 2021         | 138   | 538   | 210    | 703   | 5.3%   | 0.81 [0.63, 1.04]        |
| Ferrando-Vivas 2020 | 591  | 1459  | 2530   | 6384  | 6.8%   | 1.04 [0.92, 1.16]        |
| Gopal Rao 2021    | 174   | 679   | 166    | 514   | 5.3%   | 0.72 [0.56, 0.93]        |
| Perez Guzman 2020 | 30    | 94    | 67     | 236   | 2.7%   | 1.19 [0.70, 1.97]        |
| Russell 2020      | 4     | 6     | 21     | 78    | 0.3%   | 5.41 [0.83, 31.88]       |
| Sapely 2020       | 120   | 410   | 502    | 1540  | 5.5%   | 0.60 [0.54, 0.68]        |
| Singh 2021        | 32    | 44229 | 190    | 142781| 3.9%   | 0.54 [0.37, 0.79]        |
| Thomson 2020      | 14    | 36    | 16     | 73    | 1.3%   | 2.27 [0.95, 5.41]        |
| Yales 2021        | 863   | 3726  | 17018  | 54254 | 7.2%   | 0.60 [0.63, 0.73]        |
| Subtotal (95% CI) | 51179 | 206562| 38.4%  | 0.63 [0.50, 1.02] |
| Total events      | 1986  | 20800 |        |        |        |                         |
|                   |       |       |        |       |        | Heterogeneity: Tau² = 0.06, Chi² = 53.39, df = 8 (P < 0.00001), I² = 85% |
|                   |       |       |        |       |        | Test for overall effect: Z = 1.78 (P = 0.07) |

10.7.3 Mixed and Other

| Study or Subgroup | BAME | White | Odds Ratio | M-H, Random, 95% CI |
|-------------------|------|-------|------------|---------------------|
|                   | Events | Total | Events | Total | Weight |                         |
| Apea 2021         | 33    | 156   | 210    | 703   | 3.5%   | 0.63 [0.42, 0.96]        |
| Ferrando-Vivas 2020 | 278  | 830   | 2530   | 6384  | 6.5%   | 0.77 [0.66, 0.89]        |
| Gopal Rao 2021    | 31    | 129   | 166    | 514   | 3.3%   | 0.66 [0.43, 1.03]        |
| Perez Guzman 2020 | 3     | 17    | 67     | 236   | 0.6%   | 0.64 [0.15, 2.43]        |
| Sapely 2020       | 15    | 85    | 582    | 1540  | 2.4%   | 0.35 [0.20, 0.62]        |
| Singh 2021        | 11    | 23764 | 190    | 142761| 2.2%   | 0.35 [0.19, 0.64]        |
| Thomson 2020      | 1     | 15    | 16     | 73    | 0.2%   | 0.25 [0.03, 0.80]        |
| Yales 2021        | 1274  | 5427  | 17018  | 54254 | 7.2%   | 0.67 [0.63, 0.72]        |
| Subtotal (95% CI) | 30430 | 206562| 26.3%  | 0.64 [0.55, 0.74] |
| Total events      | 1648  | 20800 |        |        |        |                         |
|                   |       |       |        |       |        | Heterogeneity: Tau² = 0.01, Chi² = 13.73, df = 8 (P = 0.09), I² = 42% |
|                   |       |       |        |       |        | Test for overall effect: Z = 6.78 (P < 0.00001) |

Total (95% CI)

| Study or Subgroup | BAME | White | Odds Ratio | M-H, Random, 95% CI |
|-------------------|------|-------|------------|---------------------|
|                   | Events | Total | Events | Total | Weight |                         |
| Apea 2021         | 10384 | 619686| 100.0%  | 0.78 [0.70, 0.87] |
| Total events      | 4898  | 62400 |        |        |        |                         |
|                   |       |       |        |       |        | Heterogeneity: Tau² = 0.04, Chi² = 128.76, df = 26 (P < 0.00001), I² = 86% |
|                   |       |       |        |       |        | Test for overall effect: Z = 4.57 (P < 0.00001) |
|                   |       |       |        |       |        | Test for subgroups differences: Chi² = 7.46, df = 2 (P = 0.02), I² = 73.2% |
| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|------------------|----------------|------|--------|-------------------|-------------------|
| **10.8.1 Black** |                |      |        |                   |                   |
| Alaa 2020        | 0.3953         | 0.1526 | 3.1%   | 1.47 [1.09, 1.98]  |                   |
| Acea 2021        | -0.0408        | 0.1059 | 4.6%   | 0.96 [0.78, 1.18]  |                   |
| Ferrando-Vivas 2020 | 0.00425    | 0.0546 | 5.1%   | 1.00 [0.92, 1.09]  |                   |
| Field 2020       | 0.0392         | 0.0238 | 5.5%   | 1.04 [0.99, 1.09]  |                   |
| Gopal Rao 2021   | -0.2231        | 0.113 | 3.6%   | 0.80 [0.62, 1.03]  |                   |
| Perez Guzman 2020 | 0.877         | 0.166 | 2.9%   | 1.08 [0.78, 1.50]  |                   |
| Russel 2020      | -0.6349        | 0.4486 | 0.7%   | 0.53 [0.22, 1.28]  |                   |
| Sapey 2020       | -0.2357        | 0.1049 | 3.3%   | 0.79 [0.60, 1.04]  |                   |
| Singh 2021       | 0.4947         | 0.1676 | 2.7%   | 1.64 [1.16, 2.32]  |                   |
| Thomson 2020     | -0.002         | 0.007 | 8.9%   | 0.99 [0.46, 2.19]  |                   |
| Yates 2021       | -0.2977        | 0.0352 | 5.2%   | 0.75 [0.70, 0.80]  |                   |
| **Subtotal (95% CI)** |              |      | 26.8%  | 0.97 [0.83, 1.12]  |                   |
| **Heterogeneity:** Tau² = 0.03, Chi² = 64.45, df = 10 (P = 0.00001); I² = 89% | Test for overall effect: Z = 0.28 (P = 0.78) |

| **10.8.2 Asian** |                |      |        |                   |                   |
| Alaa 2020        | 0.4187         | 0.0567 | 4.2%   | 1.52 [1.26, 1.83]  |                   |
| Acea 2021        | -0.1508        | 0.0507 | 3.8%   | 0.86 [0.72, 1.03]  |                   |
| Ferrando-Vivas 2020 | 0.0198     | 0.0363 | 5.2%   | 1.02 [0.95, 1.10]  |                   |
| Field 2020       | 0.0488         | 0.0367 | 5.2%   | 1.05 [0.98, 1.13]  |                   |
| Gopal Rao 2021   | -0.2257        | 0.017 | 4.3%   | 0.79 [0.66, 0.95]  |                   |
| Perez Guzman 2020 | 0.1133        | 0.0146 | 2.6%   | 1.12 [0.78, 1.61]  |                   |
| Russel 2020      | 0.0983         | 0.0245 | 1.1%   | 2.48 [1.26, 4.88]  |                   |
| Sapey 2020       | -0.2614        | 0.0786 | 4.5%   | 0.77 [0.66, 0.90]  |                   |
| Singh 2021       | -0.6162        | 0.1029 | 2.5%   | 0.54 [0.37, 0.79]  |                   |
| Thomson 2020     | 0.5734         | 0.3041 | 1.4%   | 1.77 [0.80, 3.22]  |                   |
| Yates 2021       | -0.2744        | 0.0347 | 5.2%   | 0.76 [0.67, 0.89]  |                   |
| **Subtotal (95% CI)** |              |      | 40.5%  | 0.97 [0.84, 1.12]  |                   |
| **Heterogeneity:** Tau² = 0.04, Chi² = 168.79, df = 10 (P = 0.00001); I² = 91% | Test for overall effect: Z = 0.43 (P = 0.67) |

| **10.8.3 Mixed and Other** |                |      |        |                   |                   |
| Alaa 2020          | -0.0726        | 0.145 | 3.3%   | 0.93 [0.70, 1.24]  |                   |
| Acea 2021          | -0.3425        | 0.1689 | 2.9%   | 0.71 [0.51, 0.99]  |                   |
| Ferrando-Vivas 2020 | -0.1825       | 0.0571 | 4.9%   | 0.85 [0.76, 0.95]  |                   |
| Gopal Rao 2021     | -0.3911        | 0.1703 | 2.6%   | 0.74 [0.53, 1.03]  |                   |
| Perez Guzman 2020  | -0.478         | 0.5286 | 0.6%   | 0.62 [0.22, 1.75]  |                   |
| Russel 2020        | 0.0363         | 0.0673 | 9.3%   | 1.00 [0.31, 3.62]  |                   |
| Sapey 2020         | -0.755         | 0.2464 | 1.6%   | 0.47 [0.29, 0.86]  |                   |
| Singh 2021         | -1.0498        | 0.3117 | 1.3%   | 0.35 [0.19, 0.64]  |                   |
| Thomson 2020       | -1.1902        | 0.901 | 0.2%   | 0.30 [0.04, 2.12]  |                   |
| Yates 2021         | -0.2977        | 0.0089 | 4.5%   | 0.75 [0.64, 0.89]  |                   |
| **Subtotal (95% CI)** |              |      | 22.7%  | 0.74 [0.64, 0.88]  |                   |
| **Heterogeneity:** Tau² = 0.02, Chi² = 16.49, df = 9 (P = 0.06); I² = 45% | Test for overall effect: Z = 4.14 (P = 0.0001) |

| **Total (95% CI)** |                |      | 100.0% | 0.91 [0.84, 0.99]  |                   |
| **Heterogeneity:** Tau² = 0.03, Chi² = 226.89, df = 31 (P = 0.00001); I² = 86% | Test for overall effect: Z = 2.32 (P = 0.02) |

Test for subgroup differences: Chi² = 9.89, df = 2 (P = 0.007), I² = 79.8%.
| Study or Reference | Treatment | Weight | Mean Ratio | 95% CI | Heterogeneity | Test for overall effect | Test for subgroup differences |
|-------------------|-----------|--------|------------|--------|---------------|------------------------|----------------------------|
| 7.2.1 Analysis | Test 1 | 0.291 | 0.0137 | 0.0051 | 0.0011 | 0.0011 | | 0.0011 |
| | Test 2 | 0.291 | 0.0137 | 0.0051 | 0.0011 | 0.0011 | | 0.0011 |
| 7.2.2 Analysis | Test 1 | 0.291 | 0.0137 | 0.0051 | 0.0011 | 0.0011 | | 0.0011 |
| | Test 2 | 0.291 | 0.0137 | 0.0051 | 0.0011 | 0.0011 | | 0.0011 |
| 7.2.3 Analysis | Test 1 | 0.291 | 0.0137 | 0.0051 | 0.0011 | 0.0011 | | 0.0011 |
| | Test 2 | 0.291 | 0.0137 | 0.0051 | 0.0011 | 0.0011 | | 0.0011 |

Heterogeneity: Test for overall effect: | 0.0011 (P = 0.0011) |
Test for subgroup differences: | 0.0011 (P = 0.0011) |
| Study or Subgroup | BAME | White | Odds Ratio |
|-------------------|------|-------|------------|
|                   | Events | Total | 95% CI     |
| Apex 2621         | 63    | 340   | 1.85 (1.29, 2.65) |
| Gopal Rao 2021    | 40    | 237   | 5.60 (3.13, 10.00) |
| Perez Oyserman 2020 | 20   | 130   | 1.63 (0.96, 2.61) |
| Spain 2020        | 21    | 134   | 1.97 (1.10, 3.24) |
| Yates 2021        | 570   | 2623  | 2.29 (2.08, 2.52) |
| **Subtotal (95% CI)** | 3367 | 57246 | **2.32 (1.73, 3.11)** |
| **Total events**  | 714   | 6383  |            |
| **Heterogeneity:** | Tau² = 0.07; Chi² = 11.09; df = 4 (p = 0.032); I² = 58% |
| **Test for overall effect:** Z = 5.61 (p < 0.00061) |

9.2.2 Asian

| Study or Subgroup | BAME | White | Odds Ratio |
|-------------------|------|-------|------------|
| Apex 2621         | 108  | 638   | 2.04 (1.49, 2.80) |
| Gopal Rao 2021    | 84   | 679   | 3.89 (2.31, 6.54) |
| Perez Oyserman 2020 | 15  | 84    | 1.75 (0.87, 3.53) |
| Spain 2020        | 66   | 410   | 2.81 (2.08, 3.76) |
| Yates 2021        | 775  | 3728  | 2.05 (1.89, 2.23) |
| **Subtotal (95% CI)** | 5449 | 57246 | **2.34 (1.69, 2.96)** |
| **Total events**  | 1096 | 6383  |            |
| **Heterogeneity:** | Tau² = 0.02; Chi² = 9.57; df = 4 (p = 0.05); I² = 59% |
| **Test for overall effect:** Z = 7.92 (p < 0.00061) |

9.2.3 Mixed and Other

| Study or Subgroup | BAME | White | Odds Ratio |
|-------------------|------|-------|------------|
| Apex 2621         | 20   | 156   | 1.78 (1.11, 2.80) |
| Gopal Rao 2021    | 10   | 120   | 4.47 (2.26, 4.64) |
| Perez Oyserman 2020 | 2   | 17    | 1.23 (0.26, 6.74) |
| Spain 2020        | 0    | 0     | Not estimable |
| Yates 2021        | 1173 | 5424  | 2.10 (2.02, 2.22) |
| **Subtotal (95% CI)** | 5729 | 55766 | **2.29 (1.64, 3.11)** |
| **Total events**  | 1221 | 6250  |            |
| **Heterogeneity:** | Tau² = 0.05; Chi² = 5.45; df = 3 (p = 0.14); I² = 45% |
| **Test for overall effect:** Z = 4.59 (p = 0.00061) |

| Study or Subgroup | BAME | White | Odds Ratio |
|-------------------|------|-------|------------|
|                   | Events | Total | 95% CI     |
| Apex 2621         | 14545 | 170198 | 2.25 (2.04, 2.49) |
| **Total events**  | 3001  | 18016 |            |
| **Heterogeneity:** | Tau² = 0.64; Chi² = 22 (p = 0.00061); I² = 54% |
| **Test for overall effect:** Z = 7.92 (p < 0.00061) |
| **Test for substantive differences:** Cm² = 0.64; df = 2 (p = 0.68); I² = 0% |
| Study of Subgroup | BAME | White | Odds Ratio  |
|------------------|------|-------|-------------|
|                  | Total| Total|  IV, Random, 95% CI |
| 3.1.1 Black      |      |      |               |
| Apea 2021        | 50   | 340   | 8.4% | 1.00 [1.26, 2.81] |
| Gopal Rao 2021   | 16   | 237   | 8    | 4.09 [1.93, 10.80] |
| Perez Guzman 2020| 18   | 133   | 8    | 1.67 [0.78, 3.57]  |
| Yales 2021       | 404  | 2523  | 19.3%| 2.90 [2.65, 3.22]  |
| Subtotal (95% CI)| 5233 | 55706 | 34.4%| 2.44 [1.57, 3.57]  |
| Total events     | 485  | 3367  |      |                   |
| Heterogeneity Tau² = 0.09, Ch² = 9.23, df = 3 (P = 0.03); I² = 67% |
| Test for overall effect: Z = 4.62 (P < 0.00001) |

| 3.1.2 Asian      |      |      |               |
|                  | Total| Total|  IV, Random, 95% CI |
| Apea 2021        | 78   | 538   | 9.6% | 1.85 [1.29, 2.65]  |
| Gopal Rao 2021   | 54   | 878   | 8    | 5.46 [2.58, 11.50] |
| Perez Guzman 2020| 14   | 94    | 22   | 1.69 [0.63, 3.47]  |
| Yales 2021       | 474  | 3728  | 18.7%| 2.27 [2.04, 2.51]  |
| Subtotal (95% CI)| 5039 | 55706 | 36.1%| 2.29 [1.60, 3.11]  |
| Total events     | 620  | 3367  |      |                   |
| Heterogeneity Tau² = 0.05, Ch² = 7.11, df = 3 (P = 0.07); I² = 58% |
| Test for overall effect: Z = 5.31 (P < 0.00001) |

| 3.1.3 Mixed and Other |      |      |               |
|                      | Total| Total|  IV, Random, 95% CI |
|                      |      |      |               |
| Apea 2021            | 23   | 156   | 6.0% | 1.89 [1.13, 3.16]  |
| Gopal Rao 2021       | 12   | 129   | 9    | 6.49 [2.50, 18.23] |
| Perez Guzman 2020    | 2    | 17    | 22   | 1.29 [0.26, 6.02]  |
| Yales 2021           | 816  | 5427  | 20.4%| 2.75 [2.53, 2.99]  |
| Subtotal (95% CI)    | 5729 | 55706 | 29.9%| 2.67 [1.77, 4.01]  |
| Total events         | 853  | 3367  |      |                   |
| Heterogeneity Tau² = 0.00, Ch² = 6.32, df = 3 (P = 0.10); I² = 63% |
| Test for overall effect: Z = 4.72 (P < 0.00001) |

Total (95% CI) 14001 167118 100.0% 2.47 [2.13, 2.86]
| Study or Subgroup | log(Odds Ratio) | SE | Weight | IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-------------------|-----------------------------|
| 3.3.1 Black       |                |    |        |                   |                             |
| Apea 2021         | 0.5878         | 0.2069 | 9.6%  | 1.99 [1.20, 2.70] |                             |
| Oopal Rao 2021    | 1.3788         | 0.5174 | 2.3%  | 3.97 [1.44, 10.85]|                             |
| Yates 2021        | 0.7988         | 0.0814 | 21.3% | 2.03 [1.80, 2.29] |                             |
| Subtotal (95% CI) |                |    |        |                   | 2.03 [1.80, 2.29]           |

Heterogeneity: $\hat{\tau}^2 = 0.00$, $\chi^2 = 2.02$, df = 2 ($P = 0.36$), $I^2 = 1$

Test for overall effect: $Z = 11.59$ ($P < 0.00001$)  

3.3.2 Asian

| Study or Subgroup | log(Odds Ratio) | SE | Weight | IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-------------------|-----------------------------|
| Apea 2021         | 0.4318         | 0.1906 | 10.5% | 1.54 [1.06, 2.24] |                             |
| Oopal Rao 2021    | 1.0351         | 0.4461 | 3.0%  | 5.13 [2.14, 12.30]|                             |
| Yates 2021        | 0.3908         | 0.0598 | 21.6% | 1.49 [1.33, 1.67] |                             |
| Subtotal (95% CI) |                |    |        |                   | 1.84 [1.20, 2.80]           |

Heterogeneity: $\hat{\tau}^2 = 0.09$, $\chi^2 = 7.56$, df = 2 ($P = 0.02$), $I^2 = 74$

Test for overall effect: $Z = 2.82$ ($P = 0.005$)  

3.3.3 Mixed and Other

| Study or Subgroup | log(Odds Ratio) | SE | Weight | IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-------------------|-----------------------------|
| Apea 2021         | 0.4383         | 0.2717 | 6.6%  | 1.55 [0.91, 2.64] |                             |
| Oopal Rao 2021    | 1.6956         | 0.5014 | 2.4%  | 5.45 [2.04, 14.56]|                             |
| Yates 2021        | 0.6471         | 0.0446 | 22.6% | 1.91 [1.75, 2.08] |                             |
| Subtotal (95% CI) |                |    |        |                   | 2.09 [1.35, 3.22]           |

Heterogeneity: $\hat{\tau}^2 = 0.09$, $\chi^2 = 4.06$, df = 2 ($P = 0.08$), $I^2 = 60$

Test for overall effect: $Z = 3.32$ ($P = 0.0009$)  

Total (95% CI)

|                |        |    |        |                  |                             |
|----------------|--------|----|--------|------------------|-----------------------------|
|                | 100.0% | 1.89 | [1.61, 2.22]|                 |                             |

Heterogeneity: $\hat{\tau}^2 = 0.03$, $\chi^2 = 29.80$, df = 6 ($P = 0.0002$), $I^2 = 73$

Test for overall effect: $Z = 7.73$ ($P < 0.00001$)  

Test for subgroup differences: $\chi^2 = 0.22$, df = 2 ($P = 0.90$), $I^2 = 0$