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COVID-19 and ethnicity: A novel pathophysiological role for inflammation

Abhinav Vepa a, *, Joseph P. Bae a, Faheem Ahmed b, Manish Pareek c, Kamlesh Khunti d

a Department of Medicine, Milton Keynes University Hospital NHS Foundation Trust, Eaglestone, Milton Keynes, Buckinghamshire, UK
b NHS England, Skipton House, London, UK
c Department of Respiratory Sciences, University of Leicester, UK
d Diabetes Research Centre, University of Leicester, UK

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A B S T R A C T

Introduction: There have been recent mounting concerns regarding multiple reports stating a significantly elevated relative-risk of COVID-19 mortality amongst the Black and Minority Ethnic (BAME) population. An urgent national enquiry investigating the possible reasons for this phenomenon has been issued in the UK. Inflammation is at the forefront of COVID-19 research as disease severity appears to correlate with pro-inflammatory cytokine dysregulation. This narrative review aims to shed light on the novel, pathophysiological role of inflammation in contributing towards the increased COVID-19 mortality risk amongst the BAME population.

Methods: Searches in PubMed, Medline, Scopus, medRxiv and Google Scholar were performed to identify articles published in English from inception to 18th June 2020. These databases were searched using keywords including: ‘COVID-19’ or ‘Black and Minority Ethnic’ or ‘Inflammation’. A narrative review was synthesized using these included articles.

Results: We suggest a novel pathophysiological mechanism by which acute inflammation from COVID-19 may augment existing chronic inflammation, in order to potentiate a ‘cytokine storm’ and thus the more severe disease phenotype observed in the BAME population. Obesity, insulin resistance, cardiovascular disease, psychological stress, chronic infections and genetic predispositions are all relevant factors which may be contributing to elevated chronic systemic inflammation amongst the BAME population.

Conclusion: Overall, this review provides early insights and directions for ongoing research regarding the pathophysiological mechanisms that may explain the severe COVID-19 disease phenotype observed amongst the BAME population. We suggest ‘personalization’ of chronic disease management, which can be used with other interventions, in order to tackle this.

* Corresponding author.
E-mail address: Vepa.Abhinav@nhs.net (A. Vepa).

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1. Introduction

COVID-19 is the term used to describe the disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2). It originated in December 2019 from Wuhan, Hubei province in China, and owing to its ability to be transmitted between humans via respiratory droplets [1], has since spread globally. Within the United Kingdom (UK), there have been mounting concerns regarding multiple reports of an elevated relative-risk of COVID-19 mortality amongst the Black and Minority Ethnic (BAME) population [2–5]. After adjusting for socio-demographic characteristics and self-reported co-morbidity/disability, the Office for National Statistics (ONS) estimates that Indian females are 1.43 times, Pakistani and Bangladeshi males are 1.8 times, and Black males and females 1.9 times, more likely to die from COVID-19 relative to their White counterparts [2]. This pattern has broadly been reflected in UK critical care admission and outcome data from the Intensive Care National Audit and Research Centre report [6], as well as data from the United States of America (USA) [7]. An urgent national enquiry into the possible reasons for this phenomenon has thus been issued.

SARS CoV-2 is a positive-sense, enveloped, single-stranded RNA virus which can bind to the angiotensin converting enzyme 2 (ACE2) receptor in humans [1,8]. ACE2 receptors are expressed widely throughout the body but it is believed that SARS CoV-2 uses ACE2 receptors expressed on respiratory epithelial cells to gain entry into the host [8]. After entering the respiratory epithelium, it can replicate to cause pyroptosis and thus the release of pathogen associated molecular patterns (PAMPs) and damage associated
molecular patterns (DAMPs) [9]. DAMPs and PAMPs are recognized by the pattern recognition receptors of surrounding epithelial cells, alveolar macrophages and vascular endothelial cells, which respond by releasing a wide array of pro-inflammatory cytokines such as C-C motif chemokine-10 (CCL10), interleukin-6 (IL-6), macrophage inflammatory protein 1α (MIP1α), macrophage inflammatory protein 1β (MIP1β) and monocyte chemotactic protein 1 (MCP1). These inflammatory cytokines and chemokines can then recruit monocytes, macrophages and T-cells to the local tissue which all release further pro-inflammatory cytokines in a positive feedback loop mechanism resulting in a ‘cytokine storm’ [8]. Evidence to support this was confirmed by the levels of various inflammatory cytokines such as IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), CXCL-10, MCP1, MIP1α and tumour necrosis factor-α (TNF-α), being elevated in severe COVID-19 patients who required critical care admission, usually after the initial phase of viral infection [10].

One of the major complications of COVID-19 is acute respiratory distress syndrome (ARDS), which can lead to death by respiratory failure, and is indeed associated with systemic inflammation [11]. The aforementioned ‘cytokine storm’ can also lead to sepsis and multi-organ failure [12,13]. Another emerging frequently fatal complication of COVID-19 are venous thrombo-embolisms (VTE), namely pulmonary embolisms (PE), which are hypothesized to arise due to the pro-inflammatory and hypercoagulable state described extensively in the literature [14]. Peak IL-6 levels have now been directly associated with COVID-19 disease severity [15] and tocilizumab, an IL-6 inhibitor, is amongst many other promising anti-inflammatory drugs undergoing clinical trials to treat COVID-19 [16,17]. Inflammation is thus at the forefront of COVID-19 research [18] and it is postulated that disease severity and outcomes correlate with pro-inflammatory cytokine dysregulation [19,20]. We therefore undertook the synthesis of a narrative review, which aims to shed light on the novel, acute-on-chronic, pathophysiological role of inflammation in contributing towards the increased mortality risk of COVID-19 amongst the BAME population. We propose that the BAME population may be subject to elevated levels of chronic, systemic inflammation, due to various reasons discussed, which may augment the acute COVID-19 ‘cytokine storm’ described, to potentiate multi-organ failure and death.

2. Methods

2.1. Data sources and searches

Relevant studies were identified by searching Medline, PubMed, Scopus, medRxiv and Google Scholar to identify articles published in English from inception to 18th June 2020. The search terms included one of: ‘COVID-19’ OR ‘Black and Minority Ethnic’ OR ‘Inflammation’, AND one of: ‘Obesity’ OR ‘Diabetes Mellitus’ OR ‘Metabolic Syndrome’ OR ‘Cardiovascular Disease’ OR ‘Psychological Stress’ OR ‘Chronic Infection’ OR ‘Genetic’. The reference list of each study identified in the initial database search, and the library of each co-author, was also reviewed to identify any potentially relevant studies.

2.2. Study selection

Titles, abstracts, and key words of the studies identified in the electronic search were screened for eligibility to be included in this narrative review. All studies deemed relevant were retrieved. A standardized checklist was then used to determine the eligibility for inclusion in the review based on information within the full article. Original research articles were selected to participate in this study if they were relevant to our study hypothesis and contained the highest quality of evidence pertaining a given subject; systematic reviews were used preferentially where possible. Studies confined to local indigenous populations, or published before the year 2000, were excluded. Key epidemiological data was also extracted from government reports.

2.3. Synthesis

A narrative review was synthesized using the included articles in order to summarize key information, hypothesize pathophysiological mechanisms, draw inferences and suggest recommendations for public health policy.

3. Results

3.1. Obesity and insulin resistance

Metabolic syndrome is an inflammatory condition which encompasses insulin resistance, hypertension and obesity, all of which have been associated with COVID-19 severity. A recent meta-analysis in China of 1527 COVID-19 patients concluded that those with cardio-metabolic co-morbidity were at a significantly greater risk and had poorer prognosis [21]. Another meta-analysis of 78,993 hospitalized COVID-19 patients reported concordant data suggesting that 16.37%, 12.11% and 7.87% of patients had hypertension, cardiovascular disease, and diabetes mellitus respectively; all key components of metabolic syndrome [22]. Similarly, preliminary data from National Health Service (NHS) England has shown a higher prevalence of diabetes (19%) and chronic cardiac disease (29%), as well as an association between obesity and mortality, amongst 16,749 hospitalized UK patients with COVID-19 [23]. In the USA, the Hispanic and Black populations are also subjected to higher risks of metabolic syndrome [24], and also incidentally have poorer prognoses due to COVID-19 in preliminary reports [7]. The association between the metabolic syndrome and COVID-19 is not fully understood, but due to the extensive role of inflammation in the pathophysiology of metabolic syndrome [25,26], we build on existing evidence to suggest a potential pathophysiological role for systemic, chronic inflammation from metabolic syndrome, in order to explain the disproportionate effect of COVID-19 on the BAME population.

Insulin resistance, and subsequent Type 2 Diabetes Mellitus (T2DM), can both be described as inflammatory diseases, owing to their association with elevated inflammatory cytokines such as TNFα [27], afflicting UK minority ethnicities 2–5 times more frequently [28]. A large cross-sectional study looking at 4,976 children aged 9–10 years old, within the UK, has shown that biochemical markers of insulin resistance were significantly raised in ethnic minority children compared to Caucasian children [29]. This suggests that from childhood itself, metabolic risk in the BAME population is higher; and indeed, there is evidence to suggest a genetic predisposition to metabolic syndrome amongst the BAME population [30]. NICE recommendations provide different guidelines based on ethnicity for managing T2DM, and also state that the threshold Body Mass Index (BMI) to define ‘high risk’ is 30 for a White individual, but 27.5 for an Asian [31,32].

Obesity, like T2DM, has also been associated with severe COVID-19, the requirement for non-invasive mechanical ventilation, and death [33–36]. In the UK, 72.8% of Black adults were overweight or obese in 2017–2018 compared to 62.9% of White adults [37]. Asians and Blacks were also significantly more likely to be physically inactive, and have unhealthier diets, compared to Whites [38–40], thus suggesting a heavy influence of socioeconomic and psychological factors. Not only can obesity impair lung function via Obesity Hypoventilation Syndrome (OHS) [41], but it can also contribute to the development of Obstructive Sleep Apnoea (OSA), which is indeed more prevalent amongst Blacks in the USA [42]. OSA has been associated with an
exacerbation of metabolic syndrome [43–45], increased intubation risks [46] and respiratory failure [47]. Furthermore, obesity can contribute to non-alcoholic fatty liver disease (NAFLD), which is more commonly found in ethnic minorities [48,49]. Thus, during a COVID-19 'cytokine storm', patients with NAFLD, may be more prone to acute-on-chronic liver failure [50].

Obesity, and insulin resistance, can both also contribute to a chronic inflammatory state which may potentiate a ‘cytokine storm’ within the context of an acute COVID-19 infection. Excess fat, in particular visceral fat which is broadly measured by waist circumference, has been associated with chronic systemic inflammation [51] and COVID-19 severity [36]. In addition, preliminary reports have suggested that a 1 dm² increase in visceral fat area amongst patients with COVID-19 is associated with an over 22 times higher risk of being admitted to critical care [52]. South Asians have indeed been found to have greater proportions of visceral fat compared to Europeans [53]. As adipose tissue grows, it can receive a reduced blood supply and thus be subject to hypoxia, necrosis and subsequent inflammation [51]. Inflamed adipose tissue, as well as visceral adiposity, secretes more adipokines such as leptin, resistin, retinol binding protein-4, and visfatin, as well as less adiponectin, all of which can contribute to elevated, systemic levels of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1, MCP-1 and the complement cascade [54–56]. This adipokine induced pro-inflammatory state amongst the obese has not only been associated with increased risks of atherosclerosis, acute coronary syndrome, cancer, insulin resistance, hypertension and venous thrombo-embolism [51,57], but can also stimulate further adipokine dysregulation via a positive feedback loop mechanism [58].

3.2 Cardiovascular disease

Patients with hypertension have been found to be 2.5 times more likely to develop severe COVID-19 [59,60]. Similarly, dyslipidaemia has also been associated with a poor prognosis in patients with COVID-19 [61]. It is already well established in the literature that ethnic minority populations are more predisposed to dyslipidaemia [62,63] and hypertension [64–66], both of which are key cardiovascular risk factors, associated with chronic inflammation [67,68]. The mechanism by which COVID-19 worsens the prognosis in patients with cardiovascular risk is unknown but multiple studies have emerged indicating higher troponin levels [69] in patients with severe COVID-19 [70–72]. One hypothesis as to how this may occur states that SARS CoV-2 enters myocardial cells via the ACE2 receptor, from where it causes direct myocardial injury [73–75]. Alternatively, since seasonal influenza has been associated with a higher incidence of acute coronary syndrome (ACS) [76,77], reports have suggested that COVID-19 may be acting similarly. Attempts to explain this phenomenon have referred to the pro-inflammatory cytokine dysregulation triggered by active seasonal influenza infection, which can cause acute vascular endothelium dysfunction, atherosclerotic plaque destabilization, tachycardia and hypercoagulability; all of which increase the risk of ACS [76,77]. If COVID-19 is indeed acting similarly via vascular endothelium dysfunction [78], individuals with pre-existing cardiovascular risk factors, such as the BAME population, will be at a higher risk of ACS.

3.3 Psychological stress

Psychological stress and mental health disorders have been strongly associated with systemic inflammatory cytokine dysregulation [79,80], as well as systemic oxidative stress [81–83], across multiple systematic reviews. In fact, psychosocial trauma, occurring at any point in a lifetime, has been associated with increased levels of systemic inflammatory markers such as TNF-α, IL-6, C-reactive protein (CRP) and resistin [84]. Qualitative reports have suggested higher levels of psychological stress amongst ethnic minorities [85], and indeed, meta-analysis research has suggested that acute and chronic stress have both been associated with decreased cellular and humoral immunity [86]. There are possibly three key reasons as to why the BAME population experience increased levels of psychological stress: (i) mental health disorders, (ii) socioeconomic inequalities, and (iii) occupational hazards.

Amongst the BAME population, there is a greater social stigma attributed to mental health disorders, often making it harder for minority ethnics to present with mental health issues to healthcare providers [87,88]. Indeed, in the USA, social stigmata and cultural barriers to help-seeking behaviour amongst African Americans with mental health issues are well evidenced [89,90], and may explain why mental health services are underutilized by the African American population [91]. However, data is now emerging that mental health disorders may be more prevalent amongst the BAME population in the UK, reflected by the greater incidence of psychiatric detention amongst minority ethnics [92]. Mental health issues can not only contribute to, but can also be precipitated by, psychological stress that has been caused by traumatic life experiences. For example, incarceration has been associated with psychological stress, as well as mental health issues, and indeed there is a higher relative representation of Blacks in UK [93] and USA [91] prisons.

Secondly, deprivation and poverty, especially during childhood years, can contribute to psychological stress [94], inflammation [95,96], and now additionally COVID-19 mortality [97]. ONS data has shown that Pakistanis, Bangladeshis and Black populations within the UK have the lowest median gross hourly earnings [98]. Due to poverty, as well as cultural factors, the BAME population are more likely to live in overcrowded and multi-generational households which is as high as 9% more than Caucasians amongst the 34–55 year age category [99]. Furthermore, densely populated urban areas such as London suffered the most deaths from COVID-19 and, likewise, the population of London also comprises of over 40% BAME [100]. Not only does overcrowded housing and inner-city living pose a huge impediment for social distancing, but they are also both associated with psychological stress, mental health disorder and inflammation [101–103].

Finally, whilst 63% of COVID-19 related deaths amongst NHS frontline staff were BAME [104], only 20.8% of the NHS workforce are BAME [105]. This highlights an enormous relative risk which is greater than that of the general BAME population, raising questions regarding occupational hazard. This may partially be explained by the fact that frontline NHS workers are more likely to be exposed to higher viral loads of COVID-19. However, healthcare workers can often experience psychological stress and burn-out [106] and there is now emerging evidence that BAME NHS staff may encounter greater work-related psychological stress [107]. Amongst the non-medical NHS workforce, a hierarchal correlation can be observed whereby the prevalence of White staff positively, and BAME staff negatively, correlate with seniority [105]. Indeed, a ‘lack of decision making’ has been identified as a potent source of occupation-related psychological stress [108,109]. Similarly, various other occupations such as chefs, taxi drivers and security guards, have all encountered a disproportionately higher number of COVID-19 related deaths [110]. These occupations not only contain higher representations of minority ethnics amongst staff [111], but may also involve less decision making, as well as more night shifts, sedentary work and viral load exposure.

Overall, the mechanism as to how psychological stress can contribute to chronic inflammations is yet to be fully elucidated, but there are two mechanisms that have been described in the literature: (i) Neuroendocrine–Immune Crosstalk and (ii) Unhealthy Behaviours. Firstly, Glaser et al. explain that negative emotions,
negative life events and psychological stress, can all activate the Hypothalamic-Pituitary-Adrenal axis (HPA) and direct sympathetic innervation of lymphoid organs. Activation of the HPA contributes to elevated levels of glucocorticoids in circulation, such as cortisol, adrenocorticotropic hormone, prolactin and growth hormone, all of which can bind to respective receptors on various leukocytes, thus modulating their function. The HPA also increases circulating adrenaline and noradrenaline, which can activate the Sympathetic-Adrenal-Medullary axis (SAM). Direct sympathetic activation of lymphoid organs, coupled with activation of the SAM, can both also modulate immune cell function. Immune cell modulation may contribute to release of pro-inflammatory cytokines such as IL-1, which can then trigger a positive feedback loop mechanism to exacerbate neuroinflammation, and subsequent HPA stimulation [112]. Supporting this notion of neuroendocrine-immune crosstalk, there are promising ongoing clinical trials evaluating the use of anti-inflammatory drugs in the treatment of mental health disorders [113,114]. Secondly, the unhealthy behaviours arising from psychological stress and mental health disorder are vast, but may include sleep disruption [115], unhealthy diets and physical inactivity (which are more prevalent in BAME populations [38–40]), substance abuse [116], impulsivity and risk-taking, which can all further contribute towards chronic inflammation [117–119]. The aforementioned mechanisms may provide insight as to how psychological stress can contribute to the pathophysiology of inflammatory co-morbidities such as chronic infections [120,121], cardiometabolic disease [122,123], and perhaps additionally via reducing the threshold to trigger a cytokine storm, COVID-19.

### 3.4. Chronic infections

In addition to the well evidenced pathophysiological mechanisms discussed above, there may also be a smaller role played by chronic infections such as Tuberculosis (TB), chronic hepatitis, and Human Immunodeficiency Virus (HIV), which are more prevalent in migrants from developing countries [124–127]. TB is known to contribute to various chronic lung changes such as cavitation, fibrosis, bronchiectasis and impairment in lung function, all of which may contribute to impaired pulmonary immunity [128], thus potentially increasing the risk of other respiratory tract infections such as COVID-19. There is now also a growing body of evidence implicating hepatic impairment in COVID-19 [10,129]. Although the overall prevalence of Chronic Hepatitis infection in the UK and USA is low, it is possible that COVID-19 could exacerbate underlying Hepatitis B or C which may trigger acute-on-chronic liver failure amongst the BAME population. Finally, despite its association with cardiometabolic disease [130,131], preliminary reports, have indicated similar outcomes from COVID-19 amongst patients with HIV compared to the general population. On the other hand, these HIV patients were all also on anti-retroviral treatment, which may have conferred cross-protection against COVID-19 [132]. Overall, TB, HIV and Hepatitis are all associated with a chronic elevation in pro-inflammatory cytokines [133–135], and this may reduce the threshold for triggering a “cytokine storm” with concomitant COVID-19 infection, as shown in Fig. 1, although the evidence is unclear and requiring further study.

### 3.5. Genetics

Ellinghaus et al. describe an association between the severe COVID-19 phenotype and the 3p21.31 and 9q34.2 gene clusters, suggesting a genetic predisposition to COVID-19 mortality [136]. There is also genetic evidence to suggest that the innate immune response can vary amongst different ethnicities. Nédélec et al. report that 9.3% of macrophage-expressed genes show ancestry-associated differences in the gene regulatory response to infection, and in Black Africans, there may be a more potent inflammatory response to infection [137,138]. To support this, a cross-sectional study of 508 Black and White adults demonstrated significantly higher IL-6 and CRP levels amongst the Black participants [139]. Furthermore, patients with Sickle Cell Disease (SCD) are explicitly warned about heightened risks during the current pandemic situation [140], and there is mounting concern amongst the BAME population as SCD affects predominantly Black Africans [141]. Elevated levels of pro-inflammatory cytokines and chemokines have been well characterized in SCD [142], and within the context of a superimposed COVID-19 infection, may contribute towards an increased risk of sickle-cell crises, coagulopathy, systemic vasculopathy, and functional asplenia related immunocompromise [140].

### 3.6. Improving health inequalities

Based on the pathophysiological mechanisms identified in this review, as well as the surrounding literature, suggested multi-disciplinary interventions to reduce the health inequalities highlighted by the COVID-19 pandemic have been summarized in Table 1 below.

| Table 1 |
| --- |
| **Intervention** | **Explanation** |
| Reducing Socioeconomic Inequalities | Income inequalities for younger generations can be targeted by further investing in the education of deprived populations. Inner-city schools and universities can be given more subsidies and grants to facilitate this with scholarships, as well as career mentorship programmes. For the current working population, adult-learner courses can be further subsidized. The awareness of these government schemes should also be addressed by diversifying advertising platforms, for example, via social media. Housing inequalities can be addressed by allocating housing benefit claimants to council properties throughout the country rather than in specific inner-city areas. The barriers preventing elderly BAME individuals from utilizing care homes should be tackled to reduce overcrowded housing. |
| Improving Access to Healthcare in specific ‘at-risk’ populations | Certain populations, containing more BAME, may be excluded from receiving high quality healthcare. Firstly, in prisons, where Blacks are overrepresented, the Lammy review identifies that there is scope for improvement in the mental health awareness and health literacy amongst prison staff as they can often be the first point of contact for prisoners seeking medical attention [83]. Additionally, improving staffing levels in prisons would help overcome the added barrier of escort requirements when prisoners require secondary care. Secondly, undocumented migrants may not be entitled to non-emergency, healthcare which may delay their presentation to healthcare services due to deportation fears. The government should supportively work with these populations to prevent resultant health impairments by introducing cross-border health and social care. The BAME population are at increased risks of unhealthy behaviours such as physical inactivity, high-fat, and high-sugar diets [38–40]. Dietary advice should be offered, in multiple languages, focusing on healthy food interventions for all cuisines, rather than just Western cuisines. The importance and benefits of healthy eating and exercise should be taught in schools, social media, and certain occupations which suffered disproportionate COVID-19 deaths, for example, taxi drivers. |
| Improving Health Literacy |  |
4. Summary

The mechanisms discussed throughout this review have been summarized in Fig. 1 below.
5. Conclusion

This review aims to shed light on the ongoing national enquiry investigating the disproportionate effect of COVID-19 on the BAME population. For the first time, inflammation has been discussed in a common framework with regards to COVID-19 and ethnicity. We suggest a novel pathophysiological mechanism by which acute inflammation arising from COVID-19, may augment existing chronic inflammation secondary to medical co-morbidity, in order to potentiate a ‘cytokine storm’ and thus the more severe disease phenotype observed in the BAME population. Obesity, insulin resistance, cardiovascular disease, psychological stress, chronic infections and genetic predispositions are all relevant factors which may be contributing to elevated chronic, systemic inflammation amongst the BAME population. We suggest various interventions to reduce the prevalence of the severe COVID-19 disease phenotype amongst the BAME population.

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Declaration of competing interest

There are no relevant conflicts of interest to declare.

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