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Original Article

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

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ABSTRACT

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.

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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 recognised 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-X-C motif chemokine-10 (CXCL-10), interleukin-6 (IL-6), macrophage inflammatory protein 1α (MIP1α), macrophage inflammatory protein 1β (MIP1β) and monocyte chemoattractant 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 76,993 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 ethnics 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 dm^2 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, secrete 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 Pakistani, Bangladeshi 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 also 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 inflammation 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 multidisciplinary 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 [93]. 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.
Improving Health Literacy	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, focussing 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.

Table 1 (*continued*)

Intervention	Explanation
Community-directed health promotion	Councils in areas which suffered higher levels of COVID-19 deaths should be given subsidies to focus on health promotion. This could involve supermarket food stamps for healthy food, discounted gym memberships, more cycle lanes and cycle-to-work schemes, subsidies to convert fast-food restaurants into health food restaurants, and the delivery of healthy-lifestyle talks at community gatherings, places of worship and Gypsy communities.
Personalizing chronic disease management	The BAME population are at elevated risks of various diseases which could be contributing to their more severe COVID-19 phenotype. Guidelines should reflect this by incorporating ethnicity as a relevant risk factor to assist in determining when to initiate treatment. This may involve starting oral hypoglycaemic agents at lower HbA1c levels, the NHS provision of bariatric surgery at a lower BMI threshold, or perhaps the use of statins, aspirin and percutaneous coronary intervention at lower cardiovascular risk thresholds for BAME individuals.
Overcoming Language Barriers	Non-English speakers may lack the confidence to use NHS 111 services. It is thus imperative to increase the provision of translators and multi-lingual NHS services. Language barriers may also reduce the effectiveness of talking therapies such as cognitive behavioural therapy. For this reason, the NHS provision of evidence-based, non-verbal psychotherapies such as *yoga*, *tai-chi*, dance movement psychotherapy, and music therapy may thus be of benefit.
Improving Cultural Awareness	Cultural barriers can often influence the interaction between BAME individuals and healthcare services. For example, the stigma associated with mental health disorder is often higher amongst the BAME population. Healthcare staff, such as community mental health teams, should be equipped to deal with such stigmas as well as other cultural barriers. Furthermore, the use of alternative medicine may be more prevalent amongst the BAME population [143]. Where possible, evidence based alternative therapies such as acupuncture, mindfulness and fasting should be considered by health professionals.
BAME-targeted Healthcare Research	Various drugs such as dexamethasone, convalescent plasma, tocilizumab, and remdesivir are undergoing clinical trials to assess their efficacy in treating COVID-19 [144]. It is important to increase the BAME individuals participating in these studies, or even to conduct separate studies focussed on the BAME population. The recognition and reporting of ethnicity as a crucial demographic risk factor, like age and gender, should also be encouraged amongst healthcare research.

4. Summary

The mechanisms discussed throughout this review have been summarized in Fig. 1 below.
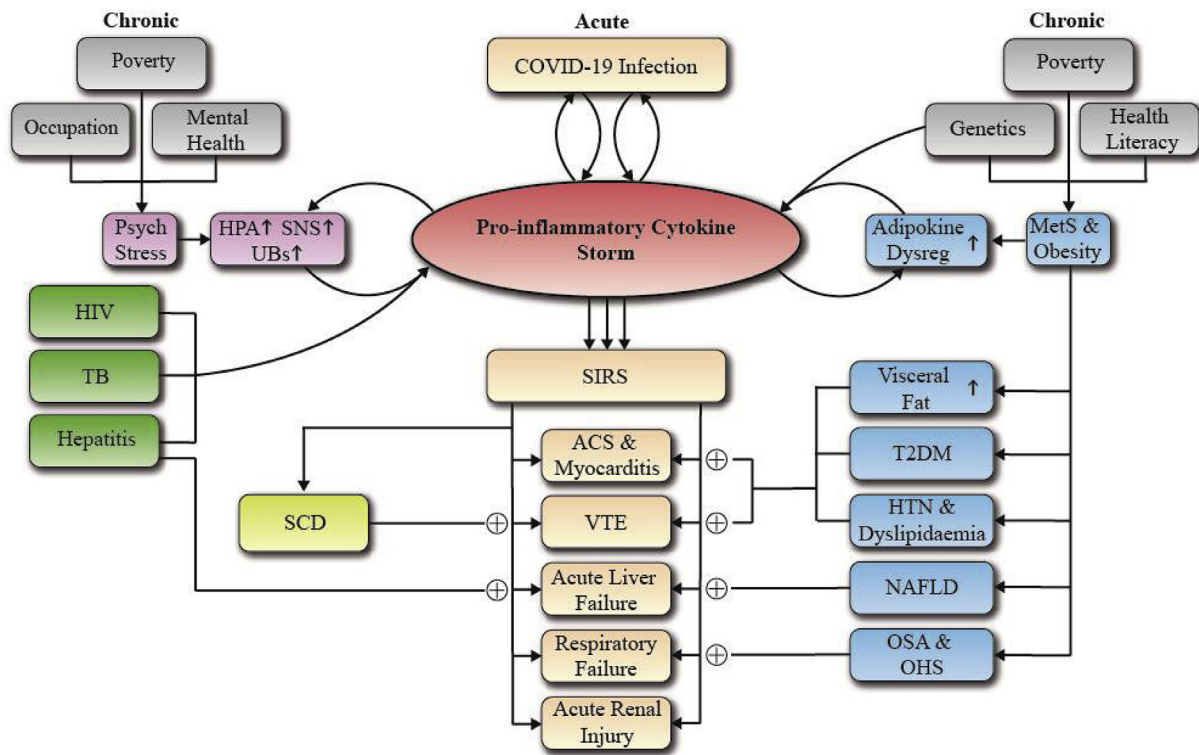
Fig. 1. Illustrating the complex, acute-on-chronic interplay between social determinants of health, acute COVID-19 pathophysiology and the chronic diseases discussed in this review, which are more prevalent in the Black and Minority Ethnic (BAME) population. Chronic diseases, and disease processes, that could be contributing to the more severe COVID-19 phenotype observed in the BAME population include Metabolic Syndrome (MetS), Type 2 Diabetes Mellitus (T2DM), Obesity, Hypertension (HTN), Dyslipidaemia, Visceral Fat, Non- Alcoholic Fatty Liver Disease (NAFLD), Obstructive Sleep Apnoea (OSA), Obesity Hypoventilation Syndrome (OHS), Psychological Stress (Psych Stress), Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Hepatitis B and C, and Sickle Cell Disease (SCD). Of particular importance in potentiating the 'cytokine storm', we draw attention to 3 positive feedback loop mechanisms involving: (i) The Hypothalamic-Pituitary- Adrenal Axis (HPA), Sympathetic Nervous System (SNS) and Unhealthy Behaviours (UBs), (ii) Adipokine Dysregulation (Adipokine Dysreg) and (iii) COVID-19 acute infection. Subsequent Systemic Immune Response Syndrome (SIRS) and multi-organ failure secondary to COVID-19 can manifest as acute coronary syndrome (ACS), myocarditis, Venous Thrombo-Embolism (VTE), acute liver failure, respiratory failure, and acute renal injury, all of which can be directly potentiated by the aforementioned, pre-existing co-morbidities.

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.

Declaration of competing interest

There are no relevant conflicts of interest to declare.

References

[1] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD. Features, evaluation and treatment Coronavirus (COVID-19). StatPearls; 2020. https://www.ncbi.nlm.nih.gov/books/NBK554776/.

[2] ONS. Coronavirus (COVID-19) related deaths by ethnic group, England and wales: 2 march 2020 to 10 april 2020. Office for National Statistics; 2020 [updated 7/05/2020; cited 2020 09/05/2020]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelateddeathsbyethnicgroupenglandandwales/2march2020to10april2020#ethnic-breakdown-of-deaths-by-age-and-sex.

[3] Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: a systematic review. EClinic Med 2020;23. https://doi.org/10.1016/j.eclinm.2020.100404.

[4] Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv 2020. https://doi.org/10.1101/2020.05.06.20092999.

[5] PHE. Disparities in the risk and outcomes from COVID-19 public health England. Public Health England; 2020 [cited 2020 11/06/2020]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/891116/disparities_review.pdf.

[6] ICNARC. ICNARC report on COVID-19 in critical care. ICNARC; 2020 [updated 10/04/2020; cited 2020 11/06/2020]. Available from: https://www.icnarc.org/DataServices/Attachments/Download/c31dd38d-d77b-ea11-9124-00505601089b.

[7] Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 states, march 1–30, 2020. MMWR (Morb Mortal Wkly Rep) 2020;69(15):458–64. https://doi.org/10.15585/mmwr.mm6915e3. https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm.

[8] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363–74. https://doi.org/10.1038/s41577-020-0311-8. https://www.nature.com/articles/s41577-020-0311-8.

[9] Yang M. Cell pyroptosis, a potential pathogenic mechanism of 2019-nCoV infection. SSRN; 2020. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3527420.

[10] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[11] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8(4):420–2. https://doi.org/10.1016/S2213-2600(20)30076-X.

[12] Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;6:1–4. https://doi.org/10.1007/s00134-020-06028-z.

[13] Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multi-organ response. Curr Probl Cardiol 2020;45(8). https://doi.org/10.1016/j.cpcardiol.2020.100618.

[14] Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. Radiology 2020:201544. https://doi.org/10.1148/radiol.2020201544.

[15] Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. Ecanc Med Sci 2020;14:1022. https://doi.org/10.3332/ecancer.2020.1022.

[16] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020;111. https://doi.org/10.1016/j.jaut.2020.102452.

[17] Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol 2020;92(7):814–8. https://doi.org/10.1002/jmv.25801.

[18] Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. J Exp Med 2020;217(6). https://doi.org/10.1084/jem.20200652.

[19] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20: 355–62. https://doi.org/10.1038/s41577-020-0331-4.

[20] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020;215:108427. https://doi.org/10.1016/j.clim.2020.108427.

[21] Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109(5):531–8. https://doi.org/10.1007/s00392-020-01626-9. https://link.springer.com/article/10.1007/s00392-020-01626-9.

[22] Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med 2020;8(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096724/.

[23] Docherty A, Harrison E, Green C, Hardwick H, Pius R, Norman L, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO clinical characterisation protocol. medRxiv; 2020. https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1.

[24] DeBoer MD. Ethnicity, obesity and the metabolic syndrome: implications on assessing risk and targeting intervention. Expet Rev Endocrinol Metabol 2011;6(2):279–89. https://doi.org/10.1586/eem.11.17.

[25] Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the west virginian population. Int J Med Sci 2016;13(1):25–38. https://doi.org/10.7150/ijms.13800.

[26] Paoletti R, Bolego C, Poli A, Cignarella A. Metabolic syndrome, inflammation and atherosclerosis. Vasc Health Risk Manag 2006;2(2):145–52. https://doi.org/10.2147/vhrm.2006.2.2.145.

[27] Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, et al. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol 2019;14(1):50–9. https://doi.org/10.15420/ecr.2018.33.1.

[28] Goff LM. Ethnicity and type 2 diabetes in the UK. Diabet Med : J Brt Diabetic Assoc 2019;36(8):927–38. https://doi.org/10.1111/dme.13895.

[29] Whincup PH, Nightingale CM, Owen CG, Rudnicka AR, Gibb I, McKay CM, et al. Early emergence of ethnic differences in type 2 diabetes precursors in the UK: the child heart and health study in England (CHASE study). PLoS Med 2010;7(4). https://doi.org/10.1371/journal.pmed.1000263.

[30] Radha V, Mohan V. Genetic predisposition to type 2 diabetes among Asian Indians. Indian J Med Res 2007;125(3):259–74. https://europepmc.org/article/med/17496355.

[31] NICE. BMI: preventing ill health and premature death in black, Asian and other minority ethnic groups NICE Guidelines. National Institute of Health and Care Excellence; 2013 [updated 03/07/2013. Available from: https://www.nice.org.uk/guidance/ph46/chapter/1-Recommendations#background.

[32] Gray LJ, Yates T, Davies MJ, Brady E, Webb DR, Sattar N, et al. Defining obesity cut-off points for migrant south asians. PloS One 2011;6(10). https://doi.org/10.1371/journal.pone.0026464.

[33] Caussy C, Wallet F, Laville M, Disse E. Obesity is associated with severe forms of COVID-19. Obesity 2020;28(7):1175-1175. https://doi.org/10.1002/oby.22842.

[34] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area.

Jama 2020;323(20):2052—9. https://doi.org/10.1001/jama.2020.6775.

[35] Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020;28(7):1195—9. https://doi.org/10.1002/oby.22831.

[36] Yates T, Razieh C, Zaccardi F, Davies J, Khunti K. Obesity and risk of COVID-19: analysis of UK Biobank. Prim Care Diabetes 2020. https://doi.org/10.1016/j.pcd.2020.05.011.

[37] GOV.UK. Overweight adults. GOV.UK; 2019 [updated 25/07/2019. Available from: https://www.ethnicity-facts-figures.service.gov.uk/health/diet-and-exercise/overweight-adults/latest#by-ethnicity-over-time.

[38] GOV.UK. Healthy eating among adults. GOV.UK; 2019 [updated 26/07/2019. Available from: https://www.ethnicity-facts-figures.service.gov.uk/health/diet-and-exercise/healthy-eating-of-5-a-day-among-adults/latest#by-ethnicity-over-time.

[39] GOV.UK. Physical inactivity. GOV.UK; 2019 [updated 14/05/2019. Available from: https://www.ethnicity-facts-figures.service.gov.uk/health/diet-and-exercise/physical-inactivity/latest#by-ethnicity.

[40] Yates T, Khunti K, Wilmot E, Brady E, Webb D, Srinivasan B, et al. Self-reported sitting time and markers of inflammation, insulin resistance, and adiposity. Am J Prev Med 2012;42(1):1—7. https://doi.org/10.1016/j.amepre.2011.09.022.

[41] Poulain M, Doucet M, Major GC, Drapeau V, Sériès F, Boulet LP, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. CMAJ (Can Med Assoc J) 2006;174(9):1293—9. https://doi.org/10.1503/cmaj.051299.

[42] Geovanini GR, Wang R, Weng J, Jenny NS, Shea S, Allison M, et al. Association between obstructive sleep apnea and cardiovascular risk factors: variation by age, sex, and race. The multi- ethnic study of atherosclerosis. Ann Am Thorac Soc 2018;15(8):970—7. https://doi.org/10.1513/AnnalsATS.201802-121OC.

[43] Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol 2013;62(7):569—76. https://doi.org/10.1016/j.jacc.2013.05.045.

[44] Kritikou I, Basta M, Tappouni R, Pejovic S, Fernandez-Mendoza J, Nazir R, et al. Sleep apnoea and visceral adiposity in middle-aged male and female subjects. Eur Respir J 2013;41(3):601—9. https://doi.org/10.1183/09031936.00183411.

[45] Yuan H, Schwab RJ, Kim C, He J, Shults J, Bradford R, et al. Relationship between body fat distribution and upper airway dynamic function during sleep in adolescents. Sleep 2013;36(8):1199—207. https://doi.org/10.5665/sleep.2886.

[46] Gonzalez H, Minville V, Delanoue K, Mazerolles M, Concina D, Fourcade O. The importance of increased neck circumference to intubation difficulties in obese patients. Anesth Analg 2008;106(4):1132—6. https://doi.org/10.1213/ane.0b013e3181679659.

[47] McSharry D, Malhotra A. Potential influences of obstructive sleep apnea and obesity on COVID-19 severity. J Clin Sleep Med 2020. https://doi.org/10.5664/jcsm.8538.

[48] Kalia HS, Gaglio PJ. The prevalence and pathobiology of nonalcoholic fatty liver disease in patients of different races or ethnicities. Clin Liver Dis 2016;20(2):215—24. https://doi.org/10.1016/j.cld.2015.10.005.

[49] Mohanty SR, Troy TN, Huo D, O'Brien BL, Jensen DM, Hart J. Influence of ethnicity on histological differences in non-alcoholic fatty liver disease. J Hepatol 2009;50(4):797—804. https://doi.org/10.1016/j.jhep.2008.11.017.

[50] Singal AK, Kamath PS. Acute on chronic liver failure in non-alcoholic fatty liver and alcohol associated liver disease. Transl Gastroenterol Hepatol 2019;4:74. https://doi.org/10.21037/tgh.2019.09.11.

[51] Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 2017;13(4):851—63. https://doi.org/10.5114/aoms.2016.58928.

[52] Antonia P, Keno B, Jakob A, Hans-Martin T, Janis V, Bernd H, et al. Obesity and COVID-19: the role of visceral adipose tissue. medRXiv 2020. https://doi.org/10.1101/2020.05.14.20101998.

[53] Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). Am J Clin Nutr 2007;86(2):353—9. https://doi.org/10.1093/ajcn/86.2.353.

[54] Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol 2010;316(2):129—39. https://doi.org/10.1016/j.mce.2009.08.018.

[55] Saddi-Rosa P, Oliveira CS, Giuffrida FM, Reis AF. Visfatin, glucose metabolism and vascular disease: a review of evidence. Diabetol Metab Syndrome 2010;2:21. https://doi.org/10.1186/1758-5996-2-21.

[56] Kim S-R, Bae Y-H, Bae S-K, Choi K-S, Yoon K-H, Koo TH, et al. Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-kappaB activation in endothelial cells. Biochim Biophys Acta 2008;1783(5):886—95. https://doi.org/10.1016/j.bbamcr.2008.01.004.

[57] Park HK, Kwak MK, Kim HJ, Ahima RS. Linking resistin, inflammation, and cardiometabolic diseases. Korean J Intern Med (Engl Ed) 2017;32(2):239—47. https://doi.org/10.3904/kjim.2016.229.

[58] Kang YE, Kim JM, Joung KH, Lee JH, You BR, Choi MJ, et al. The roles of adipokines, proinflammatory cytokines, and adipose tissue macrophages in obesity-associated insulin resistance in modest obesity and early metabolic dysfunction. PloS One 2016;11(4). https://doi.org/10.1371/journal.pone.0154003.

[59] Lippi G, Wong J, Henry BM. Hypertension in patients with coronavirus disease 2019 (COVID-19): a pooled analysis. Pol Arch Intern Med 2020;130(4):304—9. https://doi.org/10.20452/pamw.15272.

[60] Singh AK, Gupta R, Misra A. Comorbidities in COVID-19: outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. Diabetes Metab Syndr 2020;14(4):283—7. https://doi.org/10.1016/j.dsx.2020.03.016.

[61] Fan J, Wang H, Ye G, Cao X, Xu X, Tan W, et al. Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. Metabolism 2020;107:154243. https://doi.org/10.1016/j.metabol.2020.154243.

[62] Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. Circulation 2014;129(5):570—9. https://doi.org/10.1161/CIRCULATIONAHA.113.005757.

[63] Pu J, Romanelli R, Zhao B, Azar KM, Hastings KG, Nimbal V, et al. Dyslipidemia in special ethnic populations. Cardiol Clin 2015;33(2):325—33. https://doi.org/10.1016/j.ccl.2015.01.005.

[64] Balfour PC, Rodriguez CJ, Ferdinand KC. The role of hypertension in race-ethnic disparities in cardiovascular disease. Curr Cardiovasc Risk Rep 2015;9(4):18. https://doi.org/10.1007/s12170-015-0446-5.

[65] Lackland DT. Racial differences in hypertension: implications for high blood pressure management. Am J Med Sci 2014;348(2):135—8. https://doi.org/10.1097/MAJ.0000000000000308.

[66] Lip GY, Barnett AH, Bradbury A, Cappuccio FP, Gill PS, Hughes E, et al. Ethnicity and cardiovascular disease prevention in the United Kingdom: a practical approach to management. J Hum Hypertens 2007;21(3):183—211. https://doi.org/10.1038/sj.jhh.1002126.

[67] Lira F, Rosa Neto J, Antunes B, Fernandes R. The relationship between inflammation, dyslipidemia and physical exercise: from the epidemiological to molecular approach. Curr Diabetes Rev 2014;10(6). https://doi.org/10.2174/1573399810666141122210135.

[68] Miguel CD, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. Curr Hypertens Rep 2015;17(1):507. https://doi.org/10.1007/s11906-014-0507-z.

[69] Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with Coronavirus Disease 2019 (COVID-19): possible mechanisms. J Card Fail 2020;26(6):470—5. https://doi.org/10.1016/j.cardfail.2020.04.009.

[70] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.1017.

[71] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in wuhan, China. JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.0950.

[72] Yang C, Jin Z. An acute respiratory infection runs into the most common noncommunicable epidemic-COVID-19 and cardiovascular diseases. JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.0934.

[73] Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. Life Sci 2020;253:117723. https://doi.org/10.1016/j.lfs.2020.117723.

[74] Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.1105.

[75] Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med 2020. https://doi.org/10.1016/j.ajem.2020.04.048.

[76] Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378(4):345—53. https://doi.org/10.1056/NEJMoa1702090.

[77] Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 2016;1(3):274—81. https://doi.org/10.1001/jamacardio.2016.0433.

[78] Teuwen L, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol 2020;20(7):389—91. https://doi.org/10.1038/s41577-020-0343-0.

[79] Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 2017;135(5):373—87. https://doi.org/10.1111/acps.12698.

[80] Yuan N, Chen Y, Xia Y, Dai J, Liu C. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. Transl Psychiatry 2019;9:233. https://doi.org/10.1038/s41398-019-0570-y. https://www.nature.com/articles/s41398-019-0570-y.

[81] Jiménez-Fernández S, Gurpegui M, Díaz-Atienza F, Pérez-Costillas L, Gerstenberg M, Correll CU. Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta- analysis. J Clin Psychiatr 2015;76(12):1658—67. https://doi.org/10.4088/JCP.14r09179.

[82] Liu T, Zhong S, Liao X, Chen J, He T, Lai S, et al. A meta-analysis of oxidative stress markers in depression. PloS One 2015;10(10). https://doi.org/10.1371/journal.pone.0138904.

[83] Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BWJH. Is depression associated with increased oxidative stress? A systematic review and meta-

analysis. Psychoneuroendocrinology 2015;51:164–75. https://doi.org/10.1016/j.psyneuen.2014.09.025.

[84] O'Donovan A, Neylan TC, Metzler T, Cohen BE. Lifetime exposure to traumatic psychological stress is associated with elevated inflammation in the heart and soul study. Brain Behav Immun 2012;26(4):642–9. https://doi.org/10.1016/j.bbi.2012.02.003.

[85] Williams DR. Stress and the mental health of populations of color: advancing our understanding of race-related stressors. J Health Soc Behav 2018;59(4):466–85. https://doi.org/10.1177/0022146518814251.

[86] Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta- analytic study of 30 Years of inquiry. Psychol Bull 2004;130(4):601–30. https://doi.org/10.1037/0033-2909.130.4.601.

[87] Memon A, Taylor K, Mohebati LM, Sundin J, Cooper M, Scanlon T, et al. Perceived barriers to accessing mental health services among black and minority ethnic (BME) communities: a qualitative study in Southeast England. BMJ open 2016;6(11):e012337. https://doi.org/10.1136/bmjopen-2016-012337.

[88] Mantovani N, Pizzolati M, Edge D. Exploring the relationship between stigma and help- seeking for mental illness in African-descended faith communities in the UK. Health Expect 2017;20(3):373–84. https://doi.org/10.1111/hex.12464.

[89] Haynes TF, Cheney A, Sullivan G, Bryant K, Curran G, Olson M, et al. Addressing mental health needs: perspectives from african Americans living in the rural south. Psychiatr Serv 2017;68(6):573–8. https://doi.org/10.1176/appi.ps.201600208.

[90] Ward E, Wiltshire JC, Detry MA, Brown RL. African American men and women's attitude toward mental illness, perceptions of stigma, and preferred coping behaviors. Nurs Res 2013;62(3):185–94. https://doi.org/10.1097/NNR.0b013e31827bf533.

[91] Youman K, Drapalski A, Stuewig J, Bagley K, Tangney J. Race differences in psychopathology and disparities in treatment seeking: community and jail-based treatment seeking patterns. Psychol Serv 2010;7(1):11–26. https://doi.org/10.1037/a0017864.

[92] Barnett P, Mackay E, Matthews H, Gate R, Greenwood H, Ariyo K, et al. Ethnic variations in compulsory detention under the Mental Health Act: a systematic review and meta-analysis of international data. Lancet Psyc 2019;6(4):305–17. https://doi.org/10.1016/S2215-0366(19)30027-6.

[93] GOV.UK. The lammy review. GOV.UK; 2017 [updated 08/09/2017. Available from: https://www.gov.uk/government/publications/lammy-review-final-report.

[94] Blair C, Raver CC. Poverty, stress, and brain development: new directions for prevention and intervention. Acad Pediatr 2016;16(3 Suppl):S30–6. https://doi.org/10.1016/j.acap.2016.01.010.

[95] Sturgeon JA, Arewasikporn A, Okun MA, Davis MC, Ong AD, Zautra AJ. The psychosocial context of financial stress: implications for inflammation and psychological health. Psychosom Med 2016;78(2):134–43. https://doi.org/10.1097/PSY.0000000000000276.

[96] Ziol-Guest KM, Duncan GJ, Kalil A, Boyce WT. Early childhood poverty, immune-mediated disease processes, and adult productivity. Proc Natl Acad Sci U S A 2012;109(Suppl 2):17289–93. https://doi.org/10.1073/pnas.1203167109.

[97] ONS. Deaths involving COVID-19 by local area and socioeconomic deprivation: deaths occurring between 1 March and 17 April 2020:. Office for National Statistics; 2020 [updated 1/05/2020; cited 2020 05/05/2020]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingcovid19bylocalareasanddeprivation/deathsoccurringbetween1marchand17april.

[98] ONS. Ethnicity pay gaps in great britain: 2018. Office for National Statistics; 2019 [updated 09/07/2019; cited 2020 09/05/2020]. Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/articles/ethnicitypaygapsingreatbritain/2018.

[99] GOV.UK. Overcrowded households. GOV.UK; 2018 [updated 27/04/2019. Available from: ethnicity-facts-figures.service.gov.uk/housing/housing-conditions/overcrowded-households/latest.

[100] GOV.UK. Regional ethnic diversity. GOV.UK; 2018 [updated 11/07/2019. Available from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest#full-page-history.

[101] Clair A, Hughes A. Housing and health: new evidence using biomarker data. J Epidemiol Community Health 2019;73(3):256–62. https://doi.org/10.1136/jech-2018-211431.

[102] Mangrio E, Zdravkovic S. Crowded living and its association with mental ill-health among recently-arrived migrants in Sweden: a quantitative study. BMC Res Notes 2018;11:609. https://doi.org/10.1186/s13104-018-3718-6.

[103] Quinn K, Kaufman JS, Siddiqi A, Yeatts KB. Stress and the city: housing stressors are associated with respiratory health among low socioeconomic status chicago children. J Urban Health 2010;87(4):688–702. https://doi.org/10.1007/s11524-010-9465-1.

[104] Cook T, Kursumovic E, Lennane S. Exclusive: deaths of NHS staff from covid-19 analysed Health Service Journal. 2020. Available from: https://www.hsj.co.uk/exclusive-deaths-of-nhs-staff-from-covid-19-analysed/7027471.article.

[105] GOV.UK. NHS workforce. GOV.UK; 2020. updated 06/01/2020. Available from: https://www.ethnicity-facts-figures.service.gov.uk/workforce-and-business/workforce-diversity/nhs-workforce/latest.

[106] Wilkinson E. UK NHS staff: stressed, exhausted, burnt out. Lancet 2015;385(9971):841–2. https://doi.org/10.1016/S0140-6736(15)60470-6.

[107] NHS. Workforce race equality standard data reporting – 2019. NHS England; 2020 [updated 13/02/2020. Available from: https://www.england.nhs.uk/publication/workforce-race-equality-standard-data-reporting-2019.

[108] Tsai YC, Liu CH. Factors and symptoms associated with work stress and health-promoting lifestyles among hospital staff: a pilot study in Taiwan. BMC Health Serv Res 2012;12:199. https://doi.org/10.1186/1472-6963-12-199.

[109] Rao JV, Chandraiah K. Occupational stress, mental health and coping among information technology professionals. Indian J Occup Environ Med 2012;16(1):22–6. https://doi.org/10.4103/0019-5278.99686.

[110] ONS. Coronavirus (COVID-19) related deaths by occupation, England and wales: deaths registered up to and including 20 april 2020. Office for National Statistics; 2020 [updated 11/05/2020; cited 2020 16/05/2020]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/coronaviruscovid19relateddeathsbyoccupationenglandandwales/deathsregistereduptoandincluding20april2020#overview-of-coronavirus-related-deaths-by-occupation.

[111] Norrie R. The two sides OF diversity: which are the most ethnically diverse occupations? Policy Exchange [updated March 2017; cited 2020 16/05/2020]. Available from: https://policyexchange.org.uk/wp-content/uploads/2017/03/The-two-sides-of-diversity-2.pdf; 2017.

[112] Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2020;5(3):243–51. https://doi.org/10.1038/nri1571.

[113] Ma K, Zhang H, Baloch Z. Pathogenetic and therapeutic applications of tumor necrosis factor-α (TNF-α) in major depressive disorder: a systematic review. Int J Mol Sci 2016;17(5). https://doi.org/10.3390/ijms17050733.

[114] Kopschina Feltes P, Doorduin J, Klein HC, Juárez-Orozco LE, Dierckx RA, Moriguchi-Jeckel CM, et al. Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. J Psychopharmacol 2017;31(9):1149–65. https://doi.org/10.1177/0269881117711708.

[115] Kalmbach DA, Anderson JR, Drake CL. The impact of stress on sleep: pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. J Sleep Res 2018;27(6):e12710. https://doi.org/10.1111/jsr.12710.

[116] Vermeulen-Smit E, Have M, Laar M, De Graaf R. Clustering of health risk behaviours and the relationship with mental disorders. J Affect Disord 2015;15(171):111–9. https://doi.org/10.1016/j.jad.2014.09.031.

[117] Kiecolt-Glaser JK. Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. Psychosom Med 2010;72(4):365–9. https://doi.org/10.1097/PSY.0b013e3181dbf489.

[118] You T, Arsenis N, Disanzo B, Lamonte M. Effects of exercise training on chronic inflammation in obesity : current evidence and potential mechanisms. Sports Med 2013;43(4). https://doi.org/10.1007/s40279-013-0023-3.

[119] Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. Best Pract Res Clin Endocrinol Metabol 2010;24(5):775–84. https://doi.org/10.1016/j.beem.2010.08.014.

[120] Wang T, Fu H, Kaminga AC, Li Z, Guo G, Chen L, et al. Prevalence of depression or depressive symptoms among people living with HIV/AIDS in China: a systematic review and meta-analysis. BMC Psychiatr 2018;18(160). https://doi.org/10.1186/s12888-018-1741-8.

[121] Shen TC, Wang CY, Lin CL, Liao WC, Chen CH, Tu CY, et al. People with tuberculosis are associated with a subsequent risk of depression. Eur J Intern Med 2014;25(10):936–40. https://doi.org/10.1016/j.ejim.2014.10.006.

[122] Dhar AK, Barton DA. Depression and the link with cardiovascular disease. Front Psychiatr 2016;7(33). https://doi.org/10.3389/fpsyt.2016.00033.

[123] Razieh C, Khunti K, Davies MJ, Edwardson CL, Henson J, Darko N, et al. Association of depression and anxiety with clinical, sociodemographic, lifestyle and environmental factors in South Asian and white European individuals at high risk of diabetes. Diabet Med : J Brt Diabetic Assoc 2019;36(9):1158–67. https://doi.org/10.1111/dme.13986.

[124] Hargreaves S, Seedat F, Car J, Escombe R, Hasan S, Eliahoo J, et al. Screening for latent TB, HIV, and hepatitis B/C in new migrants in a high prevalence area of London, UK: a cross-sectional study. BMC Infect Dis 2014;14:657. https://doi.org/10.1186/s12879-014-0657-2.

[125] Harris RJ, Ramsay M, Hope VD, Brant L, Hickman M, Foster GR, et al. Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis. Eur J Publ Health 2020;22(2):187–92. https://doi.org/10.1093/eurpub/ckr083.

[126] GOV.UK. HIV in the United Kingdom. GOV.UK; 2020 [updated 17/01/202016/05/2020]. Available from: https://www.gov.uk/government/publications/hiv-in-the-united-kingdom.

[127] Eborall H, Wobi F, Ellis K, Willars J, Abubakar I, Griffiths C, et al. Integrated screening of migrants for multiple infectious diseases: qualitative study of a city-wide programme. EClinic Med 2020;21. https://doi.org/10.1016/j.eclinm.2020.100315.

[128] Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. Eur Respir Rev 2018;27(147). https://doi.org/10.1183/16000617.0077-2017.

[129] Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and

meta-analysis. J Infect 2020;80(6):656–65. https://doi.org/10.1016/j.jinf.2020.03.041.

[130] Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis 2011;53(11):1120–6. https://doi.org/10.1093/cid/cir627.

[131] Schouten J, Wit FW, Stolte IG, Kootstra NA, van der Valk M, Geerlings SE, et al. Cross- sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis 2014;59(12):1787–97. https://doi.org/10.1093/cid/ciu701.

[132] Härter G, Spinner CD, Roider J, Bickel M, Krznaric I, Grunwald S, et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. Infection 2020:1–6. https://doi.org/10.1007/s15010-020-01438-z.

[133] Zampino R, Marrone A, Restivo L, Guerrera B, Sellitto A, Rinaldi L, et al. Chronic HCV infection and inflammation: clinical impact on hepatic and extra-hepatic manifestations. World J Hepatol 2013;5(10):528–40. https://doi.org/10.4254/wjh.v5.i10.528.

[134] Toossi Z. The inflammatory response in Mycobacterium tuberculosis infection. Arch Immunol Ther Exp 2000;48(6). https://pubmed.ncbi.nlm.nih.gov/11197606/.

[135] Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity 2013;39(4):633–45. https://doi.org/10.1016/j.immuni.2013.10.001.

[136] Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure. https://doiorg/101056/NEJMoa2020283; 2020.

[137] Nedelec Y, Sanz J, Baharian G, Szpiech ZA, Pacis A, Dumaine A, et al. Genetic ancestry and natural selection drive population differences in immune responses to pathogens. Cell 2016;167(3):657–69. https://doi.org/10.1016/j.cell.2016.09.025. e21.

[138] Yeyeodu ST, Kidd LR, Kimbro KS. Protective innate immune variants in racial/ethnic disparities of breast and prostate cancer. Cancer Immunol Res 2019;7(9):1384–9. https://doi.org/10.1158/2326-6066.CIR-18-0564.

[139] Paalani M, Lee JW, Haddad E, Tonstad S. Determinants of inflammatory markers in a Bi- ethnic population. Ethn Dis 2011;21(2):142–9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3427005/.

[140] Roy NBA, Telfer P, Eleftheriou P, de la Fuente J, Drasar E, Shah F, et al. Protecting vulnerable patients with inherited anaemias from unnecessary death during the COVID-19 pandemic. Br J Haematol 2020;189(4):635–9. https://doi.org/10.1111/bjh.16687.

[141] ONS. Coronavirus (COVID-19) related deaths by ethnic group, England and wales: 2 march 2020 to 10 april 2020. Office for National Statistics; 2020 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelateddeathsbyethnicgroupenglandandwales/2march2020to10april2020.

[142] Conran N, Belcher JD. Inflammation in sickle cell disease. Clin Hemorheol Microcirc 2018;68(2–3):263–99. https://doi.org/10.3233/CH-189012.

[143] Cappuccio FP, Duneclift SM, Atkinson RW, Cook DG. Use of alternative medicines in a multi- ethnic population. Ethn Dis 2001;11(1):11–8. https://pubmed.ncbi.nlm.nih.gov/11289231/.

[144] BMJ. Coronavirus disease 2019 (COVID-19) - emerging treatments BMJ best practise. British Medical Journal; 2020 [Available from: https://bestpractice.bmj.com/topics/en-gb/3000168/emergingtxs.