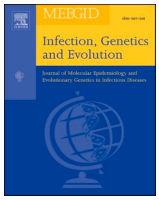
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Infection, Genetics and Evolution 103 (2022) 105338

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid



Review

The sex and gender dimensions of COVID-19: A narrative review of the potential underlying factors

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ARTICLE INFO

Keywords:
COVID-19
Gender disparities
Risk factors
Biological difference
Sociocultural effects

ABSTRACT

Multiple lines of evidence indicate that the male sex is a significant risk factor for severe disease and mortality due to coronavirus disease 2019 (COVID-19). However, the precise explanation for the discrepancy is currently unclear. Immunologically, the female-biased protection against COVID-19 could presumably be due to a more rapid and robust immune response to viruses exhibited by males. The female hormones, e.g., estrogens and progesterone, may have protective roles against viral infections. In contrast, male hormones, e.g., testosterone, can act oppositely. Besides, the expression of the ACE-2 receptor in the lung and airway lining, which the SARS-CoV-2 uses to enter cells, is more pronounced in males. Estrogen potentially plays a role in downregulating the expression of ACE-2, which could be a plausible biological explanation for the reduced severity of COVID-19 in females. Comorbidities, e.g., cardiovascular diseases, diabetes, and kidney disorders, are considered significant risk factors for severe outcomes in COVID-19. Age-adjusted data shows that males are statistically more predisposed to these morbidities—amplifying risks for males with COVID-19. In addition, many sociocultural factors and gender-constructed behavior of men and women impact exposure to infections and outcomes. In many parts of the world, women are more likely to abide by health regulations, e.g., mask-wearing and handwashing, than men. In contrast, men, in general, are more involved with high-risk behaviors, e.g., smoking and alcohol consumption, and high-risk jobs that require admixing with people, which increases their risk of exposure to the infection. Overall, males and females suffer differently from COVID-19 due to a complex interplay between many biological and sociocultural factors.

1. Introduction

Understanding the degree to which outbreaks of infectious diseases affect people across sex, gender, ethnicity, race, and age distinctively is a fundamental step to understanding the primary and secondary effects of any health emergency (Wenham et al., 2020). Such knowledge is also vital for creating equitable and effective mitigation strategies. The response to the 'once in a century' outbreak of coronavirus disease 2019 (COVID-19) is no different (Wenham et al., 2020; Gates, 2020). Sex-disaggregated infection and mortality data of COVID-19 do not explicitly show whether people of different socio-demographic backgrounds, especially across biological sex and gender, are more likely to become infected. However, existing data indicate that biology and gender norms shape the disease burden differently between males and females (Pinheiro et al., 2020; Jin et al., 2020; Liu et al., 2017). Emerging evidence hints that COVID-19 results in more adverse effects on males than females. This could be related to intrinsic differences imparted by the males and females, specific characteristics of the SARS-CoV-2 infectious process, or gender norms (Klein and Flanagan, 2016a; Gebhard et al., 2020; Spagnolo et al., 2020). Nevertheless, currently available data are still inadequate to draw any conclusions on the gendered effects of COVID-19 (Global Health 50/50, 2022).

Biological sex and gender differences are directly associated with epidemiology, symptoms, and management of diseases and hence are essential concepts in the comprehensive study of public health (van Hagen et al., 2021; Lips, 2020). Sex is the biological construct depending

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https://doi.org/10.1016/j.meegid.2022.105338
Received 28 March 2022; Received in revised form 5 July 2022; Accepted 9 July 2022
Available online 18 July 2022

on the genetic, reproductive, and endocrine organization that differentiates between males and females. As human response toward pathogens is strongly influenced by their genetic, immunological, and hormone systems, the sex difference results in disparity in how males and females are affected by the condition these pathogens cause. On the other hand, gender is the continuum of socially constructed roles, behaviors, expressions, and identities of men, women, and gender-diverse people. Gender norms impact how men or women are exposed to certain pathogens, especially when it comes to infectious diseases, and thus can cause differences in how men and women are susceptible to diseases. Sex (i.e., males and females) and gender (i.e., men and women) are inherently intertwined and entangled in complex ways, shaping how we respond to pathogens and the diseases caused by them (Springer et al., 2012).

Experience from previous outbreaks of infectious diseases shows that sex and gender differences, along with other socio-demographic factors, affect males/men and females/women differently (Mauvais-Jarvis et al., 2020; Ingersoll, 2017; vom Steeg and Klein, 2016). COVID-19, similarly, emphasizes the gendered nature of the risk that predominantly male/men individuals incur, conceivably due to sex-based physiological and immunological differences, e.g., X-linked immunity genes, sex hormone influenced immune cell function, and gendered variations, e.g., tobacco smoking and alcoholism (Wenham et al., 2020; Takahashi et al., 2020; Scully et al., 2020). Unfortunately, the interaction between biological sex and corresponding gender norms, sex-biased susceptibility to pathogens, and the direct gendered impacts remain among the underexplored topics in current public health and medicine. Efforts do not focus much on the interaction between sex and gender roles and exposure to pathogens or direct gendered impacts (Wenham et al., 2020; Muurlink and Taylor-Robinson, 2020; Smith, 2019; Klein and Flanagan, 2016b). Studies on sex and gender differences would critically shape our current understanding of vaccine and therapeutic strategy development, optimization, and administration. They can potentially fill the gap in the traditional therapeutic approach. Also, it will promote gender-specific management of post-traumatic stress symptoms (Spagnolo et al., 2020).

It has been repeatedly reported that the infection, hospitalization, and mortality rate due to COVID-19 are higher among males/men (Wenham et al., 2020; Global Health 50/50, 2022). However, there is a dearth of studies on the underlying factors precisely responsible for such differences. The socio-demographic, genetic, physiological, immunological, and cultural practice-related differences among males/men and females/women potentially have a strong influence on the sex- and gender-biased variation of COVID-19 related burden, and there has been a push to dig deeper into the pandemic's differential impacts. A clear understanding of the interaction of age, sex, gender, and risk factors, including genetic epidemiology and epigenetics, would unequivocally allow public health authorities to tailor their management strategies to better serve the people at most risk. In this write-up, we shed light upon the possible biological and physiological backgrounds and cultural norms related to the differential dimensions of COVID-19. While we recognize that gender is not a binary identity, this manuscript focused only on men and women as it sought to drill into how biological sex (male and female) and their corresponding gender (man and woman) cooperates and results in the disproportionate impact of COVID-19 in the males and females.

2. Difference in COVID-19 infection rate and mortality varies markedly by sex, gender, and age

Institutionalized gender and culturally established roles and norms play roles in determining who is most at risk of acquiring an infection or receiving a test. To date, many studies have indicated that sex and gender potentially influence infectious disease risk and outcomes. Looking at the publicly available data on sex-disaggregated case identification rates and death rates, COVID-19 appears to be no exception as males seem more disadvantaged to it. According to the global health 50/50's data, males' global case identification rate and share in the death toll due to COVID-19 are ~40% and ~ 60% higher, respectively, compared to their female counterparts (Global Health 50/50, 2022). Likewise, the proportion of death in confirmed cases is also significantly higher among males (Fig. 1). These data indicate that institutionalized gender inequality is associated with the male to female ratio of reported cases of COVID-19 across the world.

Also, data from other sources show that the death rate is not equal across sex-disaggregated age groups (Fig. 1). There was some variation across countries, although roughly, the pattern was comparable, and often the population sizes were not large enough to draw a concrete conclusion at a country-specific level (Global Health 50/50, 2022). Besides, pre-existing conditions that put patients at higher risk of dying from a COVID-19 infection include cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension, and cancer, usually affecting older people and affecting males and females differently (Fig. 1).

3. Sex difference due to immunity

Male and female responds differently against viral infections (Fig. 2). Innate biological factors, e.g., genetic, epigenetic, and hormonal factors, help females exhibit a stronger immunity against these infections (Klein and Flanagan, 2016b; Klein, 2012). Components of the cellular and extracellular systems also contribute to a stronger immunity against a vast array of pathogens.

Humans, like other multicellular eukaryotes, the initial defense against pathogens is mediated by a diverse class of ubiquitous molecules called antimicrobial peptides (AMPs). AMPs are 10–100 residue long positively charged peptides with potent antibacterial, antifungal, and especially antiviral activities, expressed by the epithelial and professional host defense cells, e.g., macrophages or neutrophils (McCann et al., 2003). LL37, a cationic peptide derived from cathelicidin, is such an AMP that creates pores on coronavirus envelope protein and causes the virus to be destroyed (Steinstraesser et al., 2005). Vitamin D is a fat-soluble essential vitamin that upregulates AMP synthesis by regulating the NF-kB signaling pathway (Subramanian et al., 2017). This vitamin helps reduce microbial infections by generating physical barriers and boosting natural immunity and adaptive immunity (Beard et al., 2011; Abhimanyu, 2017; Rondanelli et al., 2018). Several meta-analyses generated from a considerable number of observational and clinical trial studies have indicated that vitamin D deficiency is associated with greater severity of COVID-19; however, a recent Mendelian randomization study did not observe evidence to support the association (Butler-Laporte et al., 2021; Wang et al., 2021; Liu et al., 2021; Szarpak et al., 2021). It was also reported that the serum levels of vitamin D were consistently lower in males than females, especially in older ages (Sanghera et al., 2017; Orwoll et al., 2009; Mosekilde, 2005; La Vignera et al., 2020). These indicate the synthesis of antimicrobial peptide LL37 is comparatively higher in females, which might protect females from viral infection (Sanghera et al., 2017; La Vignera et al., 2020). In addition, the elevated vitamin D level may also help the females to suppress the inflammatory cytokines, leukocyte infiltration, interaction with polymorphonuclear leukocytes, complement component C3, and enhance serological response and $CD8^+$ T cell performance after being infected by SARS-CoV-2 (Teymoori-Rad et al., 2019; Grant et al., 2020; Xu et al., 1993; Risitano et al., 2020; Zheng et al., 2020; Diao, 2020). When viruses breach the initial AMP mediated defense mechanism, innate immune cells, e.g., neutrophils, and alveolar macrophages, are recruited in the infectious site. It has been reported that females have more dendritic cells (DCs), neutrophils, monocytes, and macrophages (Klein and Flanagan, 2016b). Also, phagocytic cells exhibit more vigorous activity in females (Spitzer, 1999). The DCs serve as a bridge between innate and adaptive immunity and function as an antigen-presenting cell. They promote the antigen-presenting capacity of adaptive immune cells, which is also reported to function better in females (Weinstein et al., 1984).

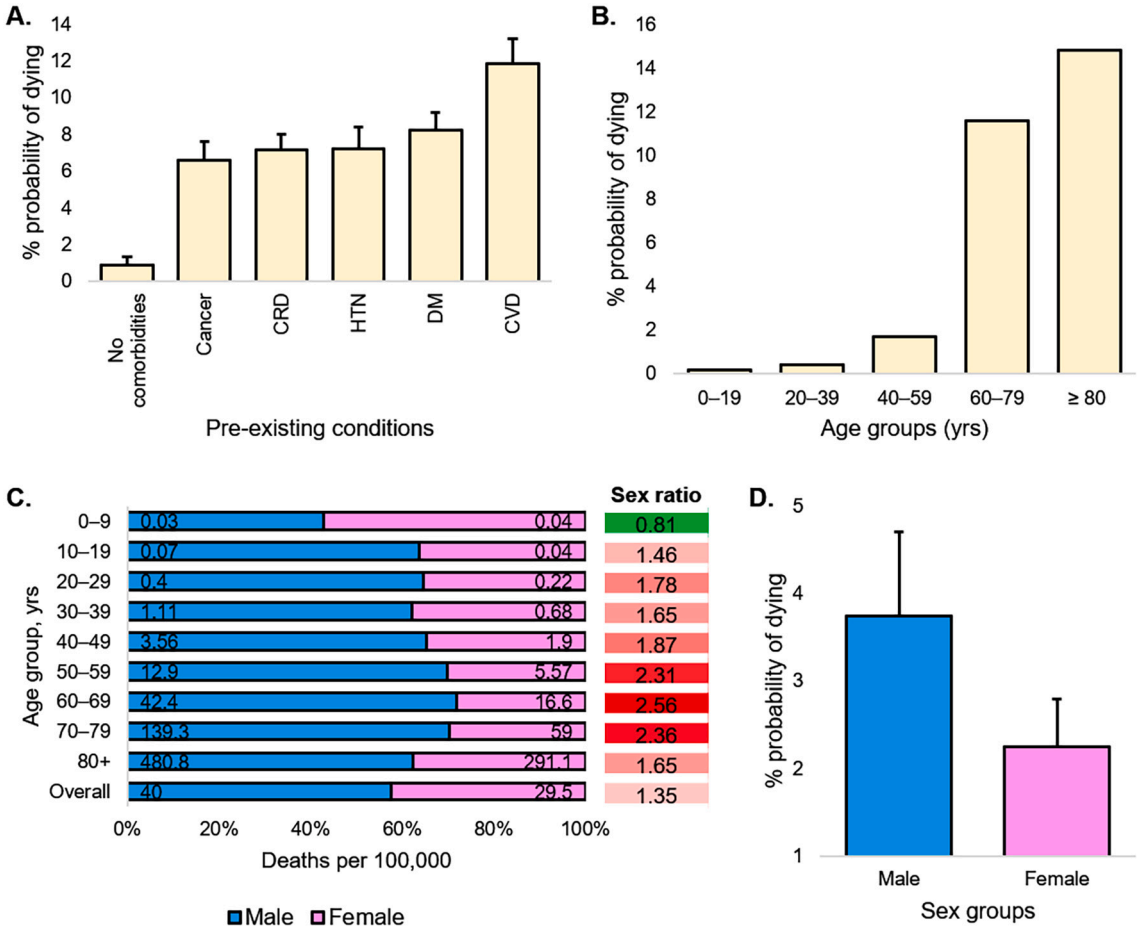


Fig. 1. Age, sex, existing conditions of COVID-19 cases and deaths. (***a***) Percent probability of dying for a patient with a given pre-existing condition. (***b***) Percent probability of dying depending on the age group. (***c***) In 10-year age bands by sex, deaths per 100,000 population and sex ratio. (***d***) Percent probability of dying for a patient by sex. *Death rate* $= \frac{No.\ of\ deaths}{No.\ of\ cases} = probability\ of\ dying\ wheninfected\ by\ the\ virus$ (%). *The* percentages shown in panels a, b, and d do not add up to 100%, as they do not represent share of deaths by condition. CRD = chronic respiratory diseases, HTN = hypertension, DM = diabetes, CVD = cardiovascular disorders.

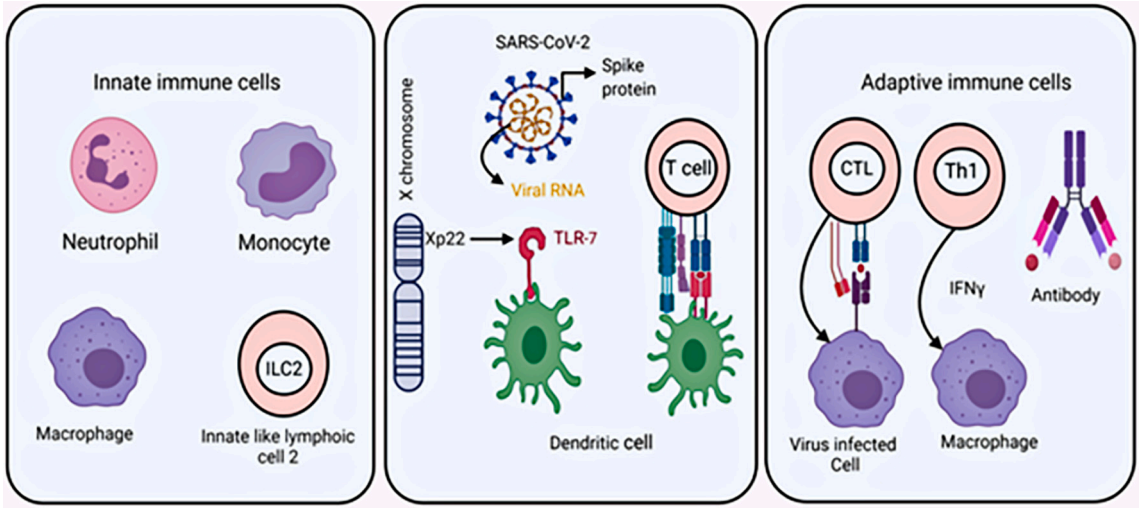


Fig. 2. A partial overview of the immune system. Left panel: innate immune cells, middle: dendritic cell (DC) as a sensor cell, it recognizes virus RNA through PRR and DC act as antigen-presenting cell, found higher in the females, right panel: Cytotoxic T cell (CTL), Th1 can kill virus-infected cells present higher in female and basal antibody is also higher.

The innate immune cells, macrophages, and dendritic cells express pattern recognition receptors (PRRs), e.g., toll-like receptors 7 and 8 (TLR-7 and TLR-8), and act as sensor cells. Using these PRRs, they recognize molecular patterns present on the pathogens, e.g., bacterial lipopolysaccharide and viral genetic material. The expression of TLR-7 and TLR-8 is prominent in plasmacytoid DCs, and myeloid lineage

cells, and they both can recognize single-strand RNA viruses (Diebold et al., 2004; Boehme and Compton, 2004). It is reported that plasmacytoid DCs expressing TLR-7 produces type 1 interferon against the influenza virus (Kaisho and Akira, 2006; Di Domizio et al., 2009). The expression of PRRs varies from male to female due to genetic differences (Berghöfer et al., 2006; Marriott and Huet-Hudson, 2006). Interestingly, studying several viral diseases, Klein et al. 2010 found ten times more interferon I responses in cell lines obtained from the females (Klein et al., 2010). The gene coding for TLR-7 is present in the X-chromosome, and as females have an additional copy of the X-chromosome than males, it provides them a female with more TLR-7 mediated immune response. This additional copy of the X-chromosome usually becomes condensed and forms an inactive Barr body to maintain proper gene dose in the females (Barr and Bertram, 1949). During the inactivation process, 10% of genes located in the non-recombinant region escape inactivation. It is reported that TLR-7 escapes the X-chromosome inactivation mechanism (Schurz et al., 2019). The inactivation of the X-chromosome's escaped genes compensates for any mutational loss in other chromosomes. Other than TLR-7, X-chromosomes contain nearly 60 immune genes, contributing to their better immunity against many pathogens (Tukiainen et al., 2017).

Innate-like lymphoid cells (ILC) originates from lymphoid progenitor also show a sex-biased response. There are three types of ILCs, such as ILC1, ILC2, ILC3, and these are prominent in the lung (De Grove et al., 2016). These ILCs recognize pathogens and provide signals to other immune cells to release cytokines. Interleukin-13 (IL-13), produced from ILC-2, has a protective role in influenza-induced lung infection in mice (Monticelli et al., 2011). The presence of an elevated number of ILC-2 cells was previously reported in female murine lung models, indicating the potential role of ILC-2 in female immunity (Cephus et al., 2017). Also, recently reported studies on human subjects suggested an age- and sex-dependent reduction in ILC-2 cell numbers in individuals over 10 years of age, and adult females, in general, possess more ILC-2 than males (Darboe et al., 2020).

The adaptive immune system also functions better in females. The females express more $CD3^+$ and $CD4^+$ T cells, which are the primary components of cellular immunity. Several clinical studies have shown that the ratio of $CD4^+$ to $CD8^+$ T cells is higher in females. The T helper 1 cell-, anti-inflammatory T helper 2 cell-, and regulatory T cell-mediated response are lower in males (Frisancho-Kiss et al., 2007). Additionally, the cytotoxic T cell level and the expression of antiviral and proinflammatory genes are higher in females due to their estrogen response element in the promoter region (Hewagama et al., 2009). The humoral immunity, basal immunoglobulin, and antibody response to viruses are higher in females (Abdullah et al., 2012; Teixeira et al., 2011).

Sex hormones, the environmental factors, can also regulate immune cells and upregulate lymphocytes, macrophages, and dendritic cells. Carreras et al. 2008 showed that dendritic cell differentiation could be stimulated by estradiol (Carreras et al., 2008). Estradiol binds with specific receptors expressed in the immune cells. It activates the NF-kB signaling pathway and interferon regulatory factors that modulate cytokine and chemokine production (Carreras et al., 2010). Estrogen, abundant in females, can foster innate and adaptive immunity, and, oppositely, testosterone, prominent in males, suppresses the immune response (Bartz et al., 2020). Robinson and colleagues reported that estrogen stimulates higher T cell response in female murine models (Robinson et al., 2014). Also, estrogen contributes to vasodilation and inhibition of viral replication by promoting the catalysis of nitric oxide (NO) from L-arginine (Wink et al., 2011; Rimmelzwaan et al., 1999). Estrogen activates the estrogen receptor, which helps initiate the transcription of the *eNOS* gene by binding to the estrogen response element in the gene's promoter, therefore contributing to the generation of NO (Wink et al., 2011; MacRitchie et al., 1997). The impact of estrogen on NO may provide an additional layer of defense against COVID-19. Besides, the testosterone level decreases with age, and the hormone deficiency upregulates the inflammatory cytokine level, e.g., TNF-α, IL1β, IL2 (Musabak et al., 2003; Bobjer et al., 2013). This might be another possible explanation of higher mortality due to COVID-19 among the older males, compared to the females of the same age group.

Growing evidence suggests that non-coding RNAs can also regulate the immune system. The expression of microRNA and long non-coding RNA varies from female to male. Viral microRNAs, for instance, modulate immune evasion and maintain chronic infection and viral diseases (Mishra et al., 2020). The X-chromosome contains nearly 10% microRNA of the human genome, whereas the Y-chromosome contains only two microRNAs. MicroRNAs are known to modulate antiviral immunity during viral infection. The X-chromosome inactivation escape might play a role in microRNA-mediated immune regulation. Besides, the immune system can also be influenced by host genetics like allelic polymorphism and copy number variation (CNV). Human leukocyte antigen (HLA) encodes MHC class I and class II molecular and other essential factors vital for antigen presentation. These HLA alleles are highly polymorphic and reported critical factors in disease severity. A recent study by Nguyen et al. 2020 also suggests that HLA polymorphism is responsible for COVID-19 severity (Nguyen et al., 2020). In addition, growing evidence indicates that CNV is associated with the pathogenesis of SARS-CoV disease (Manry and Quintana-Murci, 2013; Wang et al., 2014). A genetic variant of TLR-7 with impaired interferon I and interferon II response are reported for severe COVID-19 male patients (van der Made et al., 2020).

A couple of recent studies have explored the sex difference in immune responses to SARS-CoV-2 infection and predictors of disease progression, endeavoring to illustrate the underlying mechanism for why males are disproportionately affected by COVID-19 (Takahashi et al., 2020; Ursin et al., 2020; Lieberman et al., 2020). These reports provide evidence that males infected with SARS-CoV-2 develop elevated levels of innate immune cytokines, e.g., IL-8 and IL-18, along with robust induction of non-classical monocytes. Females infected with the virus, on the other hand, present an elevated level of activated $CD38^+$HLA-DR^+ and terminally differentiated PD-1^+TIM-3^+ T cells, enabling a more robust T-cell mediated immune reaction. Also, the poor T cell response is associated with worse disease outcomes of COVID-19 in the males but not in the females (Takahashi et al., 2020). RNA sequencing data from COVID-19 infected individuals identified at least 19 genes' expressions that could be attributed to SARS-CoV-2 infection (Lieberman et al., 2020). Expressions of these genes are related to the activities of B-cell, natural killer cell-activating receptors, and inhibitors of NF-κB signaling in males (Lieberman et al., 2020). Circulating autoantibodies neutralizing IFN-α and/or IFN-ω are detectable in one out of every seven patients who experience a severe disease outcome (Bastard et al., 2020). Strikingly, 94% of these patients were male (Bastard et al., 2020). The disproportionate presence of these neutralizing IgG autoantibodies in males suggests another possible mechanism for the observed male bias in severe outcomes of COVID-19 (Ursin et al., 2020; Bastard et al., 2020).

4. Role of sex hormone in virus entry

The spike protein of SARS-CoV-2 attaches to the human angiotensin-converting enzyme 2 (ACE2) receptor—resulting in the receptor's downregulation and ultimately impairing the renin-angiotensin system and potentially leading to acute respiratory problems (Hoffmann et al., 2020; Glowacka et al., 2010). Reports suggest that ACE2 expression in pneumocytes was higher in males than in females (Song et al., 2020; Salah and Mehta, 2021). Estradiol, a major female sex hormone, presumably regulates ACE2 expression in airway epithelial cells, kidneys, cardiac, and adipose tissues (Stelzig et al., 2020; Gupte et al., 2012; Dalpiaz et al., 2015). The polymorphism of the *ACE2* gene correlates with diabetes mellitus, cerebral stroke, and hypertension—a plausible reason these patients carry elevated risk due to COVID-19 (Fang et al., 2020). Other than the ACE2 receptor, SARS-CoV-2 requires another serine protease, transmembrane serine protease 2 (TMPRSS2), to enter

the airway epithelial cells [52]. TMPRSS2, primarily expressed in the airway epithelial cells, primes the spike protein followed by androgenic ligands and androgen receptor-regulated transcription of *TMPRSS2* (Tomlins et al., 2005; Ko et al., 2015). The transcription of TMPRSS2 is directly regulated by the androgen receptors (AR) (Lucas et al., 2014). Located on the long arm of the X-chromosome, ARs function as steroid hormones and activated transcription factors in humans. Because females have two copies of the X-chromosome, they may have better regulation systems for TMPRSS2 than males with only one copy of the chromosome (Mjaessab et al., 2020; Brown et al., 1989). Besides, the expression of ARs is low in prepubertal stages, which may explain the low incidence of severe COVID-19 infection in children (Roehrborn et al., 1987; Kashon et al., 1995). On the other hand, the weaker TMRPSS2 regulation in males resulting in the stronger receptor priming might be a plausible reason for COVID-19's progression going worse and contributing to an elevated mortality rate (Gebhard et al., 2020). Also, the male hormone testosterone helps the upregulation of TMPRSS2 and promotes viral entry (Fig. 3). This hypothesis is strengthened by higher hospitalization among bald males due to COVID-19, as androgenetic alopecia (APA; male-pattern baldness) is induced by hyperactivated androgenic receptors (Wambier and Goren, 2020; Goren et al., 2020). Sexual dimorphism in ACE2 and TMPRSS2 expression likely guides the clinical progression of COVID-19 (Wray and Arrowsmith, 2021).

5. Role of age

The case fatality rate due to COVID-19 is higher among older individuals than middle age and young adults. Human metabolism and body composition change with aging; insulin resistance, growth, and sex hormones depreciate over time (Barzilai et al., 2012). A recent study has reported that D-dimer, immune-related metabolic index, and neutrophil to lymphocyte ratio are several risk factors for COVID-19 (Zhao et al., 2021). They also found that interferon atmotherapy and activity of metabolic pathways are associated with elderly patients' survival (Zhao et al., 2021; Lipkowitz and Navarra, 2002). Similarly, aged people are vulnerable to other infectious diseases, e.g., influenza. The worst influenza outcome is reported in older adults having comorbidities, including coronary complications and pneumonia (Keilich et al., 2019). Studies indicate that several types of malignancies, e.g., lung cancer, diabetes, obesity, hypertension, vitamin D deficiency, and many cardiovascular diseases, all of which are significant risk factors for severe outcomes in COVID-19, are associated with older age and male sex (Orwoll et al., 2009; Mosekilde, 2005; Ghasemian et al., 2021). Adult females usually are reported to experience fewer comorbid conditions than males of the same age group (Roth et al., 2018). As comorbidity contributes to the severe outcomes of COVID-19, this also adds to the gendered effects of the infection. Sex steroids and immunosenescence also impact the susceptibility to seasonal influenza, as it interferes with the B-cell receptors (BCR), and T-cell receptors (TCR) repertoires (Dugan et al., 2020). Aging significantly alters the endocrine system, particularly in the sex steroids

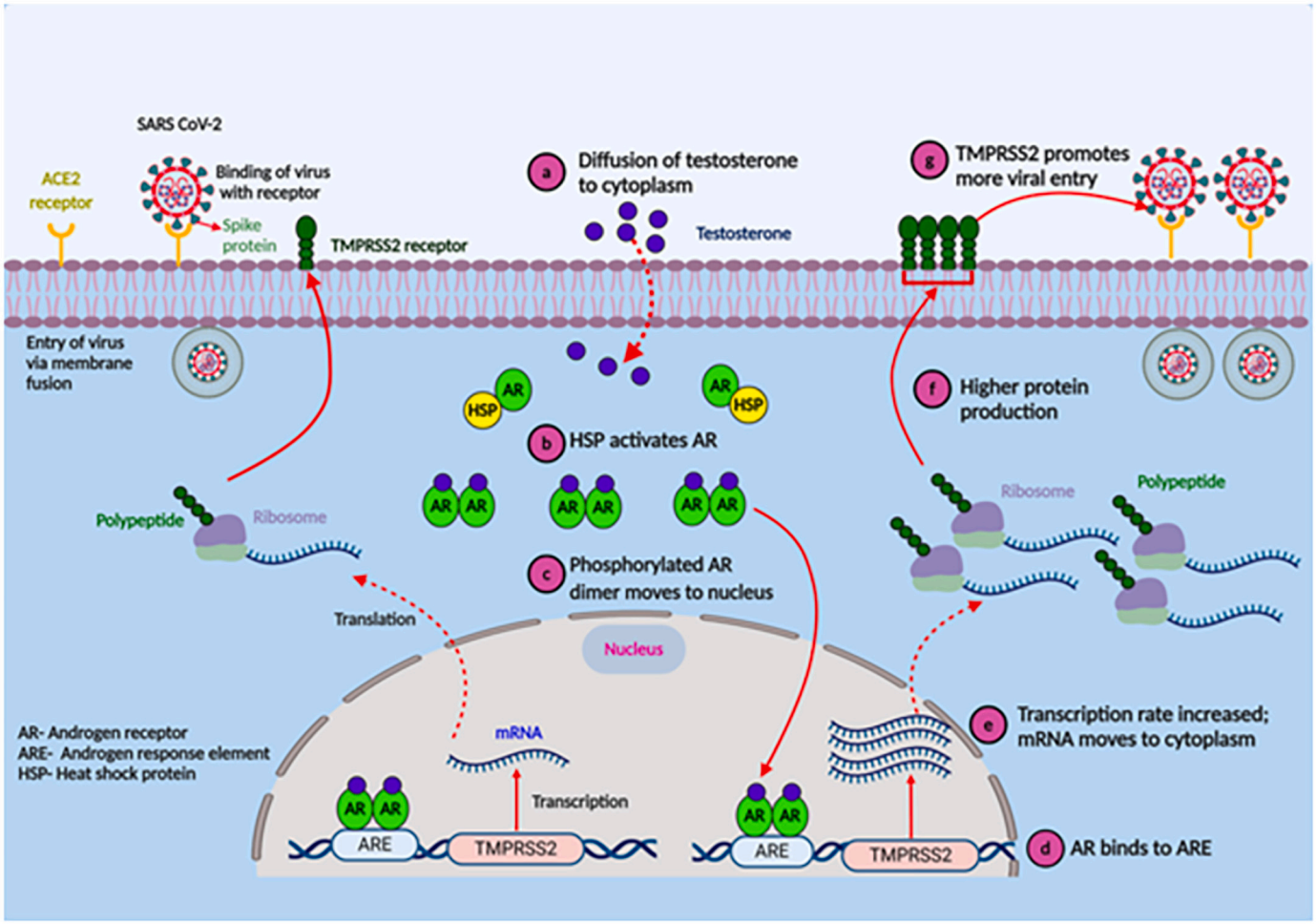


Fig. 3. Testosterone promotes viral entry via upregulating *TMPRSS2* transcription (Gebhard et al., 2020). The entry of androgen (***a***) stimulates heat shock protein (HSP) to activates androgen receptor (AR) (***b***), and phosphorylated AR homodimer translocate to the nucleus to (***c***) bind to androgen response element (ARE). This (***d***) upregulates the transcription of *TMPRSS2*. Upregulation of TMPRSS2 protein (***f***) promotes virus entry (***g***) to the cells.

and immunosenescence systems. It gives immune responses to viral infection a sex- and gendered dimension, which helps older females better defend against diseases (Gomez et al., 2019; Zarulli et al., 2018). These have helped females survive better from previous famines and epidemics and probably play a role in causing the male-biased effects of COVID-19.

Children are usually at a lower risk of developing COVID-19 and also have a milder disease than adults (Ding et al., 2020; Carsetti et al., 2020; Falahi et al., 2021). The sex-based disproportionate impact of COVID-19 is also much less pronounced among children (Falahi et al., 2021; Brizuela et al., 2021; Saatci et al., 2021; Parcha et al., 2021). Most studies, except some small cohort studies, report that the clinical outcomes of COVID-19 were similar across sex groups (Ding et al., 2020; Brizuela et al., 2021; Saatci et al., 2021; Parcha et al., 2021). The possible reasons for children not experiencing a sex-biased impact of COVID-19 could be due to many factors, e.g., stronger immune response than adults and different endothelial system functions or physiology (Falahi et al., 2021; Brodin, 2020; Lingappan et al., 2020; Mallapaty, 2021). The expression of many age-dependent genes, e.g., ACE2 (expression increases with age), contributes to the more robust immunity presented by the children. Moreover, children present less susceptibility to cytokine storms and inflammations (i.e., inflammaging) (Brodin, 2020; Lingappan et al., 2020). These contribute to a better immune response to infections by the children. Besides, while prior infections and vaccination give the adults advantages, their immune system is more trained to deal with similar pathogens. However, when it comes to dealing with a novel infection, children are naturally better and more adaptable at controlling them (Mallapaty, 2021). With the novelty of SARS-CoV-2, the children presented a better ability to combat the infection than the adults. With age, the adult immune system becomes more trained in dealing with similar infections but at the cost of its adaptability to combat new infections, perhaps in a sex-biased manner. In addition, the weakly imposed gender norms may play a role in the less disproportionate impact of COVID-19 in children. However, the precise mechanism underneath is currently unclear (Falahi et al., 2021).

6. Comorbidities

Along with the sex chromosome and hormonal difference between gender and age groups, comorbidities might be responsible for the higher death rate among males. Patients with preexisting heart conditions, diabetes, and other inflammatory diseases are more prone to SARS-CoV-2 infection. These complications are usually more prevalent among males and may contribute to elevated death incidences (Roth et al., 2018). In contrast, some pre-existing conditions, for example, thalassemia, might protect females from SARS-CoV-2 infection (Chowdhury and Anwar, 2020).

6.1. Heart disease

Many epidemiological studies have indicated that the mean age of developing a cardiovascular condition is 7–10 years lower among females (Maas and Appelman, 2010). The female hormone, estrogen, protects against coronary diseases (Merz et al., 2003), which is why females often exhibit a lower burden of cardiac diseases than males. Also, male sex is an independent risk factor for atrial fibrillation and Brugada syndrome in cardiac arrhythmias and thrombotic events, e.g., myocardial infarction, venous thromboembolism, and thrombotic stroke (Ehdaie et al., 2018; Wong et al., 2008). Consequently, the prevalence of cardiovascular diseases is considerably higher in males than in females.

People with preexisting cardiovascular conditions do not seem to be more susceptible to get COVID-19; however, acute myocardial injury, cardiac arrhythmias, microvascular dysfunction, and thrombosis are reported to contribute to a considerable proportion of COVID-19-related deaths (Huang et al., 2020; Zhou et al., 2020; Wang et al., 2020; Aggarwal et al., 2020; Iba et al., 2020; Shen and Ge, 2018). In addition, COVID-19 itself can induce myocardial injury, arrhythmia, and several other coronary complications (Nishiga et al., 2020). A considerable number of reports indicate that preexisting cardiovascular diseases are among the most common risk factors associated with severe outcomes in COVID-19, e.g., hospitalizations, intensive care support, and mortality (Zhou et al., 2020; Li et al., 2020; Deng et al., 2020). Preexisting cardiovascular conditions, thus, are thought to exacerbate the disease severity and contribute to the elevated mortality in COVID-19 patients by promoting cardiovascular injury (Medzikovic et al., 2020). However, COVID-19-induced cardiac injury is moderately modulated by sex hormones, ACE2 expression, and systemic inflammation, with the latter being less noticeable in females (Medzikovic et al., 2020; Shi et al., 2020a; Shi et al., 2020b). Also, as per a general understanding of preexisting cardiovascular conditions, sex chromosomes and hormones, ACE2 expression, drug interactions, obesity, and smoking habits may modulate disease conditions (Kaptoge et al., 2019; Ruan et al., 2018). These disease-modulating factors can predispose males and females differently to COVID-19 severity. Obesity and smoking, along with cardiovascular diseases, are risk factors with a higher burden in male patients with COVID-19, as compared to females. Altogether, these factors may explain why male COVID-19 patients seem to be at higher risk for severe disease progression and cardiovascular injury than females.

6.2. Diabetes

Diabetes does not seem to increase susceptibility to COVID-19; however, existing data show that the people with diabetes are more likely to require intensive care units (ICU) or to die due to COVID-19 (Apicella et al., 2020; Shi et al., 2020c). The precise link underlying such a worse prognosis due to COVID-19 in people with diabetes is currently unclear.

The association between diabetes and COVID-19, in general, is thought to be biunivocal, and the poorer prognosis is the likely outcome of the syndromic nature of the disease (Apicella et al., 2020). The prevalence of diabetes increases with age, and it reaches a peak in people of >65 years (Sinclair et al., 2020). People of >65 years of age are more likely to have a longer duration of diabetes and, thus, are prone to develop more diabetes-associated complications. Also, diabetes and older age often correlate with comorbidities, e.g., cardiovascular disease and hypertension. In the case of COVID-19, people with diabetes, nevertheless, have worse outcomes because of the associated conditions, e.g., hyperglycemia, older age, comorbidities, hypertension, and cardiovascular diseases, enhancing the risk (Apicella et al., 2020). Older males with diabetes are also more likely to experience diabetes-associated complications than their female counterparts (Corriere et al., 2013). On the other hand, SARS-CoV-2, because of its tropism for pancreatic ß-cells, can potentially lead to cell damage and impairment in insulin secretion, resulting in diabetes-like or hyperglycemic conditions. Impaired ß-cell function along with the inflammatory cytokine storm and counter-regulatory hormonal responses can result in more acute metabolic conditions, e.g., diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome, which is also more pronounced among males (Gannon et al., 2018). New-onset diabetes-like conditions, hyperglycemia, and acute metabolic conditions, in turn, can further worsen COVID-19 outcomes. In addition, the ACE2 receptor level is upregulated in people with type 1 and type 2 diabetes who uses ACE inhibitors and angiotensin II type-1 receptor blockers (ARBs) as treatment (Wan et al., 2020). Besides, people with diabetes often experience low vitamin D levels than healthy individuals (Abudawood et al., 2018). Lower vitamin D downregulates the antimicrobial peptide production, hence reducing the innate immune response. Alongside, diabetes-associated immune dysregulation, alveolar and endothelial dysfunction, and increased systemic coagulation may cause individuals to be more susceptible to COVID-19. Androgens play a sex-dimorphic role in diabetes, presumably through the involvement of visceral fat cells. Hyperandrogenism in

females and hypogonadism in males are reported to be risk factors for diabetes. Consequently, the male sex is regarded as a risk factor for the development of diabetes (Chen et al., 2012; Yang et al., 2010; Tracey et al., 2016; Wändell and Carlsson, 2014). Now, because males are more prone to developing diabetes and diabetes-associated complications (Nordström et al., 2016), this also partly explains why COVID-19 hits males harder.

6.3. Thalassemia

Patients with blood disorders, e.g., thalassemia, anemia, and sickle cell disease, are generally more prone to viral and bacterial infections. Many patients with blood disorders have immunocompromised conditions, e.g., splenectomized or post-transplant patients and those who receive hydroxyurea, making them more vulnerable to highly infectious diseases, e.g., COVID-19 (Chowdhury and Anwar, 2020; Lederman et al., 2014). However, blood indices evaluations in individuals with COVID-19 infection showed that most patients had a normal complete blood count and lactate dehydrogenase (LDH), and they do not usually present moderate or severe thrombocytopenia, a common finding in other viral illnesses, e.g., dengue fever (Lippi and Mattiuzzi, 2020). Hemoglobin concentration is reportedly substantially reduced in severe cases of COVID-19, which aligns with the previous evidence documented from patients with other types of pneumonia (Shang et al., 2007). Hemoglobin carries almost two-thirds of the total iron in the human body. Usually, the hemoglobin level in females is 12% lower than their male counterparts, and as such, they have less amount of iron circulating in the blood (Murphy, 2014). While this causes the females to be affected by iron deficiency complications, this also helps them stay away from complications related to excessive iron. On the other hand, transfusion-related excess iron load in the blood plasma of thalassemia patients causes the non-transferrin-bound iron to enter some cells and convert to ferritin, which becomes hemosiderin over time. Excess iron can also affect the hypothalamus or adrenal glands, potentially causing adrenal hypofunction (Nakavachara and Viprakasit, 2013; Powars et al., 1991), and contribute to a compromised ability to fight infections. It was reported that, iron overload, e.g., in the form of hemosiderin in close contact with damaged mitochondria, was associated with the severe outcomes in COVID-19 patients, e.g., hepatic failure, suggesting iron overload as a pathogenic trigger for the severe outcomes (Del Nonno et al., 2021). It is well established that females are generally less efficient than males in absorbing iron (Saljoughian, 2007); they technically are less prone to excess iron in the blood.

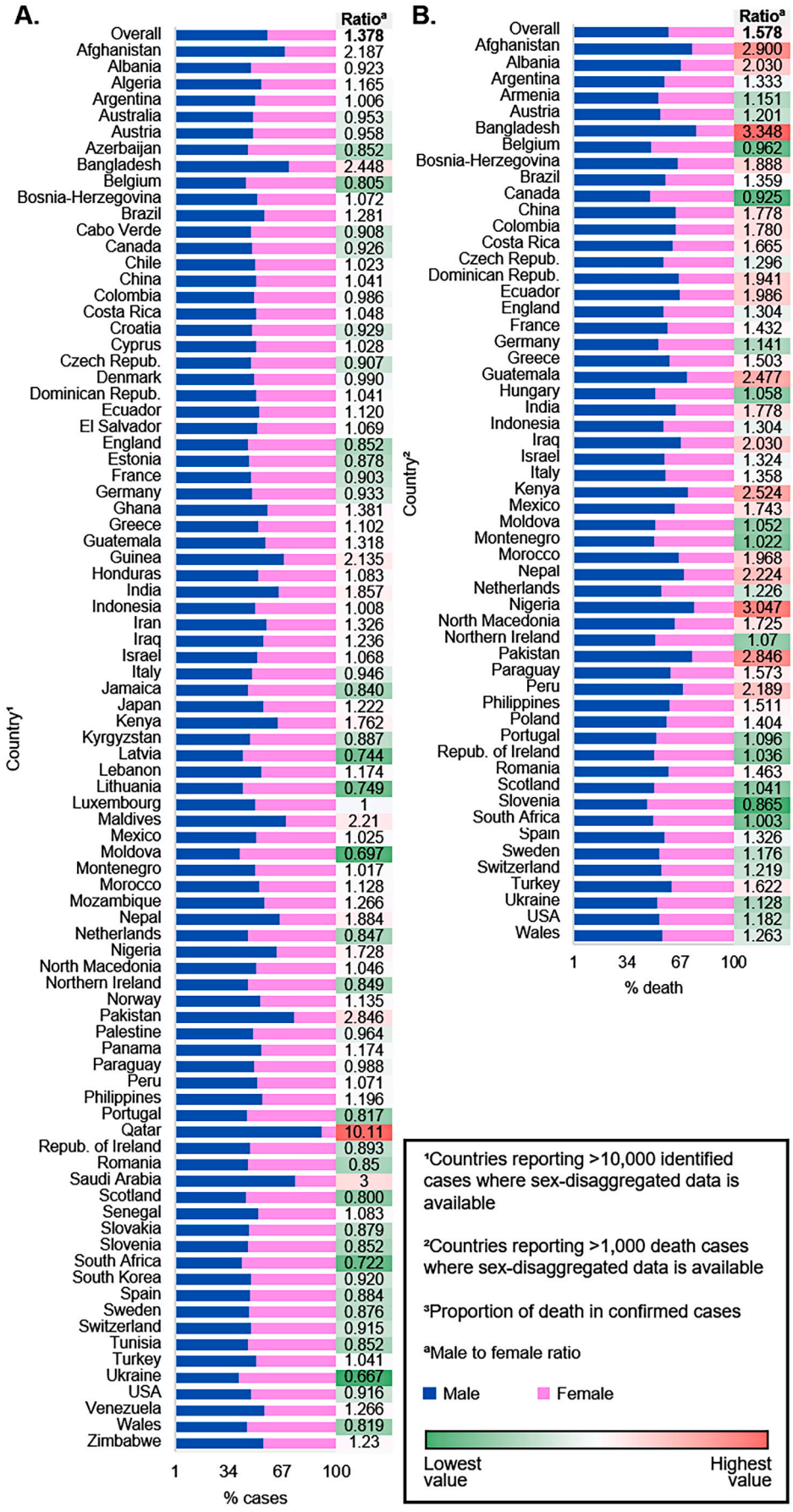
7. Racial and ethnic disparities

Over the last couple of decades, many reports have stressed that ethnic background and racial disparities potentially lead to poorer health in specific populations (Jackson et al., 2010). Especially in some racial/ethnicity groups, people with higher socioeconomic status sometimes pay a disproportionate toll on health due to biological disparities. The COVID-19 pandemics' impact on racialized and marginalized communities appears no different as it seems to hit some ethnic/racial groups harder than others.

Fig. 4 provides a global view of the sex-disaggregated data on identified cases and deaths due to COVID-19 (Global Health 50/50, 2022). Initially, the concerns about a possible association between ethnic background and outcome of COVID-19 raised after the observational analysis that a third of the patients admitted to critical care units in London were from an ethnic minority background (Siddique, 2020; Public Health England, 2020; Intensive Care National Audit and Research Centre, 2020). The report showed that the death rate due to COVID-19, adjusted for age, gender, ethnicity, and deprivation, was six times higher among people with a Bangladeshi (South Asian) background than the British White people Also, the all-cause mortality was 3–4 times higher than expected among the males in the Black and Asian population, compared to 1.7 times higher among the British White population. Similarly, in females, mortality was 2–3 times higher than expected among the Black and Asian population compared to 1.6 times in the British White population. A comparable disproportionate infection rate was reported in the US (Resnick et al., 2020). The areas where a majority of the population were Black people have three times more COVID-19 cases and over five times more death rates (Thebault et al., 2020). However, in another observational study on the COVID-19 mortality data from the Georgia and Michigan, two ethnically diverse states of the US, found that the sex disparity does not hold across racial groups while males had overall higher rates than females and Black people experienced the highest case fatality rates due to COVID-19 (Rushovich et al., 2021). In a large cohort study held at Bronx Montefiore Health System, the Black people had significantly higher mortality with COVID-19 (Golestaneh et al., 2020). Similar findings were observed in Canada: Black people and other people of color made up over two-thirds of reported cases and hospitalized patients in Toronto (Toronto Public Health, 2020). In contrast, both the case and death rate of COVID-19 was significantly higher among general Australians than Australia's Aboriginal and Torres Strait Islanders, more than one in three of whom have either cardiovascular disease, diabetes, or renal disease (Kirby, 2020). The racial disparity in COVID-19 outcomes was also reported among the children. Several large-scale studies indicate that race may plan an essential role in childhood COVID-19 outcomes as more Asian, Black, Hispanic, and mixed-race children faced adverse clinical outcomes than White children (Saatci et al., 2021; Parcha et al., 2021).

The fact that COVID-19 has disproportionately affected the racial and ethnic minority groups and race and ethnicity have an association with the worse outcomes of the infection was established by several large meta-analyses (Sze et al., 2020; Mude et al., 2021; Magesh et al., 2021). These studies revealed that individuals of Black, Hispanic, and Asian ethnicity were most likely to test positive for the infection and had the highest risk of ICU admission. By contrast, White people were the least likely to test positive for and require an ICU admission due to COVID-19. It was also indicated that, social determinants, e.g., area deprivation index and reduced access to clinical care, were positively correlated with the COVID-19 outcomes in racial and ethnic minority groups (Magesh et al., 2021).

The analysis of the US cohort of the COVID-19 patients incompletely explained the association between race and COVID-19 outcome by age, multiple reported comorbidities, and sociodemographic metrics (Golestaneh et al., 2020). Many experts have so far emphasized that the elevated rates of cases and severity in some specific ethnic groups may link with the sociodemographic, cultural, and genetic predisposition and physiological differences in infection susceptibility or response (Muurlink and Taylor-Robinson, 2020; Razaq et al., 2020; Pareek et al., 2020). An increased risk for acute respiratory tract infections, higher incidence of Vitamin D deficiency, obesity, diabetes, acute kidney diseases, the tendency of developing inflammations, and response to it, and predispositions of cardiovascular diseases in certain ethnic groups may lead to susceptibility to infections like COVID-19 (Simpson et al., 2015; Martineau et al., 2017; Miller et al., 2020; Tillin et al., 2012; Hernandez-Romieu et al., 2021; Garg et al., 2020). Evidence also shows that ethnicity/race can significantly affect the circulating 25(OH)D levels and vitamin D absorption by cells (Ghasemian et al., 2021; Correia et al., 2014). An increased interest has focused on the role of ethnically differential expression of angiotensin-converting enzyme 2 (ACE2) and serine protease 2 (TMPRSS2), the host receptor for SARS-CoV-2, as an increased incidence of cardiovascular risk factors may present in many ethnic groups (Asselta et al., 2020; Devaux et al., 2020; Cao et al., 2020; Darbani, 2020). A recent report indicated that Asian males might have a higher expression of ACE2 (Zhao et al., 2020). However, comparative genetic analyses could not identify *ACE2* mutants' presence that inhibits coronavirus binding to ACE2 among different populations (Cao et al., 2020). It also showed that the frequencies of alleles associated with higher ACE2 expression were higher among East Asian people,



C.

Country	Proportion of death[3]		
	Male %	Female %	Ratio[a]
Overall	3.381	2.488	**1.467**
Afghanistan	3.74	2.82	1.326
Albania	2.87	1.3	2.208
Argentina	3.1	2.34	1.325
Australia	3.22	3.28	0.982
Austria	1.6	1.28	1.25
Bangladesh	1.56	1.14	1.368
Belgium	3.26	2.73	1.194
Belize	2.69	1.42	1.894
Bosnia-Herzegovina	3.64	2.06	1.767
Brazil	33.56	31.61	1.062
Burkina Faso	4.63	3.0	1.543
Cabo Verde	1.29	0.74	1.743
Canada	3.21	3.21	1
Chad	7.25	5.61	1.292
Chile	1.28	0.97	1.32
China	4.7	2.8	1.676
Colombia	3.5	1.94	1.804
Costa Rica	1.55	0.97	1.598
Czech Repub.	1.98	1.39	1.424
Denmark	0.9	0.7	1.286
Dominican Repub.	2.37	1.26	1.881
Ecuador	8.64	4.87	1.774
England	11.87	7.48	1.587
Equatorial Guinea	2.17	1.31	1.656
Estonia	0.62	0.69	0.899
Eswatini	2.34	1.69	1.385
Finland	4.02	4.29	0.937
France	2.72	1.7	1.6
Germany	1.89	1.54	1.227
Greece	3.51	2.57	1.366
Guatemala	4.26	2.27	1.877
Haiti	2.61	2.21	1.181
Hong Kong	1.95	1.22	1.598
India	2.62	3.07	0.853
Indonesia	3.47	2.64	1.314
Iran	5.89	5.43	1.085
Iraq	2.74	1.67	1.641
Israel	0.93	0.75	1.24
Italy	4.01	2.79	1.437
Jamaica	2.77	1.95	1.421
Jersey	2.33	1.21	1.926
Kenya	2.01	1.4	1.436
Kyrgyzstan	1.63	0.89	1.831
Latvia	1.68	1.11	1.514
Liberia	4.9	5.05	0.970
Luxembourg	1.09	0.89	1.225
Malawi	3.43	2.31	1.485
Maldives	0.34	0.38	0.895
Mexico	11.42	6.71	1.702
Moldova	2.55	1.69	1.509
Montenegro	1.0	1.0	1.0
Morocco	2.98	1.65	1.806
Myanmar	1.0	0.26	3.846
Nepal	0.35	0.55	0.636
Netherlands	1.94	1.34	1.448
New Zealand	1.65	1.24	1.331
Nigeria	2.26	1.28	1.766
North Macedonia	3.61	2.19	1.648
Northern Ireland	2.16	1.71	1.263
Norway	0.93	0.98	0.949
Pakistan	2.14	2.12	1.009
Panama	2.78	1.89	1.471
Paraguay	2.56	1.61	1.590
Peru	4.94	2.42	2.041
Philippines	2.15	1.71	1.257
Portugal	1.87	1.4	1.336
Repub. of Ireland	3.01	2.59	1.162
Romania	3.12	1.81	1.724
Scotland	6.69	5.14	1.302
Slovenia	2.11	2.08	1.014
South Africa	2.83	2.04	1.387
South Korea	1.45	1.26	1.151
Spain	10.87	6.3	1.725
Sweden	2.6	1.94	1.340
Switzerland	1.68	1.26	1.333
Thailand	2.11	0.85	2.482
Tunisia	3.24	1.29	2.512
Turkey	3.28	2.1	1.562
Uganda	0.59	0.75	0.787
Ukraine	2.25	1.33	1.692
USA	3.51	2.76	1.272
Vietnam	1.76	3.41	0.516
Wales	3.22	2.09	1.541
Zimbabwe	3.08	2.31	1.333

(caption on next page)

Fig. 4. Sex disaggregated data on identified cases and deaths due to COVID-19 across countries included in the Global Health 50/50 tracker (as of 30 Nov 2020) (Global Health 50/50, 2022). (***a***) Male to female case identification rate in countries reporting >10,000 identified cases (N = 41,840,331) where the sex-disaggregated data is available. (***b***) Male to female death rate among male and female in countries reporting >1000 COVID-19 related death incidences (N = 1,155,509) where the sex-disaggregated data is available. The name of the countries is ordered alphabetically. (***c***) The proportion of death in male and female confirmed cases.

suggesting different susceptibility or responses to SARS-CoV-2 from diverse populations. On the other hand, preliminary studies on the role of *TMPRSS2* revealed that the variants linked with reduced expression of *TMPRSS2* might bestow less individual susceptibility to COVID-19 and favor a better clinical outcome (Russo et al., 2020).

Additionally, many disadvantaged socioeconomic and lifestyle-related features of some ethnic groups, e.g., low income, extended cohabiting families in many Southeast Asian and West African countries, may contribute to the spread of the virus. Furthermore, many Black, Asian, Western African, Indian subcontinental, and ethnic minority people, whether in their own countries or in a different country where they have migrated, face several disadvantages, including inadequate housing, overcrowding, and low income. As a result, the preventive practices to reduce the spread of COVID-19 were challenging for them, contributing to the increased case rates and death rates among these populations (Rossouw et al., 2020; Anwar et al., 2020a; Bong et al., 2020).

The overall significance of the racial and ethnic disparities of COVID-19, however, remains to be deciphered precisely. Besides, many experts argue that the racial and ethnic disparities are not due to intrinsic biological makeup but socio-cultural differences for hundreds of years, which have influenced their physiology through social determinants of health and embodiment (Racism and Genetics, 2020; Non et al., 2012; Montoya, 2011; Das, 2013). Therefore, it is crucial to take it cautiously when interpreting the data on racial disparities of COVID-19, as this disparity—as appalling as it is—may still understate the actual situation due to the incompleteness of our knowledge (Milner et al., 2020; Gravlee, 2020).

8. Gender-specific practices and cultural backgrounds

Alongside biological and ethnobiological factors, COVID-19 disease progression, severity depends on behavioral and cultural variables (Table 1). Some cultures allow men to smoke, where women smoking is treated as a social taboo. The tendency of harmful behavior such as smoking and taking alcohol is higher among men than women. According to WHO, globally men's smoking rate is 4.5 times higher than women smokers, accounting to 40% and 9%, respectively (World Health Organization, 2010). As the virus causes severe damage to the lung, the impact of smoking might be a potent cause of elevated death rate among men. Also, it was reported that middle-aged women practice more hand hygiene than men (Suen et al., 2019). Besides, air pollution impacts the outcome due to COVID-19, and men are exposed more to air pollution as more men work outside (Wu et al., 2020). A hypothesis is that postulated fine particles in air interfere with LL-37, an antimicrobial peptide (Crane-Godreau et al., 2020).

The difference between men's and women's infection rates and fatality for COVID-19 can also be related to cultural factors. A multinational study held in 2011 reports that the prevalence of an arboviral disease was remarkably high among Asian men only when over 15 years of age, when the cultural differences in work patterns, social behavior, activities, and dress come to apply (Anker and Arima, 2011). This inequality may reasonably be explained as a variation in exposure to the infection source. Also, it can be considered a plausible explanation for why the gendered effects of COVID-19 is less evident among the children. This may have a connection with the dress convention in these countries. In the countries where the definition of modesty of clothing is equivalent between men and women, the gendered effects of the infections are often disappear (Muurlink and Taylor-Robinson, 2020; da

Table 1
Potential factors influencing sex- and gender-specific outcomes in COVID-19 infections.

	Males	Females
Biological factors that contribute to the sex/gender disparities in COVID-19		
Antibody response	↓	↑
Estrogen mediated protection	×	↑
Testosterone-stimulated expression of ACE2	↑	↓
ACE2 expression/activity		
Heart	↑	↓
Kidney	↑	↓
Lung	↑	↓
Ovary	×	↓
Serum	↑	↓
Testes	↑	×
TMPRSS2 expression/activity	↑	↓
Nitric oxide levels	↓	↑
Ethnobiological backgrounds	↑	↓
Gender-constructed practices that contribute to the sex/gender disparities in COVID-19		
Smoking	↑	↓
Alcohol consumption	↑	↓
Use of personal protective equipment, compliance to health measures, hygiene	↓	↑
Risk behaviors	↑	↓
Medical reporting	↑	↓

Green arrow indicates for protective roles
Red arrow indicates for potential risk

Glória et al., 2002; Hussain, 2022). For instance, in Brazil, where the definition of clothing modesty is equivalent between men and women, the gendered difference in dengue infection rate fades away (da Glória et al., 2002). However, in a recent study in Bangladesh, which belongs to a semiconservative social structure, women were more affected by Chikungunya, another arboviral disease (Anwar et al., 2020b). Nevertheless, arboviral diseases have a different transmission mode than COVID-19, and gender risks and vulnerabilities may differ based on how diseases are transmitted (Muurlink and Taylor-Robinson, 2020). There is still a dearth of studies that systematically and comprehensively evaluating the role of clothing in the transmission efficiency of COVID-19. In addition, the public perception, knowledge, and attitude towards infectious diseases, e.g., COVID-19, is often comparable among men and women of these countries (Anwar et al., 2020c; Alberta Health Services COVID-19 Scientific Advisory Group, 2020). What this means is that the differences in knowledge, attitude, and perception of risk between men and women cannot be regarded as a major contributor to the gender disparities among these population groups. The culturally biased gendered dimension of infectious diseases is yet to be established solidly.

One significant indicator of conservative or semiconservative societies is the extent of long or modest clothing worn by both young and older people, especially women. This so-called clothing convention may involuntarily determine the extent of rapidity and degree of the spread of infectious diseases, e.g., COVID-19. Cultures that limit women's movement and clothing freedom may contribute to the fewer possibilities for pathogen transmission for women than men. One such example could be wearing a burqa (veils) and niqab (face coverings) by the women in conservative Muslim communities. This practice helps the women in these communities restrict them from touching their face, mouth, nose, and eyes. Frequent touching of the face, mouth, nose, and eyes have been a well-perceived risk factor for infection with SARS-CoV-2. The use of burqa and niqab inadvertently helps them avoid this risk factor, while many who does not wear burqa and niqab may find it challenging not to touch the face, mouth, and nose as this is instinctive and habitual (Muurlink and Taylor-Robinson, 2020; Sobh et al., 2012; Benning et al., 2020). Also, facial coverings, like the niqab, may contribute to a very low-level filtration of air-borne droplets, potentially carrying pathogenic agents (Rengasamy et al., 2010). However, the level of barrier niqab provides may not be highly significant in terms of controlling viral spread as compared to P2/N95 standard particulate filtering systems or even regular surgical masks. Besides wearing a burqa and niqab, covering the hairs also has an unintended value from the perspective of public health microbiology (Sobh et al., 2012). In contrast, the cultural predilection for mustache and beard among males of different cultures is likely to increase male exposure to pathogens like SARS-CoV-2, particularly amongst health professionals where facial hair compromises the seal P2/N95-standard particulate filtering respirators and surgical masks (Sandaradura et al., 2020).

Gender apartheid in communities influences the women's engagement in activities and roles outside the home, e.g., occupation or profession (Timmis et al., 2005; Berecki-Gisolf et al., 2008). While the reduced active engagement of women in social and professional activities beyond household and babysitting functions reduces their exposure to disease outbreaks, it, in turn, reduces the likelihood of women visiting a healthcare facility, leading to underreporting of disease incidence among them.

In the rural and remote regions where medical care facilities are not widely accessible in most cases, there is often a gender imbalance in favor of the men (Wainer et al., 2001). Often, these facilities lack workforces, and male practitioners dominate the limited workforce they have. Women originating from conservative families used not to seek medical care from male practitioners as religious and cultural factors disallow them from interacting with men outside their family and close relatives (Chaudhury and Hammer, 2003). As a result, women in these communities tend not to visit the medical care centers and remain marginalized with scarcer diagnoses using qualified methods.

Conceivably, the cultural norms and practices may have strongly influenced the reported COVID-19 infection rates' gendered dimensions and the death rates. Women may have achieved some protection by social, professional, and clothing practices related to the conservative, religious and traditional norms. Additionally, their hesitation in visiting a male medical practitioner may have led them to be underreported in the infection and fatality data. Scientifically rigorous and large-scale studies involving subjects from culturally diverse backgrounds could help establish the role of cultural practices and norms on infection rates and mortality due to outbreaks. As the COVID-19 pandemic has hit (almost) every community of the world, from a researcher's point of view, it offers an opportunity to conduct such studies to provide insights into the role of cultural factors on the rates of infection, morbidity, and mortality due to outbreaks. Indeed, such a study's findings would contribute hugely to redesigning the public health policies to combat any future outbreaks.

9. Females are more likely to suffer from long COVID-19

Several studies suggest that females are more likely to suffer from long COVID-19 (Rubin, 2020). Female sex and 40–50 years of age are considered risk factors for Long COVID (Sigfrid et al., 2021; Torjesen, 2021; Mahmud et al., 2021). While the long-lasting symptoms of most other diseases are primarily associated with adults with severe illness who spend weeks in intensive care and have older age, and comorbidities, interestingly, most of the sufferers of long COVID-19 initially face mild to moderate symptoms without requiring lengthy hospitalization and are largely unaffected by preexisting conditions (Rubin, 2020; Sigfrid et al., 2021; Stewart et al., 2021). The underlying reason behind this 'inverse sex' effect of long COVID-19 is currently unclear. Hypothetically, the disparity in risk and outcomes of long COVID-19 between sexes could be related to the effects of sex hormones (Stewart et al., 2021; Zoltán and István, 2021). The symptoms of long COVID-19, e.g., fatigue, myalgia, palpitations, cognitive impairment, and sleep disturbance, mostly overlap with those of perimenopause and menopause (Zoltán and István, 2021). Besides, the risk factors, e.g., female sex and age between 40 and 50 years, indicate the effect of the difference between pre- and postmenopausal time. As with perimenopause and menopause, the levels of estrogen and estradiol change, and so is the estradiol-stimulated immune cell activity. This change in the activity of the immune cells may have a role behind females being more affected by long COVID-19. In addition, the overlapping symptoms create diagnostic uncertainty, leading to the possibility that females with symptoms of perimenopause and menopause are misdiagnosed with long COVID-19 or the opposite (Stewart et al., 2021). More systematic studies are warranted to drill down into the mechanism causing females to suffer more from long COVID-19.

10. Need for the implementation of gender medicine

The dearth of sex and gender-specific approaches that consider sex as an analytical variable a priori in epidemiological and clinical trial studies is well recognized (Brady et al., 2021). However, the failure to explore the sex- and gender-specific risks and outcomes during outbreaks, especially during a pandemic like COVID-19, is unacceptable and linked to manifold risks (Stewart et al., 2021; Brady et al., 2021). It fails the research endeavors exploring the pathobiology and therapeutic strategy that satisfies the sex-specific biology. Besides, it endangers global women's health due to the risk of misdiagnosing, mismanagement, and in a broader sense, slipping to provide them with appropriate health care. In addition, it impairs the global post-pandemic recovery efforts and future preparedness due to the highly gendered nature of many sectors, e.g., health and social care (Wenham et al., 2020). The COVID-19 pandemic and its disproportionate impact on males and females is an awakening call for the urgent need for robust efforts to help

understand the epidemiological background and the biological mechanisms underneath for sex differences in infectious diseases and other human diseases (Wenham et al., 2020). It also calls for the systematic and sustainable application of sex-specific methodologies. In this context, several groups are working toward developing plans for implementing gender medicine, and some of them have already come out with recommendations for implementing gender medicine in the post-COVID-19 age (Organisation for Economic Co-operation and Development, 2021; Klinge and Oertelt-Prigione, 2021; Machluf et al., 2020; Jagsi et al., 2021). It is suggested that developing tailored guidelines and raising awareness of gender-specific medicine could reduce disparities and facilitate understanding of certain sub-populations' health dynamics and needs within each gender (Machluf et al., 2020; Jagsi et al., 2021). However, these studies mostly fit the context of European, American, and other high-income and upper-middle-income counties. To achieve universal sex- and gender-inclusive recovery, low- and lower-middle-income countries must develop effective and malleable plans to implement gender medicine in their regional context. Importantly, the proper implementation of these gender medicine plans across the globe without regard to the racial and economic boundaries is needed.

11. Conclusions and future perspectives

The sex and gender-based difference in the impact of the COVID-19 pandemic is not understood precisely, but it could be multifactorial as genetic, racial, certain immunological factors, and the communal psychosocial practices by men and women contribute to how they respond to infections. Females are genetically and immunologically able to mount a more robust defense against infections which serves them better in managing viral load and viral clearance than males. The sex genotype of males and females could be considered a major determinant since the X-chromosome carries a good number of immune genes in humans. Also, the hormone system in females involving estrogen and estradiol can have immune-enhancing effects, while the male system involving testosterone secreted can have immune-suppressive effects against viruses. Furthermore, comorbidity is considered a risk factor for severe outcomes in COVID-19, and the prevalence of comorbid conditions is naturally different among males and females. In addition, the aging and stress endurance of males and females may have a role to play. Besides, the gender-constructed roles of men and women put them at different levels of exposure to pathogens. A better understanding of the factors behind the sex- and gender differences in COVID-19 is necessary to tailor therapies and vaccine strategies in a step toward sex-based personalized medicine, and further research is warranted to dig deeper into the precise mechanism for these differences.

Sex and gender are strongly inter-related and to respond to infectious disease outbreaks, e.g., COVID-19, effectively and equitably, it is essential that gender norms, roles, and relations that influence women's and men's differential vulnerability to infection, exposure to pathogens, and treatment received, and how these may differ among different groups of women and men, be cautiously considered and appropriately addressed as a core component of all the efforts. The governments and health service providers need to recognize the sex and gender effects of the COVID-19 outbreak. Also, the voice of men and women need to be considered separately depending on their intrinsic immunological and genetic backgrounds, particularly on the front line of the response to COVID-19. Advocacy efforts to diminish the sex-based and gendered barriers in health service-seeking practices must be initiated. Overall, special efforts tailored and customized to meet the gender-specific and cultural demands of pandemic-affected populations, including men, women, seniors, and children, are strongly recommended to ensure that pre-existing gender-constructed social, political, and cultural differences do not amplify the impacts of the pandemic.

Authors' contributions

MH conceptualized the study. JT and SA contributed to the methodology, data collection, data visualization, and drafting the manuscript. SA revised and edited the manuscript. All authors critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

No specific grant was received for this study. JT is supported by the COSMOS Scholars Program and the American Association of University Women (AAUW). SA is supported by the Maternal and Child Health (MatCH) Scholarship program, the Women and Children's Health Research Institute (WCHRI) Graduate Studentship, and the Alberta Innovates Graduate Students Scholarship (AIGSS). MH is supported by the SUST Research Centre, the University Grant Commission (UGC) of Bangladesh, the Ministry of Science and Technology, and the Bangladesh Bureau of Educational Information and Statistics (BANBEIS), Ministry of Education, Government of Bangladesh.

Declaration of Competing Interest

The author reports no conflicts of interest in this work.

Acknowledgements

The authors wholeheartedly acknowledge Sabrina Sharmin (Wesleyan University, CT, USA) and Md. Abu Bakar Siddique (St. John's University, NY, USA). Figures 2 and 3 are created with BioRender.com.

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