Sexual dimorphism in COVID-19: potential clinical and public health implications

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Current evidence suggests that severity and mortality of COVID-19 is higher in men than in women, whereas women might be at increased risk of COVID-19 reinfection and development of long COVID. Differences between sexes have been observed in other infectious diseases and in the response to vaccines. Sex-specific expression patterns of proteins mediating virus binding and entry, and divergent reactions of the immune and endocrine system, in particular the hypothalamic–pituitary–adrenal axis, in response to acute stress might explain the higher severity of COVID-19 in men. In this Personal View, we discuss how sex hormones, comorbidities, and the sex chromosome complement influence these mechanisms in the context of COVID-19. Due to its role in the severity and progression of SARS-CoV-2 infections, we argue that sexual dimorphism has potential implications for disease treatment, public health measures, and follow-up of patients predisposed to the development of long COVID. We suggest that sex differences could be considered in future pandemic surveillance and treatment of patients with COVID-19 to help to achieve better disease stratification and improved outcomes.

Introduction

Evolution has led to a substantial divergence in endocrine, metabolic, and immune functions between males and females that is reflected in sex-specific differences in disease susceptibility and outcomes.[1,2] Factors responsible for sex-specific differences include sex hormones, gender-dependent lifestyle, and environmental aspects, such as smoking, diet, and alcohol consumption. Additionally, the sex chromosome complement, which leads to sex-specific, age-specific, and tissue-specific variations in gene transcription, contributes to these differences.[3]

A striking example of sexual dimorphism is the currently observed difference in severity and survival between men and women infected with SARS-CoV-2.[4] Early reports of COVID-19 already suggested that men are at higher risk of developing severe disease, which is associated with increased case fatality compared with women.[5,6] Sex-disaggregated data from several governments compiled by the Global Health 50/50 research initiative confirmed an increased mortality in men despite similar numbers of COVID-19 cases in men and women.[7] Biological sex is associated with life span differences in humans, with a substantially higher life expectancy in women. However, mechanisms responsible for shorter life expectancy in men have already been ruled out as major drivers of excess mortality in men with COVID-19.[8]

Patients with comorbidities such as diabetes, hypertension, and cancer are at higher risk of a severe course of SARS-CoV-2 infection, with men being significantly more likely to have these comorbidities than women.[9] Even before the onset of clinical symptoms or diagnosis of diabetes and metabolic disease, there are striking intrinsic sex hormone-dependent distinctions in metabolic regulation, including insulin sensitivity. Genetic differences are associated with disparate regulation of glycaemic control, insulin sensitivity, lipid metabolism, and adipose tissue homoeostasis; these metabolic processes are primarily, but not exclusively, controlled by sex hormones.[10,11] In an observational study of people with diabetes admitted to hospital for COVID-19, female sex was associated with a lower incidence of severe outcomes but similar mortality compared with men (NCT04324736). The authors of this study concluded that diabetes might reduce the protection that women have over men in terms of susceptibility to severe COVID-19.[12] In another cohort study of people with diabetes, male sex, among other factors, such as living in residential care, was identified as a risk factor for developing fatal or critical care unit-treated COVID-19.[13] Cardiovascular disease is the leading cause of death among men and women, although epidemiological observations indicate that women have a lower risk of major adverse cardiovascular events than age-matched men and that the manifestation of cardiovascular disease in women is delayed, as cardiovascular risk increases in women predominantly after the menopause. Thus, oestrogens are generally assumed to have protective effects on the cardiovascular system.[14]

Sex-specific differences in the regulation of the hormonal stress response and inflammatory processes might also contribute to sexual dimorphism in COVID-19.[15] This notion is supported by the fact that some diseases with an autoimmune background, such as Grave's disease, systemic lupus erythematosus, and rheumatoid arthritis, show a clear predominance in women.[16] Although the cellular and molecular basis for the sex-specific increased incidence of some diseases remains largely unknown, genetic mechanisms have been discussed in the literature. For example, expression of specific innate immune-associated genes (eg, *TLR4*, *TLR7*, *TLR8*) is X-chromosome-linked and the pattern of cytokine expression varies between sexes.[17–20] Moreover, the gene

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encoding angiotensin-converting enzyme 2 (ACE2), the host receptor that binds coronaviruses such as SARS-CoV-2[21] is located at specific sites of the X chromosome that commonly escape the inactivation of one X chromosome in mammalian XX cells. This silencing mechanism avoids redundant gene expression in female cells by up to 90%; consequently, XX cells overexpress genes such as *ACE2*.[22] Males are usually more affected by X-linked pathogenic variants, which might also contribute to the increased severity of COVID-19 in males.[23]

Moreover, susceptibility to virus infections differs between males and females. Thus, even in previous endemic infections, including SARS-CoV (2002) and MERS-CoV, men were more severely affected than women.[4] In general, men with severe acute respiratory syndrome have a significantly higher mortality rate than women.[24] Given the close link between the pathophysiological mechanism of COVID-19 and endocrine, metabolic, and immune regulation,[25–27] we argue that various aspects of sexual dimorphism should be more thoroughly considered in disease surveillance and treatment of patients with COVID-19. In this Personal View, we present the current knowledge of sexual dimorphism in COVID-19 and speculate about its clinical and public health implications.

Sex differences in COVID-19

Women are less affected by insulin resistance, have fewer cardiovascular risk factors, and have more favourable protein, microbiome, lipidome, and microRNA expression profiles than men.[28–32] Given that insulin resistance and impaired glucose metabolism are key risk factors for developing severe COVID-19, females might have a more advantageous metabolism, thereby preventing disease progression (figure 1).

Higher predisposition to inflammation in men

Infections with a range of pathogens are associated with different immune responses and disease outcomes depending on sex.[33] Men are more likely to have a less potent immune response and thus a higher susceptibility or vulnerability to infections.[33] Obesity has previously been described as a predictor of severe COVID-19 course.[34] However, beyond BMI, the distribution of fat deposits also seems to be important; it has been shown that visceral fat, which accumulates more in men than women, is associated with more severe COVID-19.[35,36] Furthermore, adipose tissue in males contains more macrophages and immune cells with higher and longer-raised cytokine concentrations than in females.[37–39] This might become the source of more rapid and intense systemic inflammation in men contributing to the detrimental rise of cytokines (cytokine storm) observed in critical SARS-CoV-2 infections. It is conceivable that this rapid cytokine response, mediated by adipose tissue among other factors, could even be beneficial initially by providing an immediate immune response. In patients with moderate

COVID-19 on no immunomodulatory medications, men had higher plasma concentrations of innate immune cytokines (eg, IL-8, IL-18) together with a more robust induction of non-classical monocytes.[40] However, women showed stronger activation of T cells than men during SARS-CoV-2 infections.[40] Furthermore, age-dependent effects on the immune system contribute to vulnerability and a more severe course of COVID-19.[41] Interestingly, immunosenescence also shows sex-specific effects. Prominent examples in this context are the observation that the number of naive T cells generally decreases with age in both men and women, with a more pronounced drop in men, while a profound decline of B cells is observed only in men.[42] In females, high oestradiol and progesterone concentrations suppress pro-inflammatory cytokine production by macrophages and stimulate anti-inflammatory cytokines in CD4+ T helper cells.[43,44] Moreover, oestradiol stimulates antibody production by B cells.[45] The stronger immune response mediated by oestradiol and progesterone in females might contribute to less severe COVID-19 infections and lower mortality rates in women compared with men (figure 1).

Sex-dependent DPP4 activity and COVID-19

In addition to ACE2, SARS-CoV-2 uses dipeptidyl peptidase-4 (DPP4) as a co-receptor when entering cells.[46] DPP4 is involved in the regulation of the immune response and autoimmune processes and has been identified as a druggable target.[47] Therefore, continued administration of DPP4 inhibitors, commonly used in people with diabetes, has been discussed in patients infected with SARS-CoV-2.[48,49] Although a retrospective analysis showed that DPP4 inhibitors can improve mortality in patients with COVID-19 and type 2 diabetes,[50] an open-label, prospective, multicenter, randomised clinical trial in three Israeli hospitals found no differences in the time to clinical improvement between hospitalised patients with diabetes and COVID-19 who received linagliptin and a control group receiving standard of care.[51]

Interestingly, in mice, notable changes in DPP4 activity occur during the oestrous cycle, with a low activity at oestrus and a high activity at dioestrus.[52] Exposure to oestrogens diminishes DPP4 activity in ovariectomised mice[52] and application of phytoestrogens leads to inhibition of DPP4 activity.[53] Conversely, DPP4 inhibitors decrease free androgens in patients with polycystic ovary syndrome[54] and might have the potential to reduce the risk of autoimmune disease and inflammation.[55] Recent evidence suggests that DPP4 inhibitors alter specific aspects of the innate immune response.[56] DPP4 inhibition could potentially also modulate the higher plasma concentrations of innate immune cytokines in males that have also been described in the context of COVID-19.[57] Sex hormone-dependent regulation of DPP4 activity could be another important factor in determining different outcomes in COVID-19 severity and mortality between men and women.

TMPRSS2 mediates sex differences in COVID-19 severity

Once SARS-CoV-2 binds to host ACE2, the transmembrane protease serine subtype 2 (TMPRSS2) mediates cleavage of SARS-CoV-2 spike proteins, allowing fusion with the cell membrane.[58,59] Age-dependent regulation of TMPRSS2 in lung epithelium, characterised by increased expression with age, might explain the relative protection of infants and children from severe respiratory illness.[60] Single-cell RNA sequencing of lung tissue from 13 healthy men and 13 healthy women revealed no sex-related differences in expression of *ACE2*, but *TMPRSS2* expression was significantly increased in men.[61] Moreover, *ACE2*+ *TMPRSS2*+ double-positive cells were more than threefold higher in men than in women.[61] The tissue-specific higher expression of *TMPRSS2* in men might be because *TMPRSS2*, like *ACE2*,[62] is a known target of the androgen receptor.[61,63] In line with this hypothesis, the anti-androgen enzalutamide lowers TMPRSS2 expression in human lung cells and mouse lungs; moreover, it significantly reduces SARS-CoV-2 entry and infection in lung cells.[64] Unfortunately, treatment with the TMPRSS2 inhibitor camostat mesilate did not shorten the time to clinical recovery and failed to reduce mortality in hospitalised patients with COVID-19 in a double-blind, randomised, placebo-controlled multicentre trial (NCT04321096).[65] This study highlights that addressing virus uptake alone might not be sufficient to improve the outcome of patients with COVID-19. Therefore, combination therapies that address viral uptake and the pro-inflammatory state, particularly in men, should be considered.

Sexual dimorphism in adrenal stress response and COVID-19

The hypothalamic–pituitary–adrenal (HPA) axis, responsible for integrating and managing internal and external stress stimuli of the organism, demonstrates a clear sex-biased activity, with striking sex differences in the neuroendocrine response particularly to acute stress.[66] Females generally present with increased glucocorticoid secretion in response to various acute stressors.[67] Adult sex differences in the neuroendocrine response to acute stress are partly the result of interactions between the HPA axis and the endocrine system, which controls reproduction. Therefore, by increasing the production of dihydrotestosterone or oestradiol, the hypothalamic–pituitary–gonadal axis modulates the function of the HPA axis in adults in a sex-dependent manner. Oestradiol treatment enhances the activity of the HPA axis, but endogenous oestrogens have also been reported to have inhibitory effects.[66] The importance of the HPA axis, and particularly of the adrenal glands, in the context of COVID-19 is supported by our recent findings demonstrating that the adrenal glands are a potential target for SARS-CoV-2 infection; the resulting cellular damage could potentially predispose patients with COVID-19 to adrenal dysfunction.[68]

Evolution has resulted in profound differences between sexes that extend to non-reproductive organs.

As an example, adrenal gland tissue renewal is highly active and sexually dimorphic, with female mice demonstrating a threefold higher turnover than males.[1] Interestingly, females employ an additional stem-cell compartment throughout life, located in the adrenal capsule. In males, these stem cells become inactive by adulthood. Sex-specific stem-cell activity in adrenal development is driven by androgens that repress
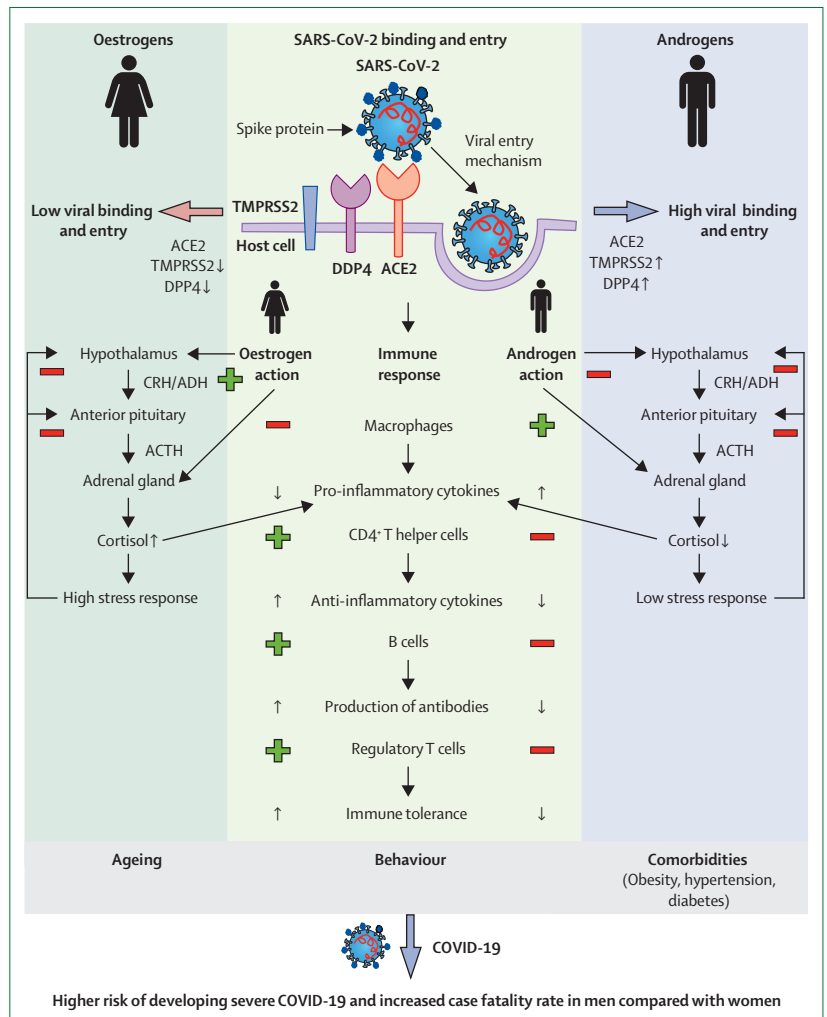

Figure 1: Systemic and molecular basis for sexual dimorphism in COVID-19
SARS-CoV-2 uses its spike glycoprotein (S) to attach to the host cell, triggering fusion between virus and lipid membrane (exocytosis). ACE2, TMPRSS2, and DPP4 are critical mediators of this process and show tissue-specific and sex-specific expression patterns. Higher expression of TMPRSS2 and DPP4 in men is associated with increased viral binding and entry, leading to higher viral load compared with women. Oestrogens and androgens regulate the subsequent immune response. Women exhibit a stronger immune response, which is characterised by, among other factors, the release of anti-inflammatory cytokines (eg, IL-6, IL-1β, TNFα). In men, on the other hand, pro-inflammatory cytokines (eg, IL-4, IL-10) dominate. Sex-related differences in the response to stress further contribute to the predisposition of men to a pro-inflammatory state. An overall increased basal activity of the hypothalamic–pituitary–adrenal axis in women, mediated by oestrogens, results in increased cortisol concentrations compared with men. Decreased concentrations of anti-inflammatory cortisol further contribute to the pro-inflammatory status in men, possibly causing more severe COVID-19 courses in men compared with women. Other factors, such as age, smoking, alcohol consumption, and presence of comorbidities further contribute to the increased risk of severe disease and higher case fatality rates in men. Plus symbols mark an activation and minus symbols mark an inhibition. ACE2=angiotensin-converting enzyme 2. ACTH=adrenocorticotropic hormone. ADH=antidiuretic hormone. CRH=corticotropin-releasing hormone. DPP4=dipeptidyl peptidase-4. TMPRSS2=transmembrane protease serine subtype 2.

recruitment of stem cells from the capsule and cell proliferation.[1]

A more robust and enhanced release of stress hormones by the adrenal glands, including glucocorticoids, in response to acute stressors might contribute to greater protection against severe COVID-19 and mortality in women (figure 1). In this context, it is not surprising that potent glucocorticoids such as dexamethasone have been shown to be the most effective therapy currently available to limit the progression of severe COVID-19 and inflammation.[69,70] In a controlled, open-label trial of 6425 hospitalised patients with COVID-19, treatment with dexamethasone resulted in lower 28-day mortality in those receiving either invasive mechanical ventilation or oxygen only at randomisation.[69] A small prospective, triple-blind, randomised controlled trial (84 patients) demonstrated superiority of methylprednisolone compared with dexamethasone in terms of clinical status and length of hospitalisation in patients with COVID-19.[71]

Besides glucocorticoid concentrations, differential action of cortisol between sexes might contribute to a more favourable response of women to severe COVID-19 (figure 1). Recently, it has been shown that cytokine secretion and responsiveness of lymphomonocytes following cortisol exposure occurs in a sex-dependent manner.[72] Thus, following cortisol exposure, the concentrations of the pro-inflammatory cytokines IL-6 and IL-8 were increased in cells derived from males, whereas in female cells, IL-6 release was unchanged and IL-8 concentrations decreased. Furthermore, anti-inflammatory cytokines such as IL-4 and IL-10 did not change in male cells but increased in female cells. Therefore, these results suggest that cortisol can differentially affect lymphomonocytes in males and females, changing the cytokine release from a pro-inflammatory pattern in male cells to a more anti-inflammatory secretion profile in females.[72] Sex differences in cytokine storm, as well as in concentrations and effects of endogenous glucocorticoids, might provide a rational pathophysiological basis for explaining the potential advantage of women in managing severe COVID-19.

Clinical and public health implications of sex-based differences in COVID-19

Since men have a higher risk of developing severe COVID-19, the question arises whether older men (≥50 years) with severe comorbidities might require special consideration concerning prevention, screening, surveillance, and vaccination strategies. Conversely, women appear to be at increased risk of some vaccine-related adverse effects, vaccine breakthroughs, and long COVID (discussed in detail later). Therefore, a sex-specific approach could be desirable in making optimal recommendations of prevention and treatment strategies in the context of the COVID-19 pandemic. However, we are only just beginning to define sex-specific preventive and therapeutic approaches for COVID-19.

Considering that we are still far away from sex-specific treatment in other areas of clinical practice, it becomes obvious that there is still a long way to go until we reach the goal of a sex-specific or even individualised treatment of our patients.

Oestrogens versus androgens: novel therapeutic approaches in COVID-19

Regarding the development of novel therapeutic approaches in COVID-19, it has been hypothesised that increased oestrogen or progesterone signalling or decreased androgen signalling can be beneficial for improving COVID-19 outcomes in men. Therefore, pharmacological intervention modulating the biological effects of oestrogens and androgens appears to be a plausible approach. Since many drugs targeting these hormonal pathways are approved and have been in clinical use for years and even decades, there are a number of registered clinical trials (eg, NCT04728802, NCT04865029, NCT05172050) addressing this question, some of which have been completed and are awaiting publication. In a small randomised controlled pilot study of 42 men hospitalised with moderate-to-severe COVID-19, subcutaneous administration of progesterone in addition to standard treatment was associated with shorter hospitalisation and reduced requirement for oxygen supplementation compared with standard treatment alone.[73] The authors of a community-based study from the Veneto region of northern Italy with 4532 patients concluded that androgen deprivation therapy—used for the treatment of prostate cancer—might reduce the risk of infection with SARS-CoV-2.[74] Data from a small prospective cohort of 77 hospitalised men suggested that anti-androgenic treatment might have beneficial effects for the clinical outcome in patients with severe COVID-19.[75]

A retrospective cohort study of 5451 women with COVID-19 found that women who received hormone replacement therapy (HRT) had a lower mortality rate than those who did not receive HRT.[76] This was somewhat expected, as HRT is associated with therapeutic benefits, including reduced incidence of cardiovascular disease.[77] In addition, postmenopausal women present with increased concentrations of pro-inflammatory cytokines (IL-6, IL-1) and the use of oestrogen-associated HRT has shown potential to decrease the cytokine concentrations to the premenopausal levels.[78] In men with COVID-19, low circulating testosterone concentrations during hospitalisation were associated with increased disease severity, inflammation, and mortality in two observational studies.[79,80] Testosterone administration might also be beneficial in men hospitalised with COVID-19, because testosterone has been reported to effectively reduce inflammation by increasing anti-inflammatory cytokines (IL-10) and decreasing pro-inflammatory cytokines (IL-1β, IL-6, and TNFα).[81]

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are precursors for sex hormones that decrease with age and are higher in males. DHEA is a powerful inhibitor of glucose-6-phosphate dehydrogenase (G6PD), which has relevance in the context of the COVID-19 pandemic since the reduction of normal G6PD activity has been shown to sensitise human cells to coronavirus 229E infections.[82] Elevated DHEA concentrations exhibit toxic effects on endothelial cells, which might enhance SARS-CoV-2-induced vascular endothelialitis.[83] These effects are of particular relevance for people with diabetes, as they already have reduced G6PD activity in blood.[84] DHEA is an over-the-counter drug in the USA and is commonly used by men to compensate for age-related decline in circulating androgens. In view of the ongoing COVID-19 pandemic, such unrestricted distribution of DHEA might contribute to a more severe course of the disease in individual men, although there are no data currently available to support this theory. Placebo-controlled studies are required to investigate the use of DHEA in elderly men in the context of COVID-19.[85]

Due to sustained high concentrations of oestrogens during gestation, maternal outcomes in pregnant women with COVID-19 were analysed in a systematic review and meta-analysis based on data from 24 articles including 1100 pregnancies.[86] The authors concluded that pregnancy itself does not substantially affect maternal and neonatal outcomes; however, patient numbers were low, especially considering that pregnant women are usually of younger age without specific comorbidities. Conversely, a large US cohort study of women of reproductive age (15–44 years; 91412 women) revealed that pregnancy (8207 women) was associated with increased risk of hospitalisation, intensive care unit admission, and requirement for mechanical ventilation, but no difference in mortality was found.[87] In another cohort study from the UK (427 pregnant women), comorbidities such as hypertension, asthma, and diabetes were identified as major risk factors for hospitalisation of pregnant women.[88] Although physiological changes during pregnancy, including hormonal status, have implications for immune response, cardiovascular function, and the respiratory system, current knowledge regarding the course and risks of COVID-19 in pregnancy is still limited.[89]

Overall, these data suggest that hormone status should be given greater consideration in COVID-19 disease stratification and might offer potential therapeutic approaches for selected patients with COVID-19, but no defined recommendations can be made at this stage. For this purpose, it should first be clarified whether treatment with sex hormones is helpful during acute COVID-19 infection, or whether preventive use is beneficial only for certain populations with increased risk. Potential side effects of sex hormones, such as the occurrence of thrombosis, should also be taken into account.

Sex-dependent effects of COVID-19 vaccines and reinfections

Data from the past 2 years suggest that sex differences might also have implications for responses to SARS-CoV-2 vaccination (figure 2) and reinfection. Smaller studies propose that COVID-19 reinfections might be associated with increased severity compared with initial infection in both sexes; moreover, there is evidence that women are more commonly affected by COVID-19 reinfections than men.[90,91] The higher rate of reinfection in women is unexpected, since women show a stronger immune response. The reasons for this apparent paradox are unclear but might be related to increased antibody responses found in male convalescent plasma donors.[57,92] Described differences in social behaviour during the COVID-19 pandemic would also suggest increased susceptibility to reinfection in men compared with women. Panel evidence suggests that women are more likely to perceive COVID-19 as a very serious health issue and therefore more likely to agree with and comply with restrictive policies.[93] A study using mobile phone data from 1·2 million devices in Austria found gender differences in social behaviour during different phases of the COVID-19 pandemic; for example,
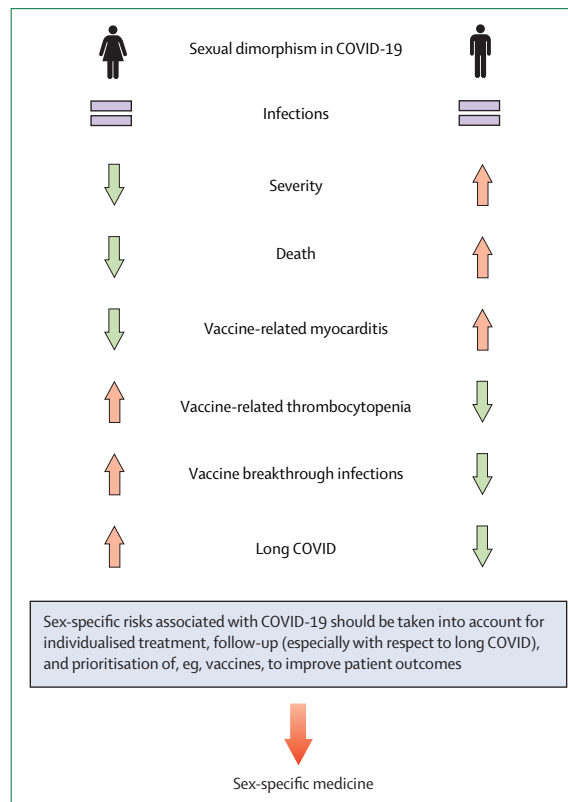

Figure 2: Sexual dimorphism in severity and mortality of COVID-19
Men experience more severe disease courses and more deaths connected to COVID-19, but women appear to be at increased risk of long COVID. Therefore, we argue that sex should be taken in consideration regarding COVID-19 treatment, follow-up, and establishment of public health measures.

women avoided larger shopping malls during lockdown, and after lockdown, men returned to their normal social behaviour faster than women.[94]

An asymptomatic or mild course of a first COVID-19 infection seems to increase the likelihood of reinfection compared with patients with symptomatic disease, which could be explained by a weaker immune response after a first infection with a mild course.[95,96] However, the COVID-19 reinfection rate associated with the beta and delta SARS-CoV-2 variants is low. Population-based data now indicate that the new omicron variant, first described in South Africa in November, 2021, is associated with a substantial ability to bypass immunity to previous infection,[97] potentially resulting in an increase in the number of reinfections.[98] COVID-19 vaccines are an effective tool to reduce the risk of reinfection.[99]

Women exhibit a more robust immune response to vaccines, associated with higher and longer-lasting protective antibody responses,[33] but report more frequently adverse side effects, including fever, pain, and inflammation, compared with vaccinated men.[100] This could be because women are more likely than men to report adverse side effects.[100] As discussed earlier, oestrogens and androgens differentially modulate immune responses (figure 1), including responses to vaccines; however, other factors, such as epigenetic and genetic differences and an additional X chromosome, are likely to play a role.

Another point of discussion is the general safety of currently available COVID-19 vaccines and, specifically, how extremely rare cases of unusual thrombocytopenia should be handled. These events, first reported after immunisation with ChAdOx1 nCoV-19 (AstraZeneca), have also been observed after administration of Ad26.COV2.S (Johnson & Johnson/Janssen)[101] and appear to occur preferentially in women below the age of 50 years.[102] The pathophysiology of these venous thromboembolic events affecting the cerebral sinus and splanchnic and pulmonary veins, and the reason why predominantly women are affected, remains largely unclear. This form of thrombocytopenia is mediated by platelet-activating autoantibodies against platelet factor 4 (PF4) and carries some resemblance to autoimmune heparin-induced thrombocytopenia.[102,103] While the European Medicines Agency continues to classify ChAdOx1 nCoV-19 (AstraZeneca) as safe and effective and recommends its use without restriction, several national and regional authorities in Europe, as well as in Australia and the UK, have restricted the use of this vaccine. In most countries, its use is recommended for people older than 60 years. Recent case reports describe rare cases of myocarditis (24 cases per million) after a second dose of mRNA-based COVID-19 vaccine, occurring predominantly in young men (18–29 years).[104,105] Moreover, rare cases of Guillain-Barré syndrome have been described after vaccination with Ad26.COV2.S (Johnson & Johnson/Janssen), particularly in men aged 50–64 years.[105] Despite these extremely rare potential adverse events, benefits of these vaccines clearly outweigh their risks.

Although all approved vaccines are highly effective, even fully vaccinated individuals can develop symptomatic or asymptomatic infection with SARS-CoV-2. Breakthrough infections in two women were reported in a fully vaccinated cohort (417 individuals), which received the second dose of BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) vaccine at least 2 weeks earlier.[106] In the USA, 10 262 SARS-CoV-2 vaccine breakthrough infections had been reported as of April 13, 2021, of which 6446 (63%) occurred in women.[107] These preliminary data indicate that females appear to be more at risk of vaccine breakthrough infections than males. With the emergence of the new omicron variant, which might bypass immunity, an adjustment of existing vaccines might be necessary to prevent increasing numbers of breakthrough infections.[98] The outlined differences between sexes with respect to susceptibility to reinfection and response to SARS-CoV-2 vaccines are rooted most likely in their specific immune responses; hence, we suggest that future recommendations for the allocation and prioritisation of certain vaccines should take biological sex into consideration.

Sex-related predisposition to long COVID

Another phenomenon with potential sex-related predisposition is long COVID (also named post-COVID syndrome), which is defined as a complex of non-specific persisting symptoms, such as chronic fatigue, muscle weakness, sleep difficulties, anxiety, and depression, that are observed in individuals after acute COVID-19 and are not explained by other diagnoses.[108] Post-virus syndromes, including chronic fatigue syndrome, are not uncommon after a variety of viral infections with extended course—eg, caused by cytomegalovirus or Epstein-Barr virus.[109,110] An increasing number of long COVID cases have been reported during the past months, and a female predominance is emerging, similar to chronic fatigue syndrome.[111,112] In a cohort study of 5838 individuals in Switzerland, women reported more frequently at least one persistent symptom, with reduced resilience being the most common symptom in both men and women.[113] In women, cardiovascular risk factors, pre-existing mental illness, and self-reported domestic stress increased the risk of long COVID.[113] Besides female sex, number of symptoms in the first week, BMI, and increasing age were found to be predictors for long COVID.[114] For long COVID in particular, as well as for any other symptoms reported to the physician, it is important to consider that there might also be sex-related differences in how symptoms are perceived and reported, which might affect outcomes of studies. For example, women with West Nile virus infection reported significantly more symptoms compared with men despite a similar viral load in men and women.[115]

Increasing evidence suggests that autoantibodies, whose concentrations exhibit also sex-specific

differences,[116,117] play a crucial role in the extended multi-organ illness in patients with long COVID.[118,119] Pre-existing asthma, which is more prevalent in women than in men, has been reported to further increase the risk of developing long COVID.[114,120] Further characterisation of predictors for long COVID, such as sex and comorbidities, might help to identify patients at high risk of developing long COVID and allow early intervention to address their individual needs and improve outcomes.

Conclusion

Taken together, there is evidence that sexual dimorphism in COVID-19 has potential implications that should be considered in treatment of COVID-19 and follow-up of patients predisposed to the development of long COVID, as well as for vaccine prioritisation. While COVID-19 infections are more frequently associated with a severe course and higher mortality in men, women appear to be predisposed to long COVID (figure 2). Although general molecular mechanisms do not differ between males and females, differences in the expression patterns of several cell surface proteins responsible for virus binding and entry, as well as sex-specific differences in the stress and immune response, likely contribute to the observed sexual dimorphism in COVID-19. Reanalysis of our own data[121] regarding sexual dimorphism suggests that male patients have a higher expression of ACE2 and inflammatory markers in the coronary tree than female patients with similar cardiovascular diseases. This might further underline a specific predisposition of men to having a higher susceptibility to severe and fatal COVID-19. Lifestyle and behavioural factors, differences in the presence of comorbidities, and sex-specific risk factors also contribute to sexual dimorphism in COVID-19 and should always be considered. Although there are no known clear mechanisms yet to explain sexual dimorphism in COVID-19, as reviewed here, there are many possible leads, some of which are worthy of further exploration. Therefore, larger prospective and mechanistic studies are required to provide scientifically robust evidence to draw improved conclusions that would allow for clear recommendations for the prevention and management of patients with COVID-19 based on sex differences.

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