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.

European Journal of Pharmacology 912 (2021) 174548

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Sex-related susceptibility in coronavirus disease 2019 (COVID-19): Proposed mechanisms

Zinnet Şevval Aksoyalp [a,*,1], Dilara Nemutlu-Samur [b,1]

[a] Izmir Katip Celebi University, Faculty of Pharmacy, Department of Pharmacology, 35620, Izmir, Turkey
[b] Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Pharmacology, 07450, Antalya, Turkey

ARTICLE INFO

Keywords:
ACE2
TMPRSS2
Immune system
Sex hormones
Vaccines
Adverse drug reactions

ABSTRACT

The importance of sex differences is increasingly acknowledged in the incidence and treatment of disease. Accumulating clinical evidence demonstrates that sex differences are noticeable in COVID-19, and the prevalence, severity, and mortality rate of COVID-19 are higher among males than females. Sex-related genetic and hormonal factors and immunological responses may underlie the sex bias in COVID-19 patients. Angiotensin-converting enzyme 2 (*ACE2*) and transmembrane protease/serine subfamily member 2 (*TMPRSS2*) are essential proteins involved in the cell entry of SARS-CoV-2. Since *ACE2* is encoded on the X-chromosome, a double copy of *ACE2* in females may compensate for virus-mediated downregulation of *ACE2*, and thus *ACE2*-mediated cellular protection is greater in females. The X chromosome also contains the largest immune-related genes leading females to develop more robust immune responses than males. Toll-like receptor-7 (TLR-7), one of the key players in innate immunity, is linked to sex differences in autoimmunity and vaccine efficacy, and its expression is greater in females. Sex steroids also affect immune cell function. Estrogen contributes to higher $CD4^+$ and $CD8^+$ T cell activation levels, and females have more B cells than males. Sex differences not only affect the severity and progression of the disease, but also alter the efficacy of pharmacological treatment and adverse events related to the drugs/vaccines used against COVID-19. Administration of different drugs/vaccines in different doses or intervals may be useful to eliminate sex differences in efficacy and side/adverse effects. It should be noted that studies should include sex-specific analyses to develop further sex-specific treatments for COVID-19.

1. Introduction

The novel Coronavirus disease 2019 (COVID-19) is severe pneumonia caused by Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) (Abate et al., 2020). It was first identified in China, then spread rapidly worldwide and declared a pandemic by the World Health Organization (WHO) (Takahashi et al., 2020). More than 4.5 million people died, and 200 million have been infected worldwide until September 2021 (Johns Hopkins University, 2021). The clinical spectrums of SARS-CoV-2 infection range from asymptomatic to fatal pneumonia. The symptoms of COVID-19 are high temperature, dry cough, myalgia, headache, fatigue, diarrhea, sore throat, and taste or smell abnormalities (Struyf et al., 2020). Besides the respiratory pathology, SARS-CoV-2 causes unpredictable cardiovascular, renal, endocrine, dermatologic, ocular, and gastrointestinal complications (Gupta et al., 2020). Mortality of COVID-19 is higher in the elderly (>80 years) or individuals with comorbidities, including diabetes mellitus, cancer, cardiovascular and respiratory diseases (Onder et al., 2020).

Although the fatality rates vary widely, available data lacks the detailed analysis of underlying contributory factors (Schiffer et al., 2020). Sex is one of the essential contributors to disparities in diseases. It may affect the susceptibility of individuals to the disease and cause differences in incidence and mortality rates between males and females (Gebhard et al., 2020). Since sex differences may alter the immunological, hormonal, and cardiovascular pathophysiological responses to SARS-CoV-2, it affects the severity and progression of the disease, as well as the efficacy of pharmacological treatment and adverse events related to the drugs used against COVID-19 (Schiffer et al., 2020). Independent of age, the prevalence of serious symptoms and mortality rate are higher in male COVID-19 patients than in their female counterparts (Schiffer

* Corresponding author. Postal address: Izmir Katip Celebi University, Faculty of Pharmacy, Department of Pharmacology, 35620 Izmir, Turkey.
E-mail addresses: zinnetsevval.aksoyalp@ikcu.edu.tr (Z.Ş. Aksoyalp), dilara.samur@alanya.edu.tr (D. Nemutlu-Samur).
[1] Z.Ş. Aksoyalp and D. Nemutlu-Samur contributed equally.

https://doi.org/10.1016/j.ejphar.2021.174548
Received 30 July 2021; Received in revised form 7 September 2021; Accepted 29 September 2021
Available online 2 October 2021

et al., 2020). The results of the COVID-19 Sex-Disaggregated Data Tracker database displayed that similar numbers of cases in males and females, but the mortality rate of males (10.4%) was higher than females (7.0%) in the vast majority of countries (Global Health 5050, 2021). Similarly, a study compiling data on the severity of COVID-19 in Europe found that males were hospitalized 50% more often than females (Gebhard et al., 2020). Mortality, intubation, and intensive care unit care in COVID-19 were independently linked with the male sex (Jun et al., 2021). In a meta-analysis, the prevalence of symptomatic COVID-19 was higher in males than females (Abate et al., 2020), and the severe COVID-19 is more common in males than females (Vahidy et al., 2021; Xu et al., 2020). Likewise, males had worse clinical outcomes, more severe complications, and more hospitalizations than female COVID-19 patients (Montopoli et al., 2020). SARS-CoV-2 RNA was found for a longer period in males, so the male sex was associated with prolonged SARS-CoV-2 RNA shedding (Xu et al., 2020).

The sex differences in COVID-19 may be due to both sex (biological) and gender (sociocultural/traditional) variable (Gebhard et al., 2020). Unfavorable lifestyle habits and age-adjusted rates of pre-existing comorbidities (cardiovascular and respiratory diseases) are higher in males than females and are associated with poor COVID-19 prognosis (Abate et al., 2020; Petrilli et al., 2020; Yang et al., 2020). Comorbidities and lifestyle differences may explain the distinct COVID-19 outcomes between males and females; however, the role of sex in COVID-19 sustain unrecognized (Gagliardi et al., 2020). In pharmacological studies, females seem underrepresented, and data are rarely disaggregated by sex. Therefore, differences in the efficacy and side/adverse effects of drugs in males and females may have been precisely undetected, and sex may affect the efficacy and side/adverse effects of treatment in COVID-19 (Bischof et al., 2020a, 2020b). A scoping review by Schiffer et al. included thirty studies investigating pharmacological treatments for COVID-19 and found that none of these studies performed sex-based randomization nor investigated sex as a potential modifier (Schiffer et al., 2020). Underrepresentation of females, lack of considering sex as a confounder, lack of sex-stratified randomization and not investigation sex as a potential effect modifier in pharmacologic study limits understanding of sex-based differences in drug responses (Schiffer et al., 2020). While some papers report sex variations, the evidence is not precise since there are some inconsistencies in the COVID-19 prevalence among males and females (Abate et al., 2020). Moreover, there are only a few systematic reviews and meta-analyses regarding sex variations in the risk for COVID-19 (Abate et al., 2020). Hence, this review aims to synthesize the current data about the proposed mechanisms of the independent role of sex in COVID-19, its effects on drug efficacy and adverse drug reactions, and the vaccine responses. We searched PubMed, Scopus, and ScienceDirect for studies on sex differences in COVID-19 until September 1st, 2021.

2. Mechanisms of sex differences in COVID-19 pathogenesis

2.1. Genetic and hormonal factors

Although the mechanisms of sex bias in respiratory viral diseases have not been elucidated yet, some hypotheses may help us predict the fundamental causatives (Gagliardi et al., 2020). The SARS-CoV-2 employs the angiotensin-converting enzyme 2 (*ACE2*) receptor and transmembrane protease/serine subfamily member 2 (*TMPRSS2*) as its entry receptor (Hoffmann et al., 2020). The virus first engaged with *ACE2* as a cell entry protein, then *TMPRSS2*-mediated proteolytic processing of the virus spike protein facilitates viral entry (Baratchian et al., 2021). *ACE2* gene is expressed widely in the heart, upper airways, lungs, intestine, testis, kidney, liver and is protective in those tissues (Gheblawi et al., 2020). On the contrary to the classical renin-angiotensin system (RAS) pathway in which the angiotensin II production leads to vasoconstriction, sodium reabsorption, and fluid retention to increase blood pressure, *ACE2*, the counterregulatory branch of the RAS, produces angiotensin 1-7 from angiotensin II (Viveiros et al., 2021). Angiotensin 1-7 then activates the Mas receptor, and *ACE2*/Angiotensin (1–7)/Mas axis exerts vascular and organ protective effects (Santos et al., 2018). *ACE2* protein is downregulated when the spike protein of SARS-CoV-2 binds to it (Hanff et al., 2020). Decrease activity of *ACE2* leads to an increase of the *ACE/ACE2* balance and activates the *ACE* arm in the RAS, which will further increase ROS production, vasoconstriction, and inflammation provoking acute respiratory failure (Pagliaro and Penna, 2020).

Serum *ACE/ACE2* activity ratios are higher in males than in females (Pagliaro and Penna, 2020). *ACE2* encoding genes are located on the X chromosome (Tipnis et al., 2000). Females' double copy of *ACE2* may compensate for virus-mediated downregulation of membrane *ACE2* (Viveiros et al., 2021). Additionally, female sex hormones impact *ACE2* expression (Hilliard et al., 2013). Estrogen downregulates *ACE* and simultaneously upregulates *ACE2*, AT2 receptor, and Mas levels in the human atrial myocardium (Bukowska et al., 2017). Since estrogen triggers the system toward the *ACE2*/Angiotensin 1-7 production, serum *ACE2* activity is higher in females than in the male serum (Hilliard et al., 2013). It also directly inhibits the SARS-CoV replication (Channappanavar et al., 2017). Moreover, estrogen inhibits *TMPRSS2*, which facilitates virus entry into cells and increases the expression of a disintegrin and metalloprotease 17 (ADAM17), which helps cleavage the *ACE2* ectodomain. Thus, higher levels of soluble *ACE2* neutralizes SARS-CoV-2 and prevent its attachment to the *ACE2* (Al-kuraishy et al., 2021). On the whole, higher levels of *ACE2* may suppress immune inflammation in females naturally, and this effect may answer why mortality rates in COVID-19 are lower in females regardless of age (Pagliaro and Penna, 2020).

ACE2 is also expressed in neurons (Yashavantha Rao and Jayabaskaran, 2020). SARS-CoV-2 could enter the central nervous system (CNS) and cause neurological diseases by impairing the crosstalk between neuronal and vascular components of the CNS (Desforges et al., 2014; Lionetti et al., 2021). SARS-CoV-2 triggers a dysfunction in endothelial cells, causing apoptosis (Varga et al., 2020). This conception is supported by the fact that microvascular endothelial cells express *ACE2* and, therefore, are susceptible to SARS-CoV-2 entry (Lionetti et al., 2021). The vascular and neuronal circulation of SARS-CoV-2 is thought to induce heart-brain axis (HBA) dysfunction (Lionetti et al., 2021). HBA can be defined as the bidirectional flow of signals between heart and brain (Baroni et al., 2021). SARS-CoV-2 can inhibit the HBA by (i) its neurotropic effects on the neural cardiovascular control centers, (ii) interfering with the local bidirectional neuronal to vascular communication or (iii) increasing the susceptibility to psychosocial factors resulting in stress or anxiety (Lionetti et al., 2021). Imbalance in the *ACE/ACE2* ratio and autonomic outflow leads to HBA dysfunction may worsen the outcomes and leads to severe multiorgan disease syndrome (MODS) in the COVID-19 patients (Lionetti et al., 2021). Genetic and hormonal factors, particular role of different mediators, and diverse regulation of RAS between sexes may underlie the sex-specific changes in HBA (Baroni et al., 2021). Although sex-related differences in HBA are not well-studied, estrogens might protect the HBA from viral infection and the detrimental consequences of RAS dysregulation since it regulates the *ACE/ACE2* ratio (Hilliard et al., 2013; Lionetti et al., 2021).

Estrogen-mediated upregulation of the Mas-receptor was protective against acute lung injury in animal models (Carey et al., 2007; Erfinanda et al., 2021). In ovariectomized mice, the acute lung injury was restored with estrogen replacement therapy (Speyer et al., 2005). Estradiol is the dominant estrogen along the reproductive period and is associated with reduced lung injury, platelet aggregation, and viral infection (Breithaupt-Faloppa et al., 2020). Estradiol was associated with the reduced mortality rates in >50 age females (Seeland et al., 2020). Since exogenous estradiol treatment has benefits on the survival rates in postmenopausal females, it may be used as an adjuvant in COVID-19 patients (Seeland et al., 2020). Garg et al., showed a higher mortality rate in postmenopausal females (12.8%) compared with premenopausal ones

(8.6%), emphasizing the protective effect of estrogen in COVID-19 (Garg et al., 2020). A short seven-day course use of estradiol via transdermal route is believed to reduce the severity of the disease in adult males and older females when administered before intubation (ClinicalTrials.gov; Identifier: NCT04359329) (Seeland et al., 2020).

Estradiol, a primary female sex steroid, binds to the cytoplasmic estrogenic receptors expressed on T cells and B cells, respectively, and triggers humoral immunity to produce antibodies against various viral infections (Al-kuraishy et al., 2021). The high estradiol levels in the periovulatory-pregnancy period are typically inhibited important proinflammatory cytokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor (TNF)-α (Straub, 2007). The low estradiol levels have no or even stimulatory effects (Straub, 2007). IL-6 is predicted to play a central role in the cytokine storms and caused severe symptoms in COVID-19 (McGonagle et al., 2020). IL-6 production is decreased by estrogens while increased by the androgens (Dorak and Karpuzoglu, 2012). Therefore, estrogen is believed to decrease strong cytokine release underlying the tissue/organ damage of COVID-19 infection (Newson et al., 2021). Estrogen receptor antagonist or ovariectomy increased mortality in female mice infected with SARS-CoV, and estrogen receptor signaling is crucial for protection in females (Channappanavar et al., 2017).

In contrast to estrogen, the male sex hormone testosterone is shown to suppress the immune system, and hypoandrogenism was associated with increased inflammatory cytokines and a decrease in T cell response (Peckham et al., 2020). Clinical and preclinical studies showed that testosterone deficiency increases proinflammatory cytokines (IL-1β, IL-6, and TNF-α) while testosterone replacement reduces. Testosterone was found to inhibit the proinflammatory cytokine release in the lung and found protective in murine models of severe influenza (Tuku et al., 2020). Dhindsa et al., showed that the testosterone levels were 65%–85% lower in males with severe COVID-19 than males with a milder disease progression (Dhindsa et al., 2021). They also mentioned that this difference was independent of other known risk factors associated with the severity of the disease, such as age, body mass index, comorbidities, smoking, and race (Dhindsa et al., 2021). Rastrelli et al., indicated that the low level of testosterone is related to cytokine storm, poor prognosis, and increased mortality rate in SARS-CoV-2-infected patients admitted to the respiratory intensive care unit with COVID-19 (Rastrelli et al., 2021). Low levels of testosterone have also been associated with increased IL-6 in older males and may increase lung damage in COVID-19 because of the upregulation of *ACE2* receptors in the lower respiratory system (Al-Lami et al., 2020; Hussain et al., 2020). Interestingly, Montopoli et al., found that androgen-deprivation therapy for prostate cancer has been associated with improved outcomes and decreased incidence for COVID-19 (Montopoli et al., 2020); however, this relationship was not further confirmed with other studies (Koskinen et al., 2020; Kwon et al., 2021). The former effects may be attributed to diminished mobility correlated with androgen deprivation-induced sarcopenia, which may have decreased the risk of exposure to the virus (Dhindsa et al., 2021).

Although SARS-CoV-2 utilizes *ACE2* for host-cell entry, higher *ACE2* expression levels are not associated with the viral load and severity of disease (Kuster et al., 2020) since other proteases such as ADAM17 (TNF-α-converting enzyme) and *TMPRSS2* are also major mechanisms for the viral entry (Valenzuela et al., 2021). The second protein, necessary for SARS-CoV-2 invasion into cells as it is involved in spike protein priming, the transmembrane serine protease *TMPRSS2*, is primarily expressed in the prostate epithelium (Gebhard et al., 2020). It is also expressed in airway epithelia, where its physiologic function is unclear (Gebhard et al., 2020). SARS-CoV-2 may enter into cells more efficiently in males because the higher expression of *TMPRSS2* facilitates virus entry (Bunders and Altfeld, 2020). Although *TMPRSS2* transcription is regulated by androgens in prostatic tissues (Tomlins et al., 2005), Baratchian et al., showed that androgens do not modulate its expression in the lungs in a similar manner (Baratchian et al., 2021). Therefore, *TMPRSS2* modulation in the lung appears different from prostatic tissues in which apparent androgen-dependent modulation is (Baratchian et al., 2021). They also indicated that *TMPRSS2* expression in human male and female lungs is not different (Baratchian et al., 2021). Moreover, in male mice, treatment with the androgen receptor antagonist enzalutamide did not decrease pulmonary *TMPRSS2* (Baratchian et al., 2021). Therefore, pulmonary *TMPRSS2* regulation seems not to count in sex differences in COVID-19 clinical outcomes (Baratchian et al., 2021).

2.2. Adaptive and innate immunity

Sex differences substantially affect the prevalence, severity, and pathogenesis of infectious diseases (Viveiros et al., 2021). A higher number of innate immune cells include monocytes, macrophages, and dendritic cells (DCs) in females than in males (Gebhard et al., 2020). The X chromosome contains the most prominent immune-related genes in the human genome (Bianchi et al., 2012). Females have a double copy of important immune genes because of their XX chromosome, whereas males have only a single copy in their XY chromosome (Abate et al., 2020). Therefore, females develop stronger inflammatory immune responses than males (Gebhard et al., 2020).

Toll-like receptors (TLRs) that recognize bacterial or viral DNA/RNA are the key innate immune pattern recognition receptors (Alwani et al., 2021). They are expressed on both the innate immunity cells (DCs, macrophages, natural killer cells) and adaptive immunity cells (T cells and B cells) (Khanmohammadi and Rezaei, 2021). There are ten different types of TLRs in the human genome as TLR1-10 (Khanmohammadi and Rezaei, 2021). The expression of TLRs is sex-specific (Pradhan and Olsson, 2020). TLR-3, TLR-7, and TLR-9 recognizing viral nucleic acids are female-biased, while TLR-2 and TLR-4 recognizing bacterial nucleic acids are male-biased (Pradhan and Olsson, 2020). Among them, TLR-7 is linked to sex differences in autoimmunity and vaccine efficacy since it escapes X chromosome inactivation, resulting in greater expression in female immune cells (Scully et al., 2020). Upon recognizing viral infection, TLR7 triggers the production of type I interferons (IFNs) with antiviral functions to control viral replication and activate an adaptive immune response to clear the infection (Alwani et al., 2021). Hadjadj et al. showed that the disease is more severe when the viral load in the blood is persistent and the levels of IFNs are low or no because of the impaired inflammatory responses (Hadjadj et al., 2020). Since TLR7 is activated by estrogen and IFN-α production is greater in adult female plasmacytoid DCs than that of adult males, COVID-19 prognosis may be better in females (Pradhan and Olsson, 2020; Scully et al., 2020).

Regarding adaptive immunity, females have higher $CD4^+$ and $CD8^+$ T cell activation levels and more B cells than males (Peckham et al., 2020), resulting in an efficient response to the infectious agents (Haitao et al., 2020). Sex steroids affect immune cell function via their specific receptors expressed in lymphoid tissue cells and immune cells (Gebhard et al., 2020). Estrogen has a dual role depends on its levels. At low doses, as seen in postmenopausal females, it has immunostimulatory properties and induces differentiation of inflammatory DCs, higher levels of IL-4 and IFN-α and promotes Th1 responses (Xu et al., 2020). Contrarily, at higher doses similar to those in premenopausal females, it increases anti-inflammatory Th2 responses and inhibits the proinflammatory innate immune response (Xu et al., 2020). Premenopausal females are at high risk for COVID-19, but the survival in <50 age is higher for females than males (Seeland et al., 2020). Moreover, nitric oxide (NO) is known to have a role in the immune system since it inhibits viral replication (Saura et al., 1999). It is known that estrogen increases NO production via estrogen receptor-mediated endothelial nitric oxide synthase (eNOS) activation (Chambliss and Shaul, 2002). The effect of estrogen on NO may provide additional protection against COVID-19 and explain why females experience less severe COVID-19.

In general, testosterone has an immunosuppressive effect, while estrogen has an immuno enhancing effect (Roved et al., 2017; Taneja,

2018). Testosterone can be converted to estrogen via the aromatase enzyme in the peripheral tissues and may act as an anti-inflammatory agent (Bianchi, 2019). Specifically, androgen receptor stimulation decreases the production of proinflammatory cytokines (Malkin et al., 2004). Androgen deficiency in males causes a high release of inflammatory cytokines and increases the CD4+/CD8+ T-cells ratio (Wehbe et al., 2021). Moreover, androgens' inhibitory effect on the differentiation of Th1 secreting IFN-γ explains the enhanced susceptibility to viral infections in males (Di Resta et al., 2021).

Once the SARS-CoV-2 enters the cell and is recognized by alveolar macrophages, the production of proinflammatory cytokines and chemokines is triggered (Wehbe et al., 2021). Studies showed that greater upregulation of proinflammatory cytokines, including IL-7, IL-16, and IL-18, in males with COVID-19 infection compared with females (Haitao et al., 2020; Takahashi et al., 2020). At the early stage of viral invasion, a more robust inflammatory response of females helps a rapid clearance of the virus (Xu et al., 2020). If the virus is not cleared timely, it causes overreaction in immune response, and excessive cytokine production leads to a cytokine storm with a widespread inflammation and multi-organ damage (Wehbe et al., 2021). The extended activation of the immune system in females may contribute to viral infection-related immunopathology (Wehbe et al., 2021). The lower immune response causes persistent viral infections in males and may contribute to increased disease severity, and thus a weak immune response can also cause significant damage (vom Steeg and Klein, 2016). As a result, it has been suggested that both weak and strong immune responses cause damage to the host.

Inflammasomes are intracellular receptors of the innate immune system and are required to produce inflammatory cytokines to various stimuli (Zhao et al., 2021). *Nucleotide-binding oligomerization domain (NOD)-like receptor containing pyrin domain 3 (NLRP3)* is the best-identified inflammasomes and plays a role in numerous inflammatory diseases (Zhao et al., 2021). Distinct physiological and biochemical features between males and females may result in variations in the activation of *NLRP3* inflammasome (Zhang et al., 2021a). Testosterone can induce the *NLRP3* inflammasome activation (Alves et al., 2020; Ma et al., 2020), and *NLRP3* mRNA expression was higher in males than in females (Wu et al., 2016). Estradiol may suppress *NLRP3* inflammasome activation and proinflammatory cytokine production in rat and mouse hippocampus (Thakkar et al., 2016; Xu et al., 2016). Progesterone may also reduce *NLRP3* inflammasome activation in rats (Espinosa-Garcia et al., 2020). The reduced immune response may be related to the dysregulated *NLRP3* inflammasome activity that causes severe COVID-19 (van den Berg and Te Velde, 2020). Overactivation of *NLRP3* inflammasome causes excessive IL-1β, IL-6, and TNF-α production, which may be responsible for the cytokine storm caused by SARS-CoV-2 (Zhang et al., 2021a). *NLRP3* inflammasome may also have a role in the respiratory, cardiovascular, and neurological complications in COVID-19 (Zhao et al., 2021). N proteins encoded by the SARS-CoV-2 genome have been shown to activate the *NLRP3* inflammasome and response (Pan et al., 2021). SARS-CoV-2 caused excessive NLRP3 inflammasome signaling by hyperactivation of the classical RAS pathway. Because SARS-CoV-2 leads to *ACE2* internalization, angiotensin II is not processed to angiotensin 1–7 (Ratajczak et al., 2021). *NLRP3* inflammasome can be a potential target for the treatment of COVID-19. Inhibitors directly targeting the *NLRP3* inflammasome, such as melatonin, statins, sirolimus, azithromycin, cyclosporine, colchicine, baricitinib, and acalabrutinib, are worth investigating in clinical trials for the COVID-19 treatment thus far (Zhao et al., 2021).

3. Sex differences in efficacy of COVID-19 drugs

According to the study of Brady et al., only 4% of registered COVID-19 studies considered sex/gender as an analytical variable, while few (21.2%) mentioned sex/gender solely as a recruitment criterion (Brady et al., 2021). Ignoring sex biases in drug efficacy and reactivity may cause increased adverse reactions or even deaths (Bischof et al., 2020b). Many drugs, including chloroquine or hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir combination, tocilizumab, convalescent plasma, and immunoglobulins, have drawn attention for their encouraging *in vitro* results and beneficial effects in the SARS and the Middle East Respiratory Syndrome (MERS), two other coronavirus diseases (Ambrosino et al., 2020). Meanwhile, only remdesivir, an antiviral medication, was approved by FDA for COVID-19 treatment (Ambrosino et al., 2020). It shortened the recovery time and decreased mortality rates of COVID-19 patients (Beigel et al., 2020). The recovery rate ratio for female patients using remdesivir was slightly higher than male ones (Beigel et al., 2020); however, the authors did not mention if this difference is statistically significant or not.

The off-label use of anti-inflammatory drugs to alleviate excessive inflammation is also noticeable. The Colchicine Coronavirus SARS-CoV-2 Trial (COLCORONA) showed that colchicine led to a lower rate of the composite of death or hospital admission than placebo (Tardif et al., 2021). However, while the primary efficacy composite endpoint was reduced by colchicine in the total cohort and males, a subgroup analysis pointed to a lower efficacy in females (Tardif et al., 2021). Furthermore, preclinical reports mentioned a higher acute oral toxicity of colchicine in female rats as than males, and that female rats were two times more susceptible to the lethal effects of colchicine than male rats (Wiesenfeld et al., 2007). According to previous studies, immunomodulators (i.e., corticosteroids, iv immunoglobulin, tocilizumab, baricitinib) may help control inflammatory responses and improve the prognosis of COVID-19 (Xu et al., 2020). However, there is no sex-based investigation of the efficiency of immune-modulatory treatment on COVID-19 (Xu et al., 2020). Only in a study evaluating the pharmacokinetics of methylprednisolone, it was found that females were more sensitive to it; however, the efficacy of methylprednisolone in females was similar to the males since females have rapid clearance and short elimination half-life (Lew et al., 1993). Because convalescent plasma contains potentially therapeutic antibodies to SARS-CoV-2, it has been widely used for COVID-19 (Joyner et al., 2021). For the proof of concept, Fink et al., showed that the transfer of antibodies from vaccinated females into naïve mice (males or females) provided better protection against influenza (Fink et al., 2018). In their prospective study, Duan et al. showed that convalescent plasma is safe, and it improves symptoms and laboratory parameters and reduces viral load (Duan et al., 2020). In another retrospective study, Joyner et al., showed that convalescent plasma with higher anti–SARS-CoV-2 IgG antibody levels were associated with a lower risk of death (Joyner et al., 2021). Although both studies include more male patients than female patients, the authors did not perform sex-specific analyses.

4. Sex differences in COVID-19 vaccine responses

Vaccines are expected to be the most effective way to handle global pandemics and prevent deaths (Fischinger et al., 2019). Biologically differences between males and females may also contribute to sex-specific vaccine outcomes (Klein et al., 2015). For instance, after vaccination against influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox, and dengue viruses, protective antibody responses are twice as high in adult females as compared with males (Klein et al., 2010). The studies with inactivated influenza vaccines reveal that adult females produce greater IL-6 and antibody responses than males, and the mentioned sex differences are decreased with aging (Potluri et al., 2019).

Since the T cell activation and antibody production are greater in females, they are more resistant to bacterial and viral infections (Klein et al., 2015). As another example of a viral vaccine eliciting a stronger response in females, the yellow fever virus vaccine-induced rapid upregulation of TLR-associated genes that activate interferon production, a trend that was not observed in males (Klein et al., 2010). However, females also tend to experience more adverse reactions following

vaccination due to this enhanced immune activation (Fischinger et al., 2019). Males generally exhibit greater susceptibility, prevalence, and severity of infection than females (Ingersoll, 2017). Sex hormones enhance or reduce the expression of cell surface molecules used for viral entry, thereby affect the susceptibility to infections. However, the exact contributors to these differences are still poorly understood (Fischinger et al., 2019). Males with elevated serum testosterone levels obtained the lowest antibody responses to the influenza vaccine, but the exact mechanism underlying this response is not clear (Furman et al., 2014). Sexual dimorphism does not draw enough attention in vaccine studies (Wehbe et al., 2021). Nor the efficacy or the adverse effects have been evaluated by considering sex differences (Wehbe et al., 2021). Following the COVID-19 vaccine injection, DCs in the area capture the particles and activate the adaptive immune system by presenting antigen to T cells (Teijaro and Farber, 2021). Natural killer cells are able to stimulate or inhibit the T-cell responses and the immune reaction to the vaccine (Crouse et al., 2015). Vulpis et al., demonstrated significant differences in the uptake of lipid nanoparticles used in vaccine development between male and female natural killer cells (Vulpis et al., 2021). Their findings revealed that vaccines to increase T cell immune responses to SARS-CoV-2 might be warranted for male patients, whereas female patients might benefit from therapies that dampen innate immune activation early during disease (Takahashi et al., 2020).

Leading vaccine companies, including Pfizer/BioNTech and Moderna, used nanoparticle-based vaccines against the COVID-19 (Vulpis et al., 2021). Recently, Pfizer-BioNTech COVID-19 Vaccine is named Comirnaty and was approved by FDA. The evaluation of sex bias for these vaccines would be more valuable than other vaccines (Vulpis et al., 2021). New reports have been shown that these vaccines have slightly better efficacy in males than in females (Vulpis et al., 2021). Pfizer/BioNTech BNT162b2 mRNA Vaccine was effective 96.4% in males, and 93.7% in females (Polack et al., 2020) and Moderna mRNA1273 vaccine was effective 95.4% in males and 93.1% in females (Baden et al., 2020) (Table 1). The interim results of the phase 3 trial of Oxford–AstraZeneca ChAdOx1 nCoV-19 vaccine indicated higher female participation due to the focus on enrolment of healthcare workers; however, authors did not clarify the contribution of sex difference on the effectiveness of the vaccine (Voysey et al., 2021). Efficacy of Ad26.COV2.S vaccine (Johnson & Johnson) against COVID-19 was 68.8% in males and 63.4% in females for cases with onset $\geq$14 days post-vaccination and was 69.8% in males and 60.3% in females for cases with onset $\geq$28 days post-vaccination (Sadoff et al., 2021). In the phase 1/2 trial of the CoronaVac (Sinovac Life Sciences) inactivated SARS-CoV-2 vaccine, the female participants were higher (Zhang et al., 2021b) whereas more males were involved in the phase 3 trial (Tanriover et al., 2021); however, no discussion about sex bias in the vaccine effects performed in those studies. The same vaccine dose or a similar vaccination schedule may not be suitable for males and females, and thus sex differences in vaccine response should be further investigated and data disaggregated by sex in COVID-19 studies.

5. Sex differences in adverse drug reactions to COVID-19 drugs and vaccines

More adverse drug reactions are reported for females worldwide (Watson et al., 2019), and this may be due to differences in sex-specific pharmacokinetics, pharmacodynamics, and fluctuations in sex hormone levels (Madla et al., 2021). Since sex/gender affects treatment success, one-size-fits-all concepts in therapeutic approaches do not work (Bischof et al., 2020b). Evidence shows that the pharmacokinetics process of antiviral drugs varies between males and females and that adverse drug reactions to antiviral drugs are more frequent in females than males (Shiau et al., 2014). It was found that when lopinavir or ritonavir is administered in the same dose, plasma concentrations of ritonavir were higher in females (Smith et al., 2014). However, atazanavir plus ritonavir combination was related to a higher risk of virologic failure in females than in males, probably because of low adherence and tolerability of atazanavir plus ritonavir in females (Smith et al., 2014). Atazanavir clearance was also slower in females, and thus, its levels were higher in females than males (Smith et al., 2014). It may be because that the glomerular filtration rate is higher in males than in females (Schwartz, 2003). Sex differences in pharmacokinetics may result from the discrepancy in body surface area, weight, and water/fat distribution between males and females. For example, gastric motility is faster in males than females, and thus the absorption of drugs is faster in males (Madla et al., 2021). Since females have higher fat mass and lower lean mass than males, lipophilic drugs tend to accumulate in females (Madla et al., 2021). Additionally, the blood concentration of the same dose of water-soluble drugs is lower in males since the total body water and blood volume are larger for males than females (Soldin and Mattison, 2009). The activity of drug-metabolizing enzymes (phase I and phase II) displays remarkable sex-dependent differences (Farkouh et al., 2020). For example, the activity of CYP2D6 and 3A4 are higher in females, whereas 1A2 is higher in males. Sulfotransferase activity is higher in males, while N-acetyltransferase is higher in females (Farkouh et al., 2020). Estrogen and progesterone change the hepatic enzyme activity and may increase the accumulation or decrease the elimination of drugs metabolized by these enzymes (Soldin and Mattison, 2009). Moreover, females may be more susceptible to adverse drug effects due to changes in pharmacodynamic mechanisms such as receptor number, binding,

Table 1
The role of sex differences in the efficacy and adverse effects of vaccines for COVID-19. Abbreviations. M: male, F: female.

Vaccines (Developer)	Type	Sex Differences in Efficacy % (95% CI)	Sex Differences in Adverse Effects	References
BNT162b2- Comirnaty (Pfizer/BioNTech)	mRNA vaccine	M: 96.4% (88.9–99.3) F: 93.7% (84.7–98.0)	Myocarditis under 30 years of age M: 41 cases per million F: 4.2 cases per million	Polack et al. (2020) Baden et al. (2020) Gargano et al. (2021)
mRN-1273 (Moderna)		M: 95.4% (87.4–98.3) F: 93.1% (85.2–96.8)		
ChAdOx1 nCoV-19 (Oxford–AstraZeneca)	Adenovirus vector vaccine	Not available	Thrombotics events F: 19 cases M: 9 cases	Tobaiqy et al. (2021)
Ad26.COV2.S Janssen COVID-19 Vaccine (Johnson & Johnson).	Adenovirus vector vaccine	M: 68.8% (60.1–75.9) F: 63.4% (53.1–71.7)	Guillain-Barré syndrome 50–64 years of age M: 15.6 cases per million Thrombosis with thrombocytopenia syndrome 30–49 years of age F: 8.8 cases per million	(Sadoff et al., 2021) (Rosenblum et al., 2021)
CoronaVac (Sinovac Life Sciences)	Inactive vaccine	Not available	Not available	Tanriover et al. (2021)

and alteration in the signal transduction pathways (Soldin and Mattison, 2009).

Although some compounds have promising effects in inhibiting the replication of SARS-CoV-2, their "off-label" use increases the risk of adverse effects such as cardiac arrhythmias and sudden cardiac death (Gebhard et al., 2020). Although recent studies showed hydroxychloroquine treatment is not beneficial in COVID-19 (Singh et al., 2021), previous reports with chloroquine and hydroxychloroquine have been shown that they trigger lethal polymorphic ventricular tachycardia (torsades de pointes) by prolonging the heart rate-corrected QT (QTc) interval (Giudicessi et al., 2020). Previous studies reveal that females are more susceptible to develop it (Abi-Gerges et al., 2004). Because testosterone has protective effects that contribute to the shorter QTc interval, drug-induced torsades de pointes are lower in males (Gebhard et al., 2020). Besides, higher enzyme activity and slower glomerular filtration rate in females may be a factor in the increased risk of QT prolongation in females with this drug because hydroxychloroquine is primarily converted to its active metabolite by CYP3A4 and 2D6 (Wahie et al., 2011), and half of the hydroxychloroquine is excreted renally (Furst, 1996). In a study that evaluated suspected adverse drug reactions with favipiravir, severe and fatal adverse reactions were more reported in males (68%) than females (32%), and most adverse reactions are hepatic enzyme increase (23.66%) and nausea and vomiting (13.98%) (Kaur et al., 2020). It has been suggested that patients using favipiravir should be monitored for the increase of hepatic enzymes. In another study with tocilizumab, drug-induced liver injury, pancreatitis, and pulmonary fibrosis were determined as unpredictable adverse events. 2, 433 cases were reported as designated medical events, and the female gender was preponderant among them (66.9%) (Gatti et al., 2021).

The relationship between adverse drug reactions and sex differences for drugs used in the treatment of COVID-19 has been evaluated (Zekarias et al., 2020). 93% of these reports consisted of the treatment with one or more drugs (hydroxychloroquine, chloroquine, lopinavir/ritonavir, azithromycin, or remdesivir) (Zekarias et al., 2020). QT-prolongation (19.07%), diarrhea (12.62%), nausea (5.68%), hepatitis (4.63%), and vomiting (4.14%) have been more reported in males, while diarrhea (18.64%), QT-prolongation (18.45%), nausea (12.66%), vomiting (11.07%), and upper abdominal pain (4.89%) have been more reported in females with COVID-19 (Zekarias et al., 2020). The most common driver was determined as hydroxychloroquine and, to a lesser extent, lopinavir/ritonavir and remdesivir treatment (Zekarias et al., 2020). On the contrary to previous reports, the percentage of serious adverse reaction reports in males (58%) was higher than in females (44%) in this study. The male predominance in the mentioned adverse drug reactions may be related to greater risk of COVID-19 in males than in females.

A recent epidemiological study aimed to investigate predictors of long COVID-19 revealed that females were more likely develop to "long COVID" which is characterized by symptoms of fatigue, headache, shortness of breath, and anosmia (Sudre et al., 2021). Thrombotic/-thromboembolic events are also prevalent in COVID-19 patients (Helms et al., 2020). Although the main reason for these events has not been discovered yet, direct viral effects, secondary hypoxia, liver impairment, or overreacted inflammatory response may be suggested (Bikdeli et al., 2020). Sex-based differences have not been reported in those papers. Only Helms et al. mentioned that 24 of the 25 patients with pulmonary emboli were male (Helms et al., 2020). Current data reveals that thromboembolism and worse outcomes are more possible in male patients with severe COVID-19 than in females because of hypercoagulability with fibrin formation and polymerization (Spiezia et al., 2020). One of the possible explanations of this finding includes that estrogen can reduce plasma levels of fibrinogen and increase antithrombin III and decrease plasminogen activator inhibitor type 1 (PAI-1) (Li et al., 2020). On the other hand, testosterone enhances endothelial NO production, thereby potently inhibiting platelet activation (Kalra et al., 2020). The antithrombotic effect of the testosterone might be lost in hypogonadism state in older males or with comorbidities, which may further aggravate morbidity and mortality rates in COVID-19 in males (Kalra et al., 2020). Particularly, vaccine-associated thrombocytopenia and vascular adverse events have led to some restrictions in their use (Simpson et al., 2021). For example, ChAdOx1 (Oxford–AstraZeneca) was found to be associated with a small increased risk of arterial thromboembolic and haemorrhagic events, while there were no positive associations with BNT162b2 (Pfizer/BioNTech) (Simpson et al., 2021). Moreover, 28 thrombotic events were found to be linked to the AstraZeneca vaccine out of 54,571 adverse reactions and 19 of these thrombotic events were reported by females (Tobaiqy et al., 2021) (Table 1). Females were higher likely to report adverse effects than males after the first dose of BNT162b2 (16.2% vs. 9.3%) and ChAdOx1 nCoV-19 (39.3% vs. 26.2%) (Menni et al., 2021). An increased risk of myocarditis was observed seven days after the second dose of mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) (Gargano et al., 2021). This risk was found higher in males under 30 years of age (41 cases per million) than in females (4.2 cases per million) and older males (2.4 cases per million) (Gargano et al., 2021) (Table 1). The benefits of the mRNA vaccine were greater because myocarditis and pericarditis cases were rare and treatable. After Janssen COVID-19 vaccination, an overage number of Guillain-Barré syndrome cases were more reported in males aged 50–64 years (15.6 cases per million), and thrombosis with thrombocytopenia syndrome (TTS) cases were highest in females aged 30–49 years (8.8 cases per million) (Rosenblum et al., 2021). In the CoronaVac (Sinovac Life Sciences) phase 3 study, the incidence of adverse events in the vaccine group was low (18.9%) without deaths or grade 4 adverse events (Tanriover et al., 2021). The most frequent systemic and local adverse event was fatigue (8.2%) and injection-site pain (2.4%) (Tanriover et al., 2021). More males (57.4%) were involved in this study; however, no clear causal effect or sex-related difference of the events was confirmed. Other than the vascular adverse effects, injection site reactions and hypersensitivity are more commonly reported after vaccination in females (Cook, 2009; Griffioen and Halsey, 2014). Stronger immune responses of females may increase the efficacy of vaccines but also leads to more adverse reactions (fever, pain, and inflammation) (Fischinger et al., 2019; Klein et al., 2015). Administration of vaccines in different doses or intervals or administering different vaccine candidates to males and females may prevent negative consequences related to sex differences (Fathi et al., 2020).

6. Conclusion

The current data emphasize the importance of considering the effect of sex in evaluating biological responses to the drugs and vaccines and developing personalized treatment strategies in COVID-19. Mortality and severity of COVID-19 in males are higher than in females. Comorbidities, aging, lifestyle, and, most importantly, biological sex differences play a role in this difference. The findings point out that the sex differences in genes, chromosomes, and hormones affect the immune responses to SARS-CoV-2 and may change the disease's progress differently in males and females. The independent effects of sex differences in infection risk and severity of the disease have not yet been fully elucidated. This gap in the literature highlights that sex remains an underappreciated variable when interrogating outcomes in infectious diseases. More research should be performed to reveal the mechanisms underlying the discrepant outcomes in COVID-19, and sex bias should be taken into account when designing and interpreting the results of preclinical and clinical trials.

CRediT authorship contribution statement

Zinnet Şevval Aksoyalp: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing. **Dilara Nemutlu-Samur:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors report no conflicts of interest.

References

Abate, B.B., Kassie, A.M., Kassaw, M.W., Aragie, T.G., Masresha, S.A., 2020. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ Open 10, e040129. https://doi.org/10.1136/bmjopen-2020-040129.

Abi-Gerges, N., Philp, K., Pollard, C., Wakefield, I., Hammond, T.G., Valentin, J.P., 2004. Sex differences in ventricular repolarization: from cardiac electrophysiology to Torsades de Pointes. Fundam. Clin. Pharmacol. 18, 139–151. https://doi.org/10.1111/j.1472-8206.2004.00230.x.

Al-kuraishy, H.M., Al-Gareeb, A.I., Faidah, H., Al-Maiahy, T.J., Cruz-Martins, N., Batiha, G.E.-S., 2021. The looming effects of estrogen in covid-19: a rocky rollout. Front. Nutr. 8 https://doi.org/10.3389/fnut.2021.649128.

Al-Lami, R.A., Urban, R.J., Volpi, E., Algburi, A.M.A., Baillargeon, J., 2020. Sex hormones and novel corona virus infectious disease (COVID-19). Mayo Clin. Proc. 95, 1710–1714. https://doi.org/10.1016/j.mayocp.2020.05.013.

Alves, J.V., da Costa, R.M., Pereira, C.A., Fedoce, A.G., Silva, C.A.A., Carneiro, F.S., Lobato, N.S., Tostes, R.C., 2020. Supraphysiological levels of testosterone induce vascular dysfunction via activation of the NLRP3 inflammasome. Front. Immunol. 11, 1647. https://doi.org/10.3389/fimmu.2020.01647.

Alwani, M., Yassin, A., Al-Zoubi, R.M., Aboumarzouk, O.M., Nettleship, J., Kelly, D., Al-Qudimat, A.R., Shabsigh, R., 2021. Sex-based differences in severity and mortality in COVID-19. Rev. Med. Virol. https://doi.org/10.1002/rmv.2223, 10.1002/rmv.2223.

Ambrosino, I., Barbagelata, E., Corbi, G., Ciarambino, T., Politi, C., Moretti, A.M., 2020. Gender differences in treatment of coronavirus disease-2019. Monaldi Arch. Chest Dis. 90 https://doi.org/10.4081/monaldi.2020.1508.

Baden, L.R., El Sahly, H.M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S.A., Rouphael, N., Creech, C.B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., Janes, H., Follmann, D., Marovich, M., Mascola, J., Polakowski, L., Ledgerwood, J., Graham, B.S., Bennett, H., Pajon, R., Knightly, C., Leav, B., Deng, W., Zhou, H., Han, S., Ivarsson, M., Miller, J., Zaks, T., 2020. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N. Engl. J. Med. 384, 403–416. https://doi.org/10.1056/NEJMoa2035389.

Baratchian, M., McManus, J.M., Berk, M.P., Nakamura, F., Mukhopadhyay, S., Xu, W., Erzurum, S., Drazba, J., Peterson, J., Klein, E.A., Gaston, B., Sharifi, N., 2021. Androgen regulation of pulmonary AR, TMPRSS2 and ACE2 with implications for sex-discordant COVID-19 outcomes. Sci. Rep. 11, 11130 https://doi.org/10.1038/s41598-021-90491-1.

Baroni, C., Lionetti, V., Pharmacology, 2021. The impact of sex and gender on heart–brain axis dysfunction: current concepts and novel perspectives. Can. J. Physiol. Pharmacol. 99, 151–160.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, B.S., Kalil, A.C., Hohmann, E., Chu, H.Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T.F., Paredes, R., Sweeney, D.A., Short, W.R., Touloumi, G., Lye, D.C., Ohmagari, N., Oh, M.D., Ruiz-Palacios, G.M., Benfield, T., Fatkenheuer, G., Kortepeter, M.G., Atmar, R.L., Creech, C.B., Lundgren, J., Babiker, A.G., Pett, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Green, M., Makowski, M., Osinusi, A., Nayak, S., Lane, H.C., Members, A.-S.G., 2020. Remdesivir for the treatment of covid-19 - final report. N. Engl. J. Med. 383, 1813–1826. https://doi.org/10.1056/NEJMoa2007764.

Bianchi, V.E., 2019. The anti-inflammatory effects of testosterone. J Endocr Soc 3, 91–107. https://doi.org/10.1210/js.2018-00186.

Bianchi, I., Lleo, A., Gershwin, M.E., Invernizzi, P., 2012. The X chromosome and immune associated genes. J. Autoimmun. 38, J187–J192. https://doi.org/10.1016/j.jaut.2011.11.012.

Bikdeli, B., Madhavan, M.V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., Nigoghossian, C., Ageno, W., Madjid, M., Guo, Y., Tang, L.V., Hu, Y., Giri, J., Cushman, M., Quere, I., Dimakakos, E.P., Gibson, C.M., Lippi, G., Favaloro, E.J., Fareed, J., Caprini, J.A., Tafur, A.J., Burton, J.R., Francese, D.P., Wang, E.Y., Falanga, A., McLintock, C., Hunt, B.J., Spyropoulos, A.C., Barnes, G.D., Eikelboom, J. W., Weinberg, I., Schulman, S., Carrier, M., Piazza, G., Beckman, J.A., Steg, P.G., Stone, G.W., Rosenkranz, S., Goldhaber, S.Z., Parikh, S.A., Monreal, M., Krumholz, H.M., Konstantinides, S.V., Weitz, J.I., Lip, G.Y.H., , Global Covid-19 Thrombosis Collaborative Group, E.b.t.I.N.E., the Iua, S.b.t.E.S.C.W.G.o.P.C., Right Ventricular, F., 2020. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J. Am. Coll. Cardiol. 75, 2950–2973. https://doi.org/10.1016/j.jacc.2020.04.031.

Bischof, E., Oertelt-Prigione, S., Morgan, R., Klein, S.L., The, S., , Gender In Covid Clinical Trials Working Group, Gender, S., Covid Working, G., 2020a. Towards precision medicine: inclusion of sex and gender aspects in COVID-19 clinical studies-acting now before it is too late-A joint call for action. Int. J. Environ. Res. Publ. Health 17. https://doi.org/10.3390/ijerph17103715.

Bischof, E., Wolfe, J., Klein, S.L., 2020b. Clinical trials for COVID-19 should include sex as a variable. J. Clin. Invest. 130, 3350–3352. https://doi.org/10.1172/JCI139306.

Brady, E., Nielsen, M.W., Andersen, J.P., Oertelt-Prigione, S., 2021. Lack of consideration of sex and gender in COVID-19 clinical studies. Nat. Commun. 12, 4015. https://doi.org/10.1038/s41467-021-24265-8.

Breithaupt, Faloppa, A.C., Correia, C.J., Prado, C.M., Stilhano, R.S., Ureshino, R.P., Moreira, L.F.P., 2020. 17beta-Estradiol, a potential ally to alleviate SARS-CoV-2 infection. Clinics 75, e1980. https://doi.org/10.6061/clinics/2020/e1980.

Bukowska, A., Spiller, L., Wolke, C., Lendeckel, U., Weinert, S., Hoffmann, J., Bornfleth, P., Kutschka, I., Gardemann, A., Isermann, B., Goette, A., 2017. Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. Exp. Biol. Med. 242, 1412–1423. https://doi.org/10.1177/1535370217718808.

Bunders, M.J., Altfeld, M., 2020. Implications of sex differences in immunity for SARS-CoV-2 pathogenesis and design of therapeutic interventions. Immunity 53, 487–495. https://doi.org/10.1016/j.immuni.2020.08.003.

Carey, M.A., Card, J.W., Voltz, J.W., Germolec, D.R., Korach, K.S., Zeldin, D.C., 2007. The impact of sex and sex hormones on lung physiology and disease: lessons from animal studies. Am. J. Physiol. Lung Cell Mol. Physiol. 293, L272–L278. https://doi.org/10.1152/ajplung.00174.2007.

Chambliss, K.L., Shaul, P.W., 2002. Estrogen modulation of endothelial nitric oxide synthase. Endocr. Rev. 23, 665–686. https://doi.org/10.1210/er.2001-0045.

Channappanavar, R., Fett, C., Mack, M., Ten Eyck, P.P., Meyerholz, D.K., Perlman, S., 2017. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J. Immunol. 198, 4046–4053. https://doi.org/10.4049/jimmunol.1601896.

Cook, I.F., 2009. Sex differences in injection site reactions with human vaccines. Hum. Vaccine 5, 441–449. https://doi.org/10.4161/hv.8476.

Crouse, J., Xu, H.C., Lang, P.A., Oxenius, A., 2015. NK cells regulating T cell responses: mechanisms and outcome. Trends Immunol. 36, 49–58. https://doi.org/10.1016/j.it.2014.11.001.

Desforges, M., Le Coupanec, A., Stodola, J.K., Meessen-Pinard, M., Talbot, P.J., 2014. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res. 194, 145–158. https://doi.org/10.1016/j.virusres.2014.09.011.

Dhindsa, S., Zhang, N., McPhaul, M.J., Wu, Z., Ghoshal, A.K., Erlich, E.C., Mani, K., Randolph, G.J., Edwards, J.R., Mudd, P.A., Diwan, A., 2021. Association of circulating sex hormones with inflammation and disease severity in patients with COVID-19. JAMA Network Open 4. https://doi.org/10.1001/jamanetworkopen.2021.11398 e2111398-e2111398.

Di Resta, C., Ferrari, D., Viganò, M., Moro, M., Sabetta, E., Minerva, M., Ambrosio, A., Locatelli, M., Tomaiuolo, R., 2021. The gender impact assessment among healthcare workers in the SARS-CoV-2 vaccination—an analysis of serological response and side effects. Vaccines 9. https://doi.org/10.3390/vaccines9050522.

Dorak, M.T., Karpuzoglu, E., 2012. Gender differences in cancer susceptibility: an inadequately addressed issue. Front. Genet. 3, 268. https://doi.org/10.3389/fgene.2012.00268.

Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., Zhou, M., Chen, L., Meng, S., Hu, Y., Peng, C., Yuan, M., Huang, J., Wang, Z., Yu, J., Gao, X., Wang, D., Yu, X., Li, L., Zhang, J., Wu, X., Li, B., Xu, Y., Chen, W., Peng, Y., Hu, Y., Lin, L., Liu, X., Huang, S., Zhou, Z., Zhang, L., Wang, Y., Zhang, Z., Deng, K., Xia, Z., Gong, Q., Zhang, W., Zheng, X., Liu, Y., Yang, H., Zhou, D., Yu, D., Hou, J., Shi, Z., Chen, S., Chen, Z., Zhang, X., Yang, X., 2020. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc. Natl. Acad. Sci. U. S. A. 117, 9490–9496. https://doi.org/10.1073/pnas.2004168117.

Erfinanda, L., Ravindran, K., Kohse, F., Gallo, K., Preissner, R., Walther, T., Kuebler, W. M., 2021. Oestrogen-mediated upregulation of the Mas receptor contributes to sex differences in acute lung injury and lung vascular barrier regulation. Eur. Respir. J. 57 https://doi.org/10.1183/13993003.00921-2020.

Espinosa-Garcia, C., Atif, F., Yousuf, S., Sayeed, I., Neigh, G.N., Stein, D.G., 2020. Progesterone attenuates stress-induced NLRP3 inflammasome activation and enhances autophagy following ischemic brain injury. Int. J. Mol. Sci. 21 https://doi.org/10.3390/ijms21113740.

Farkouh, A., Riedl, T., Gottardi, R., Czejka, M., Kautzky-Willer, A., 2020. Sex-related differences in pharmacokinetics and pharmacodynamics of frequently prescribed drugs: a review of the literature. Adv. Ther. 37, 644–655. https://doi.org/10.1007/s12325-019-01201-3.

Fathi, A., Addo, M.M., Dahlke, C., 2020. Sex differences in immunity: implications for the development of novel vaccines against emerging pathogens. Front. Immunol. 11, 601170 https://doi.org/10.3389/fimmu.2020.601170.

Fink, A.L., Engle, K., Ursin, R.L., Tang, W.-Y., Klein, S.L., 2018. Biological sex affects vaccine efficacy and protection against influenza in mice. Proc. Natl. Acad. Sci. U.S. A. 115, 12477–12482. https://doi.org/10.1073/pnas.1805268115.

Fischinger, S., Boudreau, C.M., Butler, A.L., Streeck, H., Alter, G., 2019. Sex differences in vaccine-induced humoral immunity. Semin. Immunopathol. 41, 239–249. https://doi.org/10.1007/s00281-018-0726-5.

Furman, D., Hejblum, B.P., Simon, N., Jojic, V., Dekker, C.L., Thiebaut, R., Tibshirani, R. J., Davis, M.M., 2014. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc. Natl. Acad. Sci. U. S. A. 111, 869–874. https://doi.org/10.1073/pnas.1321060111.

Furst, D.E., 1996. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus 5 (Suppl. 1), S11–S15.

Gagliardi, M.C., Tieri, P., Ortona, E., Ruggieri, A., 2020. ACE2 expression and sex disparity in COVID-19. Cell Death Dis. 6, 37. https://doi.org/10.1038/s41420-020-0276-1.

Garg, R., Agrawal, P., Gautam, A., Pursnani, N., Agarwal, M., Agarwal, A., Parihar, A., Pandey, A., 2020. COVID-19 outcomes in postmenopausal and perimenopausal females: is estrogen hormone attributing to gender differences? J. Mid Life Health 11, 250–256. https://doi.org/10.4103/jmh.jmh_287_20.

Gargano, J.W., Wallace, M., Hadler, S.C., Langley, G., Su, J.R., Oster, M.E., Broder, K.R., Gee, J., Weintraub, E., Shimabukuro, T., Scobie, H.M., Moulia, D., Markowitz, L.E., Wharton, M., McNally, V.V., Romero, J.R., Talbot, H.K., Lee, G.M., Daley, M.F., Oliver, S.E., 2021. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices - United States, june 2021. MMWR Morb. Mortal. Wkly. Rep. 70, 977–982. https://doi.org/10.15585/mmwr.mm7027e2.

Gatti, M., Fusaroli, M., Caraceni, P., Poluzzi, E., De Ponti, F., Raschi, E., 2021. Serious adverse events with tocilizumab: pharmacovigilance as an aid to prioritize monitoring in COVID-19. Br. J. Clin. Pharmacol. 87, 1533–1540. https://doi.org/10.1111/bcp.14459.

Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H.K., Morgan, R., Klein, S.L., 2020. Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex Differ. 11, 29. https://doi.org/10.1186/s13293-020-00304-9.

Gheblawi, M., Wang, K., Viveiros, A., Nguyen, Q., Zhong, J.C., Turner, A.J., Raizada, M. K., Grant, M.B., Oudit, G.Y., 2020. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ. Res. 126, 1456–1474. https://doi.org/10.1161/CIRCRESAHA.120.317015.

Giudicessi, J.R., Noseworthy, P.A., Friedman, P.A., Ackerman, M.J., 2020. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin. Proc. 95, 1213–1221. https://doi.org/10.1016/j.mayocp.2020.03.024.

Global Health 5050, 2021. Sex, Gender and Covid-19.

Griffioen, M., Halsey, N., 2014. Gender differences in immediate hypersensitivity reactions to vaccines: a review of the literature. Publ. Health Nurs. 31, 206–214. https://doi.org/10.1111/phn.12073.

Gupta, A., Madhavan, M.V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T.S., Bikdeli, B., Ahluwalia, N., Ausiello, J.C., Wan, E.Y., Freedberg, D.E., Kirtane, A.J., Parikh, S.A., Maurer, M.S., Nordvig, A.S., Accili, D., Bathon, J.M., Mohan, S., Bauer, K.A., Leon, M.B., Krumholz, H.M., Uriel, N., Mehra, M.R., Elkind, M.S.V., Stone, G.W., Schwartz, A., Ho, D.D., Bilezikian, J.P., Landry, D.W., 2020. Extrapulmonary manifestations of COVID-19. Nat. Med. 26, 1017–1032. https://doi.org/10.1038/s41591-020-0968-3.

Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Smith, N., Péré, H., Charbit, B., Bondet, V., Chenevier-Gobeaux, C., Breillat, P., Carlier, N., Gauzit, R., Morbieu, C., Pène, F., Marin, N., Roche, N., Szwebel, T.A., Merkling, S.H., Treluyer, J.M., Veyer, D., Mouthon, L., Blanc, C., Tharaux, P.L., Rozenberg, F., Fischer, A., Duffy, D., Rieux-Laucat, F., Kernéis, S., Terrier, B., 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 369, 718–724. https://doi.org/10.1126/science.abc6027.

Haitao, T., Vermunt, J.V., Abeykoon, J., Ghamrawi, R., Gunaratne, M., Jayachandran, M., Narang, K., Parashuram, S., Suvakov, S., Garovic, V.D., 2020. COVID-19 and sex differences: mechanisms and biomarkers. Mayo Clin. Proc. 95, 2189–2203. https://doi.org/10.1016/j.mayocp.2020.07.024.

Hanff, T.C., Harhay, M.O., Brown, T.S., Cohen, J.B., Mohareb, A.M., 2020. Is there an association between COVID-19 mortality and the renin-angiotensin system? A call for epidemiologic investigations. Clin. Infect. Dis. 71, 870–874. https://doi.org/10.1093/cid/ciaa329.

Helms, J., Tacquard, C., Severac, F., Leonard-Lorant, I., Ohana, M., Delabranche, X., Merdji, H., Clere-Jehl, R., Schenck, M., Fagot Gandet, F., Fafi-Kremer, S., Castelain, V., Schneider, F., Grunebaum, L., Anglés-Cano, E., Sattler, L., Mertes, P.-M., Meziani, F., Group, C.T., 2020. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 46, 1089–1098. https://doi.org/10.1007/s00134-020-06062-x.

Hilliard, L.M., Sampson, A.K., Brown, R.D., Denton, K.M., 2013. The "his and hers" of the renin-angiotensin system. Curr. Hypertens. Rep. 15, 71–79. https://doi.org/10.1007/s11906-012-0319-y.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Kruger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Muller, M.A., Drosten, C., Pohlmann, S., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280. https://doi.org/10.1016/j.cell.2020.02.052 e278.

Hussain, A.N., Hussain, F., Hashmi, S.K., 2020. Role of testosterone in COVID-19 patients - a double-edged sword? Med. Hypotheses 144. https://doi.org/10.1016/j.mehy.2020.110287, 110287-110287.

Ingersoll, M.A., 2017. Sex differences shape the response to infectious diseases. PLoS Pathog. 13 https://doi.org/10.1371/journal.ppat.1006688 e1006688-e1006688.

Johns Hopkins University, 2021. COVID-19 dashboard by the center for systems science and engineering (CSSE) at johns Hopkins university (JHU). Access date: 01.09.2021. https://coronavirus.jhu.edu/map.html.

Joyner, M.J., Carter, R.E., Senefeld, J.W., Klassen, S.A., Mills, J.R., Johnson, P.W., Theel, E.S., Wiggins, C.C., Bruno, K.A., Klompas, A.M., Lesser, E.R., Kunze, K.L., Sexton, M.A., Diaz Soto, J.C., Baker, S.E., Shepherd, J.R.A., van Helmond, N., Verdun, N.C., Marks, P., van Buskirk, C.M., Winters, J.L., Stubbs, J.R., Rea, R.F., Hodge, D.O., Herasevich, V., Whelan, E.R., Clayburn, A.J., Larson, K.F., Ripoll, J.G., Andersen, K.J., Buras, M.R., Vogt, M.N.P., Dennis, J.J., Regimbal, R.J., Bauer, P.R., Blair, J.E., Paneth, N.S., Fairweather, D., Wright, R.S., Casadevall, A., 2021. Convalescent plasma antibody levels and the risk of death from covid-19. N. Engl. J. Med. 384, 1015–1027. https://doi.org/10.1056/NEJMoa2031893.

Jun, T., Nirenberg, S., Weinberger, T., Sharma, N., Pujadas, E., Cordon-Cardo, C., Kovatch, P., Huang, K.-l.J.C.M., 2021. Analysis of Sex-specific Risk Factors and Clinical Outcomes in COVID-19, vol. 1, pp. 1–8.

Kalra, S., Bhattacharya, S., Kalhan, A., 2020. Testosterone in COVID-19 - foe, friend or fatal victim? Eur. Endocrinol. 16, 88–91. https://doi.org/10.17925/EE.2020.16.2.88.

Kaur, R.J., Charan, J., Dutta, S., Sharma, P., Bhardwaj, P., Sharma, P., Lugova, H., Krishnapillai, A., Islam, S., Haque, M., Misra, S., 2020. Favipiravir use in COVID-19: analysis of suspected adverse drug events reported in the WHO database. Infect. Drug Resist. 13, 4427–4438. https://doi.org/10.2147/IDR.S287934.

Khanmohammadi, S., Rezaei, N., 2021. Role of Toll-like receptors in the pathogenesis of COVID-19. J. Med. Virol. 93, 2735–2739. https://doi.org/10.1002/jmv.26826.

Klein, S.L., Jedlicka, A., Pekosz, A., 2010. The Xs and Y of immune responses to viral vaccines. Lancet Infect. Dis. 10, 338–349. https://doi.org/10.1016/S1473-3099(10)70049-9.

Klein, S.L., Marriott, I., Fish, E.N., 2015. Sex-based differences in immune function and responses to vaccination. Trans. R. Soc. Trop. Med. Hyg. 109, 9–15. https://doi.org/10.1093/trstmh/tru167.

Koskinen, M., Carpen, O., Honkanen, V., Seppänen, M.R.J., Miettinen, P.J., Tuominen, J. A., Raivio, T., 2020. Androgen deprivation and SARS-CoV-2 in men with prostate cancer. Ann. Oncol. 31, 1417–1418. https://doi.org/10.1016/j.annonc.2020.06.015.

Kuster, G.M., Pfister, O., Burkard, T., Zhou, Q., Twerenbold, R., Haaf, P., Widmer, A.F., Osswald, S., 2020. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur. Heart J. 41, 1801–1803. https://doi.org/10.1093/eurheartj/ehaa235.

Kwon, D.H., Vashisht, R., Borno, H.T., Aggarwal, R.R., Small, E.J., Butte, A.J., Huang, F. W., 2021. Androgen-deprivation therapy and SARS-CoV-2 in men with prostate cancer: findings from the University of California Health System registry. Ann. Oncol. 32, 678–679. https://doi.org/10.1016/j.annonc.2021.01.067.

Lew, K.H., Ludwig, E.A., Milad, M.A., Donovan, K., Middleton Jr., E., Ferry, J.J., Jusko, W.J., 1993. Gender-based effects on methylprednisolone pharmacokinetics and pharmacodynamics. Clin. Pharmacol. Ther. 54, 402–414. https://doi.org/10.1038/clpt.1993.167.

Li, Y., Jerkic, M., Slutsky, A.S., Zhang, H., 2020. Molecular mechanisms of sex bias differences in COVID-19 mortality. Crit. Care 24, 405. https://doi.org/10.1186/s13054-020-03118-8.

Lionetti, V., Bollini, S., Coppini, R., Gerbino, A., Ghigo, A., Iaccarino, G., Madonna, R., Mangiacapra, F., Miragoli, M., Moccia, F., Munaron, L., Pagliaro, P., Parenti, A., Pasqua, T., Penna, C., Quaini, F., Rocca, C., Samaja, M., Sartiani, L., Soda, T., Tocchetti, C.G., Angelone, T., 2021. Understanding the heart-brain axis response in COVID-19 patients: a suggestive perspective for therapeutic development. Pharmacol. Res. 168, 105581 https://doi.org/10.1016/j.phrs.2021.105581.

Ma, X., Zhou, Y., Qiao, B., Jiang, S., Shen, Q., Han, Y., Liu, A., Chen, X., Wei, L., Zhou, L., Zhao, J., 2020. Androgen aggravates liver fibrosis by activation of NLRP3 inflammasome in CCl4-induced liver injury mouse model. Am. J. Physiol. Endocrinol. Metab. 318, E817–E829. https://doi.org/10.1152/ajpendo.00427.2019.

Madla, C.M., Gavins, F.K.H., Merchant, H.A., Orlu, M., Murdan, S., Basit, A.W., 2021. Let's talk about sex: differences in drug therapy in males and females. Adv. Drug Deliv. Rev., 113804 https://doi.org/10.1016/j.addr.2021.05.014.

Malkin, C.J., Pugh, P.J., Jones, R.D., Kapoor, D., Channer, K.S., Jones, T.H., 2004. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J. Clin. Endocrinol. Metabol. 89, 3313–3318. https://doi.org/10.1210/jc.2003-031069.

McGonagle, D., Sharif, K., O'Regan, A., Bridgewood, C., 2020. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun. Rev. 19, 102537 https://doi.org/10.1016/j.autrev.2020.102537.

Menni, C., Klaser, K., May, A., Polidori, L., Capdevila, J., Louca, P., Sudre, C.H., Nguyen, L.H., Drew, D.A., Merino, J., Hu, C., Selvachandran, S., Antonelli, M., Murray, B., Canas, L.S., Molteni, E., Graham, M.S., Modat, M., Joshi, A.D., Mangino, M., Hammers, A., Goodman, A.L., Chan, A.T., Wolf, J., Steves, C.J., Valdes, A.M., Ourselin, S., Spector, T.D., 2021. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect. Dis. 21, 939–949. https://doi.org/10.1016/S1473-3099(21)00224-3.

Montopoli, M., Zumerle, S., Vettor, R., Rugge, M., Zorzi, M., Catapano, C.V., Carbone, G. M., Cavalli, A., Pagano, F., Ragazzi, E., Prayer-Galetti, T., Alimonti, A., 2020. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). Ann. Oncol. 31, 1040–1045. https://doi.org/10.1016/j.annonc.2020.04.479.

Newson, L., Manyonda, I., Lewis, R., Preissner, R., Preissner, S., Seeland, U., 2021. Sensitive to infection but strong in defense—female sex and the power of oestradiol in the COVID-19 pandemic. Front. Global Women's Health 2. https://doi.org/10.3389/fgwh.2021.651752.

Onder, G., Rezza, G., Brusaferro, S., 2020. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. J. Am. Med. Assoc. 323, 1775–1776. https://doi.org/10.1001/jama.2020.4683.

Pagliaro, P., Penna, C., 2020. ACE/ACE2 ratio: a key also in 2019 coronavirus disease (Covid-19)?, 335-335 Front. Med. 7. https://doi.org/10.3389/fmed.2020.00335.

Pan, P., Shen, M., Yu, Z., Ge, W., Chen, K., Tian, M., Xiao, F., Wang, Z., Wang, J., Jia, Y., Wang, W., Wan, P., Zhang, J., Chen, W., Lei, Z., Chen, X., Luo, Z., Zhang, Q., Xu, M., Li, G., Li, Y., Wu, J., 2021. SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. Nat. Commun. 12, 4664. https://doi.org/10.1038/s41467-021-25015-6.

Peckham, H., de Gruijter, N.M., Raine, C., Radziszewska, A., Ciurtin, C., Wedderburn, L. R., Rosser, E.C., Webb, K., Deakin, C.T., 2020. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat. Commun. 11, 6317. https://doi.org/10.1038/s41467-020-19741-6.

Petrilli, C.M., Jones, S.A., Yang, J., Rajagopalan, H., O'Donnell, L., Chernyak, Y., Tobin, K.A., Cerfolio, R.J., Francois, F., Horwitz, L.I., 2020. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease

2019 in New York City: prospective cohort study. BMJ 369, m1966. https://doi.org/10.1136/bmj.m1966.
Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Moreira, E.D., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck, R.W., Hammitt, L.L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Şahin, U., Jansen, K.U., Gruber, W.C., 2020. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N. Engl. J. Med. 383, 2603–2615. https://doi.org/10.1056/NEJMoa2034577.
Potluri, T., Fink, A.L., Sylvia, K.E., Dhakal, S., Vermillion, M.S., vom Steeg, L., Deshpande, S., Narasimhan, H., Klein, S.L., 2019. Age-associated changes in the impact of sex steroids on influenza vaccine responses in males and females. NPJ Vaccines 4, 29. https://doi.org/10.1038/s41541-019-0124-6.
Pradhan, A., Olsson, P.E., 2020. Sex differences in severity and mortality from COVID-19: are males more vulnerable? Biol. Sex Differ. 11, 53. https://doi.org/10.1186/s13293-020-00330-7.
Rastrelli, G., Di Stasi, V., Inglese, F., Beccaria, M., Garuti, M., Di Costanzo, D., Spreafico, F., Greco, G.F., Cervi, G., Pecoriello, A., Magini, A., Todisco, T., Cipriani, S., Maseroli, E., Corona, G., Salonia, A., Lenzi, A., Maggi, M., De Donno, G., Vignozzi, L., 2021. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. Andrology 9, 88–98. https://doi.org/10.1111/andr.12821.
Ratajczak, M.Z., Bujko, K., Ciechanowicz, A., Sielatycka, K., Cymer, M., Marlicz, W., Kucia, M., 2021. SARS-CoV-2 entry receptor ACE2 is expressed on very small CD45 (-) precursors of hematopoietic and endothelial cells and in response to virus spike protein activates the Nlrp3 inflammasome. Stem Cell Rev Rep 17, 266–277. https://doi.org/10.1007/s12015-020-10010-z.
Rosenblum, H.G., Hadler, S.C., Moulia, D., Shimabukuro, T.T., Su, J.R., Tepper, N.K., Ess, K.C., Woo, E.J., Mba-Jonas, A., Alimchandani, M.J.M., Report, M.W., 2021. Use of COVID-19 Vaccines after Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices—United States, July 2021, vol. 70, p. 1094.
Roved, J., Westerdahl, H., Hasselquist, D., 2017. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. Horm. Behav. 88, 95–105. https://doi.org/10.1016/j.yhbeh.2016.11.017.
Sadoff, J., Gray, G., Vandebosch, A., Cardenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P.A., Truyers, C., Fennema, H., Spiessens, B., Offergeld, K., Scheper, G., Taylor, K.L., Robb, M.L., Treanor, J., Barouch, D.H., Stoddard, J., Ryser, M.F., Marovich, M.A., Neuzil, K.M., Corey, L., Cauwenberghs, N., Tanner, T., Hardt, K., Ruiz-Guinazu, J., Le Gars, M., Schuitemaker, H., Van Hoof, J., Struyf, F., Douoguih, M., Group, E.S., 2021. Safety and efficacy of single-dose Ad26.COV2.S vaccine against covid-19. N. Engl. J. Med. 384, 2187–2201. https://doi.org/10.1056/NEJMoa2101544.
Santos, R.A.S., Sampaio, W.O., Alzamora, A.C., Motta-Santos, D., Alenina, N., Bader, M., Campagnole-Santos, M.J., 2018. The ACE2/angiotensin-(1-7)/MAS Axis of the renin-angiotensin system: focus on angiotensin-(1-7). Physiol. Rev. 98, 505–553. https://doi.org/10.1152/physrev.00023.2016.
Saura, M., Zaragoza, C., McMillan, A., Quick, R.A., Hohenadl, C., Lowenstein, J.M., Lowenstein, C.J., 1999. An antiviral mechanism of nitric oxide: inhibition of a viral protease. Immunity 10, 21–28. https://doi.org/10.1016/s1074-7613(00)80003-5.
Schiffer, V., Janssen, E., van Bussel, B.C.T., Jorissen, L.L.M., Tas, J., Sels, J.E.M., Bergmans, D., Dinh, T.H.T., van Kuijk, S.M.J., Hana, A., Mehagnoul-Schipper, J., Scheeren, C.I.E., Mesotten, D., Stessel, B., Marx, G., Hof, A., Spaanderman, M.E.A., van Mook, W., van der Horst, I.C.C., Ghossein-Doha, C., 2020. The "sex gap" in COVID-19 trials: a scoping review. EClinicalMedicine 29, 100652. https://doi.org/10.1016/j.eclinm.2020.100652.
Schwartz, J.B., 2003. The influence of sex on pharmacokinetics. Clin. Pharmacokinet. 42, 107–121. https://doi.org/10.2165/00003088-200342020-00001.
Scully, E.P., Haverfield, J., Ursin, R.L., Tannenbaum, C., Klein, S.L., 2020. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat. Rev. Immunol. 20, 442–447. https://doi.org/10.1038/s41577-020-0348-8.
Seeland, U., Coluzzi, F., Simmaco, M., Mura, C., Bourne, P.E., Heiland, M., Preissner, R., Preissner, S., 2020. Evidence for treatment with estradiol for women with SARS-CoV-2 infection. BMC Med. 18, 369. https://doi.org/10.1186/s12916-020-01851-z.
Shiau, S., Kuhn, L., Strehlau, R., Martens, L., McIlleron, H., Meredith, S., Wiesner, L., Coovadia, A., Abrams, E.J., Arpadi, S.M., 2014. Sex differences in responses to antiretroviral treatment in South African HIV-infected children on ritonavir-boosted lopinavir- and nevirapine-based treatment. BMC Pediatr. 14 https://doi.org/10.1186/1471-2431-14-39.
Simpson, C.R., Shi, T., Vasileiou, E., Katikireddi, S.V., Kerr, S., Moore, E., McCowan, C., Agrawal, U., Shah, S.A., Ritchie, L.D., Murray, J., Pan, J., Bradley, D.T., Stock, S.J., Wood, R., Chuter, A., Beggs, J., Stagg, H.R., Joy, M., Tsang, R.S.M., de Lusignan, S., Hobbs, R., Lyons, R.A., Torabi, F., Bedston, S., O'Leary, M., Akbari, A., McMenamin, J., Robertson, C., Sheikh, A., 2021. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat. Med. 27, 1290–1297. https://doi.org/10.1038/s41591-021-01408-4.
Singh, B., Ryan, H., Kredo, T., Chaplin, M., Fletcher, T., 2021. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst. Rev. 2, Cd013587 https://doi.org/10.1002/14651858.CD013587.pub2.
Smith, K.Y., Tierney, C., Mollan, K., Venuto, C.S., Budhathoki, C., Ma, Q., Morse, G.D., Sax, P., Katzenstein, D., Godfrey, C., Fischl, M., Daar, E.S., Collier, A.C., Team, A.C.T. G.S., 2014. Outcomes by sex following treatment initiation with atazanavir plus ritonavir or efavirenz with abacavir/lamivudine or tenofovir/emtricitabine. Clin. Infect. Dis. 58, 555–563. https://doi.org/10.1093/cid/cit747.
Soldin, O.P., Mattison, D.R., 2009. Sex differences in pharmacokinetics and pharmacodynamics. Clin. Pharmacokinet. 48, 143–157. https://doi.org/10.2165/00003088-200948030-00001.
Speyer, C.L., Rancilio, N.J., McClintock, S.D., Crawford, J.D., Gao, H., Sarma, J.V., Ward, P.A., 2005. Regulatory effects of estrogen on acute lung inflammation in mice. Am. J. Physiol. Cell Physiol. 288, C881–C890. https://doi.org/10.1152/ajpcell.00467.2004.
Spiezia, L., Boscolo, A., Poletto, F., Cerruti, L., Tiberio, I., Campello, E., Navalesi, P., Simioni, P., 2020. COVID-19-Related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb. Haemostasis 120, 998–1000. https://doi.org/10.1055/s-0040-1710018.
Straub, R.H., 2007. The complex role of estrogens in inflammation. Endocr. Rev. 28, 521–574. https://doi.org/10.1210/er.2007-0001.
Struyf, T., Deeks, J.J., Dinnes, J., Takwoingi, Y., Davenport, C., Leeflang, M.M., Spijker, R., Hooft, L., Emperador, D., Dittrich, S., Domen, J., Horn, S.R.A., Van den Bruel, A., Cochrane, C.-D.T.A.G., 2020. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database Syst. Rev. 7, CD013665 https://doi.org/10.1002/14651858.CD013665.
Sudre, C.H., Murray, B., Varsavsky, T., Graham, M.S., Penfold, R.S., Bowyer, R.C., Pujol, J.C., Klaser, K., Antonelli, M., Canas, L.S., Molteni, E., Modat, M., Jorge Cardoso, M., May, A., Ganesh, S., Davies, R., Nguyen, L.H., Drew, D.A., Astley, C.M., Joshi, A.D., Merino, J., Tsereteli, N., Fall, T., Gomez, M.F., Duncan, E.L., Menni, C., Williams, F.M.K., Franks, P.W., Chan, A.T., Wolf, J., Ourselin, S., Spector, T., Steves, C.J., 2021. Attributes and predictors of long COVID. Nat. Med. 27, 626–631. https://doi.org/10.1038/s41591-021-01292-y.
Takahashi, T., Ellingson, M.K., Wong, P., Israelow, B., Lucas, C., Klein, J., Silva, J., Mao, T., Oh, J.E., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Liu, F., Meir, A., Sun, J., Wang, E.Y., Casanovas-Massana, A., Wyllie, A.L., Vogels, C.B.F., Earnest, R., Lapidus, S., Ott, I.M., Moore, A.J., Anastasio, K., Askenase, M.H., Batsu, M., Beatty, H., Bermejo, S., Bickerton, S., Brower, K., Bucklin, M.L., Cahill, S., Campbell, M., Cao, Y., Courchaine, E., Datta, R., DeIuliis, G., Geng, B., Glick, L., Handoko, R., Kalinich, C., Khoury-Hanold, W., Kim, D., Knaggs, L., Kuang, M., Kudo, E., Lim, J., Linehan, M., Lu-Culligan, A., Malik, A.A., Martin, A., Matos, I., McDonald, D., Minasyan, M., Mohanty, S., Muenker, M.C., Naushad, N., Nelson, A., Nouws, J., Nunez-Smith, M., Obaid, A., Ott, I., Park, H.-J., Peng, X., Petrone, M., Prophet, S., Rahming, H., Rice, T., Rose, K.-A., Sewanan, L., Sharma, L., Shepard, D., Silva, E., Simonov, M., Smolgovsky, M., Song, E., Sonnert, N., Strong, Y., Todeasa, C., Valdez, J., Velazquez, S., Vijayakumar, P., Wang, H., Watkins, A., White, E.B., Yang, Y., Shaw, A., Fournier, J.B., Odio, C.D., Farhadian, S., Dela Cruz, C., Grubaugh, N.D., Schulz, W.L., Ring, A.M., Ko, A.I., Omer, S.B., Iwasaki, A., Yale, I.R. T., 2020. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 588, 315–320. https://doi.org/10.1038/s41586-020-2700-3.
Taneja, V., 2018. Sex hormones determine immune response. Front. Immunol. 9, 1931. https://doi.org/10.3389/fimmu.2018.01931.
Tanriover, M.D., Doganay, H.L., Akova, M., Guner, H.R., Azap, A., Akhan, S., Kose, S., Erdinc, F.S., Akalin, E.H., Tabak, O.F., Pullukcu, H., Batum, O., Simsek Yavuz, S., Turhan, O., Yildirmak, M.T., Koksal, I., Tasova, Y., Korten, V., Yilmaz, G., Celen, M. K., Altin, S., Celik, I., Bayindir, Y., Karaoglan, I., Yilmaz, A., Ozkul, A., Gur, H., Unal, S., CoronaVac Study, G., 2021. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 398, 213–222. https://doi.org/10.1016/S0140-6736(21)01429-X.
Tardif, J.C., Bouabdallaoui, N., L'Allier, P.L., Gaudet, D., Shah, B., Pillinger, M.H., Lopez-Sendon, J., da Luz, P., Verret, L., Audet, S., Dupuis, J., Denault, A., Pelletier, M., Tessier, P.A., Samson, S., Fortin, D., Tardif, J.D., Busseuil, D., Goulet, E., Lacoste, C., Dubois, A., Joshi, A.Y., Waters, D.D., Hsue, P., Lepor, N.E., Lesage, F., Sainturet, N., Roy-Clavel, E., Bassevitch, Z., Orfanos, A., Stamatescu, G., Grégoire, J.C., Busque, L., Lavallée, C., Hétu, P.O., Paquette, J.S., Deftereos, S.G., Levesque, S., Cossette, M., Nozza, A., Chabot-Blanchet, M., Dubé, M.P., Guertin, M.C., Boivin, G., 2021. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. Lancet Respir Med. https://doi.org/10.1016/s2213-2600(21)00222-8.
Teijaro, J.R., Farber, D.L., 2021. COVID-19 vaccines: modes of immune activation and future challenges. Nat. Rev. Immunol. 21, 195–197. https://doi.org/10.1038/s41577-021-00526-x.
Thakkar, R., Wang, R., Sareddy, G., Wang, J., Thiruvaiyaru, D., Vadlamudi, R., Zhang, Q., Brann, D., 2016. NLRP3 inflammasome activation in the brain after global cerebral ischemia and regulation by 17beta-estradiol. Oxid Med Cell Longev 2016, 8309031. https://doi.org/10.1155/2016/8309031.
Tipnis, S.R., Hooper, N.M., Hyde, R., Karran, E., Christie, G., Turner, A.J., 2000. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J. Biol. Chem. 275, 33238–33243. https://doi.org/10.1074/jbc.M002615200.
Tobaiqy, M., Elkout, H., MacLure, K., 2021. Analysis of thrombotic adverse reactions of COVID-19 AstraZeneca vaccine reported to EudraVigilance database. Vaccines (Basel) 9. https://doi.org/10.3390/vaccines9040393.
Tomlins, S.A., Rhodes, D.R., Perner, S., Dhanasekaran, S.M., Mehra, R., Sun, X.W., Varambally, S., Cao, X., Tchinda, J., Kuefer, R., Lee, C., Montie, J.E., Shah, R.B., Pienta, K.J., Rubin, M.A., Chinnaiyan, A.M., 2005. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 310, 644–648. https://doi.org/10.1126/science.1117679.
Tuku, B., Stanelle-Bertram, S., Sellau, J., Beck, S., Bai, T., Kouassi, N.M., Preuß, A., Hoenow, S., Renné, T., Lotter, H., Gabriel, G., 2020. Testosterone protects against severe influenza by reducing the pro-inflammatory cytokine response in the murine lung. Front. Immunol. 11, 697. https://doi.org/10.3389/fimmu.2020.00697.

Vahidy, F.S., Pan, A.P., Ahnstedt, H., Munshi, Y., Choi, H.A., Tiruneh, Y., Nasir, K., Kash, B.A., Andrieni, J.D., McCullough, L.D., 2021. Sex differences in susceptibility, severity, and outcomes of coronavirus disease 2019: cross-sectional analysis from a diverse US metropolitan area. PLoS One 16, e0245556. https://doi.org/10.1371/journal.pone.0245556.

Valenzuela, R., Pedrosa, M.A., Garrido-Gil, P., Labandeira, C.M., Navarro, G., Franco, R., Rodriguez-Perez, A.I., Labandeira-Garcia, J.L., 2021. Interactions between ibuprofen, ACE2, renin-angiotensin system, and spike protein in the lung. Implications for COVID-19. Clin. Transl. Med. 11, e371 https://doi.org/10.1002/ctm2.371.

van den Berg, D.F., Te Velde, A.A., 2020. Severe COVID-19: NLRP3 inflammasome dysregulated. Front. Immunol. 11, 1580. https://doi.org/10.3389/fimmu.2020.01580.

Varga, Z., Flammer, A.J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A.S., Mehra, M.R., Schuepbach, R.A., Ruschitzka, F., Moch, H., 2020. Endothelial cell infection and endotheliitis in COVID-19. Lancet 395, 1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5.

Viveiros, A., Rasmuson, J., Vu, J., Mulvagh, S.L., Yip, C.Y.Y., Norris, C.M., Oudit, G.Y., 2021. Sex differences in COVID-19: candidate pathways, genetics of ACE2, and sex hormones. Am. J. Physiol. Heart Circ. Physiol. 320, H296–h304. https://doi.org/10.1152/ajpheart.00755.2020.

vom Steeg, L.G., Klein, S.L., 2016. SeXX matters in infectious disease pathogenesis. PLoS Pathog. 12, e1005374 https://doi.org/10.1371/journal.ppat.1005374.

Voysey, M., Clemens, S.A.C., Madhi, S.A., Weckx, L.Y., Folegatti, P.M., Aley, P.K., Angus, B., Baillie, V.L., Barnabas, S.L., Bhorat, Q.E., Bibi, S., Briner, C., Cicconi, P., Collins, A.M., Colin-Jones, R., Cutland, C.L., Darton, T.C., Dheda, K., Duncan, C.J.A., Emary, K.R.W., Ewer, K.J., Fairlie, L., Faust, S.N., Feng, S., Ferreira, D.M., Finn, A., Goodman, A.L., Green, C.M., Green, C.A., Heath, P.T., Hill, C., Hill, H., Hirsch, I., Hodgson, S.H.C., Izu, A., Jackson, S., Jenkin, D., Joe, C.C.D., Kerridge, S., Koen, A., Kwatra, G., Lazarus, R., Lawrie, A.M., Lelliott, A., Libri, V., Lillie, P.J., Mallory, R., Mendes, A.V.A., Milan, E.P., Minassian, A.M., McGregor, A., Morrison, H., Mujadidi, Y.F., Nana, A., O'Reilly, P.J., Padayachee, S.D., Pittella, A., Plested, E., Pollock, K.M., Ramasamy, M.N., Rhead, S., Schwarzbold, A.V., Singh, N., Smith, A., Song, R., Snape, M.D., Sprinz, E., Sutherland, R.K., Tarrant, R., Thomson, E.C., Török, M.E., Toshner, M., Turner, D.P.J., Vekemans, J., Villafana, T.L., Watson, M.E. E., Williams, C.J., Douglas, A.D., Hill, A.V.S., Lambe, T., Gilbert, S.C., Pollard, A.J., Aban, M., Abayomi, F., Abeyskera, K., Aboagye, J., Adam, M., Adams, K., Adamson, J., Adelaja, Y.A., Adewetan, G., Adlou, S., Ahmed, K., Akhalwaya, Y., Akhalwaya, S., Alcock, A., Ali, A., Allen, E.R., Allen, L., Almeida, T.C.D.S.C., Alves, M.P.S., Amorim, F., Andritsou, F., Anslow, R., Appleby, M., Arbe-Barnes, E.H., Ariaans, M.P., Arns, B., Arruda, L., Azi, P., Azi, L., Babbage, G., Bailey, C., Baker, K. F., Baker, M., Baker, N., Baker, P., Baldwin, L., Baleanu, I., Bandeira, D., Bara, A., Barbosa, M.A.S., Barker, D., Barlow, G.D., Barnes, E., Barr, A.S., Barrett, J.R., Barrett, J., Bates, L., Batten, A., Beadon, K., Beales, E., Beckley, R., Belij-Rammerstorfer, S., Bell, J., Bellamy, D., Bellei, N., Belton, S., Berg, A., Bermejo, L., Berrie, E., Berry, L., Berzenyi, D., Beveridge, A., Bewley, K.R., Bexhell, H., Bhikha, S., Bhorat, A.E., Bhorat, Z.E., Bijker, E., Birch, G., Birch, S., Bird, A., Bird, O., Bisnauthsing, K., Bittaye, M., Blackstone, K., Blackwell, L., Bletchly, H., Blundell, C. L., Blundell, S.R., Bodalia, P., Boettger, B.C., Bolam, E., Boland, E., Bormans, D., Borthwick, N., Bowring, F., Boyd, A., Bradley, P., Brenner, T., Brown, P., Brown, C., Brown-O'Sullivan, C., Bruce, S., Brunt, E., Buchan, R., Budd, W., Bulbulia, Y.A., Bull, M., Burbage, J., Burhan, H., Burn, A., Buttigieg, K.R., Byard, N., Cabera Puig, I., Calderon, G., Calvert, A., Camara, S., Cao, M., Cappuccini, F., Cardoso, J.R., Carr, M., Carroll, M.W., Carson-Stevens, A., Carvalho, Y.d.M., Carvalho, J.A.M., Casey, H.R., Cashen, P., Castro, T., Castro, L.C., Cathie, K., Cavey, A., Cerbino-Neto, J., Chadwick, J., Chapman, D., Charlton, S., Chelysheva, I., Chester, O., Chita, S., Cho, J.-S., Cifuentes, L., Clark, E., Clark, M., Clarke, A., Clutterbuck, E.A., Collins, S. L.K., Conlon, C.P., Connarty, S., Coombes, N., Cooper, C., Cooper, R., Cornelissen, L., Corrah, T., Cosgrove, C., Cox, T., Crocker, W.E.M., Crosbie, S., Cullen, L., Cullen, D., Cunha, D.R.M.F., Cunningham, C., Cuthbertson, F.C., Da Guarda, S.N.F., da Silva, L. P., Damratoski, B.E., Danos, Z., Dantas, M.T.D.C., Darroch, P., Datoo, M.S., Datta, C., Davids, M., Davies, S.L., Davies, H., Davis, E., Davis, J., Davis, J., De Nobrega, M.M. D., De Oliveira Kalid, L.M., Dearlove, D., Demissie, T., Desai, A., Di Marco, S., Di Maso, C., Dinelli, M.I.S., Dinesh, T., Docksey, C., Dold, C., Dong, T., Donnellan, F.R., Dos Santos, T., dos Santos, T.G., Dos Santos, E.P., Douglas, N., Downing, C., Drake, J., Drake-Brockman, R., Driver, K., Drury, R., Dunachie, S.J., Durham, B.S., Dutra, L., Easom, N.J.W., van Eck, S., Edwards, M., Edwards, N.J., El Muhanna, O. M., Elias, S.C., Elmore, M., English, M., Esmail, A., Essack, Y.M., Farmer, E., Farooq, M., Farrar, M., Farrugia, L., Faulkner, B., Fedosyuk, S., Felle, S., Feng, S., Ferreira Da Silva, C., Field, S., Fisher, R., Flaxman, A., Fletcher, J., Fofie, H., Fok, H., Ford, K.J., Fowler, J., Fraiman, P.H.A., Francis, E., Franco, M.M., Frater, J., Freire, M.S.M., Fry, S.H., Fudge, S., Furze, J., Fuskova, M., Galian-Rubio, P., Galiza, E., Garlant, H., Gavrila, M., Geddes, A., Gibbons, K.A., Gilbride, C., Gill, H., Glynn, S., Godwin, K., Gokani, K., Goldoni, U.C., Goncalves, M., Gonzalez, I.G.S., Goodwin, J., Goondiwala, A., Gordon-Quayle, K., Gorini, G., Grab, J., Gracie, L., Greenland, M., Greenwood, N., Greffrath, J., Groenewald, M.M., Grossi, L., Gupta, G., Hackett, M., Hallis, B., Hamaluba, M., Hamilton, E., Hamlyn, J., Hammersley, D., Hanrath, A.T., Hanumunthadu, B., Harris, S.A., Harris, C., Harris, T., Harrison, T.D., Harrison, D., Hart, T.C., Hartnell, B., Hassan, S., Haughney, J., Hawkins, S., Hay, J., Head, I., Henry, J., Hermosin Herrera, M., Hettle, D.B., Hill, J., Hodges, G., Horne, E., Hou, M.M., Houlihan, C., Howe, E., Howell, N., Humphreys, J., Humphries, H.E., Hurley, K., Huson, C., Hyder-Wright, A., Hyams, C., Ikram, S., Ishwarbhai, A., Ivan, M., Iveson, P., Iyer, V., Jackson, F., De Jager, J., Jaumdally, S., Jeffers, H., Jesudason, N., Jones, B., Jones, K., Jones, E., Jones, C., Jorge, M.R., Jose, A., Joshi, A., Júnior, E.A.M.S., Kadziola, J., Kailath, R., Kana, F., Karampatsas, K., Kasanyinga, M., Keen, J., Kelly, E.J., Kelly, D.M., Kelly, D., Kelly, S., Kerr, D., Kfouri, R.d.Á., Khan, L., Khozoee, B., Kidd, S., Killen, A., Kinch, J., Kinch, P., King, L.D.W., King, T.B., Kingham, L., Klenerman, P., Knapper, F., Knight, J.C., Knott, D., Koleva, S., Lang, M., Lang, G., Larkworthy, C.W., Larwood, J.P.J., Law, R., Lazarus, E.M., Leach, A., Lees, E.A., Lemm, N.-M., Lessa, A., Leung, S., Li, Y., Lias, A.M., Liatsikos, K., Linder, A., Lipworth, S., Liu, S., Liu, X., Lloyd, A., Lloyd, S., Loew, L., Lopez Ramon, R., Lora, L., Lowthorpe, V., Luz, K., MacDonald, J.C., MacGregor, G., Madhavan, M., Mainwaring, D.O., Makambwa, E., Makinson, R., Malahleha, M., Malamatsho, R., Mallett, G., Mansatta, K., Maoko, T., Mapetla, K., Marchevsky, N.G., Marinou, S., Marlow, E., Marques, G.N., Marriott, P., Marshall, R.P., Marshall, J.L., Martins, F.J., Masenya, M., Masilela, M., Masters, S.K., Mathew, M., Matlebjane, H., Matshidiso, K., Mazur, O., Mazzella, A., McCaughan, H., McEwan, J., McGlashan, J., McInroy, L., McIntyre, Z., McLenaghan, D., McRobert, N., McSwiggan, S., Megson, C., Mehdipour, S., Meijs, W., Mendonça, R.N.Á., Mentzer, A.J., Mirtorabi, N., Mitton, C., Mnyakeni, S., Moghaddas, F., Molapo, K., Moloi, M., Moore, M., Moraes-Pinto, M.I., Moran, M., Morey, E., Morgans, R., Morris, S., Morris, S., Morris, H.C., Morselli, F., Morshead, G., Morter, R., Mottal, L., Moultrie, A., Moya, N., Mpelembue, M., Msomi, S., Mugodi, Y., Mukhopadhyay, E., Muller, J., Munro, A., Munro, C., Murphy, S., Mweu, P., Myasaki, C.H., Naik, G., Naker, K., Nastouli, E., Nazir, A., Ndlovu, B., Neffa, F., Njenga, C., Noal, H., Noé, A., Novaes, G., Nugent, F.L., Nunes, G., O'Brien, K., O'Connor, D., Odam, M., Oelofse, S., Oguti, B., Olchawski, V., Oldfield, N.J., Oliveira, M.G., Oliveira, C., Oosthuizen, A., O'Reilly, P., Osborne, P., Owen, D.R.J., Owen, L., Owens, D., Owino, N., Pacurar, M., Paiva, B.V.B., Palhares, E.M.F., Palmer, S., Parkinson, S., Parracho, H.M.R.T., Parsons, K., Patel, D., Patel, B., Patel, F., Patel, K., Patrick-Smith, M., Payne, R.O., Peng, Y., Penn, E.J., Pennington, A., Peralta Alvarez, M.P., Perring, J., Perry, N., Perumal, R., Petkar, S., Philip, T., Phillips, D.J., Phillips, J., Phohu, M.K., Pickup, L., Pieterse, S., Piper, J., Pipini, D., Plank, M., Du Plessis, J., Pollard, S., Pooley, J., Pooran, A., Poulton, I., Powers, C., Presa, F.B., Price, D.A., Price, V., Primeira, M., Proud, P.C., Provstgaard-Morys, S., Pueschel, S., Pulido, D., Quaid, S., Rabara, R., Radford, A., Radia, K., Rajapaska, D., Rajeswaran, T., Ramos, A.S.F., Ramos Lopez, F., Rampling, T., Rand, J., Ratcliffe, H., Rawlinson, T., Rea, D., Rees, B., Reiné, J., Resuello-Dauti, M., Reyes Pabon, E., Ribiero, C.M., Ricamara, M., Richter, A., Ritchie, N., Ritchie, A.J., Robbins, A.J., Roberts, H., Robinson, R.E., Robinson, H., Rocchetti, T.T., Rocha, B.P., Roche, S., Rollier, C., Rose, L., Ross Russell, A.L., Rossouw, L., Royal, S., Rudiansyah, I., Ruiz, S., Saich, S., Sala, C., Sale, J., Salman, A.M., Salvador, N., Salvador, S., Sampaio, M., Samson, A.D., Sanchez-Gonzalez, A., Sanders, H., Sanders, K., Santos, E., Santos Guerra, M.F.S., Satti, I., Saunders, J.E., Saunders, C., Sayed, A., Schim van der Loeff, I., Schmid, A.B., Schofield, E., Screaton, G., Seddiqi, S., Segireddy, R.R., Senger, R., Serrano, S., Shah, R., Shaik, I., Sharpe, H.E., Sharrocks, K., Shaw, R., Shea, A., Shepherd, A., Shepherd, J.G., Shiham, F., Sidhom, E., Silk, S.E., da Silva Moraes, A.C., Silva-Junior, G., Silva-Reyes, L., Silveira, A.D., Silveira, M.B.V., Sinha, J., Skelly, D.T., Smith, D.C., Smith, N., Smith, H.E., Smith, D.J., Smith, C.C., Soares, A., Soares, T., Solórzano, C., Sorio, G.L., Sorley, K., Sosa-Rodriguez, T., Souza, C.M.C.D.L., Souza, B.S.D.F., Souza, A.R., Spencer, A.J., Spina, F., Spoors, L., Stafford, L., Stamford, I., Starinskij, I., Stein, R., Steven, J., Stockdale, L., Stockwell, L.V., Strickland, L.H., Stuart, A.C., Sturdy, A., Sutton, N., Szigeti, A., Tahiri-Alaoui, A., Tanner, R., Taoushanis, C., Tarr, A.W., Taylor, K., Taylor, U., Taylor, I.J., Taylor, J., te Water Naude, R., Themistocleous, Y., Themistocleous, A., Thomas, M., Thomas, K., Thomas, T.M., Thombrayil, A., Thompson, F., Thompson, A., Thompson, K., Thompson, A., Thomson, J., Thornton-Jones, V., Tighe, P.J., Tinoco, L.A., Tiongson, G., Tladinyane, B., Tomasicchio, M., Tomic, A., Tonks, S., Towner, J., Tran, N., Tree, J., Trillana, G., Trinham, C., Trivett, R., Truby, A., Tsheko, B.L., Turabi, A., Turner, R., Turner, C., Ulaszewska, M., Underwood, B.R., Varughese, R., Verbart, D., Verheul, M., Vichos, I., Vieira, T., Waddington, C.S., Walker, L., Wallis, E., Wand, M., Warbick, D., Wardell, T., Warimwe, G., Warren, S. C., Watkins, B., Watson, E., Webb, S., Webb-Bridges, A., Webster, A., Welch, J., Wells, J., West, A., White, C., White, R., Williams, P., Williams, R.L., Winslow, R., Woodyer, M., Worth, A.T., Wright, D., Wroblewska, M., Yao, A., Zimmer, R., Zizi, D., Zuidewind, P., 2021. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397, 99–111. https://doi.org/10.1016/S0140-6736(20)32661-1.

Vulpis, E., Giulimondi, F., Digiacomo, L., Zingoni, A., Safavi-Sohi, R., Sharifi, S., Caracciolo, G., Mahmoudi, M., 2021. The possible role of sex as an important factor in development and administration of lipid nanomedicine-based COVID-19 vaccine. Mol. Pharm. 18, 2448–2453. https://doi.org/10.1021/acs.molpharmaceut.1c00291.

Wahie, S., Daly, A.K., Cordell, H.J., Goodfield, M.J., Jones, S.K., Lovell, C.R., Carmichael, A.J., Carr, M.M., Drummond, A., Natarajan, S., Smith, C.H., Reynolds, N.J., Meggitt, S.J., 2011. Clinical and pharmacogenetic influences on response to hydroxychloroquine in discoid lupus erythematosus: a retrospective cohort study. J. Invest. Dermatol. 131, 1981–1986. https://doi.org/10.1038/jid.2011.167.

Watson, S., Caster, O., Rochon, P.A., den Ruijter, H., 2019. Reported adverse drug reactions in women and men: aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine 17, 100188. https://doi.org/10.1016/j.eclinm.2019.10.001.

Wehbe, Z., Hammoud, S.H., Yassine, H.M., Fardoun, M., El-Yazbi, A.F., Eid, A.H., 2021. Molecular and biological mechanisms underlying gender differences in COVID-19 severity and mortality. Front. Immunol. 12 https://doi.org/10.3389/fimmu.2021.659339.

Wiesenfeld, P.L., Garthoff, L.H., Sobotka, T.J., Suagee, J.K., Barton, C.N., 2007. Acute oral toxicity of colchicine in rats: effects of gender, vehicle matrix and pre-exposure to lipopolysaccharide. J. Appl. Toxicol. 27, 421–433. https://doi.org/10.1002/jat.1198.

Wu, X., Cakmak, S., Wortmann, M., Hakimi, M., Zhang, J., Bockler, D., Dihlmann, S., 2016. Sex- and disease-specific inflammasome signatures in circulating blood leukocytes of patients with abdominal aortic aneurysm. Mol. Med. 22, 505–518. https://doi.org/10.2119/molmed.2016.00035.

Xu, Y., Sheng, H., Bao, Q., Wang, Y., Lu, J., Ni, X., 2016. NLRP3 inflammasome activation mediates estrogen deficiency-induced depression- and anxiety-like behavior and hippocampal inflammation in mice. Brain Behav. Immun. 56, 175–186. https://doi.org/10.1016/j.bbi.2016.02.022.

Xu, K., Chen, Y., Yuan, J., Yi, P., Ding, C., Wu, W., Li, Y., Ni, Q., Zou, R., Li, X., Xu, M., Zhang, Y., Zhao, H., Zhang, X., Yu, L., Su, J., Lang, G., Liu, J., Wu, X., Guo, Y., Tao, J., Shi, D., Yu, L., Cao, Q., Ruan, B., Liu, L., Wang, Z., Xu, Y., Liu, Y., Sheng, J., Li, L., 2020. Factors associated with prolonged viral RNA shedding in patients with coronavirus disease 2019 (COVID-19). Clin. Infect. Dis. 71, 799–806. https://doi.org/10.1093/cid/ciaa351.

Yang, J., Zheng, Y., Gou, X., Pu, K., Chen, Z., Guo, Q., Ji, R., Wang, H., Wang, Y., Zhou, Y., 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int. J. Infect. Dis. 94, 91–95. https://doi.org/10.1016/j.ijid.2020.03.017.

Yashavantha Rao, H.C., Jayabaskaran, C., 2020. The emergence of a novel coronavirus (SARS-CoV-2) disease and their neuroinvasive propensity may affect in COVID-19 patients. J. Med. Virol. 92, 786–790. https://doi.org/10.1002/jmv.25918.

Zekarias, A., Watson, S., Vidlin, S.H., Grundmark, B., 2020. Sex differences in reported adverse drug reactions to COVID-19 drugs in a global database of individual case safety reports. Drug Saf. 43, 1309–1314. https://doi.org/10.1007/s40264-020-01000-8.

Zhang, H., Tang, Y., Tao, J., 2021a. Sex-related overactivation of NLRP3 inflammasome increases lethality of the male COVID-19 patients. Front Mol Biosci 8, 671363. https://doi.org/10.3389/fmolb.2021.671363.

Zhang, Y., Zeng, G., Pan, H., Li, C., Hu, Y., Chu, K., Han, W., Chen, Z., Tang, R., Yin, W., Chen, X., Hu, Y., Liu, X., Jiang, C., Li, J., Yang, M., Song, Y., Wang, X., Gao, Q., Zhu, F., 2021b. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect. Dis. 21, 181–192. https://doi.org/10.1016/S1473-3099(20)30843-4.

Zhao, N., Di, B., Xu, L.L., 2021. The NLRP3 inflammasome and COVID-19: activation, pathogenesis and therapeutic strategies. Cytokine Growth Factor Rev. https://doi.org/10.1016/j.cytogfr.2021.06.002.