Chapter 16
Sex Differences in the Coronavirus Disease 2019

Sergio E. Chiarella, Christina Pabelick, and Y. S. Prakash

Abstract There are profound sex differences in coronavirus disease 2019 (COVID-19) outcomes, with higher morbidity and mortality in males compared to females. The possible mechanisms implicated in this sex bias include the direct effects of sex hormones on the innate and adaptive immune systems, as well as the differential activity of immune-related genes in sex chromosomes. These male-female differences in COVID-19 outcomes highlight the need for sex-disaggregated data to elaborate effective public health policies and the importance of including biological sex as a key variable in future therapeutic and vaccine trials.

Keywords Sex · Gender · Lung · Intrinsic · Structure · Function

16.1 Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a once-in-a-generation health crisis that continues to devastate communities across the globe. As of this writing, the Johns Hopkins Coronavirus Resource Center reported over 26 million confirmed COVID-19 cases and more than 880,000 deaths worldwide (Johns Hopkins University 2020). Importantly, demographic and clinical data gathered by multiple health agencies and governments have demonstrated profound sex differences in COVID-19 outcomes. Overall, the rate of SARS-CoV-2 infection is similar between the sexes. However, males have a higher risk of developing severe COVID-19 and dying when compared to females (Klein et al. 2020b). In this
chapter, we describe in detail the sex differences in COVID-19 outcomes and discuss the possible mechanisms behind them.

There is a significant sex bias in the immune response to viral infections, which is thought to be mostly the result of male-female differences in sex chromosomes and sex hormone milieu. Sex-specific immune responses to a diverse array of viral pathogens, including hantavirus, cytomegalovirus, human immunodeficiency virus, influenza virus, coxsackieviruses, herpes simplex virus, and hepatitis B virus, have been previously described (Bongen et al. 2019; Ghosh and Klein 2017; Piasecka et al. 2018; Schurz et al. 2019; vom Steeg and Klein 2016). In addition, there are significant differences in the immune responses to viral vaccines of males and females (Klein and Flanagan 2016; Markle and Fish 2014). In the case of coronavirus infections, there have been reports of sex differences during prior outbreaks. For instance, data from the Hong Kong Department of Health showed that, during the 2003 severe acute respiratory syndrome (SARS) outbreak, males had a higher case fatality rate (CFR) than females (21.9% versus 13.2%; \(p\)-value <0.0001) (Karlberg et al. 2004). Researchers in Singapore reported similar findings, with male sex being a significant univariate predictor of poor outcome in patients with SARS (odds ratio [OR], 3.1; 95% confidence interval [CI] 1.64–5.87; \(p\)-value <0.001) (Leong et al. 2006). There was also a male predominance during the Middle East respiratory syndrome (MERS) coronavirus epidemic, both in the number of deaths (74% of the fatalities were male) and the CFR (52% in males versus 23% in females) (Alghamdi et al. 2014).

The first reports of sex bias in COVID-19 came from China’s Hubei province, where the pandemic is thought to have started. In a retrospective multicenter cohort study from Wuhan, Zhou and colleagues reported the outcomes of adult patients admitted to the hospital with COVID-19. Of the 191 individuals included in the study, 62% were male. Furthermore, of the 54 patients who died, 70% were male. The protective effect of female sex did not reach statistical significance (univariate logistic regression analysis showed an OR for female versus male sex, 0.61; 95% CI 0.31–1.2; \(p\)-value, 0.15), but a trend started to emerge (Zhou et al. 2020). Similarly, in a subsequent retrospective case series from China, 274 patients with COVID-19 were studied. In this cohort, males represented 62% of the cases and 73% of the deaths, but the authors did not provide a statistical analysis of these sex differences (Chen et al. 2020a).

In another case series from Wuhan, Jin and colleagues reported a similar rate of infection between sexes. Despite this, the mortality rate was 2.4 times higher in males compared to females (70.3% versus 29.7%; \(p\)-value = 0.016), independent of age (Jin et al. 2020). Survival analysis of 269 patients admitted to Tongji Hospital (Wuhan, China) with severe COVID-19 showed that male sex was associated with higher mortality (adjusted hazard ratio of 1.72; 95% CI 1.05–2.82; \(p\)-value = 0.032) (Li et al. 2020b). Other reports have shown significant sex differences in comorbidities and laboratory tests (neutrophil/lymphocyte ratio, C-reactive protein, aspartate aminotransferase, and serum creatinine) among 168 patients with severe COVID-19 (Meng et al. 2020). Finally, a more recent meta-analysis by Li and colleagues, which included the demographic and clinical information of 1994
COVID-19 patients from 10 different publications, showed that males represent 60% of the cases (95% CI, 0.54–0.65) (Li et al. 2020a). Unfortunately, the authors did not present sex-disaggregated data on the CFR.

Other Asian countries have also reported significant sex differences in their COVID-19 outcomes. In a study from the Republic of Korea, data from 7755 individuals with confirmed SARS-CoV-2 infection were collected and analyzed. Interestingly, 62% of the cases were female individuals. Conversely, the CFR was higher in males (1.19% in men versus 0.52% in women) (Dudley and Lee 2020). Iran has also reported on sexual dimorphism in COVID-19 outcomes, with one study showing higher mortality in males (OR, 1.45; 95% CI 1.08–1.96; p-value, 0.01) (Nikpouraghdam et al. 2020).

Sex-disaggregated data from Europe has also shown significant male predominance in COVID-19 morbidity and mortality, which suggests these findings are not specific to Asian populations. In this regard, one of the first reports came from Lombardy, Italy. In their retrospective case series, Grasselli and colleagues found that 82% of 1591 consecutive patients with confirmed COVID-19 requiring admission to the intensive care unit (ICU) were males (Grasselli et al. 2020). A subsequent European study described the clinical and laboratory differences between cohorts of bacterial community-acquired pneumonia (CAP) and SARS-CoV-2 pneumonia. In this study, it was noted that 89.3% of the patients who developed severe respiratory failure due to SARS-CoV-2 were males. This is in stark contrast with data from their bacterial CAP cohort, in which only 48.2% of the patients who developed severe respiratory failure were males (Giamarellos-Bourboulis et al. 2020). In another Italian study evaluating the radiological abnormalities in patients infected with SARS-CoV-2, it was noted that males between the ages of 50 and 79 had a significantly worse radiographic score when compared to their female counterparts (Borghesi et al. 2020). Finally, in a study involving COVID-19 data from six European countries (Italy, Spain, Germany, Switzerland, Belgium, and Norway), the authors found a greater rate of SARS-CoV-2 infection among 10- to 50-year-old women, when compared to men of the same age. Nevertheless, among all age groups, males had a higher fatality rate when compared to females (Marina and Lorenzo 2020).

In the United States, most of the states have made public sex-disaggregated data on COVID-19 morbidity and mortality. In an article published in June of 2020, Klein and colleagues reported that data from 16 states suggests a female bias in SARS-CoV-2 infections (1 to 0.9/0.8 male to female ratio). In the states where sex-disaggregated information regarding COVID-19 deaths has been made available, the data shows that men are twice as likely to die from COVID-19 when compared to women (Klein et al. 2020b). This is consistent with data from the Chinese and European studies discussed above. In a case series of 5700 patients hospitalized with COVID-19 from 12 hospitals in the state of New York, the authors showed that 60.3% of them were male. Furthermore, when analyzing the patient’s discharge disposition at 10-year age intervals, the data showed that from 20 years onward, a higher proportion of males died. As an example, in the age interval of
50–59 years, 12.2% of males died compared to only 6.9% of females (Richardson et al. 2020).

A more recent study of moderate COVID-19 cases dissected the sex differences in the immune response to SARS-CoV-2. In this cohort from Yale University, males had higher plasma levels of interleukin (IL)-8, IL-18, and chemokine ligand 5 (CCL5), while females had higher CD4 and CD8 T cell activation (Takahashi et al. 2020). Intriguingly, a recent study from Johns Hopkins University using convalescent plasma showed higher microneutralization and IgG responses to SARS-CoV-2 in males compared to females. The authors also reported that a greater IgG response correlated with worse COVID-19 outcomes (Klein et al. 2020a). These findings warrant further evaluation, as it seemingly contradicts prior studies showing that females have a more robust adaptive immune system than males (Klein and Flanagan 2016).

In a more global study that analyzed data from 38 countries, Scully and colleagues found that, on average, males had a 1.7 higher CFR compared to females (7.3 versus 5.4; \( p \)-value < 0.0001). When analyzing age-disaggregated data, males 30 years and older had a consistently higher risk of dying from COVID-19 (Scully et al. 2020). The authors obtained some of the information from the Global Health 50/50 COVID-19 data tracker, a notable source of sex-disaggregated data during the COVID-19 pandemic (Global Health 2020).

Interestingly, these male-female differences in coronavirus infections have also been noted in preclinical murine studies. In a pivotal study from 2017, investigators infected age-matched B6 mice from both sexes with different doses of mouse-adapted SARS-CoV (MA15). When infecting mice with 5000 plaque-forming units (PFUs) of MA15, 90% of male mice died versus only 20% of female mice. Increasing the infection dose to 10,000 PFUs resulted in the death of all male mice, while 40% of female mice survived. These sex differences in MA15-induced mortality were more pronounced with increasing age of the mice (Channappanavar et al. 2017).

In summary, there is a male predominance in almost every country reporting sex-disaggregated data on COVID-19 outcomes. In the following section, we will explore the possible mechanisms involved in this sex bias. These include differences in the sex hormone milieu and the copy numbers of X-linked genes relevant to the immune response against SARS-CoV-2.

### 16.2 Sex Chromosomes and COVID-19

X chromosome inactivation and female mosaicism (Lyon 1961) are particularly relevant to the sex bias observed in COVID-19 outcomes. Early in development, one of the female X chromosomes becomes transcriptionally inactive. This process, termed X chromosome inactivation, is random, and the result is two populations of somatic cells that differ in their active X chromosome, i.e., female mosaicism (Machiela et al. 2016). Importantly, the X chromosome has a high number of
immune-related genes, including some involved in cytokine and toll-like receptor (TLR) signaling ($IL1RAPL1$, $IL1RAPL2$, $IL2RG$, $IL13RA1$, $IL13RA2$, $CXCR3$, $TLR7$, and $TLR8$), NF-κB and MAPK signaling ($IKBKG$, $NKRF$, $NKAP$, and $MKP4$), and apoptosis ($XIAP$, $AIFM1$, and $IGBP1$) (Spolarics et al. 2017). X chromosome inactivation and female mosaicism can directly impact immune function and a patient’s response to viral infections and vaccines. As an example, Fink and colleagues have demonstrated that epigenetic regulation of $TLR7$ is implicated in the sex differences observed in vaccine-induced antibody responses (Fink et al. 2018). The presence of the Y chromosome in males can also significantly impact immunity. For instance, genetic variation in the Y chromosome has been shown to impact influenza-induced lung inflammation via the activation of IL-17-producing γδ T cells (Krementsov et al. 2017). Overall, male-female differences in sex chromosomes can significantly impact the immune response to viral infections, which is highly relevant in the setting of the COVID-19 pandemic.

The impact of male-female chromosomal differences on COVID-19 outcomes is also highlighted by the gene encoding the human angiotensin-converting enzyme 2 (ACE2). ACE2 serves as the receptor for the spike (S) protein of SARS-CoV and SARS-CoV-2 (Chen et al. 2020b; Ge et al. 2013; Hoffmann et al. 2020; Li et al. 2003, 2005a, b) and plays a pivotal role in their infectivity. Such is the significance of ACE2 that it is being considered as a potential therapeutic target for COVID-19 (Zhang et al. 2020). Importantly, although the $ACE2$ gene is located in the X chromosome, it can escape X inactivation and be expressed from both the active and inactive X chromosome (Carrel and Willard 2005). This has been shown to lead to sex differences in $ACE2$ gene expression (Gemmati et al. 2020; Li et al. 2020c; Tukiainen et al. 2017), which have potential consequences for the vulnerability to SARS-CoV-2.

Sex differences in TLR signaling and the interferon (IFN) response might also play a role in the sex bias observed in COVID-19. Several TLRs are encoded in the X chromosome (Libert et al. 2010) and have been implicated in sex-specific immune responses to viral infections (Meier et al. 2009). TLR7 is able to recognize SARS-CoV-specific GU-rich single-stranded RNA (ssRNA), activating downstream signaling events which lead to the upregulation of pro-inflammatory cytokines such as the tumor necrosis factor-alpha (TNF-α), interleukin IL-6, and IL-12 (Cervantes-Barragan et al. 2007; Li et al. 2016). As mentioned above, the gene for TLR7 is located in the X chromosome. As with the case of the $ACE2$ gene, the $TLR7$ gene can also avoid X inactivation (Souyris et al. 2018). TLR4 signaling genes, such as IL-1 receptor-associated kinase (IRAK) 1, have also been implicated in sex-specific susceptibility to infections (O’Driscoll et al. 2017). In addition, sexual dimorphism in the response to TLR3 activation has been reported (Chavez-Valdez et al. 2019). Interestingly TLR3 signaling through TRIF adaptor protein has been shown to protect mice from a lethal SARS-CoV disease (Totura et al. 2015). Finally, an abnormal interferon response has been associated with COVID-19, with low levels of type I and II IFNs (Blanco-Melo et al. 2020). There have been reports of sex differences in IFN production from plasmacytoid dendritic cells (pDCs), with higher levels in females compared to males (Berghofer et al. 2006; Meier et al. 2009).
Finally, X-linked genetic variability and mosaicism might also influence the cytokine storm reported in severe cases of COVID-19. This cytokine storm is characterized by elevated plasma levels of IL-2, IL-6, IL-7, granulocyte-colony stimulating factor, IFN-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and TNF-α (Huang et al. 2020; Mehta et al. 2020). Furthermore, IL-6 levels have been shown to be a good predictor of severity and death in patients with COVID-19 (Grifoni et al. 2020). Interestingly, females express lower levels of IL-6 in response to viral infections (Conti and Younes 2020).

16.3 The Roles of Estrogen and Progesterone in COVID-19

The diverse effects of estrogen on the immune system have been described in prior publications, and the reader is referred to other excellent reviews on this topic (Han et al. 2018; Straub 2007; Townsend et al. 2012). Notably, estrogen can regulate viral replication in nasal epithelial cells. Peretz and colleagues showed that 17β-estradiol, via ERβ, decreased the viral titer in human nasal epithelial cells from female donors, but not in the cells from male donors (Peretz et al. 2016). Estrogen could potentially have similar effects during a SARS-CoV-2 infection, limiting viral replication.

Estrogen can also regulate the expression of SARS-CoV-2 viral entry receptors, such as ACE2 and the transmembrane protease, serine 2 (TMPRSS2). As mentioned above, SARS-CoV-2 uses membrane-bound ACE2 (mACE2) as a cellular receptor, and TMPRSS2 is required for S protein priming (Hoffmann et al. 2020). It has been hypothesized that sex differences in lung mACE2 might be directly implicated in the sex bias of COVID-19 (Majdic 2020). The A disintegrin and metalloproteinase 17 (ADAM-17) enzyme can cleave mACE2, shedding soluble ACE2 (sACE2) (Heurich et al. 2014; Haga et al. 2008; Patel et al. 2014). Interestingly, Sward and colleagues have reported that females age 15 and older have lower levels of sACE2 when compared to age-matched males (Sward et al. 2020). Furthermore, the serum activity of ACE2 is higher in older women (age 55 or older) when compared to younger women (Gebhard et al. 2020). The authors of this last study speculate that this increase in ACE2 activity with age might be related to changes in sex hormones, particularly estrogen.

In the bronchial epithelium, ACE2 is primarily expressed in transient secretory cells (Lukassen et al. 2020). Our group has shown that estrogen can regulate the expression of ACE2 in differentiated airway epithelial cells. We treated normal human bronchial epithelial (NHBE) cells with estrogen or vehicle during their differentiation process in air-liquid interface. When compared to control, estrogen treatment led to a significant reduction in ACE2 (Stelzig et al. 2020). Other researchers have also identified estrogen effects on ACE2. Liu and colleagues have shown that ACE2 activity and enzyme velocity is higher in male mice, when compared to their female counterparts. A series of elegant experiments by this group using XX and XY gonadal females and XX and XY gonadal males determined that these sex differences are estrogen-dependent and sex chromosome-independent (Liu 2020).
et al. 2010). In addition, estrogen treatment of oophorectomized rats led to a reduction in cardiac ACE2 expression (Wang et al. 2013). Interestingly, deletion of estrogen-related receptor alpha (ERRα) also leads to an upregulation of ACE2 (Tremblay et al. 2010).

Although less studied, estrogen has also been shown to have an effect on the TMPRSS2:v-ets erythroblastosis virus E26 oncogene homolog (TMPRSS2-ERG) expression in malignant prostate cells. Treatment with an ERβ agonist led to a decrease in the expression of TMPRSS2-ERG, while treatment with an ERα agonist had the opposite effect (Setlur et al. 2008). Of note, in our studies using differentiated airway epithelial cells, we found no significant effect of estrogen on the expression of TMPRSS2 (Stelzig et al. 2020).

As mentioned previously, the sex-specific interferon response to SARS-CoV-2 might contribute to the sex bias in COVID-19. The pDC TLR-mediated type I interferon response to viruses is higher in females compared to males (Berghofer et al. 2006; Meier et al. 2009). By targeting ERα in pDCs, estrogen can promote this interferon response (Seillet et al. 2012). Conversely, inhibiting ER signaling during pDC development leads to a diminished production of interferon (Laffont et al. 2014). Finally, genetic deletion of ERα in mice results in a reduction in the expression of IRF5 and the downstream interferon response (Griesbeck et al. 2015).

The protective effects of estrogen signaling in the context of coronavirus infections have also been shown in murine studies. In a seminal paper, Channappanavar and colleagues showed that oophorectomized female mice had a higher mortality when infected with MA15, the mouse-adapted SARS-CoV. Furthermore, treatment with an estrogen receptor antagonist increased the susceptibility of female mice to this viral infection, while treatment with tamoxifen decreased it (Channappanavar et al. 2017).

Progesterone can also regulate several components of the innate and adaptive immune system. By interacting with progesterone receptors in macrophages, dendritic cells, natural killer cells, T cells, and B cells, progesterone can affect mucosal immunity in the respiratory tract (Hall and Klein 2017). Relevant to the COVID-19 pandemic, progesterone has been shown to regulate lung inflammation and promote tissue repair after a viral infection by increasing the production of epidermal growth factor amphiregulin (Hall et al. 2016). In a murine model of influenza A virus infection, progesterone had a protective effect on naïve female mice, but not in the mice that had undergone a prior viral challenge (Hall et al. 2017).

### 16.4 The Role of Androgens in COVID-19

The effects of androgen signaling on the innate and adaptive immune system are diverse and have been previously reviewed (Gubbels Bupp and Jorgensen 2018; Kissick et al. 2014; Lai et al. 2012; Trigunaite et al. 2015). So far, it is unclear if low or high androgen levels contribute to severe outcomes in COVID-19. Some have shown that elevated testosterone levels correlate with low antibody levels to
vaccines (Furman et al. 2014). Others hypothesize that SARS-CoV-2 infection might trigger acute male hypogonadism with low androgen levels, which may contribute to increased COVID-19 morbidity and mortality (Channappanavar et al. 2017; Salonia et al. 2020). As an example, Rastrelli and colleagues have shown that, in males with SARS-CoV-2 pneumonia, low total testosterone (less than 5 nmol/L) and low calculated free testosterone (less than 100 pmol/L) are associated with higher rates of ICU transfer and death (Rastrelli et al. 2020). Interestingly, human studies have shown that testosterone can upregulate IL-1 and downregulate IL-1β, IL-6, and TNF-α, leading to a suppression of inflammation (Mohamad et al. 2019; Pozzilli and Lenzi 2020). Future studies investigating the effects of androgen levels on COVID-19 should consider the timing of the androgen measurement in the course of the SARS-CoV-2 infection (Strope et al. 2020).

Another mechanism by which testosterone might predispose males to worse COVID-19 outcomes is by regulating the expression of TMPRSS2 (Giagulli et al. 2020; Stopsack et al. 2020). In the context of coronavirus infections, TMPRSS2 is not only a key element for S protein activation and virus-cell fusion but can also decrease viral recognition by neutralizing antibodies (Glowacka et al. 2011). TMPRSS2 is highly expressed in urogenital organs, such as the prostate (Chakravarty et al. 2020). Therefore, it is not surprising that testosterone regulation of TMPRSS2 expression was first identified in studies of prostate cancer biology. In prostate cancer cells, the TMPRSS2 gene is commonly fused to ETS transcription factors, such as ERG or ETV1. Androgen-responsive elements within TMPRSS2 mediate the increased expression of ERG or ETV1, which in turn has important prognostic implications for prostate cancer patients (Fernandez et al. 2015; Hagglof et al. 2014; Lucas et al. 2014; Tomlins et al. 2005). Importantly, androgen-induced upregulation of TMPRSS2 has also been reported in a human lung adenocarcinoma-derived (A549) cell line (Mikkonen et al. 2010).

16.5 Clinical Trials for COVID-19 Involving Sex Steroid Signaling

Given the marked sex bias in COVID-19 outcomes and multiple preclinical studies demonstrating the ability of sex hormones to regulate different aspects of SARS-CoV-2 infectivity, several clinical trials targeting sex steroid signaling have been initiated across the globe. These clinical studies have been summarized in Table 16.1. For example, investigators at Stony Brook University Hospital in New York are conducting a study to evaluate if the administration of estradiol (100 micrograms per day for 7 days) through a patch can decrease symptom severity in patients with confirmed or presumptive COVID-19. Others have even proposed the use of conjugated estrogens to prevent SARS-CoV-2 infections (Suba 2020). Another randomized controlled trial is testing the efficacy of progesterone (100 milligrams subcutaneously twice daily for 5 days) plus standard of care (SOC) versus
SOC alone as a therapeutic strategy for males with COVID-19. Finally, several ongoing clinical trials are using antagonists of the androgen receptor to treat patients with COVID-19. For instance, researchers at Johns Hopkins Hospital are studying if adding bicalutamide (150 mg by mouth daily for 7 days) to SOC can improve the rate of clinical improvement in patients with COVID-19 requiring hospitalization. Other clinical trials targeting the androgen receptor use spironolactone and enzalutamide.

Future clinical studies should also investigate the effects of estrogen replacement therapy and androgen deprivation therapy (ADT) on COVID-19 outcomes. Italian researchers have reported a lower risk of SARS-CoV-2 infection in patients with prostate cancer receiving ADT than those not receiving ADT (OR, 4.05; 95% CI

Table 16.1  COVID-19 clinical trials targeting sex hormone pathways

| Drug                   | Drug effect                        | ClinicalTrials.gov identifier | Primary outcome measure(s)                                                                 | Location                                      |
|------------------------|------------------------------------|-------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------|
| Degarelix              | Antagonist of the GnRH receptor   | NCT04397718                  | A composite endpoint of mortality, ongoing need for hospitalization, or requirement for mechanical ventilation or ECMO | VA healthcare systems in CA, NY, and WA, USA |
| Estrogen               | Agonist of the estrogen receptors | NCT04359329                  | Rate of hospitalization, rate of transfer to intensive care unit, rate of intubation, and rate of death | Stony Brook University Hospital, NY, USA     |
| Tamoxifen (in combination with isotretinoin) | Agonist of the estrogen receptors | NCT04389580                  | Lung injury score                                                                       | Kafrelsheikh university, Egypt               |
| Progesterone           | Agonist of the progesterone receptors | NCT04365127                | Change in clinical status                                                                | Cedars Sinai medical center, CA, USA         |
| Bicalutamide           | Antagonist of the androgen receptor | NCT04374279                | Percentage of participants who have clinical improvement                                  | Johns Hopkins Hospital, MD, USA              |
| Spironolactone         | Antagonist of the androgen receptor | NCT04345887                | p/f ratio (improvement in oxygenation)                                                     | Istanbul University, Turkey                  |
| Spironolactone (in combination with bromhexine) | Antagonist of the androgen receptor | NCT04424134                | Change from baseline in clinical assessment score COVID-19                                 | Lomonosov Moscow State University, Russian Federation |
| Enzalutamide           | Antagonist of the androgen receptor | NCT04475601                | Time to worsening of disease and time to improvement of disease                           | Norrlands university hospital, region Västerbotten, Sweden |
1.55–10.59; \( p \)-value = 0.0043) (Montopoli et al. 2020). Others have shown that abiraterone, an androgen biosynthesis inhibitor, has in vitro anti-SARS-CoV-2 activity, reducing the virus-induced cytopathic effects by approximately 70% (Yuan et al. 2020).

The study of individuals with COVID-19 who have comorbidities such as polycystic ovarian syndrome or androgenetic alopecia (AGA; also known as male pattern hair loss) could also shed light on the effects of sex steroid signaling on this disease. For instance, Goren and colleagues noted that 71% of Caucasian males (\( n = 41 \)) who were admitted with bilateral SARS-CoV-2 pneumonia had clinically significant AGA (Goren et al. 2020). A subsequent study by the same research group confirmed this observation, finding that 67% of patients (\( n = 175 \)) with COVID-19 had AGA (Wambier et al. 2020). The authors speculate the increased androgen sensitivity might predispose patients with AGA to more severe forms of COVID-19.

In addition to the efforts to conduct clinical trials specifically targeting steroid signaling pathways, it is of paramount importance to include sex as a biological variable in all other COVID-19 therapeutic studies. Medications can have sex-specific pharmacogenomic, pharmacokinetic, and pharmacodynamics properties (Bartz et al. 2020; Franconi and Campesi 2014). Furthermore, multiple studies with immunotherapies (such as antiviral agents, convalescent plasma, and vaccines) have already demonstrated the importance of biologic sex when studying drug efficacy (Grassadonia et al. 2018; Jawaheer et al. 2012; Klein and Morgan 2020).

Preclinical studies involving mice have shown that serum from female mice is better at protecting naïve mice than serum from male mice (Fink et al. 2018). In addition, it is important to consider the sex differences in adverse drug reactions, since they tend to be more prevalent in female patients (Bischof et al. 2020). Finally, biological sex should even be a key variable in studies addressing mechanical ventilation strategies, as male-female differences in lung volumes could impact the COVID-19 outcomes of mechanically ventilated patients (Han et al. 2018).

### 16.6 Gender Differences in COVID-19

Sex is a biological variable, while gender is defined as the socially constructed roles, behaviors, and expressions of men and women. Although not the primary focus of this chapter, gender can also contribute to differences in COVID-19 outcomes. For example, there are marked gender differences in smoking habits among certain populations. In China, 288 million men smoke versus only 12.6 million women (Cai 2020). Importantly, smoking has been shown to be a risk factor for adverse outcomes in COVID-19, which may disproportionately affect men (Vardavas and Nikitara 2020). There are also significant gender differences in comorbidities (Sharma et al. 2020). Importantly, the CFR for COVID-19 is elevated for patients with cardiovascular disease (10.5%), diabetes (7.3%), chronic pulmonary disease (6.3%), hypertension (6%), and cancer (5.6%) (Wu and McGoogan 2020). In general, these comorbidities tend to be more prevalent in men.
In certain communities, women are the predominant caregivers at home and in healthcare settings. This places them at an increased risk of becoming infected with SARS-CoV-2 (Wenham et al. 2020). Women are also at increased risk for psychiatric disorders (Liu et al. 2020) and social isolation (Senst et al. 2016) during the pandemic, which might result in worse outcomes. Even the gendered behavior of handwashing, which is lower in men, can have an impact on the rate of SARS-CoV-2 infections (Gebhard et al. 2020). Overall, COVID-19 will bring to the forefront several structural gender health disparities that will need to be addressed in order to effectively mitigate the pandemic (Spagnolo et al. 2020).

16.7 Conclusion

There are profound sex differences in the vulnerability to COVID-19. The mechanisms involved in this sex bias are still unclear, but experts in the field agree that differences in sex chromosomes and the direct action of sex steroids are likely contributing. Further mechanistic studies are required to address this knowledge gap. Biological sex is also an important variable to incorporate into future COVID-19 therapeutic and vaccine trials. Finally, the authors believe that sex-disaggregated data and sex-specific interventions are crucial to establishing efficient public health policies in order to manage and mitigate the adverse outcomes of the COVID-19 pandemic.

Acknowledgments This book chapter was supported by NIH grants K08 AI141765 (SEC), R01 HL142061 (CMP, YSP), and R01 HL088029, R01 HL056470 (YSP).

References

Alghamdi IG, Hussain II, Almalki SS, Alghamdi MS, Alghamdi MM, El-Sheemy MA (2014) The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. Int J Gen Med 7:417–423. https://doi.org/10.2147/IJGM.S67061

Bartz D, Chitnis T, Kaiser UB, Rich-Edwards JW, Rexrode KM, Pennell PB, Goldstein JM, O’Neal MA, LeBoff M, Behn M, Seely EW, Joffe H, Manson JE (2020) Clinical advances in sex- and gender-informed medicine to improve the health of all: a review. JAMA Intern Med 180:574. https://doi.org/10.1001/jamainternmed.2019.7194

Berghofer B, Frommer T, Haley G, Fink L, Bein G, Hackstein H (2006) TLR7 ligands induce higher IFN-alpha production in females. J Immunol 177(4):2088–2096. https://doi.org/10.4049/jimmunol.177.4.2088

Bischof E, Wolfe J, Klein SL (2020) Clinical trials for COVID-19 should include sex as a variable. J Clin Invest 130(7):3350–3352. https://doi.org/10.1172/JCI139306

Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR (2020) Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 181 (5):1036–1045. e1039. https://doi.org/10.1016/j.cell.2020.04.026
Bongen E, Lucian H, Khatri A, Fragiadakis GK, Bjornson ZB, Nolan GP, Utz PJ, Khatri P (2019)
Sex differences in the blood transcriptome identify robust changes in immune cell proportions
with aging and influenza infection. Cell Rep 29(7):1961–1973. e1964. https://doi.org/10.1016/j.
celrep.2019.10.019

Borghesi A, Zigliani A, Masciullo R, Golemi S, Maculotti P, Farina D, Maroldi R (2020)
Radiographic severity index in COVID-19 pneumonia: relationship to age and sex in 783 Italian
patients. Radiol Med 125(5):461–464. https://doi.org/10.1007/s11547-020-01202-1

Cai H (2020) Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir
Med 8(4):e20. https://doi.org/10.1016/S2213-2600(20)30117-X

Carrel L, Willard HF (2005) X-inactivation profile reveals extensive variability in X-linked gene
expression in females. Nature 434(7031):400–404. https://doi.org/10.1038/nature03479

Cervantes-Barragan L, Zust R, Weber F, Spiegel M, Lang KS, Akira S, Thiel V, Ludewig B (2007)
Control of coronavirus infection through plasmacytoid dendritic-cell-derived type I interferon.
Blood 109(3):1131–1137. https://doi.org/10.1182/blood-2006-05-023770

Chakravarty D, Nair SS, Hammouda N, Ratnani P, Gharib Y, Wagaskar V, Mohamed N, Llundon D, Dovey Z, Kyprianou N, Tewari AK (2020) Sex differences in SARS-CoV-2 infection rates and the potential link to prostate cancer. Commun Biol 3(1):374. https://doi.org/10.1038/s42003-020-1088-9

Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S (2017) Sex-based
differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J
Immunol 198(10):4046–4053. https://doi.org/10.4049/jimmunol.1601896

Chavez-Valdez R, Mottaedeen A, Stridh L, Yellowhair TR, Jantzie LL, Northington FJ, Mallard C
(2019) Evidence for sexual dimorphism in the response to TLR3 activation in the developing
neonatal mouse brain: a pilot study. Front Physiol 10:306. https://doi.org/10.3389/fphys.2019.
00306

Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W,
Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q (2020a) Clinical
characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study.
BMJ 368:m1091. https://doi.org/10.1136/bmj.m1091

Chen Y, Guo Y, Pan Y, Zhao ZJ (2020b) Structure analysis of the receptor binding of 2019-nCoV.
Biochem Biophys Res Commun 525:135. https://doi.org/10.1016/j.bbrc.2020.02.071

Conti P, Younes A (2020) Coronavirus COV-19/SARS-CoV-2 affects women less than men:
clinical response to viral infection. J Biol Regul Homeost Agents 34(2):339–343. https://doi.
org/10.23812/Editorial-Conti-3

Dudley JP, Lee NT (2020) Disparities in age-specific morbidity and mortality from SARS-CoV-2 in
China and the Republic of Korea. Clin Infect Dis 71(15):863–865. https://doi.org/10.1093/cid/ciaa354

Fernandez EV, Reece KM, Ley AM, Troutman SM, Sissung TM, Price DK, Chau CH, Figg WD
(2015) Dual targeting of the androgen receptor and hypoxia-inducible factor 1alpha pathways
synergistically inhibits castration-resistant prostate cancer cells. Mol Pharmacol 87
(6):1006–1012. https://doi.org/10.1124/mol.114.097477

Fink AL, Engle K, Ursin RL, Tang WY, Klein SL (2018) Biological sex affects vaccine efficacy
and protection against influenza in mice. Proc Natl Acad Sci U S A 115(49):12477–12482.
https://doi.org/10.1073/pnas.1805268115

Franconi F, Campesi I (2014) Pharmacogenomics, pharmacokinetics and pharmacodynamics:
interaction with biological differences between men and women. Br J Pharmacol 171
(3):580–594. https://doi.org/10.1111/bph.12362

Furman D, Hejblum BP, Simon N, Jocic V, Dekker CL, Thiebaut R, Tibshirani RJ, Davis MM
(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(2):869–874. https://doi.
org/10.1073/pnas.1321060111

Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C,
Zhang YJ, Luo CM, Tan B, Wang N, Zhu Y, Cramer G, Zhang SY, Wang LF, Daszak P, Shi
ZL (2013) Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503(7477):535–538. https://doi.org/10.1038/nature12711

Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL (2020) Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ 11(1):29. https://doi.org/10.1186/s13293-020-00304-9

Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V (2020) COVID-19 and individual genetic susceptibility/receptivity: role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 compared to the single X-chromosome in males? Int J Mol Sci 21(10). https://doi.org/10.3390/ijms21103474

Ghosh S, Klein RS (2017) Sex drives dimorphic immune responses to viral infections. J Immunol 198(5):1782–1790. https://doi.org/10.4049/jimmunol.1601166

Giagulli VA, Guastamacchia E, Magrone T, Jirillo E, Lisco G, De Pergola G, Triggiani V (2020) Worse progression of COVID-19 in men: is testosterone a key factor? Andrology. https://doi.org/10.1111/andr.12836

Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrina K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A (2020) Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 27(6):992–1000. e1003. https://doi.org/10.1016/j.chom.2020.04.009

Global Health 50/50 (2020) Sex, gender and COVID-19: overview and resources. https://globalhealth5050.org/covid19/

Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, Steffen I, Tsegaye TS, He Y, Gniirss K, Niemeyer D, Schneider H, Drosten C, Pohlmann S (2011) Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol 85(9):4122–4134. https://doi.org/10.1128/JVI.02232-10

Goren A, Vano-Galvan S, Wambier CG, McCoy J, Gomez-Zubiaur A, Moreno-Arrones OM, Shapiro J, Sinclair RD, Gold MH, Kovacevic M, Mesinkovska NA, Goldust M, Washenik K (2020) A preliminary observation: male pattern hair loss among hospitalized COVID-19 patients in Spain – a potential clue to the role of androgens in COVID-19 severity. J Cosmet Dermatol 19(7):1545–1547. https://doi.org/10.1111/jocd.13443

Grassadonia A, Sperduti I, Vici P, Iezzi L, Brocco D, Gamucci T, Pizzutti L, Mauger-Sacca M, Marchetti P, Cognetti G, De Tursi M, Natoli C, Barba M, Tinari N (2018) Effect of gender on the outcome of patients receiving immune checkpoint inhibitors for advanced Cancer: a systematic review and meta-analysis of phase III randomized clinical trials. J Clin Med 7(12). https://doi.org/10.3390/jcm7120542

Grasselli G, Zaninotto A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cerda D, Colucciello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cescon M, Pesenti A, Network C-LI (2020) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region. Italy JAMA 323:1574. https://doi.org/10.1001/jama.2020.5394

Griesbeck M, Ziegler S, Laffont S, Smith N, Chauveau L, Tomezsko P, Sharei A, Kourjian G, Porichis F, Hart M, Palmer CD, Sirignano M, Beisel C, Hildebrandt H, Cencac C, Villani AC, Diefenbach TJ, Le Gall S, Schwartz O, Herbeuval JP, Atraun B, Guery JC, Chang JJ, Aitfeld M (2015) Sex differences in Plasmacytoid dendritic cell levels of IRF5 drive higher IFN-alpha production in women. J Immunol 195(11):5327–5336. https://doi.org/10.4049/jimmunol.1501684

Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, Vannucchi V, Moroni F, Pelagatti L, Tarquini R, Landini G, Vanni S, Masotti L (2020) Interleukin-6 as prognosticator in patients with COVID-19. J Infect 81(3):452–482. https://doi.org/10.1016/j.jinf.2020.06.008
Liu J, Ji H, Zheng W, Wu X, Zhu JJ, Arnold AP, Sandberg K (2010) Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17beta-oestradiol-dependent and sex chromosome-independent. Biol Sex Differ 1(1):6. https://doi.org/10.1186/2042-6410-1-6

Liu N, Zhang F, Wei C, Jia Y, Shang Z, Sun L, Wu L, Sun Z, Zhou Y, Wang Y, Liu W (2020) Prevalence and predictors of PTSS during COVID-19 outbreak in China hardest-hit areas: gender differences matter. Psychiatry Res 287:112921. https://doi.org/10.1016/j.psychres.2020.11.2921

Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, Morrissey C, Corey E, Montgomery B, Mostaghel E, Clegg N, Coleman I, Brown CM, Schneider EL, Craik C, Simon JA, Bedalov A, Nelson PS (2014) The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 4(11):1310–1325. https://doi.org/10.1158/2159-8290.CD-13-1010

Lukassen S, Chua RL, Trefzer T, Kahn NC, Schneider MA, Muley T, Winter H, Meister M, Veith C, Boots AW, Hennig BP, Kreuter M, Conrad C, Eils R (2020) SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. EMBO J 39(10):e105114. https://doi.org/10.15252/embj.20105114

Lyon MF (1961) Gene action in the X-chromosome of the mouse (Mus musculus L.). Nature 190:372–373. https://doi.org/10.1038/190372a0

Machiela MJ, Zhou W, Karlins E, Sampson NJ, Freedman ND, Yang Q, Hicks B, Dagnall C, Hautman C, Jacobs KB, Abnet CC, Aldrich MC, Amos C, Amundaddotir LT, Arslan AA, Beane-Freeman LE, Berndt SI, Black A, Blot WJ, Bock CH, Bracci PM, Brinton LA, Bueno-de-Mesquita HB, Burdett L, Buring JE, Butler MA, Canzian F, Carreon T, Chaffee KK, Chang IS, Chatterjee N, Chen C, Chen C, Chen K, Chung CC, Cook LS, Crous Bou M, Cullen M, Davis FG, De Vivo I, Ding T, Doherty J, Duell EI, Epstein CG, Fan JH, Figueroa JD, Fraumeni JF, Friedenreich CM, Fuchs CS, Gallinger S, Gao YT, Gapstur SM, Garcia-Closas M, Gaudet MM, Gaziano JM, Giles GG, Gillanders EM, Giovannucci EL, Goldin L, Goldstein AM, Haiman CA, Hallmans G, Hankinson SE, Harris CC, Henriksson R, Holly EA, Hong YC, Hoover RN, Hsuang CA, Hu N, Hu W, Hunter DJ, Hutchinson A, Jemal A, Johansen C, Khaw KT, Kim HN, Kim YH, Kim YT, Klein AP, Kleijn R, Koh WP, Kolonel LN, Kooperberg C, Krogh V, Kurtz RC, LaCroix A, Lan Q, Landi MT, Marchand LL, Li D, Liang X, Liao LM, Lin D, Liu J, Lissowska J, Lu L, Magliocco AM, Malats N, Matsuo K, MeNeill LH, McWilliams RR, Melin BS, Mirabello L, Moore L, Olson SH, Orlov I, Park JY, Patino-Garcia A, Peplonska B, Peters U, Petersen GM, Pooler L, Prescott J, Prokunina-Olsson L, Purdue MP, Qiao YL, Rajaraman P, Real FX, Riboli E, Risch HA, Rodriguez-Santiago B, Ruder AM, Savage SA, Schumacher F, Schwartz AG, Schwartz KL, Seow A, Wendy Setiawan V, Severi G, Shen H, Sheng X, Shih MH, Shu XO, Silverman DT, Spitz MR, Stevens VL, Stolzenberg-Solomon R, Stram D, Tang ZZ, Taylor PR, Teras LR, Tobias GS, Van Den Berg D, Visvanathan K, Wacholder S, Wang JC, Wang Z, Wentzensen N, Wheeler W, White E, Wiencek JK, Wolpin BM, Wong MP, Wu C, Wu T, Wu X, Wu YL, Wunder JS, Xia L, Yang HP, Yang PC, Yu K, Zanetti KA, Zeleniuch-Jacquotte A, Zheng W, Zhou B, Ziegler RG, Perez-Jurado LA, Caporaso NE, Rothman N, Tucker M, Dean MC, Yeager M, Chanock SJ (2016) Female chromosome X mosaicism is age-related and preferentially affects the inactivated X chromosome. Nat Commun 7:11843. https://doi.org/10.1038/ncomms11843

Majdic G (2020) Could sex/gender differences in ACE2 expression in the lungs contribute to the large gender disparity in the morbidity and mortality of patients infected with the SARS-CoV-2 virus? Front Cell Infect Microbiol 10:327. https://doi.org/10.3389/fcimb.2020.00327

Marina S, Lorenzo P (2020) Gender and age effects on the rates of infection and deaths in individuals with confirmed SARS-CoV-2 infection in six european countries

Majdle G, Fish EN (2014) SeXX matters in immunity. Trends Immunol 35(3):97–104. https://doi.org/10.1016/j.it.2013.10.006
Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLh Across Speciality Collaboration UK (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 395(10229):1033–1034. https://doi.org/10.1016/S0140-6736(20)30628-0
Meier A, Chang JJ, Chan ES, Pollard RB, Sidhu HK, Kulkarni S, Wen TF, Lindsay RJ, Orellana L, Mildvan D, Bazner S, Streeck H, Alter G, Liffson JD, Carrington M, Bosch RJ, Robbins GK, Altfield M (2009) Sex differences in the toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat Med 15(8):955–959. https://doi.org/10.1038/nm.2004
Meng Y, Wu P, Lu W, Liu K, Ma K, Huang L, Cai J, Zhang H, Qin Y, Sun H, Ding W, Gui L, Wu P (2020) Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: a retrospective study of 168 severe patients. PLoS Pathog 16(4):e1008520. https://doi.org/10.1371/journal.ppat.1008520
Mikkonen L, Pihlajamaa P, Sahu B, Zhang FP, Jänne OA (2010) Androgen receptor and androgen-dependent gene expression in lung. Mol Cell Endocrinol 317(1–2):14–24. https://doi.org/10.1016/j.mce.2009.12.022
Mohamad NV, Wong SK, Wan Hasan WN, Jolly JJ, Nur-Farhana MF, Ima-Nirwana S, Chin KY (2019) The relationship between circulating testosterone and inflammatory cytokines in men. Aging Male 22(2):129–140. https://doi.org/10.1080/13685538.2018.1482487
Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, Carbone GM, 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. https://doi.org/10.1016/j.annonc.2020.04.479
Nikpouraghdam M, Jalali Farahani A, Alishiri G, Heydari S, Ebrahimmia M, Samadinia H, Sepandi M, Safari NJ, Izadi M, Qazvini A, Dorostkar R, Tat M, Shahriary A, Farnoosh G, Hosseini Zijoud SR, Taghdir M, Alimohamadi Y, Abbaszadeh S, Gouvarchin Gahale HE, Bagheri M (2020) Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: a single center study. J Clin Virol 127:104378. https://doi.org/10.1016/j.jcv.2020.104378
O’Driscoll DN, De Santi C, McKiernan PJ, McEneaney V, Molloy EJ, Greene CM (2017) Expression of X-linked toll-like receptor 4 signaling genes in female vs. male neonates. Pediatr Res 81(5):831–837. https://doi.org/10.1038/pr.2017.2
Patel VB, Clarke N, Wang Z, Fan D, Parajuli N, Basu R, Kassiri Z, Turner AJ, Oudit GY (2014) Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. J Mol Cell Cardiol 66:167–176. https://doi.org/10.1016/j.yjmcc.2013.11.017
Peretz J, Pekosz A, Lane AP, Klein SL (2016) Estrogenic compounds reduce influenza a virus replication in primary human nasal epithelial cells derived from female, but not male, donors. Am J Physiol Lung Cell Mol Physiol 310(5):L415–L425. https://doi.org/10.1152/ajplung.00398.2015
Piasecka B, Duffy D, Urrutia A, Quach H, Patin E, Posseme C, Bergstedt J, Charbit B, Rouilly V, MacPherson CR, Hasan M, Albaud B, Gentien D, Fellay J, Albert ML, Quintana-Murci L, Milieu Interieur C (2018) Distinctive roles of age, sex, and genetics in shaping transcriptional variation of human immune responses to microbial challenges. Proc Natl Acad Sci U S A 115(3):E488–E497. https://doi.org/10.1073/pnas.1714765115
Pozzilli P, Lenzi A (2020) Commentary: testosterone, a key hormone in the context of COVID-19 pandemic. Metabolism 108:154252. https://doi.org/10.1016/j.metabol.2020.154252
Rastrelli G, Di Stasi V, Inglese F, Beccaria M, Garuti M, Di Costanzo D, Spezafico F, Greco GF, Cervi G, Pecoriello A, Magini A, Todisco T, Cipriani S, Maseroni E, Corona G, Salonia A, Lenzi A, Maggi M, De Donno G, Vignozzi L (2020) Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. Andrology. https://doi.org/10.1111/andr.12821
Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, the Northwell C-RC, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin H, Hajjizadeh N, Harvin TG, Hirschwerk
DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 323:2052. https://doi.org/10.1001/jama.2020.6775

Salonia A, Corona G, Giwercman A, Maggi M, Minhas S, Nappi RE, Sofikitis N, Vignozzi L (2020) SARS-CoV-2, testosterone and frailty in males (PROTEGGIMI): a multidimensional research project. Andrology. https://doi.org/10.1111/andr.12811

Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Moller M (2019) The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genomics 13(1):2. https://doi.org/10.1186/s40246-018-0185-z

Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL (2020) Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 20(7):442–447. https://doi.org/10.1038/s41577-020-0348-8

Seillet C, Laffont S, Tremollieres F, Rouquie N, Ribot C, Arnal JF, Douin-Echinard V, Gourdy P, Guery JC (2012) The TLR-mediated response of plasmacytoid dendritic cells is positively regulated by estradiol in vivo through cell-intrinsic estrogen receptor alpha signaling. Blood 119(2):454–464. https://doi.org/10.1182/blood-2011-08-371831

Senst L, Baimoukhametova D, Sterley TL, Bains JS (2016) Sexually dimorphic neuronal responses to social isolation. elife 5:e18726. https://doi.org/10.7554/eLife.18726

Setlur SR, Mertz KD, Hoshida Y, Demichelis F, Lupien M, Perner A, Pawitan Y, Andren O, Johnson LA, Tang J, Adami HO, Calza S, Chinnaiyan AM, Rhodes D, Tomlins S, Fall K, Mucci LA, Kantoff PW, Stampler MJ, Andersson SO, Varenhorst E, Johansson JE, Brown M, Golub TR, Rubin MA (2008) Estrogen-dependent signaling in a molecularly distinct subclass of aggressive prostate cancer. J Natl Cancer Inst 100(11):815–825. https://doi.org/10.1093/jnci/djn150

Sharma G, Volgman AS, Michos ED (2020) Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected? JACC Case Rep 2:1407. https://doi.org/10.1016/j.jaccas.2020.04.027

Souris M, Cenc A, Azar P, Daviaud D, Canivet A, Grunenwald S, Pienkowski C, Chaumeil J, Mejia JE, Guery JC (2018) TLR7 escapes X chromosome inactivation in immune cells. Sci Immunol 3(19):eaap8855. https://doi.org/10.1126/sciimmunol.aap8855

Spagnolo PA, Manson JE, Joffe H (2020) Sex and gender differences in health: what the COVID-19 pandemic can teach us. Ann Intern Med 173:385. https://doi.org/10.7326/M20-1941

Spolarsics Z, Pena G, Qin Y, Donnelly RJ, Livingston DH (2017) Inherent X-linked genetic variability and cellular mosaicism unique to females contribute to sex-related differences in the innate immune response. Front Immunol 8:1455. https://doi.org/10.3389/fimmu.2017.01455

Stelzig KE, Canepa-Escaro F, Schilio M, Berdnikovs S, Prakash YS, Chiarella SE (2020) Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. Am J Physiol Lung Cell Mol Physiol 318(6):L1280–L1281. https://doi.org/10.1152/ajplung.00153.2020

Stopnick KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW (2020) TMPRSS2 and COVID-19: serendipity or opportunity for intervention? Cancer Discov 10(6):779–782. https://doi.org/10.1158/2159-8290.CD-20-0451

Straub RH (2007) The complex role of estrogens in inflammation. Endocr Rev 28(5):521–574. https://doi.org/10.1210/er.2007-0001

Strope JD, Chau CH, Figg WD (2020) Are sex discordant outcomes in COVID-19 related to sex hormones? Semin Oncol 47:335. https://doi.org/10.1053/j.seminoncol.2020.06.002

Suba Z (2020) Prevention and therapy of COVID-19 via exogenous estrogen treatment for both male and female patients. J Pharm Pharm Sci 23(1):75–85. https://doi.org/10.18433/jpps31069

Sward P, Edsfeldt A, Reepalu A, J héppson L, Rosengren BE, Karlsson MK (2020) Age and sex differences in soluble ACE2 may give insights for COVID-19. Crit Care 24(1):221. https://doi.org/10.1186/s13054-020-02942-2
Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, Silva J, Mao T, Oh JE, Tokuyama M, Lu P, Venkataraman A, Park A, Liu F, Meir A, Sun J, Wang EY, Casanovas-Massana A, Wyllie AL, Vogels CB, Earnest R, Lapidus S, Ott IM, Moore AJ, Iry T, Shaw A, Fournier JB, Odio CD, Farhadian S, Dela Cruz C, Grubaugh ND, Schulz WL, Ring AM, Ko AI, Omer SB, Iwasaki A (2020) Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. https://doi.org/10.1038/s41586-020-2700-3

Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, Lee C, Montie JE, Shah RB, Pienta KJ, Rubin MA, Chinnaiyan AM (2005) Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 310(5748):644–648. https://doi.org/10.1126/science.1117679

Trotta AL, Whittome A, Agnihotram S, Schafre A, Katze MG, Heise MT, Baric RS (2015) Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio 6(3):e00638–e00615. https://doi.org/10.1128/mBio.00638-15

Townsend EA, Miller VM, Prakash YS (2012) Sex differences and sex steroids in lung health and disease. Endocr Rev 33(1):1–47. https://doi.org/10.1210/er.2010-0031

Tremblay AM, Dufour CR, Ghahremani M, Reudelhuber TL, Giguere V (2010) Physiological genomics identifies estrogen-related receptor alpha as a regulator of renal sodium and potassium homeostasis and the renin-angiotensin pathway. Mol Endocrinol 24(1):22–32. https://doi.org/10.1210/me.2009-0254

Trigunaite A, Dimo J, Jorgensen TN (2015) Suppressive effects of androgens on the immune system. Cell Immunol 294(2):87–94. https://doi.org/10.1016/j.cellimm.2015.02.004

Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R, Aguirre M, Gauthier L, Fleharty M, Kirby A, Cummings BB, Castel SE, Karczewski KJ, Aguett F, Byrnes A, Consortium GT, Laboratory DA, Coordinating Center -Analysis Working G, Statistical Methods groups-Analysis Working G, Enhancing Gg, Fund NIHC, Nih/Nci, Nih/Nhgrt, Nih/Nilmh, Nih/Nida, Biospecimen Collection Source Site N, Biospecimen Collection Source Site R, Biospecimen Core Resource V, Brain Bank Repository-University of Miami Brain Endowment B, Leidos Biomedical-Project M, Study E, Genome Browser Data I, Visualization EBI, Genome Browser Data I, Visualization-Ucsc Genomics Institute UoCSC, Lappalainen T, Regev A, Ardlie KG, Hacohen N, MacArthur DG (2017) Landscape of X chromosome inactivation across human tissues. Nature 550(7675):244–248. https://doi.org/10.1038/nature24265

Vardavas CI, Nikitara K (2020) COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 18:20. https://doi.org/10.18332/tid/119324

Wambier CG, Vano-Galvan S, McCoy J, Gomez-Zubiaur A, Herrera S, Hermosa-Gelbard A, Moreno-Arrones OM, Jimenez-Gomez OM, Gonzalez-Cantero A, Fonda-Pascual P, Segurado-Miravalles G, Shapiro J, Perez-Garcia B, Goren A (2020) Androgenetic alopecia present in the majority of patients hospitalized with COVID-19: the “Gabrin sign”. J Am Acad Dermatol 83(2):680–682. https://doi.org/10.1016/j.jaad.2020.05.079

Wang H, Jessup JA, Zhao Z, Da Silva J, Lin M, MacNamara LM, Ahmad S, Chappell MC, Ferrario CM, Groban L (2013) Characterization of the cardiac renin angiotensin system in oophorectomized and estrogen-replete mRen2.Lewis rats. PLoS One 8(10):e76992. https://doi.org/10.1371/journal.pone.0076992

Wenham C, Smith J, Morgan R, Gender, Group C-W (2020) COVID-19: the gendered impacts of the outbreak. Lancet 395(10227):846–848. https://doi.org/10.1016/S0140-6736(20)30526-2

Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the chinese center for disease control and prevention. JAMA 323:1239. https://doi.org/10.1001/jama.2020.2648
Yuan S, Chan JFW, Chik KKH, Chan CCY, Tsang JOL, Liang R, Cao J, Tang K, Chen LL, Wen K, Cai JP, Ye ZW, Lu G, Chu H, Jin DY, Yuen KY (2020) Discovery of the FDA-approved drugs bexarotene, cetilistat, diiodohydroxyquinoline, and abiraterone as potential COVID-19 treatments with a robust two-tier screening system. Pharmacol Res 159:104960. https://doi.org/10.1016/j.phrs.2020.104960

Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 46(4):586–590. https://doi.org/10.1007/s00134-020-05985-9

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229):1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3