Sex differences in COVID-19: candidate pathways, genetics of ACE2, and sex hormones

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Abstract

Biological sex is increasingly recognized as a critical determinant of health and disease, particularly relevant to the topical COVID-19 pandemic caused by the SARS-CoV-2 coronavirus. Epidemiological data and observational reports from both the original SARS epidemic and the most recent COVID-19 pandemic have a common feature: males are more likely to exhibit enhanced disease severity and mortality than females. Sex differences in cardiovascular disease and COVID-19 share mechanistic foundations, namely, the involvement of both the innate immune system and the canonical renin-angiotensin system (RAS). Immunological differences suggest that females mount a rapid and aggressive innate immune response, and the attenuated antiviral response in males may confer enhanced susceptibility to severe disease. Furthermore, the angiotensin-converting enzyme 2 (ACE2) is involved in disease pathogenesis in cardiovascular disease and COVID-19, either to serve as a protective mechanism by deactivating the RAS or as the receptor for viral entry, respectively. Loss of membrane ACE2 and a corresponding increase in plasma ACE2 are associated with worsened cardiovascular disease outcomes, a mechanism attributed to a disintegrin and metalloproteinase (ADAM17). SARS-CoV-2 infection also leads to ADAM17 activation, a positive feedback cycle that exacerbates ACE2 loss. Therefore, the relationship between cardiovascular disease and COVID-19 is critically dependent on the loss of membrane ACE2 by ADAM17-mediated proteolytic cleavage. This article explores potential mechanisms involved in COVID-19 that may contribute to sex-specific susceptibility focusing on the innate immune system and the RAS, namely, genetics and sex hormones. Finally, we highlight here the added challenges of gender in the COVID-19 pandemic.

ACE2; cardiovascular disease; gender; SARS-CoV-2; sex; sex differences

INTRODUCTION

The importance of sex differences in clinical disease outcomes is increasingly recognized. A field that has pioneered this dialogue is cardiovascular disease (CVD), including heart failure (HF), myocardial infarction, and hypertension (1, 2). Sex differences underlie the manifestation of HF; aged women preferentially develop HF with preserved left ventricular ejection fraction (HFpEF) with a background of hypertension, whereas men present with HF with reduced ejection fraction (HFrEF) associated with coronary artery disease (CAD) (3, 4). Furthermore, women with HF have improved survival compared with men after adjusting for age in the Framingham study (4). Acute myocardial infarction commonly presents with chest pain in both sexes; however, healthcare providers are more likely to associate symptoms in women with heart-independent conditions in the prodromal stage (5). Hypertension incidence is higher for men than age-matched, premenopausal women (6).

Similarly, sex differences are implicated in the severity of COVID-19 caused by the SARS-CoV-2 virus (Figs. 1 and 2). Epidemiological data from the related 2002–2003 SARS coronavirus epidemic suggested sex dependency in clinical disease outcomes, including intensive care unit (ICU) admission and death, favoring men, a pattern maintained after adjusting for age (7, 8). The sex disparity in COVID-19 is consistent in most countries, with a similar incidence of infection (percent of cases) in both sexes; however, men consistently demonstrate a more severe phenotype and increased mortality across age-groups on a global level (Figs. 1 and 2).
This review investigates the relationship between CVD and COVID-19 and provides a rationale for the involvement and targeting of two candidate pathways in the pathogenesis of COVID-19, namely, immune responses and the counterregulatory branch of the renin-angiotensin system (RAS). We highlight here sex hormones and sex chromosomes as two potential explanations for sexual dimorphism in these pathways. Finally, we briefly discuss the added challenges of gender in the COVID-19 pandemic.

**CVD AND COVID-19**

The relationship between CVD and COVID-19 is multifaceted; a significant complication in COVID-19 is the development of CVD, including myocarditis, arrhythmias, and HF, while preexisting CVD enhances the probability of detrimental outcomes in SARS-CoV-2 infection (11–14). Vascular effects are prominent in patients with COVID-19 with endothelial damage, intussusive angiogenesis, and microthrombi formation following lung morphological examination (15, 16). Notably, the pathogeneses of CVD and COVID-19 overlap in key signaling pathways, namely, the innate immune system and the RAS.

Extensive immune activation is implicated in severe cases of COVID-19 and predicts severity and mortality [reviewed in (9, 17, 18)]. In accordance, chronic immune activation is implicated in the pathogenesis of CVD in some instances. In fact, autoimmune diseases, such as rheumatoid arthritis and periodontal disease, are associated with increased cardiovascular risk from accelerated atherosclerosis and subsequent morbidities.

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**Figure 1.** Global reported COVID-19 epidemiological data of percent of cases disaggregated by sex. The red line represents the average cases for males across all countries (53.5%). All countries with available and complete sex-disaggregated data were included (78 in total). The list of included countries and raw data plotted can be accessed as Supplemental Data S1. The data presented are a summary of publicly available data compiled by Global Health 5050. The compiled data are from various sources, which include national governments, official media/social media communications, national surveillance centers, and global/regional coordinating bodies. Figures created are based on data directly from data source (no calculations were made). Numbers presented may not reflect the actual current cases since not all the available data are disaggregated by sex. Data accessed November 11, 2020.
premature CAD (19). As women are more susceptible to inflammatory and autoimmune diseases, autoimmune-associated CVD is of particular concern (18). The emerging role of the innate immune system in CVD is characterized by Toll-like receptor (TLR) signaling that contributes to myocardial damage and adverse remodeling when stress-activated cytokine production is sustained. Furthermore, the expression profile of innate immune genes is distinct in the failing heart compared with nonfailing explanted human hearts, whereby the data suggest an increase in innate immune system activation in heart failure (20, 21).

COVID-19 and CVD share another common feature in that angiotensin-converting enzyme 2 (ACE2) is implicated in the pathogenesis of both. ACE2 is protective in CVD to counteract the canonical renin-angiotensin system (RAS), and loss of this protein (genetic knockout or proteolytic cleavage) exacerbates dysfunction (22–26). In accordance, increased plasma ACE2 concentration was correlated with a worsened prognosis in HF, and male sex was the strongest predictor of elevation (27). Premenopausal women are protected from developing CVD and hypertension, including stroke; however, male androgens may contribute to these conditions’ incidence and progression (6, 28). Therapies indicated for the prevention, treatment, or management of CVD include drugs targeting the RAS, namely, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) (29). Interestingly, despite common clinical manifestations of HF, treatment response in men and women is variable: women may be incorrectly dosed in HFrEF with ACEi (30), women are more likely to have cough-induced...
intolerance of ACEi, and women are twice as likely as men to develop HFpEF—a clinical phenotype without adequate therapy (31, 32). Overall, there is substantial evidence for inflammation and immunity and aberrant RAS activity in the pathogenesis of CVD, which we will explore in the context of delineating sex differences in COVID-19.

**CANDIDATE PATHWAYS FOR SEX DIFFERENCES**

**Innate Immunity**

The innate immune system drives the initial response to viral infection. It is initiated when host-cell pattern recognition receptors (PRRs), such as RIG-I-like receptors and Toll-like receptors (TLRs), identify pathogen-associated molecular patterns of viral components, subsequently activating a signaling cascade to combat the infection (33). Immunological sex differences play a substantial role in the prevalence, severity, and pathogenesis of infectious diseases. Adult women mount a rapid and aggressive innate and adaptive immune response to combat invading pathogens (18). In contrast, men have a dampened immune response and are more susceptible to viral infections [reviewed in (17, 34)].

In accordance, in SARS-CoV infection, the innate immune response is a primary driver of viral clearance and pathogenesis if activity is uncoordinated and prolonged (33). Specifically, type I interferons (IFNs), including IFNα, limit viral infection, initiate tissue repair, and program the adaptive immune system to foster viral elimination. The robust, delimited, and timely IFN-1 response is considered protective; however, left unchecked, aberrant cytokine and chemokine production (many of which are interferon-stimulated genes) contribute to dysfunction in SARS-CoV infection, including the development of acute respiratory distress syndrome (33,35). In the context of SARS-CoV-2, enhanced severity in men is correlated with increased plasma cytokine levels of the innate immune system, including IL-8 and IL-18. In contrast, reduced severity in females corresponds with higher T-cell activation (10). Furthermore, increases in TNF-α and IL-6 immunological activation are significant and independent predictors of severity and mortality in COVID-19 (17).

**Counterregulatory RAS: ACE2**

ACE2, a counterregulatory monocarboxypeptidase, has garnered enhanced interest as the receptor for SARS-CoV-2 (22, 26, 36). However, the negative connotation should be refrained, as ACE2 is essential to deactivate the detrimental effects of the RAS, reported particularly in the context of CVD (23). ACE2 is ubiquitously expressed and exerts protective effects in the cardiovascular system, lungs, kidneys, and gut. Indeed, symptoms of SARS-CoV-2 are intimately linked with the expression pattern of ACE2 (22, 37). The canonical RAS pathway involves sequential catalytic steps that culminate in angiotensin (Ang) II formation, promoting vasoconstriction, sodium reabsorption, and fluid retention to increase blood pressure. Ang II imparts these effects by binding and activating the Ang II receptor type 1 (AT1R) (38). A counterregulatory branch of the RAS was subsequently discovered, namely, the ACE2 axis. ACE2 deactivates Ang II by conversion to Ang 1–7, a peptide with anti-inflammatory, antifibrotic, and vasodilatory properties through activation of the Mas receptor (MasR) (22, 26, 39, 40).

SARS-CoV-2 requires ACE2 for cellular entry and downregulates protective ACE2 (36). Following viral entry, SARS-CoV and SARS-CoV-2 activate a disintegrin and metalloproteinase (ADAM17); a cellular event that differentiates mild and severe coronavirus infections (22, 41). Specifically, Haga et al. (41) examined the differences in activated signaling cascades between SARS-CoV and HNL63-CoV, the latter a coronavirus that causes mild symptoms attributed to the common cold. Despite common binding to ACE2, the HNL63-CoV spike protein does not induce ACE2 shedding or ADAM17 activation. Furthermore, ADAM17 mobilizes and activates TNF-α and determines IL-6 signaling through cleavage of the IL-6 receptor α (42). Importantly, activation of the canonical RAS (ACE-Ang II-AT1R) pathway leads to enhanced ADAM17 activity (22). Therefore, RAS overactivity would promote disease severity, especially for patients with comorbid CVD (43). ADAM17 may provide the critical link between aberrant immune system activation and exacerbating the loss of protective ACE2, thus fostering enhanced susceptibility to severe COVID-19.

**MECHANISM OF SEX DIFFERENCES**

**Sex Chromosomes**

The female advantage lies in harboring an additional X chromosome than males, therefore conferring the benefit of mosaicism, skewed inactivation, and escaping X inactivation to bypass the deleterious effects of X-linked mutations and offer functional diversity in responses (44). We will focus on X-linked genes escaping silencing, as this mechanism is relevant for both the innate immune system and ACE2 in females (Fig. 4A). Physiologically X inactivation occurs for dosage compensation; however, ~15% of X genes escape inactivation in humans; thus, they are found at a higher copy number in females over males (18). Although not elucidated entirely, one mechanism of X inactivation is dominantly controlled by two long noncoding RNAs (lncRNAs), namely, X-inactivation specific transcript and X-active specific transcript responsible for X-silencing and maintaining an active X-chromosome, respectively (44). The probability of escape from X-chromosome inactivation is determined by the specific gene’s dosage sensitivity and location on the X chromosome (44). Generally, X inactivation of the maternal or paternal X chromosome occurs randomly, thereby producing a mosaic in females, whereas skewed inactivation describes the genetic selection of the inactivated chromosome. A skewed inactivation pattern confers a sex-specific phenotype in females, and this phenomenon increases with age. Therefore, this may offer females a protective mechanism against deleterious mutations by restricting their expression (44). Many immune-associated genes are X linked, including but not limited to PRRs (such as TLR7, TLR8) and fundamental regulators of TLR signaling [interleukin-1 receptor-associated kinase 1 (IRAK1) for example], with females having two copies of these genes (44). We will focus on TLR7, a receptor localized to dendritic cells that responds to single-stranded viral RNA, thus relevant for SARS-CoV-2 infection. Increased TLR7
gene expression has been detected in females over males, thus suggesting the TLR7 gene, as it is X linked, may escape inactivation (18, 45). Similarly, IFNα production is enhanced by female-derived peripheral blood mononuclear cells (PBMCs) stimulated in vitro with TLR7 ligands (18, 46). However, despite this increase, Berghofer et al. (46) reported anticipated gene silencing of one of the TLR7 alleles in females; therefore, the differences were not attributed to X-gene escape in this study. However, female upregulation of TLR7 is estrogen dependent (18).

The ACE2 gene resides in the Xp22.2 region of the X chromosome and is recognized as an escape gene. As described, X-gene escape generally confers a female bias in expression (47). Therefore, in theory, females have a double dose of ACE2 that may compensate for SARS-CoV-2-mediated loss of membrane ACE2. In fact, heterozygous knockout of ACE2 is sufficient to enhance heart disease susceptibility and reduce ACE2 protein levels in female mice, demonstrating a gene-dosing effect fundamentally dependent on the ACE2 locus (48). Further research efforts are required to investigate the putative female bias in ACE2 expression; however, sex hormones may modulate this mechanism (47, 49). Of note, many articles draw conclusions based exclusively on expression profiles of ACE2, which may limit our complete understanding of the impact on the ACE2 protein and its function. Indeed, ACE2 expression may not correlate with enzyme activity (50), as ACE2 is highly regulated by proteolytic cleavage (23) and is predicted to be regulated by microRNAs (miRNAs) (51). Indeed, the ability of ACE2 to deactivate the RAS complex, and the sex-specific function and control of ACE2 requires investigation at the transcriptional, translational, and posttranslational levels.

**Sex Hormones**

Sex hormones confer differential susceptibility of the sexes to viral infections, which we will discuss in the context of innate immunity and the counterregulatory RAS (ACE2) pathway. Immunological differences between males and females are exemplified by the fact that androgen response elements and estrogen response elements reside in the promoters of several genes of the innate immune system (18, 52). Seoul hantavirus challenge in female rats saw transcriptional upregulation of genes associated with the innate immune system, namely, Tlr7, Tlr3, Rig-i, as well as proinflammatory genes including Ifnβ, Ifnar1, and interferon regulatory factor 7 (Irf7) — a transcription factor for the induction of type I interferons (52). The enhanced antiviral response in females resulted in a reduced viral RNA copy number and reduced expression of viral antigens, thus improved viral handling over males in a sex hormone-dependent manner (18, 52). In accordance, male mice infected with SARS-CoV demonstrated increased viral load, vascular permeability, and alveolar edema compared with age-matched females, an effect attributed to sex-hormone dependent innate immunity (53).

17β-estradiol possesses cell type-dependent effects, namely, fostering an increased neutrophil number in response to viral infection (54) and an increased number of natural killer cells, yet reducing their cytotoxicity (55). Furthermore, 17β-estradiol demonstrates a bipartite effect on monocytes and macrophages: at low doses, the hormone stimulates the release of IL-1, IL-6, and TNF-α; however, at high concentrations, it limits the production of proinflammatory cytokines (18). In contrast, androgens are immunosuppressive; exogenous testosterone administration reduced TLR4 in isolated mouse macrophages, effectively diminishing the propensity to activate the innate immune response (34). Therefore, although sex hormones elicit cell type-specific effects, the hormonal modulators, genetics, and environmental factors culminate in female bias in both the innate and the adaptive immune response (Fig. 4B) (9, 18). Although the role of sex hormones is compelling, in the context of SARS-CoV-2 infection, this mechanism would be absent upon reproductive senescence; a period characterized by a rapid decline of sex hormones (estrogens) in females and a progressive decline of...
androgens in males (18). Therefore, sex hormones may not entirely explain the sex discrepancy, as differences persist in aged males and females (Fig. 3, Supplemental Data S1; all Supplemental Material is available at https://figshare.com/s/2d52921a0b00e648199c).

Interestingly, ACE2 expression and enzyme activity changes throughout life in a sex-specific manner. Normal aging is characterized by increased ACE2 expression in both sexes; however, only males demonstrated an increase in ACE2 activity from studies in sheep (50). In support, ACE2 had a male-biased expression pattern in humans, which is counterintuitive to ACE2 escaping X-gene inactivation (47). In this case, the female bias in escape is counteracted by sex-hormone-dependent regulation. Renal ACE2 mRNA, protein levels, and activity are increased in male mice under basal conditions. Furthermore, 17β-estradiol inhibited ACE2 activity posttranscriptionally (47, 49). In contrast, 17β-estradiol upregulated ACE2 and conferred renal protection in animal models of hypertension—an effect lost in ovariectomized rats and restored upon exogenous administration of Ang 1–7 or 17β-estradiol (56).

In another study investigating sex differences in response to high-fat diet-induced obesity, females exhibited an estrogen-dependent increase in adipose ACE2 activity and Ang 1–7 despite increased body weight and fat mass compared with males. In contrast, male animals exhibited increased plasma Ang II, decreased Ang 1–7, and reduced renal ACE2 activity, thus greater susceptibility to obesity-induced hypertension (57). Taken together, these studies suggest that a male bias in ACE2 expression and activity is characteristic of normal aging; however, females may harbor a sex hormone-dependent compensatory mechanism to upregulate ACE2 in disease.

The positive feedback mechanism of ACE2 downregulation driven by aberrant RAS and ADAM17 activation may explain the enhanced susceptibility of males to COVID-19. As described, RAS pathogenesis is contingent on Ang II activating AT1R. Although the expression of AT1R followed no sex-specific pattern in a mouse model of vascular injury, studies demonstrated that females have a greater capacity to

**Figure 4.** Candidate mechanisms of sex-specific susceptibility of males to COVID-19. A: TLR7 and ACE2 are localized to the Xp22.2 region of the X chromosome and escape X-chromosome inactivation in females. B: differences in the innate and adaptive immune responses between males and females. In general, neutrophils in females have a higher phagocytic capacity; however, males have higher Toll-like receptor (TLR) expression. Macrophages from females have higher activation, phagocytic capacity, and IL-10 production, whereas males have increased proinflammatory cytokine generation. Dendritic cells from females have higher TLR7 and type 1 interferon activity. Males have an increased number of natural killer cells. Females have generally higher B-cell numbers and antibody production. Females have a higher number of CD4⁺ T-cells and activated T-cells and T-cell proliferation than males. C: summarized sex differences and bidirectional susceptibility in COVID-19 and cardiovascular disease (CVD). In COVID-19, females have an increased IFN-α secretion and early virus sensing and prompt antiviral response upon TLR7 stimulation in dendritic cells. Gene dosing imbalances in females result from innate immune genes escaping X inactivation. Males have increased proinflammatory cytokine and chemokine production in COVID-19 associated with enhanced severity, specifically IL-8 and IL-18. In CVD, males have increased heart failure with reduced ejection fraction (HFrEF) with a background of coronary artery disease (CAD), whereas females are more likely to have HF with preserved left ventricular ejection fraction (HFpEF) with a background of hypertension (Htn) and autoimmune-related CAD.
upregulate expression of the antagonistic AT$_1$R, which elicits anti-inflammatory and protective effects in CVD (58). Ovariectomy in spontaneously hypertensive rats increases the expression of AT$_1$R in mesenteric vascular beds and reduces kidney AT$_1$R expression in Wistar–Hanover rats. Exogenous supplementation of estradiol decreases AT$_1$R and increases AT$_2$R expression. Testosterone may mediate opposing effects; however, the evidence remains controversial (6). Female mice have a greater capacity to upregulate ACE2 than males following Ang II infusion-induced hyper-tension, resulting in enhanced catabolism of Ang II and reduced glomerular AT$_1$R expression (59). Although these associations have not been addressed directly in COVID-19, this suggests that females have attenuated RAS activation in disease, which may correspond to reduced activation of the ADAM17-mediated positive-feedback pathway that augments ACE2 loss. Altogether, the bidirectional susceptibility of COVID-19 and CVD is fundamentally dependent on ACE2 shedding, thus highlighting ADAM17 as a potential therapeutic target (Fig. 4C).

**IMPACT OF GENDER**

Gender plays a fundamental role in health and disease outcomes. Considering the COVID-19 pandemic, gender norms, culture, and societal roles collectively influence viral exposure, infection susceptibility, and treatment access. Differences in the incidence of infectious diseases, such as SARS-CoV-2, are more likely to be impacted by alternate exposure rather than differences in biological immunity (8). Examples of differing exposure include occupational risk and gender roles in providing care, resulting in discrepancies in contracting viral infections. Women constitute the majority of frontline healthcare workers globally, with 70% of the world’s healthcare staff composed of women (60). Moreover, women are exposed in caregiving roles and caretaking occupations, whereas men have greater exposure outside the home (8). Additional strain is placed on women in childcare roles due to the existing family structure (8, 61). Differential exposure may be particularly relevant in SARS-CoV-2 infection due to the modest positive association between viral load and shedding duration with the degree of COVID-19 severity (62). In summary, the interplay between gender and biological sex represents an added challenge to delineate COVID-19 outcomes.

**LIMITATIONS**

Sex-disaggregated data are not available from all countries, and consistent reporting of data based on sex and age interaction is limited (63). All cases documented are both reported and confirmed cases; therefore, if nonsevere or access to testing is limited, these will not be included. Furthermore, asymptomatic cases will not likely be reported. Outbreaks in long-term care facilities are substantial and may lead to a bias in statistics due to women’s higher life expectancy and the overrepresentation of women in these facilities. However, the discrepancy in male severity is still represented across age-groups, including the aged cohorts (Fig. 3B), and the number of cases does not favor older women (Fig. 3A). Additional limitations include a lack of reliable test rate data and varying test methods with different specificity and sensitivity, thus challenging the ability to draw conclusions based on globally reported statistics.

**CONCLUSIONS AND PERSPECTIVE**

Sex differences in COVID-19 are represented in the initial handling of viral infections, hormonal signaling pathways, and a differential risk profile based on sociocultural factors. The literature suggests that females have an enhanced capacity to mount an initial innate immune response and a reduced propensity to upregulate canonical RAS activity in disease, both of which are critically dependent on genetics and sex hormones. Therefore, these candidate pathways and molecular mechanisms offer a multifaceted explanation for greater COVID-19 severity and mortality in males compared with females. As canonical RAS overactivation drives pathogenesis in CVD and potentially COVID-19, upregulation of the ACE2-Ang 1–7-MasR axis or blocking ADAM17-mediated ACE2 shedding both offer potential disease-modifying approaches to ameliorate enhanced severity in males. Therefore, the precise temporal upregulation of ACE2 will likely confer protection following SARS-CoV-2 mediated loss of ACE2, which may be achieved through repurposing existing pharmacotherapies (i.e., ACEis and ARBs). Overall, the impact of biological sex is an essential consideration in the study and reporting of COVID-19 outcomes and clinical assessment, thus highlighting the necessity of consistent reporting of sex- and age-disaggregated data.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

A.V. prepared figures; A.V., S.L.M., C.Y.Y.Y., C.M.N., and G.Y.O. drafted manuscript; A.V., J.R., J.V., and G.Y.O. edited and revised manuscript; A.V. and G.Y.O. approved final version of manuscript.

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