


# The immune response to COVID-19: Does sex matter?

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic has created unprecedented challenges worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and has a complex interaction with the immune system, including growing evidence of sex-specific differences in the immune response. Sex-disaggregated analyses of epidemiological data indicate that males experience more severe symptoms and suffer higher mortality from COVID-19 than females. Many behavioural risk factors and biological factors may contribute to the different immune response. This review examines the immune response to SARS-CoV-2 infection in the context of sex, with emphasis on potential biological mechanisms explaining differences in clinical outcomes. Understanding sex differences in the pathophysiology of SARS-CoV-2 infection will help promote the development of specific strategies to manage the disease.

## KEYWORDS

COVID-19, gender, immune system, SARS-CoV-2, sex, sex hormones

## BIOLOGICAL SEX AND COVID-19

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), produced enormous global health challenges. Recent epidemiological studies have uncovered critical differences between men and women with

respect to COVID-19 outcomes. Males and females have similar proportions of COVID-19 cases, suggesting similar infection rates.<sup>1</sup> However, males exhibit higher disease severity and are at a higher risk of succumbing to the disease.<sup>2,3</sup> Older age is associated with higher risk of death in both sexes, but even after accounting for age, males are still more likely than females to die from

SARS-CoV-2 infection.<sup>1,4-9</sup> Though males were less likely to be diagnosed with COVID-19 in one study, their mortality rate was about twice that of females.<sup>4</sup> Mortality rates were higher amongst males across all age groups above 20 years in multiple European countries.<sup>10</sup> Certain groups of females with COVID-19 are more likely to have worse clinical outcomes. For example, pregnant females with COVID-19 are at increased risk of severe illness, hospitalization, intensive care unit (ICU) admission, pre-term delivery and mortality.<sup>11-15</sup> Concerns have also been raised about the use of hormonal contraception in females with COVID-19. Combined oral contraceptives are associated with a higher risk of venous thromboembolism (VTE), and COVID-19 disease is associated with hypercoagulability.<sup>16-18</sup> Further studies are needed to evaluate the risk of VTE in females with COVID-19 and using combined oral contraceptives.

Sex-specific differences in clinical outcomes and immune response to other viruses have been documented. Higher mortality amongst males has been observed in other human coronavirus infections, including SARS-CoV-1 and Middle East respiratory syndrome-related coronavirus (MERS-CoV).<sup>19,20</sup> Females infected with the human immunodeficiency virus (HIV) mount stronger antiviral responses than males, possibly due to increased toll-like receptor 7 (TLR7) and interferon alpha (IFN $\alpha$ ) activation.<sup>21,22</sup> Higher hepatitis B surface antibody (anti-HBs) titres have been reported in women compared with men following hepatitis B virus (HBV) vaccination.<sup>23</sup>

There are many possible explanations for the difference in COVID-19 outcomes between men and women, including certain behavioural and social factors.<sup>24</sup> However, biological factors such as sex-related genes and sex hormones that influence immune system regulation may also play an important role.<sup>25</sup> This review will focus on our current understanding of biological mechanisms underlying sex differences in the immune response to SARS-CoV-2 infection.

## SEX DIFFERENCES IN THE IMMUNE RESPONSE TO SARS-COV-2 INFECTION

Females and males have different immune responses to pathogens, which may explain the differing disease severity and mortality due to SARS-CoV-2 infection.<sup>26</sup> The immune system's interaction with SARS-CoV-2 consists of viral entry into the human cell, followed by recognition of the virus and activation of the host innate immune response, which subsequently leads to the activation of the adaptive immune response (Figure 1).<sup>10</sup> Gene expression in immune cells

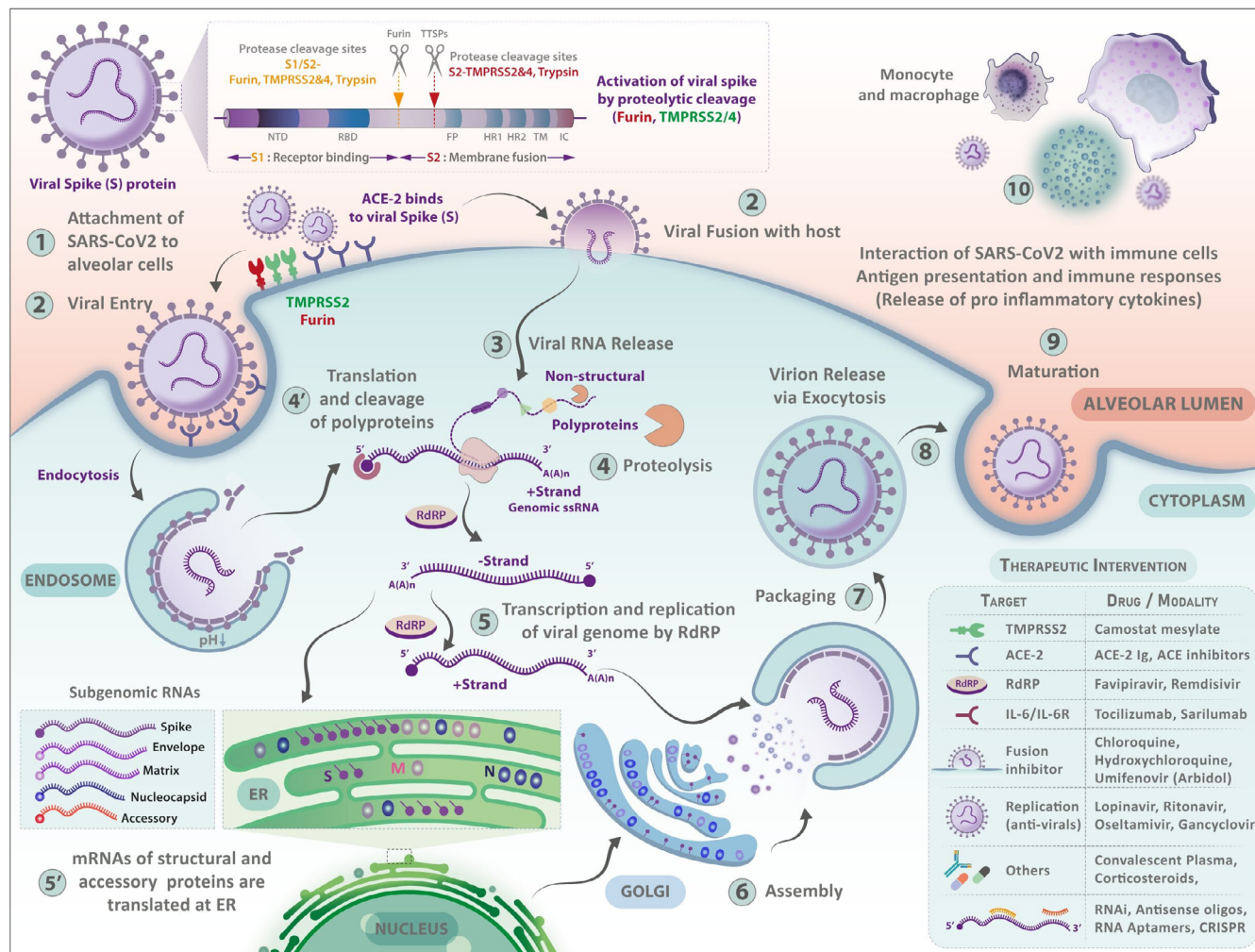
exhibits different patterns based on sex, being most pronounced in autosomal genes.<sup>10,27</sup> The sex chromosomes (X and Y) also carry a number of immune response-related genes and are involved in immunoregulation as well. For example, transcriptional regulation of immunoregulatory genes can be influenced by the mosaic loss of the Y chromosome in leucocytes.<sup>28</sup>

## Viral entry

Coronaviruses are pleomorphic, enveloped, positive-sense, single-stranded RNA viruses.<sup>29</sup> The viral membrane includes the envelope (E) protein, transmembrane (M) glycoprotein, and spike (S) glycoprotein.<sup>30</sup> Due to the surface spikes, coronaviruses appear like crowns. The viral life cycle within the host involves attachment, penetration, biosynthesis, maturation, and release. After the virus binds to receptors of the host cell (attachment), it enters through receptor-mediated endocytosis or membrane fusion (penetration). The initial cells infected are usually those along the upper respiratory tract. The corona spikes bind to the angiotensin-converting enzyme 2 (ACE2) receptors on the surface of upper respiratory tract cells, which can facilitate entry into the cells. The normal function of the ACE2 receptor, which includes decreasing inflammation, becomes affected when the virus binds.<sup>31,32</sup> This decrease in anti-inflammatory response may exacerbate tissue damage.<sup>33,34</sup> Located on the cell surface and intracellularly, furin is a subtilisin-like proprotein convertase and calcium-dependent serine endoprotease that cleaves the spike protein to make it functional for priming and activation.<sup>35,36</sup> The spike protein is primed by proteases: transmembrane serine protease 2 (TMPRSS2) and a disintegrin and metalloprotease 17 (ADAM17). Subsequently, the virus uses those cells to produce more progenies for invasion of surrounding cells.<sup>2,37</sup>

A computational study demonstrated that the Omicron variant had a greater affinity for ACE2 compared with the Delta variant because of numerous mutations in the SARS-CoV-2 receptor-binding domain.<sup>38</sup> Preliminary research also showed that Omicron preferred infecting the upper airways rather than the lungs.<sup>39</sup> These characteristics may contribute to the higher transmissibility and lower disease severity of Omicron.<sup>40-43</sup>

Males have been found to have elevated expression of ACE2 in some studies, although the relationship between sex and ACE2 levels is highly complex.<sup>44-46</sup> One hypothesis is that men have a higher prevalence of hypertension and heart failure, which may explain the higher ACE2 compared with women.<sup>47</sup> It has also been shown that



**FIGURE 1** The life cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (1) The cycle begins with the virus entering cells of the airway. Viral attachment is mediated by the interaction between the viral spike (S) protein and host ACE2 receptors with the serine protease TMPRSS2 co-receptors. Furin cleaves the spike protein to make it functional for priming and activation. (2) Either by endocytosis or membrane fusion, the virus enters the host cell. (3) This event is followed by the release of viral ssRNA into the host cell. The release of the viral genome triggers the signals for activation of intracellular pattern recognition receptors such as TLR7 that usually lead to the synthesis of antiviral interferons. (4 & 4') Subsequently, the translation and cleavage of the viral polymerase protein occur in the cytoplasm. (5 & 5') RNA replication depends on the viral RNA-dependent RNA polymerase (RdRp). Translation of viral structural proteins occurs via the ribosomes in the endoplasmic reticulum (ER). (6) Virion assembly occurs at ER-Golgi junctions in concurrence with (7) the formation of mature virions inside Golgi vesicles. (8) Post-assembly, the infective virions are released via exocytosis or through cell lysis. The inset table shows possible intervention points for SARS-CoV-2 at multiple stages of its life cycle. These repurposed drugs intercept the SARS-CoV-2 infection at crucial points, including inhibiting the viral proteins or interfering with viral entry, translation of viral proteins, assembly of new virions, viral budding, etc. Many repurposed/experimental drugs also possess off-target side-effects contributing to drug-induced cytotoxicity, local tissue damage, and systemic immunosuppression

soluble ACE2 (sACE2) levels are similar between males and females up to age 12 years. However, by age 15, sACE2 levels in males surpass those of females.<sup>48</sup> Consistent with that idea, one study demonstrated that a lower dose of ACE inhibitors is needed in females compared with males for optimal therapeutic effect.<sup>49</sup> More research will hopefully further elucidate the relationship between sex-related differential expression of ACE2 and vulnerability to SARS-CoV-2 infection.<sup>10</sup>

## Innate immune response

Females usually mount stronger innate and adaptive immune responses against pathogens than their male counterparts, which could explain their lower COVID-19 disease severity and mortality.<sup>26</sup> Early immune responses to the virus involve innate viral detection, interferon (IFN) production and inflammasome activation.<sup>50</sup> Although cross-reactive adaptive immune cells have been

detected in SARS-CoV-2 unexposed individuals, the disease outcome is largely thought to be shaped by initial innate immune responses.<sup>51,52</sup>

Pattern recognition receptors (PRRs) such as toll-like receptor 7 (TLR7) that sense single-stranded RNA may play a major role in the initial innate immune response against RNA viruses such as SARS-CoV-2.<sup>53</sup> Women may be able to clear early SARS-CoV-2 infection better than men because TLR7 expression in innate immune cells can be upregulated by the female sex steroid oestrogen and, furthermore, TLR7 might escape X chromosome inactivation in some cells.<sup>54,55</sup> Escaping X-inactivation allows the TLR7 gene to be expressed more highly in females, who have two copies of the X chromosome.

After detection by PRRs, two major arms of innate antiviral responses are activated to curb the spread of the virus. Specifically, viral replication and dissemination are restricted by type I and type III IFNs, and antiviral immune cells are recruited by cytokines and chemokines. In COVID-19, the cytokine/chemokine response is stronger than the IFN response, possibly because SARS-CoV-2 can more effectively evade IFN responses.<sup>56,57</sup>

Sex differences in early SARS-CoV-2 infection may be linked to differences in the IFN response.<sup>58</sup> TLR7 is a crucial sensor in plasmacytoid dendritic cells (pDCs) for the production of type I IFN. IFN $\alpha$  production from pDCs is greater in women than in men, with oestrogen modulating this effect.<sup>59–63</sup> Females with COVID-19 have higher plasma concentrations of IFN $\alpha$ .<sup>64</sup> IFN regulatory factor 5 (IRF5), a critical transcription factor in IFN signalling, is also more highly expressed in pDCs of females, contributing to stronger type I IFN responses.<sup>10,53</sup> Besides these differences in IFN induction, in a group of severely ill COVID-19 patients consisting mostly of older males, type I IFN signalling was found to be inhibited by autoantibodies.<sup>65</sup>

Innate immune cells produce proinflammatory cytokines in response to viral infections. Elevated inflammatory cytokine levels have been associated with severe COVID-19 pathology, and clinical studies in patients indicate sex differences. Interleukin 6 (IL-6) production after viral infection is lower in females and is associated with better prognosis.<sup>66</sup> Though stronger cytokine responses are typically seen in females with viral infections, COVID-19 is an exception. Instead, higher levels of innate proinflammatory cytokines (e.g., IL-8 and IL-18) are seen in males.<sup>64</sup> Elevated plasma proinflammatory cytokines and chemokines, especially IL-6 and inflammation-associated IL-1 $\beta$  and IL-18, are seen in people with severe COVID-19, culminating in cytokine storm.<sup>67,68</sup> An extraordinary amount of IL-1 and tumour necrosis factor (TNF) release can lead to acute inflammation and death.<sup>66,69</sup> Males have been found to have higher serum levels of IL-8, IL-18 and C-C motif chemokine ligand

5 (CCL5) than females, and a significant correlation has been found between elevated serum levels of IL-8 and reduction in antiviral lymphocytes. There is also an association between systemic inflammation and lung involvement, such as infiltration by monocytes and neutrophils, and elevated neutrophil count is linked to worse clinical outcomes.<sup>70</sup> Research in female mice has shown not only lower SARS-CoV-1 viral titres, but also lower infiltration by monocytes and macrophages and production of cytokines, resulting in milder lung injury and lower mortality compared with males.<sup>71</sup>

## Adaptive immune response

Antibody-based protection has been shown to be a key in our fight against SARS-CoV-2. Females usually have greater humoral responses to viral infection and vaccination, although they also show greater autoreactivity.<sup>72–79</sup> Multiple mechanisms, which may be mediated by oestrogen, help account for differences in antibody production between the sexes: germinal centre formation, selection against autoreactive B cells, somatic hypermutation enhancement, and epigenetic accessibility of B cell-specific loci.<sup>10</sup>

Similar to that of humoral responses, the role of sex-based differences in T-cell responses in COVID-19 has also been emerging. Regulatory T-cell (Treg) development,<sup>80–83</sup> lymphocyte subset distribution,<sup>84</sup> and quality of T-cell responses are all affected by sex.<sup>85,86</sup> Higher oestradiol levels increase Tregs,<sup>87</sup> and women have a higher ratio of CD4/CD8 T cells.<sup>88</sup> Researchers did not identify a connection between T-cell responses and human outcomes in the SARS outbreak.<sup>89</sup> However, CD4+ T cells may be involved based on murine experiments.<sup>90</sup> Low lymphocyte levels predict COVID-19 disease progression and are associated with severe COVID-19 disease.<sup>91–93</sup> Males with COVID-19 have lower lymphocyte count and higher neutrophil-to-lymphocyte ratios and serum C-reactive protein (CRP) concentrations compared with females.<sup>94</sup> Elderly females with early SARS-CoV-2 infection have more robust T-cell activation than their male counterparts. Poorer outcomes are seen in males with COVID-19, along with weak activation of T cells during early disease, but this is not seen in females.<sup>64</sup> More research is necessary to characterize sex differences in the role of T cells in acute infection and lung injury<sup>95</sup> as well as vaccine targets.<sup>10</sup>

The epigenetic status of immune cells also differs based on sex. The epigenetic landscape of immune cells in males changes immensely from age 62 to 64, leading to faster immunosenescence.<sup>24</sup> This includes elevated expression of innate proinflammatory genes and decreased expression of adaptive immune system genes. Males exhibit a more

notable decline in certain naïve T cells with ageing,<sup>24</sup> and only males exhibit a notable decrease in B cells after age 65.<sup>77</sup> On the other hand, females exhibit large epigenetic changes in immune cells about 5–6 years later than males.<sup>57</sup> Overexpression of immune genes on the X chromosome in T cells has been associated with T-cell-specific X-chromosome epigenetic modifications and incomplete X-inactivation.<sup>96,97</sup>

In addition, females may be more efficient at clearing SARS-CoV-2, as studies demonstrated that the virus is detected for a longer period in males.<sup>98,99</sup> To assess the efficacy of immune responses, the viral clearance rate should be further evaluated.<sup>10</sup>

## Long-term effects

Female sex is associated with long or post-COVID syndrome, which involves symptoms that persist after recovering from COVID-19.<sup>100–103</sup> In one study, fatigue was observed to be the most common sequela of post-COVID syndrome and associated with higher IL-6 levels and female sex. Dyspnoea was more likely in men and not associated with higher IL-6 levels.<sup>101</sup> Sex-specific autoimmune responses may influence the course of recovery from COVID-19.<sup>104,105</sup> A study found that, after asymptomatic infection, the overall autoantibody (AAB)

**TABLE 1** Relationship between sex hormones and immune response to SARS-CoV-2 infection

Sex hormones	Potential effect on the immune response to SARS-CoV-2 infection	References
Androgens	<ul style="list-style-type: none"> <li>Exact role is unclear; current literature suggests that high and low androgen levels can both have harmful effects</li> <li>Regulate furin</li> <li>Stimulate TMPRSS2, which may facilitate SARS-CoV-2 entry into the host cell</li> <li>Suppress thymic function and T-cell development</li> <li>Decrease proinflammatory cytokine release (e.g., IFN<math>\gamma</math> and TNF)</li> <li>Increase anti-inflammatory cytokine release (e.g., IL-4 and IL-10)</li> <li>Reduce Th1 and Th17 differentiation</li> <li>Induce Treg differentiation</li> <li>Regulate B-cell development and humoral immune responses</li> <li>Low testosterone levels are correlated with more severe COVID-19 and higher levels of inflammatory cytokines</li> </ul>	35,107,108,113,119,120, 137–140,143,144
Oestrogens	<ul style="list-style-type: none"> <li>Regulate ACE2, furin, TMPRSS2, and ADAM17, which may help prevent SARS-CoV-2 entry into host cells</li> <li>Suppress DPP4, another potential point of entry for SARS-CoV-2</li> <li>Activate adenosine receptors, which may have anti-inflammatory effects</li> <li>Activate TLR7, which is involved in the innate immune response</li> <li>Inhibit NLRP3 inflammasome activation</li> <li>Regulate the RAGE pathway, which may reduce lung injury</li> <li>Decrease CCR2, CCL2, and CXCR3, and inhibit migration of cells in the innate immune system (e.g., monocytes and neutrophils)</li> <li>Regulate eosinophils</li> <li>Activate anti-inflammatory cytokines (IL-4, IL-10)</li> <li>Inhibit NF-<math>\kappa</math>B pathway and reduce inflammatory cytokines (IL-1<math>\beta</math>, IL-6, IL-17, TNF)</li> <li>Inhibit Th1 and promote Th2 and Treg</li> <li>Affect B-cell development and stimulate plasma cells to produce antibodies</li> <li>Regulate pDCs, which secrete type I IFNs</li> <li>Increase nitric oxide and decrease platelet aggregation</li> </ul>	36,54,55,61–63,151–160
Progesterone	<ul style="list-style-type: none"> <li>Has anti-inflammatory properties that oppose cytokine storm development</li> <li>Increases Treg differentiation</li> <li>Enhances IFN<math>\alpha</math> pathways</li> <li>Promotes lung repair by inducing amphiregulin</li> <li>Reduces Th17 responses</li> <li>Disrupts endocytic pathways used by viruses</li> </ul>	169

Abbreviations: ACE, angiotensin-converting enzyme. ADAM, a disintegrin and metalloprotease. CCR, C-C motif chemokine receptor. CCL, C-C motif chemokine ligand, CXCR, C-X-C motif chemokine receptor. COVID-19, coronavirus disease 2019. DPP, dipeptidyl peptidase. IFN, interferon. IL, interleukin. NF- $\kappa$ B, nuclear factor kappa B. NLRP, nucleotide-binding oligomerization domain-like receptor, pyrin domain containing. pDCs, plasmacytoid dendritic cells. RAGE, receptor for advanced glycation end products. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Th, T-helper cell. TLR, toll-like receptor. TMPRSS, transmembrane serine protease. TNF, tumour necrosis factor. Treg, regulatory T cell.

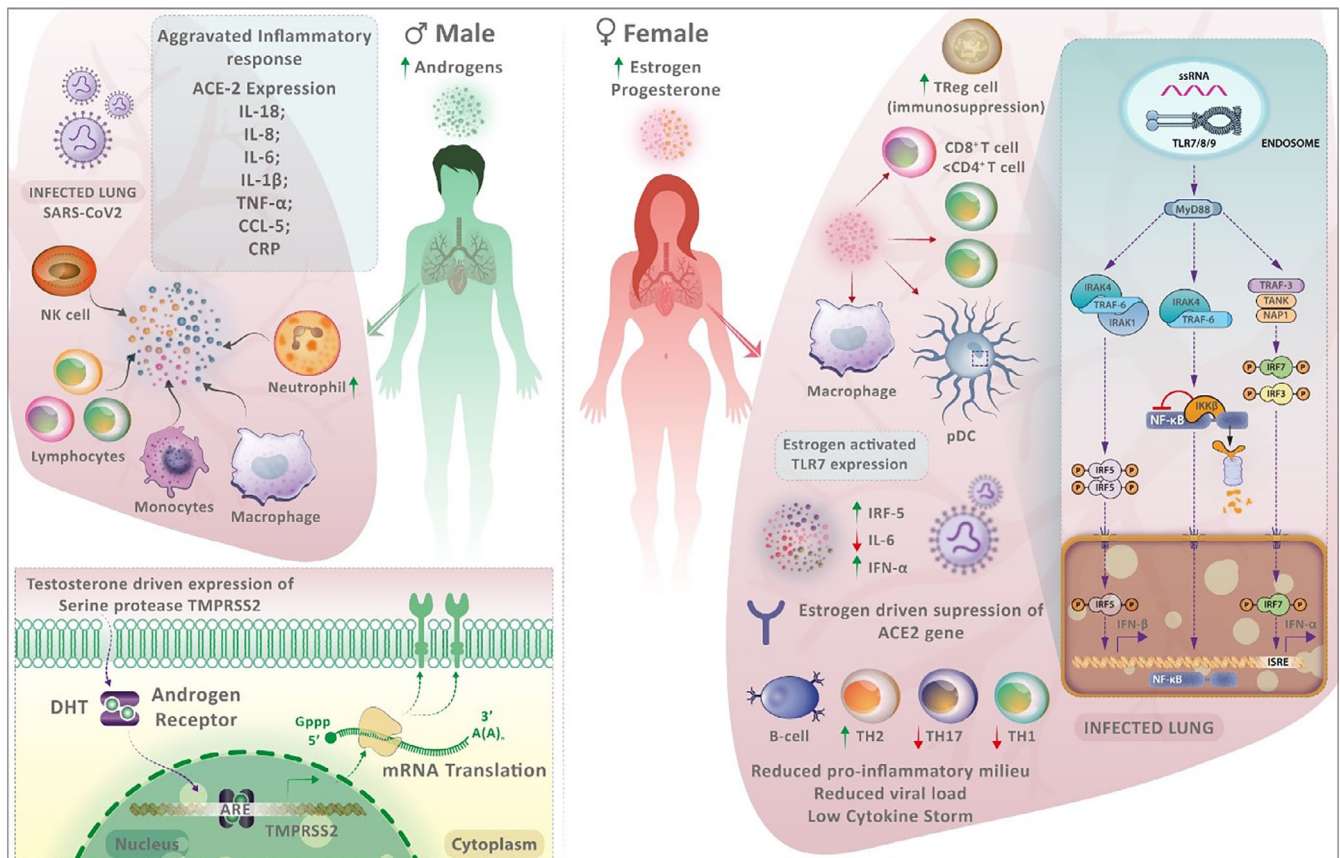
response was greater in women. However, after ‘at least mildly symptomatic infection,’ the ‘breadth and extent of AAB reactivity’ was greater in men.<sup>105</sup>

## CRUCIAL ROLE OF SEX HORMONES IN MODULATING THE IMMUNE RESPONSE TO SARS-COV-2 INFECTION

### Androgens

The progression of COVID-19 is likely associated with sex hormones (Table 1). Females have more oestrogen and

progesterone, whilst males have more androgens, including testosterone and dihydrotestosterone (Figure 2).<sup>106</sup> Androgens may regulate furin. Studies suggest that the androgen receptor influences furin and other proprotein convertases in prostate cancer cells.<sup>35,107,108</sup> TMPRSS2, a gene regulated by testosterone, may be more highly expressed in men,<sup>109,110</sup> which may, in turn, account for the greater COVID-19 severity in males.<sup>111,112</sup> The genetic expression of TMPRSS2 is regulated and can be increased by the androgen receptor.<sup>113</sup> As a result, SARS-CoV-2 entry into host cells can be affected by the expression of androgen receptors and TMPRSS2. Higher androgen receptor expression may increase the risk of more severe COVID-19 disease.<sup>114</sup> This is supported by clinical evidence of an association between



**FIGURE 2** The sex differences in the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Males have more testosterone and dihydrotestosterone, whilst females have higher oestrogen and progesterone levels. Men experience aggravated immune responses to SARS-CoV-2 infection due to various factors. The expression of transmembrane serine protease 2 (TMPRSS2), which facilitates viral entry, is regulated by androgen receptors and higher in males. Males with coronavirus disease 2019 (COVID-19) have higher neutrophil-to-lymphocyte ratios, lower lymphocyte count and greater serum C-reactive protein levels. Older males have decreased naïve T and B cells. Males experience hyperinflammation and cytokine storms, which translate into increased COVID-19 severity. In females, SARS-CoV-2 infection is better controlled due to the efficient sensing of the viral genome by endosomally expressed TLR7 in immune cells. TLR7 expression is enhanced by higher levels of oestrogen in females. Such intracellular detection of the viral genome in immune cells amplifies the production of type I interferon (IFN), which confers antiviral immunity. In plasmacytoid dendritic cells of females, IRF5 expression is higher, which may explain the greater production of type I IFN in females. Additionally, oestradiol promotes regulatory T cells, and women also have increased CD4<sup>+</sup>:CD8<sup>+</sup> T-cell ratios, which may have an impact on COVID-19 progression. Females exhibit more robust adaptive immunity compared with males, with pronounced effects on reducing dysregulated inflammation.

androgenic alopecia and severe COVID-19.<sup>115</sup> Smoking has also been associated with higher expression of ACE2 and TMPRSS2, possibly through upregulating the androgen pathway.<sup>116–118</sup>

Androgen-related treatments may provide further insight into the role of androgens in COVID-19 progression. One study showed a lower risk of COVID-19 infection amongst prostate cancer patients who were on androgen deprivation therapy (ADT) compared with those who were not.<sup>119</sup> It is thought that virus binding to the cell can be inhibited by ADT. Fewer activated androgen receptors to upregulate TMPRSS2 would be expected in patients on ADT, decreasing the risk of SARS-CoV-2 infection.<sup>120</sup> However, multiple recent studies observed that ADT did not improve COVID-19 outcomes, including infection risk, ICU admission, hospitalization, and mortality.<sup>121–126</sup> Another study showed that prostate cancer patients with COVID-19 had higher rates of hospitalization and mortality compared with non-prostate genitourinary cancer patients with COVID-19.<sup>127</sup>

TMPRSS2 expression and SARS-CoV-2 entry in human lung cells have been reduced by antiandrogens.<sup>128–130</sup> Clinical trial results on antiandrogens have been mixed. A randomized controlled trial (RCT) treated COVID-19 patients undergoing nitazoxanide and azithromycin therapy with dutasteride and found decreased viral shedding, inflammatory markers and time-to-remission compared with placebo.<sup>131</sup> Another RCT found that proxalutamide decreased the 30-day hospitalization rate and risk ratio amongst men with COVID-19.<sup>132</sup> In contrast, a third RCT determined that COVID-19 patients treated with enzalutamide had longer hospitalization.<sup>126</sup>

Semen samples from males with COVID-19 have been shown to contain SARS-CoV-2 genetic material.<sup>133</sup> ACE2 and TMPRSS2 are also expressed in the testes.<sup>134</sup> However, the expression of TMPRSS2 in lung tissue was not significantly different between sexes, according to one study.<sup>135</sup> Currently, it remains unclear whether pulmonary expression of TMPRSS2 may be influenced by androgens during SARS-CoV-2 infection.<sup>136</sup> Whether SARS-CoV-2 viral load can be influenced by the level of TMPRSS2 expression is also uncertain.

Additionally, androgens have numerous immunosuppressive effects. They can suppress thymic function and T-cell development, have direct or indirect effects (via antigen-presenting cells) on T cells to decrease proinflammatory cytokine release (e.g., IFN $\gamma$  and TNF) or increase anti-inflammatory cytokine release (e.g., IL-4 and IL-10), reduce T helper 1 (Th1) and T helper 17 (Th17) cell differentiation, induce Treg differentiation and regulate B-cell development and humoral immune responses.<sup>137–140</sup>

Testosterone-dependent Gr1<sup>+</sup> cells in male autoimmune BWF1 mice inhibited T follicular helper cell development, which, in turn, controlled the formation of germinal centres and differentiation of plasma cells.<sup>141</sup> Furthermore, higher testosterone levels are associated with lower neutralizing antibody responses after influenza vaccination.<sup>142</sup>

Paradoxically, these immunosuppressive effects of testosterone might be beneficial to overcome the heightened inflammatory environment that predisposes to severe COVID-19. Recent research has revealed that males with COVID-19 have lower testosterone levels and higher luteinizing hormone (LH) levels than healthy subjects.<sup>143</sup> Moreover, there is a negative association between testosterone/LH ratio and serum CRP levels.<sup>143</sup> Another study found a negative association between total testosterone levels and biochemical markers of COVID-19 severity.<sup>144</sup> In a prospective cohort study of COVID-19 patients, lower testosterone concentrations were associated with higher concentrations of IL-6, CRP, IL-1 receptor antagonist, hepatocyte growth factor, and IFN $\gamma$ -inducible protein 10.<sup>145</sup> In young men, there is a negative association between androgen levels and inflammatory markers.<sup>146</sup> Therefore, testosterone deficiency appears to be associated with higher levels of proinflammatory cytokines, whilst testosterone can decrease these cytokines.<sup>147</sup>

The available evidence on the role of androgens in COVID-19 leaves many questions unanswered. It appears that both high and low androgen levels can be associated with poor COVID-19 outcomes.<sup>35</sup> Additional research is needed to investigate the relationship.

## Oestrogens

A different line of reasoning argues that oestrogen promotes beneficial immune system activation, which may protect against severe COVID-19.<sup>148</sup> Oestrogen receptors are expressed on cells of the immune system and known to impact immune-related gene expression. In female mouse models, oestrogen decreased the severity of influenza virus infection, and mortality after SARS-CoV-1 infection increased when oestrogen was suppressed.<sup>71,149</sup> Amongst hospitalized patients, a negative association between oestradiol levels and COVID-19 severity was found.<sup>150</sup> In addition to androgens, there is evidence that oestrogens also regulate furin. In one study, human breast cancer cells were transfected with the cDNAs of PC1 and furin, which are both proprotein convertases. Lower oestradiol concentration was associated with

slower growth in the transfected cells relative to the wild-type cells. In mice, tamoxifen therapy led to slower regression of tumours from transfected cells compared with those from wild-type cells. These results suggest that over-expressing proprotein convertases can lead to higher dependence on oestrogen and resistance to antioestrogens.<sup>151</sup> Another study revealed that oestradiol and oestrogen receptor agonists regulated the expression of furin in peripheral blood leucocytes.<sup>152</sup> Oestrogen regulates three other molecules involved in SARS-CoV-2 entry into host cells: ACE2, TMPRSS2, and ADAM17.<sup>153–155</sup> Oestrogen can also suppress dipeptidyl peptidase 4 (DPP4), helping prevent another potential means of entry for SARS-CoV-2.<sup>154</sup> Moreover, oestradiol can activate adenosine receptors (part of the DPP4/adenosine pathway), which may have anti-inflammatory effects.<sup>154</sup>

Several other pathways that contribute to heightened inflammation in COVID-19 are regulated by oestrogen. Oestrogen inhibits nucleotide-binding oligomerization domain-like receptor, pyrin domain containing 3 (NLRP3) inflammasome activation and may regulate the receptor for advanced glycation end products (RAGE) pathway to reduce lung injury.<sup>154</sup> Oestrogen can also decrease C-C motif chemokine receptor 2 (CCR2), CCL2 and C-X-C motif chemokine receptor 3 (CXCR3), inhibit recruitment of cells of the innate immune system (e.g., monocytes and neutrophils) and regulate eosinophils.<sup>156–158</sup> In addition, oestrogen activates anti-inflammatory cytokines (IL-4, IL-10), inhibits the nuclear factor kappa B (NF- $\kappa$ B) pathway and decreases the release of inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-17, and TNF), thereby reducing inflammation in innate immune responses.<sup>154,159,160</sup> The hormone can inhibit Th1 cells, promote T helper 2 (Th2) and Treg cells, affect B-cell development, and stimulate plasma cells to produce antibodies.<sup>158</sup> Oestrogen also participates in the regulation of pDCs, which are involved in the antiviral immune response by producing IFN $\alpha$ .<sup>61</sup> In response to viruses, females produce much more IFN $\alpha$  than males, leading to a stronger priming of the adaptive immune response.<sup>62,63</sup> Oestrogen can increase nitric oxide for vasodilation of vessels and decrease platelet aggregation to prevent thrombosis. Through these various mechanisms, oestrogen may have therapeutic potential for managing COVID-19.<sup>161</sup>

Given the important role of oestrogen in the immune system, there has been increased interest in and concerns about interventions that modulate the effects of oestrogen.<sup>162,163</sup> Researchers are currently examining the effect of selective oestrogen receptor modulators (SERMs) on COVID-19.<sup>164–166</sup> An ongoing RCT is investigating the efficacy of an oestradiol and progesterone therapy for reducing COVID-19 disease severity in hospitalized adults.<sup>167</sup>

## Progesterone

Progesterone is another hormone that may influence COVID-19 disease progression. In hypoxemic men hospitalized with COVID-19, short-term subcutaneous progesterone improved clinical outcomes.<sup>168</sup> The anti-inflammatory effects of progesterone may decrease the risk of hyperinflammation and cytokine storm.<sup>169</sup> Progesterone has been shown to increase Treg differentiation, enhance IFN $\alpha$  pathways, promote lung repair by inducing amphiregulin, reduce T helper cell 17 (Th17) responses and disrupt endocytic pathways used by viruses to enter host cells.<sup>169</sup> Taken together, the current evidence suggests that the effects of sex hormones on the immune system are highly complex and context dependent. Further investigation into the underlying pathways targeted by these sex steroids and their clinical correlation will allow us to fine-tune our treatment approaches across the sexes.

## SEX DIFFERENCES IN THE IMMUNE RESPONSE TO VACCINES

Vaccines are amongst the most critical components in our arsenal to control the spread of a rapidly spreading pandemic. They induce immunological memory using components of the pathogen, such that when exposed to the actual pathogen, immunological memory can be reactivated to rapidly mount a stronger immune response to eliminate the pathogen. Vaccine efficacy is affected by various factors including age and sex. Females generally show stronger humoral and cell-mediated immune responses to vaccines.<sup>53,170</sup> Data from a randomized, prospective, single-blind investigation on humoral immune responses have shown that healthy women (age 18–64) produce a stronger protective antibody response to a trivalent inactivated influenza vaccine than their male counterparts.<sup>171</sup> Antibody responses of females to a half dose of influenza vaccine were comparable to antibody responses of males to the full dose. Moreover, a positive association was found between levels of antibodies to the monovalent 2009 H1N1 vaccine and circulating oestradiol concentrations in females.<sup>172</sup> These findings explain why sex differences should be taken into account as a biological variable for adjusting sex-personalized vaccine dosage and considering vaccine efficacy. Because adverse events are also more common in women,<sup>173</sup> the increased immune response to vaccines should be balanced with vaccine safety.<sup>170</sup>

Similar sex-related factors that influence the immune response to pathogens can potentially affect the immune



response to vaccines. Hormonal differences, including oestrogen and androgen levels, may lead to discrepancies in the vaccine response.<sup>174</sup> In addition, X chromosomes have been proposed as one possible factor for the stronger and sometimes longer lasting immunological responses in women, since females have two, whilst males have only one. Higher expression of immune-related molecules in females could be due to the X chromosome having abundant genes that produce immunological components (e.g., TLR7, cytokines, and chemokines) as well as regulatory molecules such as micro-RNAs.<sup>55,175–177</sup> Ageing is another factor in immune response modulation that should not be overlooked.<sup>178</sup> As discussed earlier, males exhibit faster immunosenescence than females.<sup>24</sup>

Females and males also experience different pathogen-specific and non-specific effects (NSEs) of vaccines.<sup>179</sup> NSEs are effects beyond those that protect against the targeted diseases.<sup>180</sup> They can be beneficial for certain vaccines and harmful for others and generally affect females more than males.<sup>181–184</sup> Many factors are involved in NSEs of vaccines, including innate and adaptive immune responses, heterologous immunity, and the effects of other vaccines. Potential reasons for sex differences in NSEs include the effect of X-linked (and Y-linked) genes, sex hormones, micro-RNAs, and sex differences in the microbiota.<sup>179</sup>

A CDC report showed that of 13.8 million doses of COVID-19 vaccine administered in the United States from mid-December 2020 to mid-January 2021, women received 61% of the doses but accounted for 79% of the reported adverse events.<sup>185</sup> A systematic review and meta-analysis revealed that COVID-19 vaccination had higher efficacy in preventing COVID-19 disease in men compared with women.<sup>180,186</sup> Further research is necessary to determine the role of sex differences in the immune response to the COVID-19 vaccine.

## CONCLUDING REMARKS

The purpose of this review was to explore the biological mechanisms driving sex differences in the immune response to SARS-CoV-2 infection and to help elucidate the complex relationship between sex and immune regulation in the context of COVID-19. As discussed in this review, there are sex-specific differences at various stages of SARS-CoV-2 infection, including viral entry, the innate immune response and the adaptive immune response. Sex hormones, including androgens, oestrogens and progesterone, may have a major role in regulating the immune system to combat the virus. Studies have also identified potential differences between females and males in the vaccine immune response. These sex-specific differences at the cellular and molecular levels may

contribute to the dissimilar clinical outcomes between females and males. Because sex is a complex, non-binary biological trait that involves the sex chromosomes, sex hormones, and reproductive organs and because sex-related genes and sex hormones affect the immune system—and thus disease progression and outcome—in many known and potentially unknown ways, sex should be considered in basic, translational and clinical COVID-19 research as a biological factor that may influence therapeutic response. Further enquiry into the role of biological sex in COVID-19 could help enhance the specificity of preventive and therapeutic strategies and improve health and well-being.

## AUTHOR CONTRIBUTIONS

J.Q.H, M.R.S, B.B and S.Z- Conceptualization and design, Writing Original draft. J.Q.H, M.R.S, B.B, T.S, R.E, P.C, V.S, L.B, G.H and S.Z, Writing – Review & Editing. All authors read and approved the final version of the manuscript.

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## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## DATA AVAILABILITY STATEMENT

Not applicable.

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