

# The Coronavirus Disease 2019 Outbreak Highlights the Importance of Sex-sensitive Medicine

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## Abstract

The novel coronavirus disease 2019 (COVID-19) pandemic has revealed important differences between the sexes in epidemiology, risk factors, clinical course, mortality and socioeconomic dimensions of the disease in all populations worldwide. This has emphasised the need for a better understanding of diversity aspects in healthcare to improve prevention, treatment and long-term consequences. In this article, the authors describe the most relevant knowledge thus far on sex differences regarding COVID-19.

## Keywords

COVID-19, gender differences, inflammation, SARS-CoV-2, sex differences, coronavirus

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While 2020 is only halfway through, we have already experienced a historical year in global healthcare with a high societal impact. When the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were reported in China at the end of 2019, few people realised we would all be affected by a global pandemic several months later.

Women are less susceptible than men to many viral infections, such as coxsackievirus B, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome.<sup>1-3</sup> This is partially because of a different innate immunity, the influence of steroid hormones and factors related to sex chromosomes.<sup>2-4</sup> Testosterone, estradiol and progesterone influence the functioning of immune cells. Several immune-related genes are encoded on the X chromosome and there is some evidence of greater activation of X-linked genes in immune cells from women than men.<sup>5</sup>

Sex-related differences in gene expression and distribution of angiotensin-converting enzyme 2 (ACE2), which serves as the entry receptor for SARS-CoV-2, are also possibly connected to the reported differences in novel coronavirus disease 2019 (COVID-19) between women and men.<sup>6</sup> Sex hormones can modulate the expression of ACE2, as can risk factors such as hypertension and obesity. Cardiac injury occurs in more than one in three patients affected by COVID-19, who often have pre-existing heart disease, who present with heterogeneous cardiac manifestations that may also differ between male and female patients.<sup>7-9</sup>

In addition to sex-linked biological differences, we have learned from the COVID-19 outbreak that lifestyle factors, age, comorbidities and

environmental factors are crucial modulators of gender-related susceptibility, affecting the course of the disease and mortality.

Ethnicity also appears to be an important determinant of outcomes.<sup>10-12</sup> People from ethnic minority groups in European countries often live in extended, cohabiting families, which potentially increases the risk of virus transmission.

About two-thirds of patients who have died worldwide are men, which needs to be further investigated to better understand the various patient phenotypes and to develop tailored directions for treatment and prevention.<sup>13-15</sup>

Last but not least, the socioeconomic and cultural roles of women both at work and at home are important in the course of this pandemic and its long-term consequences. Women make up the majority of the workforce at the frontline of the pandemic whereas men are more often in leading positions.<sup>16</sup> Women are more likely to be the primary caregivers within a household, increasing the risk of psychosocial stress. The consequences of lockdown situations have already translated into a 30% increase in intimate partner violence and, as women are more likely to have part-time and freelance jobs, their economic situation is seriously at stake.<sup>17</sup> This applies even more for women from ethnic minority groups and those living in low-income countries. The decline in finances because of job loss may lead to a deterioration in health in the years ahead. As such, the COVID-19 pandemic may have a higher impact on women than men. The need for equal treatment opportunities for all is of utmost importance towards ending this global pandemic.

## Sex Hormones and Genetic Differences in SARS-CoV2 Infections

Several steps of the SARS-CoV-2 virus infection process are susceptible to sex-specific influences. Analogously to the SARS-S virus, the viral haemagglutinin of the SARS-CoV-2 virus employs (ACE2) as the entry receptor.<sup>6,18</sup> The viral haemagglutinin is then cleaved by serine protease TMPRSS2 on the host cell to activate the internalisation of the virus.<sup>18,19</sup>

The ACE2 receptor gene is located on the X chromosome and displays marked heterogeneity of expression across different tissues.<sup>20</sup> A recent, as yet unpublished report has described a significant overexpression in testicular tissue, suggesting that the testis could potentially be a reservoir for the virus.<sup>21</sup> In addition to these differences in expression, the dynamic interaction of the virus with host tissue needs to be taken into account. During SARS-S infection, ACE2 appears to provide protection from lung injury and the virus itself downregulates its expression.<sup>22</sup> It is not yet known whether SARS-CoV-2 directly interferes with ACE2 expression.

The role of the TMPRSS2 protease in SARS-CoV-2 needs to be further investigated, but information on other diseases points towards sex-specific differences. For example, TMPRSS2 serine protease appears essential to infection with the influenza virus. Single-nucleotide polymorphisms associated with a higher expression of TMPRSS2 correlate with a higher susceptibility to influenza virus infection in distinct cohorts.<sup>23</sup> In TMPRSS2 knockout mice, female animals infected by H1N1 virus had a significantly attenuated course of infection compared with wild-type mice.<sup>24</sup> The impact of hormones on the serine protease has been investigated in the field of oncology and androgens appear to upregulate its expression.<sup>25</sup> In addition to androgen susceptibility, a potential role of oestrogens as modulators of TMPRSS2 in prostate cancer has also been postulated.<sup>26</sup> The role of these hormonal regulation pathways warrants further investigation, especially in the context of SARS-CoV-2 infection. Given the impact of this mechanism in different respiratory viruses and the previously described sex differences in susceptibility to influenza infection and vaccine response, this appears to be a promising future area of investigation.<sup>4</sup>

## Sex Differences in Cardiac Manifestations of COVID-19

Cardiovascular complications are common in patients with COVID-19, in a range of 20–40% in hospitalised patients' series.<sup>27</sup> Many different complications may occur as direct or indirect effects of the infection. These vary from arrhythmias, heart failure, acute fulminant myocarditis, acute coronary syndromes (ACS; both type I and type II ACS) to (micro-) thromboembolic events. It is estimated that half of patients with serious cardiac problems had pre-existing comorbidities, especially hypertension, diabetes, prior ischaemic heart disease (IHD), pulmonary diseases and cancer.

Sex-specific data about patients with COVID-19 are still scarce. A small study of 43 patients from Wuhan showed no differences in age and symptoms between hospitalised men and women.<sup>28</sup> However, the clinical course was more severe in men, with a more than two-fold higher mortality; specific cardiac data were not reported. In a review of 28 patients with ST-elevation MI in the Lombardy region in Italy, two-thirds were men.<sup>29</sup>

At coronary angiography, 40% of patients were classified as having an MI with no obstructive coronary artery disease, significantly higher than the

average. This may be related to the hypotension, hypoxaemia and hypovolaemia that frequently occur in severely affected COVID-19 patients, which may cause this type of ACS. A recent European position statement on invasive management of ACS during the COVID-19 pandemic emphasised that the use of coronary angiography for COVID-19-positive patients with elevation in troponin-c should be restricted to those in whom type I ACS is suspected.<sup>30</sup> This occurs more often in men than women and its diagnosis may be delayed in people needing long-term ventilation.<sup>31</sup>

In the Lombardy region, a striking increase in out-of-hospital cardiac arrests of 58% was seen compared to a year earlier, of which more than 77% were related to COVID-19 infections.<sup>32</sup> There was no mention, however, of the sex of the patients. The diffuse myocardial damage caused by the cytokine storm in the most severe stage of the infection seems to be more detrimental to men than women.<sup>27</sup> It is speculated that the adverse impact of obesity on survival in men may be associated with a lower testosterone:estradiol ratio in visceral fat tissue, which may increase the inflammatory reaction to the virus.<sup>33</sup> Other studies, however, postulate that sex differences in inflammatory regulation in obesity are not dependent on sex steroids.<sup>34</sup>

Sex differences in the binding of SARS-CoV-2 to the ACE2 receptor have been identified as an important contributor to the initiation and course of the disease.<sup>6,7,27</sup> Women are at an advantage as the ACE2 gene is located on the X chromosome, so they have higher ACE2 levels, which has a protective effect.<sup>35</sup> It has been disputed whether the use of angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers should be discontinued, but there is no evidence so far that they are harmful.<sup>35</sup> In contrast, by providing a better control of blood pressure, the dysregulated immune system may be better restored in patients with hypertension.<sup>27,35,36</sup> Sex differences regarding potential protective effects of renin-angiotensin-aldosterone system inhibitors in SARS-CoV-2 infections are as yet unknown.<sup>37</sup>

## Sex Differences in Long-term Health Sequelae in COVID19

As this pandemic unfolds and we gather new data, the impact of SARS-CoV2 infection on the human body appears more complex than initially described. At the outset, COVID-19 was classified mainly as a respiratory disease. By now, we know that the virus can infect any organ of the human body and that at least four symptom clusters are present: respiratory, musculoskeletal, enteric and mucocutaneous.<sup>38,39</sup>

In certain groups of patients, symptoms persist for weeks or months, so there is a need for individualised long-term support.<sup>40</sup> Patients treated with invasive ventilation could need long-term rehabilitation and may experience irreparable disability. Men make up the greater proportion of this group, and will possibly have extensive, long-term therapy needs.<sup>41</sup> Men appear to have better access to cardiovascular rehabilitation overall and a potential need to make services sex-specific has been suggested.<sup>42</sup>

An important aspect to consider in this context is the potential loss of a stereotypically masculine role in younger patients because of long-term disability. Work ability, expectation and role distribution in households might change, which could foster a more equal distribution of tasks between partners or put additional strain on unequal relationships. Patients should be adequately counselled and potential options to mitigate this impact discussed.

This pandemic has the potential to significantly affect the mental health of the affected population. In addition to previously described sex differences in the incidence of depression or anxiety, unequally distributed mental load and sources of stress during the pandemic and in its aftermath have to be considered.<sup>43</sup> In the acute phase of the infection, during quarantine and in the recovery period, care tasks might be unequally allocated in households, particularly burdening women. The economic downturn and the redundancy of specific fields of work will affect women and men differently. Loss of jobs and livelihoods is an additional stressor to the immediate existential fears of infection, illness and mortality. Women make up a larger proportion of the healthcare and essential workers who have to provide services in times of quarantine.<sup>44</sup> This could increase strain on already overburdened women, who are having to juggle caring for children and relatives with intensive work schedules and mental stressors. In addition to the effects on mental health, an increased risk for stress-related cardiovascular illness is another possible consequence for the female population.

## Experiences with COVID-19 and Sex-specific Medicine

After years of campaigning for more attention to the impact of sex on healthcare, COVID-19 has provided the discipline with an unexpected increase in validation. Likely higher mortality rates in men, a receptor encoded on an X-linked gene and sex differences in the immune response seem convincing even to many skeptics.

Nevertheless, reporting of sex-disaggregated data is still not the standard, not even in COVID-19 research. Lack of disaggregated data can severely limit our ability to predict the clinical course of patients and mitigate the wider inequities potentially connected to the disease. It is still unknown if symptoms at presentation differ between women and men and if they respond differently to therapy, including experiencing different side effects. We do not know if people caring for infected patients in their homes need specific protective equipment depending on the age or severity of the patient. We do not know if women and men adhere differently to preventive measures and if they need to be motivated differently. Finally, we do not know if the mental health impact of the pandemic will differ according to sex.

## Sex and Gender Medicine

Gender medicine gives us guidance and tools to approach these questions and provide answers that can aid the treatment of our patients and possibly prevent infection at the population level. We have the opportunity to witness on a large scale how the investigation of sex differences could help identify disease mechanisms, improve prognosis and aid in identifying therapeutic targets. The COVID-19 pandemic is forcing us to rethink many healthcare processes and consider changes to our practices for the future; we urge that a systematic attention to sex be one of them. ■

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