
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

# Gender differences in COVID-19

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Epidemiological data have consistently shown since the beginning of the pandemic that both the severity and the mortality of coronavirus disease (COVID-19) are higher in men than in women [1,2]. The Global Health 50/50 research initiative confirmed a greater mortality in men despite similar numbers of COVID-19 cases in both genders worldwide [3]. On the other hand, women appear to be at greater risk of reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Also, the persistence of symptoms over a long period of time after infection, a condition known as long COVID, is more common in women than in men [1,4,5]. Another interesting observation is that women are more likely to experience, or at least to report more frequently, side-effects after COVID-19 vaccination, including fever and pain at the site of injection [4,5]. Moreover, it seems that the transient endothelial and inflammatory response after vaccination is larger in women, which may indicate greater protection in women [6].

The two genders of course have chromosomal differences, namely in one of our 23 pairs of chromosomes, XY for men and XX for women. This chromosomal variation results in different transcription and expression of some genes. Chromosomal variation is responsible for different gonads, testes and ovaries, which in turn secrete sex hormones, oestrogens and androgens, in different concentrations. However, differences between the two sexes are not only genetic or hormonal. In many societies, their lifestyle and social habits, such as smoking, diet, and alcohol consumption, can be quite different [4]. Interestingly, the substantial divergence in various characteristics and functions between males and females is reflected in sex-specific differences in disease susceptibility and outcomes. Biological sex is ultimately associated with a difference in human life span, as women have a higher life expectancy [5].

How do the above gender differences affect the clinical course of COVID-19? Overall lower life expectancy in men has already been ruled out as a major contributor to their increased mortality due to COVID-19 [4,5]. However, patients with comorbidities, such as diabetes mellitus, hypertension and cardiovascular disease, have a higher risk of serious disease [7]. Indeed, men are more likely to present such comorbidities than women [1,4,5]. Moreover, there are distinct gender differences in metabolism regulation, including insulin sensitivity and lipid metabolism [8]. These differences are especially evident before menopause. Women also present lower risk of cardiovascular events compared with men of the same age, while this risk becomes somewhat similar after menopause. Oestrogens are generally thought to have a protective role in metabolism and the cardiovascular system [4,5,8].

Hormonal differences between the two genders seem to significantly affect our response to stress, as well as the inflammatory processes that follow [9]. Furthermore, SARS-CoV-2 binding or proliferation is possibly affected at a cellular or molecular level, reflecting of both genetic and hormonal differences. For example, specific genes associated with the immune system, such as toll-like receptors TLR4, TLR7, TLR8, are located on chromosome X [10]. The gene encoding the major SARS-CoV-2 receptor (angiotensin-converting enzyme 2, ACE2) is also expressed on chromosome X, in regions that usually escape the inactivation of an X chromosome in XX cells [5,11]. In addition to ACE2, SARS-CoV-2 uses dipeptidyl peptidase-4 (DPP4) as a co-receptor. Experimental data, mainly from mice, have shown that exposure to oestrogens may reduce DPP4 activity [5].

A recent large study from Sweden, including 14.685 women in total, provided evidence that among postmenopausal women with COVID-19, those taking oestrogen as hormone replacement therapy (HRT) were less than half as likely (55% reduced risk) to die from COVID-19 compared with those who did not receive such treatment [12]. These data highlight the role of hormonal differences between the two genders in the clinical course of COVID-19. Moreover, it is possible that drugs that increase oestrogen levels may reduce the severity of COVID-19 [5]. Of course, this should be properly studied in randomized controlled trials.

In conclusion, men and women present significant differences regarding COVID-19. These differences can be partly explained by known genetic, hormonal, physiological and other gender variations. Such differences between men and women should be considered in the treatment and follow-up of patients with COVID-19. Moreover, they are

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important for the formulation of public health policies.

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