

# Sex and Gender Differences in Health: What the COVID-19 Pandemic Can Teach Us

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**S**ex; biological and physiologic traits characterizing males and females; and gender, a continuum of socioculturally constructed roles and behaviors associated with men, women, and gender-spectrum diversity, are among the most important determinants of health and disease outcomes. However, these fundamental factors are often ignored in biomedical research and are rarely incorporated into clinical care. We call for sex- and gender-specific and differentiating factors to be urgently included in the research, prevention, and therapeutics implementation response to the coronavirus disease 2019 (COVID-19) pandemic.

Although available sex-disaggregated data for COVID-19 show equal numbers of cases between sexes, current evidence indicates that fatality rates are higher in men than in women. A recent report (23 April 2020) from the Italian National Institute of Health shows that of 23 188 deaths from COVID-19 infection in Italy, approximately 70% were in men. In the United States, provisional death counts for COVID-19 from February to April 2020 similarly indicate a sex bias in fatality rates: Of 37 308 deaths reported by the National Center for Health Statistics, 59% were in men. Similar trends have been reported in China (1) and South Korea (2).

Taken together, these preliminary data suggest that sex- and gender-related factors may be implicated in COVID-19 vulnerability. As scientists, we may consider this an interesting observation to be explored in post hoc analyses, using available sex and gender data. Or we can investigate a priori the specific role of these factors and potentially leverage the mechanisms implicated in sex and gender differences in COVID-19 risk, progression, and outcomes, to identify effective prevention and treatment interventions for the entire population. Adopting a sex- and gender-informed perspective in research has already shown to improve patient care for cardiovascular diseases and other conditions that affect both women and men (3).

Translating this perspective to the study of COVID-19 infection requires the first and essential step of collecting large-scale sex- and gender-disaggregated data. This task may pose some methodological challenges for gender, given the lack of validated tools to assess gender. Using sex when reporting biological factors and gender when reporting gender identity or sociocultural factors, and asking individuals about both their sex assigned at birth and their current gender identity, may facilitate data collection and improve comparability across studies.

However, truly sex- and gender-informed research exceeds mere stratification by these variables. Researchers should also systematically assess biological (such as hormonal state, immune function, comorbid

conditions, and concurrent treatments) and gender-related (such as lifestyle and socioeconomic status) factors in patients with COVID-19. Furthermore, as clinical trials investigating novel therapeutics to prevent and treat COVID-19 infection are being launched worldwide, it is imperative to incorporate sex- and gender-related data into these trials and to analyze and report treatment outcomes disaggregated by sex and gender.

Taking these actions will be crucial to address several fundamental questions related to COVID-19. For example, we may elucidate to what extent sex biases in COVID-19 outcomes are linked to differences in sex hormone profiles. Sex hormones contribute to different immunologic responses in men and women: As a general rule, estrogens promote both innate and adaptive immune responses, which result in faster clearance of pathogens and greater vaccine efficacy. Conversely, testosterone has largely suppressive effects on immune function, which may explain the greater susceptibility to infectious diseases observed in men (3). Notably, changes in sex hormone may further shape the immune response to pathogens, highlighting the importance of studying factors that affect such levels (for example, age, pregnancy, menstrual cycle, exogenous sex-hormone therapies, men, and transgender individuals).

Sex-related biological data may also be critical to investigate the contribution of sex hormones to sex differences in inflammatory response. In particular, reduction in testosterone levels in aging men has been associated with increased proinflammatory cytokine levels (4), which may contribute to worse COVID-19 progression in older men. Sex differences in disease progression may also be linked to estrogen-induced decreased expression of angiotensin-converting enzyme 2 (5), which acts as a functional receptor for SARS-CoV-2 (the virus causing COVID-19) to enter host target cells.

Investigating sex hormone-influenced mechanisms and, more broadly, conducting sex- and gender-informed research may optimize the development of novel therapeutics and shed light on drug efficacy, safety profiles, and adherence to treatments currently tested for COVID-19, given that sex differences in pharmacokinetics and pharmacodynamics influence therapeutic effects and risk profiles of numerous medications, and that gender-related factors affect adherence to treatment, access to health care, and health-seeking behaviors (3).

Stress-related disorders and the long-term consequences of COVID-19 on health outcomes highlight another important effect of sex and gender. Beyond being a pandemic infectious disease, COVID-19 also acts as a potent stressor, with millions of individuals experi-

encing fear and social isolation over a prolonged period. Exposure to persistent stress is associated with increased vulnerability to and severity of stress-related psychiatric disorders (such as posttraumatic stress disorder, panic disorder, and major depression), which occur more frequently in women than men (6). Indeed, preliminary evidence from China during the initial phase of the COVID-19 outbreak shows an increased prevalence and severity of depressive, anxious, and posttraumatic symptoms in women than in men (7).

This gender bias is supported by evidence of sex differences in stress response systems, which increase endocrine, affective, and arousal responses to stress in females (6, 8), who also appear to be more susceptible to social isolation (9). Gender-related factors, such as the predominant roles of women as family caregivers and as frontline health care workers, further exacerbate stress exposure. We have the unprecedented opportunity to conduct large longitudinal studies to directly test whether the relationship between stress exposures and the prevalence and presentation of stress-related psychiatric disorders is mediated by sex- and gender-related factors.

On the basis of these observations, we call on scientists and biomedical institutions to recognize the importance of investigating sex- and gender-specific and differentiating effects of COVID-19 to develop and implement prevention and treatment interventions able to address the acute and long-term effects of this pandemic on the health and well-being of the population. By doing so, we will reshape the way we think about diseases as we conceive and conduct research, thus optimizing health for the entire population.

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