

# Why males may have a worse response to COVID-19

13 October 2020, by Meghan E. Rebuli



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If you ask most women about how their male relatives, partners and friends respond to being sick, they'll often tell you with an accompanying eye roll, "He's such a baby." "He's extra whiny." Or "he exaggerates so much." But there may be a biological explanation for this behavior.

Dubbed the "man flu," this phenomenon has [been validated in a review](#) of previously published, large epidemiological studies, as well as in studies of influenza in animals. In these studies, males were sick longer, with more severe symptoms and had a weaker response to vaccination. Laboratory tests with animals infected with the [influenza virus](#) also underscore that there are sex-based differences in [immune response](#) that influence outcomes observed in humans. But are these more [severe symptoms](#) and outcomes unique to cold and flu?

As a [respiratory toxicologist and researcher](#) investigating sex differences in the respiratory system, I was intrigued to read a [recent study](#) on sex-specific responses to COVID-19 that suggest that men are, actually, more vulnerable and suffer more from this disease.

## Sex differences in COVID-19

These findings may apply to other respiratory viruses like SARS-CoV-2, which causes COVID-19. For example, reports of SARS-CoV-2 [infection rates are similar between males and females](#), but male sex is a significant risk factor for more serious COVID-19 disease and death. In fact, one study revealed that men are [2.4 times more likely to die from COVID-19](#). I find it interesting that [higher death rates](#) in men also occurred in other coronavirus diseases like [severe acute respiratory syndrome](#), caused by SARS-CoV, and [Middle East respiratory syndrome](#).

Based on data from the Centers for Disease Control and Prevention as of Oct. 5, 2020, the risk of death from COVID-19 in men 30-49 years old was also [found to be more than twice that of females](#).

In other age groups, the risk of COVID-19-related death in males was also higher than the same female age cohort. But it was not as high as in the 30- to 49-year-old age group.

This contrasts with almost equal rates of SARS-CoV-2 infection in those same age groups, leading scientists to wonder why might males be more susceptible.

## Study identifies why men may be more susceptible to COVID-19

[The recent report published in Nature explores](#) how males and females respond differently to COVID-19.

This study examined samples including nasal swabs, saliva, and blood, which were either collected from healthy individuals or COVID-19 patients. These samples were used to better understand what the immune response to the infection looks like and how it differs in people with

more severe disease.

Similar to CDC data on infection rates, no sex difference in the concentration of virus or the amount of virus present was observed in either the nasal swab or the saliva. There were also no differences in [antibody levels](#)—a signal the body had identified the virus—detected in infected men and women.

### **Males with SARS-CoV-2 show greater inflammation**

However, the authors identified major sex differences during the early immune response that occurs soon after someone is infected with the SARS-CoV-2 virus.

The blood samples were analyzed for a variety of cytokines—some of the first signaling molecules that help immune cells respond to pathogens. The levels of these signals rise and fall to provide an adequate response to fight an invading pathogen. But large quantities of these molecules can severely damage the body. This is the case in a cytokine storm.

The authors of the *Nature* report observed sex differences in the strength of the cytokine response. Men showed higher levels of cytokines that trigger inflammation, like IL-8 and IL-18, than women. Higher quantities of these cytokines are linked to more severe disease. In severe cases of COVID-19, [fluid builds up in the lungs](#), reducing the oxygen available in the body for normal functions. This can lead to tissue damage, shock and potentially the failure of multiple organs.

### **Females with SARS-CoV-2 are better prepared to eliminate the virus**

In addition to sex differences in cytokine levels, the authors also found sex differences in the function of immune cells.

Compared to men, women had a higher number of T cells—essential for eliminating the virus—that were activated, primed and ready to respond to the SARS-CoV-2 infection. Men with lower levels of these activated T-cells were more likely to have

severe disease.

Thus, there are several aspects of the human immune response to SARS-CoV-2 that differ between men and women. Understanding these differences can inform how doctors treat patients and can help researchers develop sex-specific therapies.

### **Increased COVID-19 susceptibility in men is likely biological**

These results contradict speculation that male susceptibility to SARS-CoV-2 infection is due to [more risky behaviors](#). Those include downplaying the seriousness of the virus, joining large gatherings and ignoring social distancing guidelines, as well as lower rates of hand-washing and wearing masks. Instead, rates of infection are actually similar between males and females, while males are more at risk of serious COVID-19 disease, suggesting biological differences in response to infection.

This paper is one of the first of its kind to delve into mechanisms of susceptibility [sex differences](#). With greater innate biological risk for severe disease and death in men, this suggests that males might need to be hypervigilant about social distancing, hand-washing and mask-wearing.

Greater adherence to infection prevention protections, especially in men, would not only reduce their risk of [infection](#), but also combat their increased risk of severe [disease](#) and death from COVID-19.

The take-home message of this new paper is that researchers need to consider strategies to ensure [treatments and vaccines are equally effective for both women and men](#), especially when one is more susceptible than another.

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