

Why COVID-19 poses greater risks for men than women

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While it's not exactly clear why, the finding itself is certain: Men are suffering worse fates than women when it comes to COVID-19, regardless of geography or age. A variety of data from outbreaks across the world has established this fact, and experts like Johns Hopkins biologist Sabra Klein are trying to understand more.

Last month, Klein contributed to a viewpoint in the *Journal of Critical Investigations* calling for broader study of how biological sex differences between men and women affect outcomes with COVID-19—which she and colleagues believe should be a significant consideration for developing effective treatments and vaccines.

Earlier this week, Klein joined fellow Johns Hopkins University researchers in for a webinar exploring sex and gender dimensions of coronavirus. That talk was hosted by two research units Klein co-chairs, the Center for Women's Health, Sex, and Gender and a specialized center under the National Institutes of Health that studies sex and age differences in influenza immunity.

The Hub reached out to Klein for more insights on what the scientific community knows so far about the different outcomes between men and women who contract COVID-19.

What is the evidence showing different outcomes for men and women who contract COVID-19?

Around the world, on every continent, we're observing that men are significantly more likely to be hospitalized with severe COVID-19, and men are also significantly more likely to die from COVID-19. Some studies are showing the risks are twofold for men. Women are contracting the virus at same rates as men, but they are more likely to recover.

Because these findings are cutting across social and cultural boundaries, that strongly suggests the biological difference between males and females is contributing. That likely doesn't tell the full story, however—social and [lifestyle factors](#) may certainly be influencing the trends, but we need to understand more.

What might be the possible explanations for the discrepancy?

I am hypothesizing that because women typically have a more rapid and robust immune response to viruses than men, this may be one factor contributing to female-biased protection against SARS-CoV-2, the virus that causes COVID-19. There are data from early outbreaks in Wuhan, China, for example, that show women clear the virus more quickly than men.

A sex difference in immune responses that control and clear SARS-CoV-2 suggests there's a difference between sexes affecting immunity. We have data for other viruses illustrating that sex differences in immunity are caused by genetic as well as hormonal differences between women and men. For example, in females, hormones such as estrogen and progesterone may be protective against the virus, and it's possible testosterone does the opposite for men.

Scientists are also looking into the role of the ACE-2 receptor, which is found on the cells lining the lung and airways and is used by the SARS-CoV-2 virus to enter cells. From what we know about this receptor, from other conditions such as hypertension and [kidney disease](#), ACE-2 expression is greater in males than in females. We also know from work in the kidneys that estrogen downregulates the expression of ACE-2, which could be a plausible biological explanation for reduced severity of the virus in women.

How is the factor of age overlapping with all of this?

It turns out the male bias severity is happening across a diverse range of ages. A very large *JAMA* study on cases in New York City, for example, looked at ages 30 through 90, and found that males were significantly

more likely to be hospitalized or die regardless of age. Another study in *The Lancet* examining ages 20 upwards in European countries also shows this trend across ages. What we're seeing in ages 60 years and older is that this is where we find the most severe outcomes of death.

You said that social and cultural factors may also be playing a role.

My colleague Rosemary Morgan, in international health, is studying this; she specializes in gender-associated factors that impact health and disease, including COVID-19. We know that biological differences are only part of the story of what make men and women different. It also has to do with our behavior and even the social and cultural norms that define our roles and responsibilities. For example, females may be more likely to be frontline workers, which could create more risks for exposure. In terms of lifestyle, men tend to be more likely to be smokers, which is a risk factor, and they're less likely to seek out medical care when there's a problem. And with COVID-19, if men are less likely to engage in behaviors like mask-wearing and hand-washing, that may increase risks.

There are also underlying conditions such as hypertension, heart disease, and diabetes, which men are statistically more likely to have and some of which can be attributed to lifestyle factors, that also amplify risks with COVID-19.

What are the implications of all of this for treatment and vaccines?

As my colleagues and I wrote in the *Journal of Critical Investigations*, we need to be ensuring a large prism of men and women take part in the numerous clinical trials for vaccines and we need to be able compare outcome data between men and women. Formulating vaccines should

take into account the differences.

Vaccines are just one arm of how we're addressing protections from COVID-19, however. Another is therapeutics. We have data from the past showing more adverse reactions for women than men with antiviral drugs, and it's important to be aware of that. We don't want the reaction to the drug to be worse than the condition it's trying to treat.

What are you researching right now related to this issue?

I'm one of the partners working with Hopkins immunologist Arturo Casadevall on the promising treatment of convalescent plasma, which uses antibodies of recovered COVID-19 patients to boost immunity in others. Personally, that's giving me lots of fabulous serological data to use to characterize differences between men and [women](#) in antibody responses to SARS-CoV-2.

My colleague Sean Leng at the School of Medicine and I have also won a grant to study differences in immune responses to the virus in older adults, the people who are most at risks of severe outcomes.

Lastly, I'm collaborating with other School of Public Health and Medicine colleagues on animal models that can provide us with mechanistic insights on SARS-CoV-2.

More information: Evelyne Bischof et al. Clinical trials for COVID-19 should include sex as a variable, *Journal of Clinical Investigation* (2020). [DOI: 10.1172/JCI139306](https://doi.org/10.1172/JCI139306)

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