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More men dying from COVID-19 than women, but as with so much about this disease, the reasons are unclear

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Published 7:00 a.m. CT June 15, 2020



Coronavirus (Photo: zetat, Getty Images/iStockphoto)

COVID-19 discriminates, killing more men than women, a fact often noted in scientific journals, but less often explained.

In Wisconsin, men make up just under half of those infected by the new coronavirus, but account for 55% of those killed by it. Nationwide, the pandemic death toll has been 54% male.

Worldwide, the difference is even more stark. Men account for approximately 60% of deaths reported from COVID-19, according to a new pre-print of a study by Yale researchers posted on the website medRxiv. The study has not yet been peer-reviewed.

"A growing body of evidence reveals that male sex is a risk factor for a more severe disease, including death," the authors reported.

Their study examined a group of 93 COVID-19 patients and a control group of 103 health care workers, studying plasma, nasal swabs, saliva samples and highly specialized immune cells called PBMCs.

Researchers found that early in the infection women generated significantly more immune system T cells than men. That's important because T cells kill off the cells that have been infected by the virus, and activate other parts of the immune system.

For their part, men with COVID-19 have higher levels of a protein that attracts neutrophils, the first responders in the immune system. On the surface that might seem like an advantage for men, but it appears to be just the opposite. Neutrophils are great at killing bacteria and fungi, but they are not well designed to fight viruses.

When battling a virus, neutrophils help promote an inflammatory response that can end up hurting, rather than helping. The response can actually damage the lungs.

The Yale study found that women do face one disadvantage in fighting off COVID-19. Their immune system comes out roaring early in the disease, which can lead to a deadly overreaction called a cytokine storm. This overreaction results in the immune system killing both healthy and infected tissue, and often leads to death.

"We were surprised to see such a clear-cut difference in the male vs. female patients' immune response during COVID-19," said Akiko Iwasaki, one of the study authors and a Yale professor of immunobiology and molecular, cellular and developmental biology.

Potential differences in treatment

Iwasaki and her colleagues said their study results suggest potential differences in treatment for men and women with COVID-19.

They wrote that male patients might benefit from vaccines and therapies that boost the T cell immune response to the virus. Female patients, however, might be better served by treatments that dampen their immune response early in the illness, reducing their risk of generating a cytokine storm.

"Earlier with the SARS virus (Severe Acute Respiratory Syndrome), the same observation was made that men had worse outcomes than women, but the scale of this, as a pandemic, drew attention to it on a whole different level," said Hadine Joffe, executive director of the Mary Horrigan Connors Center for Women's Health at Brigham and Women's Hospital in Boston. Both SARS and the virus that causes COVID-19 are in the coronavirus family.



Madonna Multinational Home for Funerals in Passaic, N.J., has seen a three-fold increase in the number of funerals they are performing due to deaths attributed to Covid-19. (Photo: AMY NEWMAN, NORTHJERSEY.COM/ USA TODAY NETWORK)

The higher number of male deaths from COVID-19 is all the more striking, Joffe said, because more women have been at greater risk of exposure to the new coronavirus.

The reason: They make up the majority of frontline health care doctors, nurses and nursing home workers. Even nursing home residents are overwhelmingly female — about 70%, according to a study by the AARP Policy Institute.

Some experts believe the higher mortality rate among men could reflect fundamental differences in the male and female immune systems.

"In general, it's thought that there are immune responses that are biologically different," Joffe said. "In general, for example, women have more robust responses to vaccines."

Not everyone believes the immune system differences explain why more men are dying from COVID-19 than women.

"Essentially looking at the differences in male and female immune systems could be quite fascinating," said Mary Beth Graham, a professor at the Medical College of Wisconsin and medical director of infection prevention and control at Froedtert Hospital. Still, she cautioned that the differences are complex, and "whether getting more information on the differences will translate into therapies or vaccines, is totally unclear."

Graham said studies showing that men have higher levels of a receptor that attracts the new coronavirus — ACE2 — are more likely to explain the higher mortality rate among men. She said the higher ACE2 levels in men may also provide a more promising avenue in the search for ways to reduce male deaths from COVID-19.

Inequity varies by disease, gender

Inequity between sexes in pandemics has actually been common throughout history, sometimes favoring women, and other times favoring men.

Men died in higher numbers from the 1918 Spanish flu, though the difference is less likely to have been explained by immune responses than by the large numbers of male soldiers packed into cramped barracks during World War I.

"In the United States, during the 1957 H2N2 pandemic, mortality was higher among females than males 1-44 years of age," wrote the authors of a 2012 paper in the *Journal of Leukocyte Biology*.

"Worldwide, as of 2008, females were 1.6 times less likely to survive H5N1 (bird flu) infection than males. During the first and second wave of the 2009 H1N1 (swine flu) pandemic, a significant majority of the patients hospitalized were young adult females (15-49 years of age)."

The differences aren't confined to pandemics either. Many diseases have a bias toward men or women. For example, men face twice the risk of dying from malignant cancer. On the other hand, 80% of autoimmune diseases occur in women, according to a 2016 paper in the journal *Nature Reviews Immunology*.

"There's a price women pay for having a stronger immune system," said John K. Amory, a professor of medicine at the University of Washington School of Medicine in Seattle.

Still, it is difficult to translate immune system differences into distinct male and female treatments for COVID-19 and many other illnesses that discriminate.

"We can give people hormones and take them away, but at the end of the day we don't understand it all," Amory said. "There are just so many moving parts of the immune system that the net effect is difficult to predict."

Some researchers favor treating COVID-19 patients with repurposed drugs like remdesivir because they kill the virus directly, rather than getting the immune system to perform better.

In a larger sense, the differences between men and women almost appear to be a biological balancing act. Men have higher mortality rates than women throughout their lifetimes. At the same time, Amory said, more babies — about 51% — are born male than female.

"It's almost like nature knows that men are the weaker sex," he said. "It makes more of them because they're going to die at a higher rate."



Mark Johnson has written in-depth stories about health, science and research for the *Journal Sentinel* since 2000. He is a three-time Pulitzer Prize finalist and, in addition, was part of a team that won the 2011 Pulitzer Prize in Explanatory Reporting for a series of reports on the groundbreaking use of genetic technology to save a 4-year-old boy.

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