

1. Mark your confusion.
2. Show evidence of a close reading.
3. Write a 1+ page reflection.

Why the Coronavirus Is Killing More Men than Women

Men have weaker immune systems that, in some cases, may actually sabotage the body's response to an invader. But social and cultural factors may also play a role.

Source: Ben Guarino, *Washington Post*, October 17, 2020

Early in the coronavirus outbreak, hospital data from China revealed a startling disparity: Covid-19, the disease caused by the virus, was killing far more men than women. That difference persisted in other Asian countries, such as South Korea, as well as in European countries, such as Italy. Then, it appeared in the United States.

By mid-October, the coronavirus had killed almost 17,000 more American men than women, according to data from the Centers for Disease Control and Prevention. For every 10 women claimed by the disease in the United States, 12 men have died, found an analysis by Global Health 50/50, a U.K.-based initiative to advance gender equality in health care. That disparity was one of many alarming aspects of the new virus. It bewildered those unfamiliar with the role of gender in disease.

But the specialized group of researchers who study that relationship was not surprised. It prepared an array of hypotheses. One possible culprit was male behavior. Perhaps men were more likely to be exposed to the virus due to social factors; a disproportionately male workforce, for instance, could place more men in contact with infected people. Or men's lungs might be more vulnerable because they were more likely to smoke in the earliest countries to report the differences.

What has become more evident, 10 months into this outbreak, is that men show comparatively weaker immune responses to coronavirus infections, which may account for those added deaths. "If you look at the data across the world, there are as many men as women that are infected. It's just the severity of disease that is stronger in most populations in men," Franck Mauvais-Jarvis, a Tulane University physician who studies gender differences in such diseases as diabetes. In such cases, biology can help explain why.

The male immune response

Women generally have stronger immune systems, thanks to sex hormones, as well as chromosomes packed with immune-related genes. About 60 genes on the X chromosome are involved in immune function, Johns Hopkins University microbiologist Sabra Klein told *The Washington Post* in April. People with two X chromosomes can benefit from the double helping of some of those genes.

Akiko Iwasaki, who studies immune defenses against viruses at Yale University, wanted to see how sex differences might play out in coronavirus infections. She and her colleagues cast a proverbial net into the immune system to fish out schools of microscopic fighters. "We did a holistic look at everything we can measure immunologically," Iwasaki said, listing a litany of the molecules and cells that form the body's bulwark against pathogens: "cytokines, chemokines, T cells, B cells, neutrophils. Everything that we had access to."

In male patients, the T-cell response was weaker, the scientists found. Not only do T cells detect infected cells and kill them, they also help direct the antibody response. "It's like a master regulator of immune response. And when you have a drop in T cells, or in their ability to become activated, you basically lose the conductor of an orchestra," Iwasaki said.

The power of the immune system wanes as people age, regardless of sex. But what is a gentle decline for women is an abrupt dive off a cliff for men: Iwasaki's work indicates the T-cell response of men in their 30s and 40s is equivalent to that of a woman in her 90s. And T cells aren't the only immune feature disproportionately impaired in men. Another paper, published in September in *PLOS Biology*, examined anonymous human genetic material collected along with viruses in nasal swabs.

That study found throttled defense signals in men. When a cell detects a virus, it performs the molecular equivalent of yanking the fire alarm, said one of the study's author, Nicole Lieberman, a

research scientist at the University of Washington. That alarm is manifest in genetic messengers, called RNA, which react almost immediately. The reaction should cause cells to churn out the first lines of defense, such as interferons, immune system molecules that, as the name suggests, interfere with the virus's ability to reproduce. Other molecules summon specialized immune cells to destroy the pathogens. "You want the fire alarm to go off for long enough that you can get the fire department there," Lieberman said. Lieberman and her co-authors, however, found that in men and some older populations, the fire alarm shuts off early — maybe even before the firefighters have arrived. "That, I think, is the functional consequence, potentially, of what we're seeing here," she said.

Harmful autoantibodies

Not only is the immune system in men weaker, but in some severe cases of the coronavirus, it may hobble itself. A study of nearly 1,000 patients with life-threatening covid-19, published in *Science* in September, found evidence of molecular self-sabotage. Immune system fighters were acting against the body's defenses, like rebellious castle guards splintering their own gates. This flaw was much more prevalent in men than women.

Specifically, the researchers detected what are called autoantibodies, molecules that bind and neutralize parts of the immune system. Those neutralizers disabled a subset of defender molecules known as type-1a interferon. Simply put, having autoantibodies led to more viral replication.

Ninety-five of 101 people with autoantibodies against interferon were male. "Somehow males are probably more prone to develop such autoantibodies, but we do not know why," said study author Petter Brodin, a pediatrician at Sweden's Karolinska Institute who studies the immune system.

Interferon molecules come in several types, so it's possible these patients could be treated with another flavor of interferon, Brodin said. But that may be difficult, he acknowledged, because interferons are most helpful early in the course of an infection, before the disease progresses to life-threatening stages.

The lack of killer T cells, coupled with neutralizing antibodies, is "like a double whammy," Iwasaki said, "that would then ultimately increase the viral load in these men." What's unusual about this result is that most autoantibody immune disorders appear in women, as is the case with the chronic disease lupus.

Iwasaki's research is examining whether female immune systems may play a role in people with long-lasting covid-19, nicknamed long-haulers. "There are thousands of people suffering from chronic symptoms," which may be debilitating, Iwasaki said. Many long-haulers are young and the majority of them, though not all, are women.

Men behaving differently

Beyond these biological differences, it would be simplistic to ignore how gender's other aspects, such as behavior and social norms, may also influence the pandemic. Broadly speaking, men may be less likely to be worried about covid-19 than women, fitting the pattern that women generally treat health risks more seriously. Women took a more cautious approach to the disease, a recent poll found, expressing more concern they could return to workplaces safely. Women are also more likely to follow expert advice such as mask-wearing and social distancing, according to another study that included surveys and observations of pedestrians' behavior in New York, Connecticut and New Jersey.

Sarah Hawkes, a professor of global public health at University College London who, with her husband, co-directs Global Health 50/50, said that the image of men as risk-takers extends back hundreds of years to John Graunt, one of the first people to participate in the field now known as epidemiology. After he reviewed England's death records, Graunt postulated in 1662 that "men, being more intemperate than women, die as much by reason of their Vices" — that is, male behavior was to blame. Hawkes argues that "350 years later," Graunt's point still stands. "It is undoubtedly a mixture of both biology and behavior" responsible for the health differences in men and women, she said.

The share of coronavirus deaths in women also rises with their share of the full-time workforce, according to a report by University of Oxford economist Renee Adams that used Global Health 50/50 data. "The more you have women participating in the workforce, the smaller your sex difference becomes," Hawkes said. That lines up with gender inequalities — men are more likely to work in

environments where they are exposed to air pollution and other harms, Hawkes said. When women start to enter those traditionally masculine spaces, she said, it “turns out, women can get as sick as men.”

The gender disparities discovered in the response to covid-19 have sparked a surge of interest in such differences more broadly. “Almost nobody, apart from the people working in the field, were interested in that difference between men and women in disease until February or March,” when the first results showed that more men were dying, Mauvais-Jarvis said.

Even agencies at the forefront of public health, such as the CDC, were initially slow to reveal sex-disaggregated coronavirus data, Hawkes said. The U.K. public health surveillance system was similarly late. Hawkes took those delays as a sign of just how unimportant people considered this data, since it is so readily available: When people die, their death certificates state whether they were male, female or, in some places, nonbinary.

The CDC data finally made that information accessible in mid-April. The male-skewed patterns revealed in those deaths conform to what was seen in earlier outbreaks of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), both within the family of coronaviruses. And it is in line with other viral responses. “We know that women develop much better antibody response to flu vaccines,” Iwasaki said.

Some of those experts are hoping to capitalize on this moment to shine a spotlight on other gender differences in health. The coronavirus, after all, isn’t the only problem to afflict men and women unequally — so, too, do cancer, asthma, heart disease and other common illnesses, as Mauvais-Jarvis noted in a recent paper in the *Lancet*.

“The kinds of differences that we’re seeing and outcomes in covid-19 are not unexpected. They’re not exceptional,” Hawkes said. If there’s surprise, it only demonstrates the widespread underestimation of the differences in men and women that persist even among physicians, she said.

Mauvais-Jarvis referred to this faulty approach as “bikini medicine” — in which clinicians view female patients as interchangeable with male ones, except for the organs covered by swimwear.

The coronavirus has helped accelerate the trend away from that outdated view. The “one positive that’s come out of the pandemic,” Hawkes said, is the sudden realization that gendered social factors and biology “may have a relationship with your life expectancy, your experience with illness, your risk of illness. It has made that conversation a little bit more real.”

Possible Response Questions:

- What are your thoughts about how the virus affects different genders? Explain.
- Pick a word/line/passage from the article and respond to it.
- Discuss a “move” made by the writer in this piece that you think is good/interesting. Explain.