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**Sex differences**

**Men hit harder by covid-19**

From lifestyle to immune system differences, there are a number of reasons why men may be more affected by covid-19, reports Graham Lawton

WE KNOW that older people are more vulnerable to covid-19, but another major risk factor has emerged: being male.

The first signs of a sex difference in covid-19 severity emerged from hospital records in Wuhan, China, shortly after the city locked down. On 30 January, a team at Shanghai Jiaotong University School of Medicine published a report on 99 covid-19 patients who were admitted to Jinyintan Wuhan hospital between 1 and 20 January. The researchers found that among those admitted, men outnumbered women by more than two to one.

There has also been a sex difference among deaths. Mortality data from 21 hospitals in Wuhan between 21 and 30 January, for example, revealed that 75 per cent of those who died were men.

Since then, larger studies from other countries have backed up these earlier findings. In England, Wales and Northern Ireland, for example, around 70 per cent of critically ill patients admitted to intensive care have been male, and a higher proportion of men than women have died. A study of more than 4,000 covid-19 patients in New York City hospitals found that 62 per cent were male (medRxiv, doi.org/ggsjbw).

The difference doesn’t appear to be caused by differential rates of infection: the New York study, for example, found that equal numbers of men and women catch the virus. But men are more likely to progress to severe illness and death.

Two previous emerging coronavirus diseases, SARS and MERS, have also been found to disproportionately affect men. But this isn’t the case with respiratory infections generally. The report on England, Wales and Northern Ireland also looked at sex data on patients critically ill with viral pneumonia between 2017 and 2019, mostly due to influenza. There was an excess of men in this cohort too, but the ratio was less stark: 54 male deaths for every 46 female deaths.

One possible reason for the sex difference is smoking. In China, over half of men smoke, but only 5 per cent of women do. Tobacco smoke appears to cause lung cells to produce more of a surface protein called ACE2, which the virus exploits to infect cells. This may mean that smoking makes cells more susceptible to the virus.

However, according to an analysis by Hua Linda Cai at the University of California, Los Angeles, this hypothesis isn’t supported by the data. Current smokers only make up about 12.5 per cent of people severely ill with covid-19 in China, she says, which is much lower than the proportion of smokers in the general population.

Another possibility is that men – older men in particular – are in generally worse health than women. They tend to have higher rates of obesity, high blood pressure, diabetes, cancer and lung and cardiovascular disease, all of which have been linked to covid-19 severity.

**Hormones and hygiene**

One key difference is that women have two X chromosomes per cell whereas men have one. “A number of critical immune genes are located on the X chromosome,” says immunologist Philip Goulder, in particular the gene for a protein called TLR7, which detects single-stranded RNA viruses like the coronavirus. “As a result, this protein is expressed at twice the dose on many immune cells in females compared with males, and the immune response to coronavirus is therefore amplified in females,” he says.

While one X chromosome is usually inactivated in each female cell, the TLR7 gene somehow escapes this in some immune cells, meaning women produce more of the protein.

There is also some evidence that female sex hormones such as oestrogen and progesterone boost the immune system, but this hasn’t been specifically investigated in covid-19 yet.

Another possibility is that men are simply less hygienic. They are less likely to comply with basic sanitation measures such as hand washing, says Kunihiro Matsushita of Johns Hopkins University in Maryland.

A study of sex differences in China found that men with covid-19 in hospital were more likely than women to be carrying other viruses, including flu, and bacteria. It is possible that carrying more microbial pathogens may contribute to the severity of covid-19 symptoms.

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**A medical centre screens a man for infection with the coronavirus**

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**62%**

of covid-19 patients in New York City hospitals are male

When the authors of the New York study factored these conditions into their analysis, they found that sex was no longer one of the main risk factors for severe covid-19.

Another, not necessarily unrelated, idea is that women may naturally have stronger immune defences. “There are substantial differences in the immune system between males and females and these have a significant impact on outcome from a wide range of infectious diseases,” says immunologist Philip Goulder at the University of Oxford.

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**A study of sex differences in covid-19 severity**

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