Sex difference and smoking predisposition in patients with COVID-19

The outbreak of novel coronavirus disease 2019 (COVID-19) is quickly turning into a pandemic. Although the disease is now better contained in China, 32 702 cases remain as of March 2, 2020. 10 566 cases and 166 deaths outside of China had been reported as of March 3 (WHO situation report 43), which is a large increase from the 2918 cases and 44 deaths reported on Feb 26 (WHO situation report 37). Rapid progress has been made with diagnostic reagents (eg, nucleic acid and IgM or IgG detection, or both), drug repurposing (eg, remdesivir and chloroquine), and vaccine production. Studies on the biology of viral infection and clinical management of the disease have also been published, some of which have demonstrated that differences in COVID-19 disease prevalence and severity are associated with sex, and smoking is related to higher expression of ACE2 (the receptor for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), so that might also be a factor. One study (preprint),[1] using single-cell sequencing, found that expression of ACE2 was more predominant in Asian men, which might be the reason for the higher prevalence of COVID-19 in this subgroup of patients than in women and patients of other ethnicities. One study of 140 patients with COVID-19 in China,[2] found the sex distribution equal; whereas, in a study of critically ill patients,[3] more men were affected (67%) than women. In a latest report[4] of 1099 patients with COVID-19 from 552 hospitals in 30 provinces in China, 58% of the patients were men. Taken together, these data seem to indicate that there might be a sex predisposition to COVID-19, with men more prone to being affected.

This sex predisposition might be associated with the much higher smoking rate in men than in women in China (288 million men *vs* 12·6 million women were smokers in 2018). Of note, one study (preprint)[5] found that although ACE2 expression was not significantly different between Asian and white people, men and women, or subgroups aged older and younger than 60 years, it was significantly higher in current smokers of Asian ethnicity than Asian non-smokers; although no difference was found between smokers and non-smokers who were white. Nonetheless, the current literature does not support smoking as a predisposing factor in men or any subgroup for infection with SARS-CoV-2. In the study by Zhang and colleagues,[2] only 1·4% of patients were current smokers, although this number was much higher at 12·6% in the study by Guan and colleagues.[4] The relatively small proportion of current smokers in each of these two studies compared with the proportion of male smokers in China (50·5%) are unlikely to be associated with incidence or severity of COVID-19. A trend towards an association was seen between smoking and severity of COVID-19 in the study by Zhang and colleagues[2] (11·8% of smokers had non-severe disease *vs* 16·9% of smokers with severe disease), but it was not significant. Without strong evidence of an association between smoking and prevalence or severity of COVID-19 in Asian men compared with other subgroups, no firm conclusions can be drawn. With more cases being examined from different ethnic and genetic backgrounds worldwide, ACE2 expression variation can be better analysed and compared to establish whether it contributes to susceptibility to COVID-19 across the different subgroups.

I declare no competing interests.

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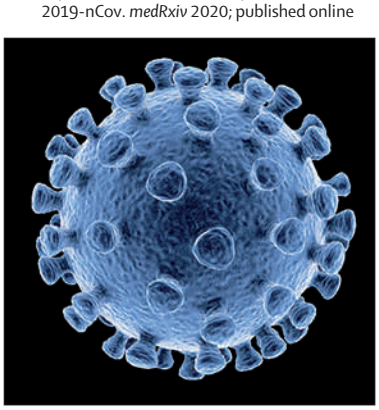

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For the **WHO COVID-19 report 43** see https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200303-sitrep-43-covid-19.pdf?sfvrsn=2c21c09c_2

For the **WHO COVID-19 report 37** see https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200226-sitrep-37-covid-19.pdf

Smoking or Vaping May Increase the Risk of a Severe Coronavirus Infection

SA scientificamerican.com/article/smoking-or-vaping-may-increase-the-risk-of-a-severe-coronavirus-infection1

Tanya Lewis

Smoking or vaping could make you more vulnerable to a severe infection with the novel coronavirus, some experts say.

Although there have not been many studies investigating this link specifically, a wealth of evidence suggests that smoking suppresses immune function in the lungs and triggers inflammation. There have been far fewer investigations of vaping, but preliminary research suggests it may do similar damage. And both long-term smokers and e-cigarette users are at a heightened risk of developing chronic lung conditions, which have been associated with more severe cases of COVID-19, as the disease caused by the new virus is called. Scientists say it therefore seems reasonable to assume that smoking —and possibly vaping—could increase the risk of developing a serious infection from the coronavirus.

“All these things make me believe that we are going to have more severe cases—especially [in] people who are [long-term] smokers or vapers,” says Melodi Pirzada, chief of pediatric pulmonology at NYU Winthrop Hospital on Long Island.* She has not treated COVID-19 patients herself, “but it is definitely common sense to think that once you have a history of smoking or vaping, the whole airways, the defense mechanism of your lungs —everything changes,” she says.

Very little research has looked directly at whether smoking or vaping increases a person’s risk of severe COVID-19. A preprint study in China found that men were slightly more likely than women to be hospitalized for coronavirus infections, and scientists say this observation could be related to the fact that in the country, vastly more men than women smoke. (The paper, which has not been peer-reviewed, has been withdrawn because it was based on early data. It will be replaced with a more up-to-date version soon, the authors write.) Another study, which has been published online in the *Chinese Medical Journal*, involved 78 patients with COVID-19 and found that those with a history of smoking were 14 times as likely to develop pneumonia.**

There is substantial scientific literature showing that smoking inflames the lungs and suppresses immune function. “For regular smoking, we know it inhibits the ciliary clearance of the airways,” Pirzada says. “We have these little [hairlike] structures known as cilia, and they are responsible for taking the toxins and the mucus out of our airways and clearing the lungs when we cough. We know that that is affected when you smoke and when you vape.”

During a respiratory infection in the lungs, there tends to be an influx of white blood cells called neutrophils—the first responders that start killing the pathogen—followed by an influx of lymphocytes—which are responsible for clearing the infection. “There’s a very coordinated series of events that take place when you do become infected with a virus,” says Ray Pickles, an associate professor of microbiology and immunology at the University of North Carolina at Chapel Hill. “These are probably the events that take place in the vast majority of us as individuals, whether we’re infected by influenza or whether we’re infected by SARS-CoV-2,” as the new coronavirus is known. “I think once you start perturbing this sequence of events in any which way or direction, that’s when things can go awry.”

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Smoking is a known risk factor for influenza, says Robert Tarran, a professor of cell biology and physiology at Chapel Hill. “People who smoke are immunosuppressed to some degree,” Tarran says. “They make more mucus. It doesn’t clear the lungs as well. There are pro-inflammatory changes; immune cells are changed as well. And all that leads up to, basically, they’re more likely to get viruses and have a worse outcome.”

Vapers’ risk of viral infections has not been studied much, although there are some epidemiological studies suggesting they are more likely to get respiratory infections, Tarran says. And animal studies provide some clues. Mice that were exposed to e-cigarette aerosol and then inoculated with *Streptococcus pneumoniae* bacteria or influenza A were less likely to survive. And vaping may interfere with neutrophil function, some studies suggest. Scientists at Chapel Hill have shown that e-cigarette use suppresses the activity of immune- and inflammatory-response genes in nasal cells—more so even than smoking. And a preprint study found that the gene that encodes the receptor ACE2, which the novel coronavirus uses to infect cells, is more active in smokers than nonsmokers.

Of course, none of these studies directly show that smoking or vaping increases the severity of COVID-19 infections; it is not clear to what extent they can be extrapolated to the current pandemic. But given that smoking and vaping do well-established harm to the immune system, it seems prudent to assume they might make coronavirus infections worse.

“I think that a sensible thing to do for people is to stop smoking and stop vaping—and avoid secondhand exposure,” says Stanton Glantz,director of the Center for Tobacco Control Research and Education at the University of California, San Francisco. “We don’t have every little detail on this nailed down,” he says. “But based on what we know, generally, about smoking and e-cigarettes—and in particular about smoking and COVID-19 from people who are already sick, from one study in China—it stands to reason that you would lower your risk if you stopped doing these things.” After all, Glantz adds, “what’s the downside?”

**Editor’s Note (3/17/20): This sentence was edited after posting to update Melodi Pirzada’s title.*

***Editor’s Note (3/19/20): This sentence was edited after posting to correct the figure for the increased risk of pneumonia.*

Read more about the coronavirus outbreak here.

Reduce your risk of serious lung disease caused by corona virus by quitting smoking and vaping

tobacco.ucsf.edu/reduce-your-risk-serious-lung-disease-caused-corona-virus-quitting-smoking-and-vaping

When someone's lungs are exposed to flu or other infections the adverse effects of smoking or vaping are much more serious than among people who do not smoke or vape.

Smoking is associated with increased development of acute respiratory distress syndrome (ARDS) in people with a risk factor like severe infection, non-pulmonary sepsis (blood infection), or blunt trauma. People who have *any* cotinine (a metabolite of nicotine) in their bodies – even at the low levels associated with secondhand smoke – have substantially increased risk of acute respiratory failure from ARDS (paper 1, paper 2, paper 3).

The recent excellent summary of the evidence on the pulmonary effects of e-cigarettes reported multiple ways that e-cigarettes impair lungs' ability to fight off infections:

Effects on immunity

Reporting of respiratory symptoms by e-cigarette users suggests increased susceptibility to and/or delayed recovery from respiratory infections. A study of 30 healthy non-smokers exposed to e-cigarette aerosol found decreased cough sensitivity.82 If human ciliary dysfunction is also negatively affected, as suggested by animal and cellular studies,83 the combination of reduced coughing and impaired mucociliary clearance may predispose users to increased rates of pneumonia. Exposure to e-cigarettes may also broadly suppress important capacities of the innate immune system. Nasal scrape biopsies from non-smokers, smokers, and vapers showed extensive immunosuppression at the gene level with e-cigarette use.84 Healthy non-smokers were exposed to e-cigarette aerosol, and bronchoalveolar lavage was obtained to study alveolar macrophages.46 The expression of more than 60 genes was altered in e-cigarette users' alveolar macrophages two hours after just 20 puffs, including genes involved in inflammation. Neutrophil extracellular trap (NET) formation, or NETosis, is a mode of innate defense whereby neutrophils lyse DNA and release it into the extracellular environment to help to immobilize bacteria, a process that can also injure the lung.85 Neutrophils from chronic vapers have been found to have a greater propensity for NET formation than those from cigarette smokers or non-smokers.57 Given that e-cigarettes may also impair neutrophil phagocytosis,86 these data suggest that neutrophil function may be impaired in e-cigarette users. [emphasis added]

Studies in animals reinforce and help explain these human effects:

Two weeks of exposure to e-cigarette aerosol in mice decreased survival and increased pathogen load following inoculation with either *Streptococcus pneumoniae* or influenza A, two leading causes of pneumonia in humans.97 Furthermore, the aerosol exposure may lead to enhanced upper airway colonization with pathogens and to virulent changes in pathogen phenotype, as shown with *Staphylococcus aureus*.98 99 Thus, although more studies are needed, ***the animal data suggesting that vaping leads to an increased susceptibility to infection would seem to correlate with the population level data in young adult humans, whereby vapers have increased rates of symptoms of chronic bronchitis.***23 [emphasis added]

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Consistent with this science, analysis of deaths from corona virus in China shows that men are more likely to die than women, something that may be related to the fact that many more Chinese men smoke than women. However, one study from China that evaluated predictors of death among all people hospitalized with COVID-19 did not find an association with smoking. Another study from China of patients diagnosed with COVID-19 associated pneumonia who had been in the hospital for two weeks reported that the odds of disease progression (including to death) were 14 times higher among people with a history of smoking compared to those who did not smoke. This was the strongest risk factor among those examined. A review of the available literature done in mid-March 2020 found 5 relevant papers, all from China. Three of the five papers did not find statisticaly significant differences between smokers and nonsmokers in terms of disease progression, but the studies were generally small, which means they had low power to detect an effect if it was there. One did not report a p value and the other (noted earlier in thins paragraph) found worse outcomes for smokers. The general pattern in the non-significant studies was for worse outcomes among the smokers. The authors concluded, "with the limited available data, and although the above results are unadjusted for other factors that may impact disease progression, smoking is most likely associated with the negative progression and adverse outcomes of COVID-19."

Dr. Nora Volkow, director of the National Institute on Drug Abuse, posted an article on her blog "COVID-19: Potential Implications for Individuals with Substance Use Disorders," that stared off by saying

As people across the U.S. and the rest of the world contend with coronavirus disease 2019 (COVID-19), the research community should be alert to the possibility that it could hit some populations with substance use disorders (SUDs) particularly hard. Because it attacks the lungs, the coronavirus that causes COVID-19 could be an especially serious threat to those who smoke tobacco or marijuana or who vape.

She goes on to address other drug use and how COVID-19 could interact with them, including noting that

Vaping, like smoking, may also harm lung health. Whether it can lead to COPD is still unknown, but emerging evidence suggests that exposure to aerosols from e-cigarettes harms the cells of the lung and diminishes the ability to respond to infection. In one NIH-supported study, for instance, influenza virus-infected mice exposed to these aerosols had enhanced tissue damage and inflammation.

The whole blog post is worth reading.

In addition, an article in *Scientific American,* "Smoking or Vaping May Increase the Risk of a Severe Coronavirus Infection," summarizes how smoking and vaping affect the lungs and the immune system that is consistent with the view that using these products increases the risk of infection and worse outcomes. *CNN* also has a good story, "How smoking, vaping and drug use might increase risks from Covid-19."

CDC, FDA, the Surgeon General, state health departments and everyone (including comedians, such as John Oliver who spent his whole show on the issue last weekend) working to educate the public on how to lower risk of serious complications from covid-19 should ***add stopping smoking, vaping, and avoiding secondhand exposure to their list of important preventive measures***.

This would also be a good time for cities, states private employers and even individual families ***to strengthen their smokefree laws and policies*** – including e-cigarettes -- to protect nonsmokers from the effects of secondhand smoke and aerosol on their lungs and to create an environment that will help smokers quit.

(updated March 20, 2020)

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(updated March 20, 2020)

Coronavirus' Top Targets: Men, Seniors, Smokers

webmd.com/lung/news/20200226/coronavirus-top-targets-men-seniors-smokers

By Karen Weintraub

Editor's Note: For the latest updates on the 2020 coronavirus outbreak, see our news coverage.

Feb. 26, 2020 -- Viruses can strike one group more severely than another. The 1918 flu, which claimed 50 million lives worldwide, particularly affected young adults. The Zika outbreak that raged through Brazil in 2015-2016 had an especially devastating effect on pregnant women, attacking the brains of the fetuses they carried.

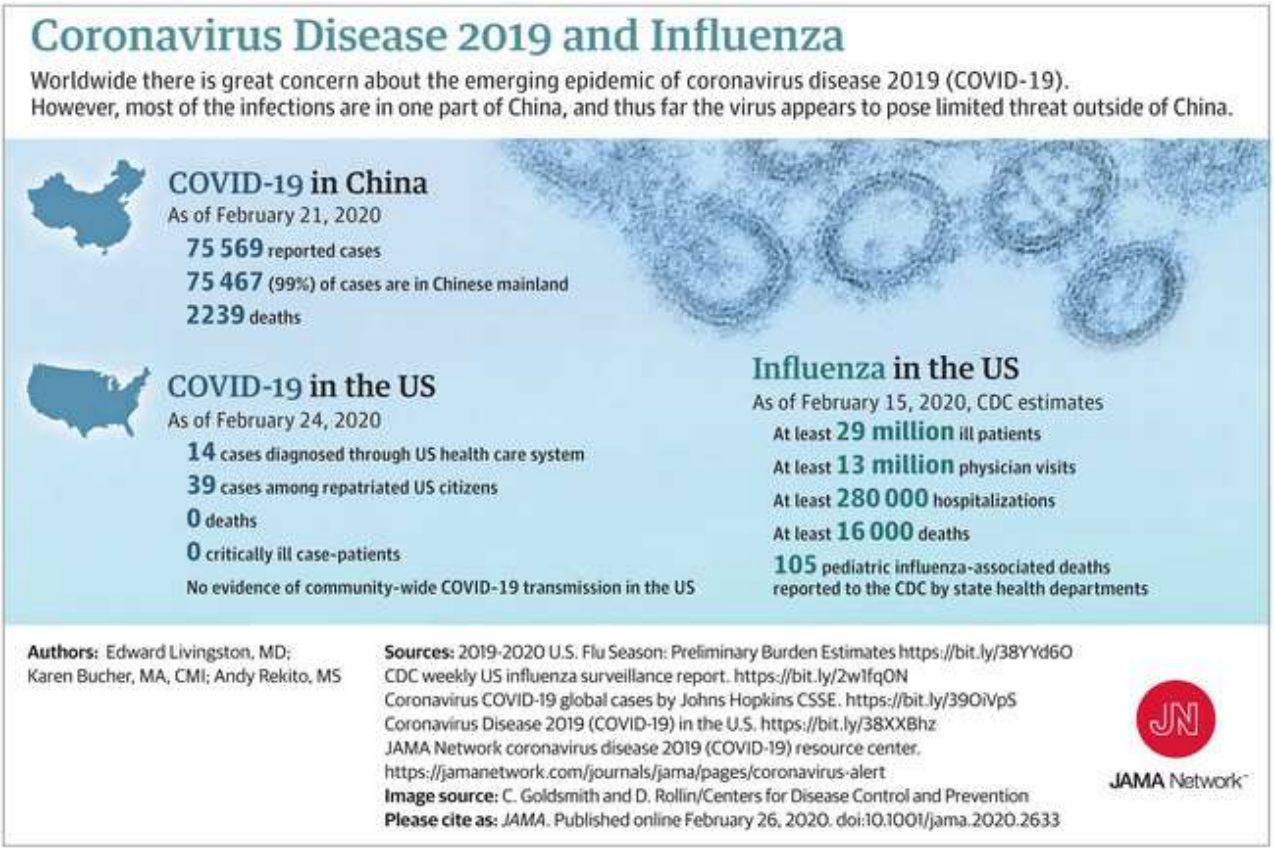
COVID-19, the disease caused by the new coronavirus that originated in China, appears to get more dangerous with age, says Michael Mina, MD, PhD, an assistant professor of epidemiology at the Harvard T.H. Chan School of Public Health.

“There seems to be this threshold -- below [age] 35 we’re seeing practically zero [cases],” he says. “As people increase in age from their 40s to 80s, we’re seeing mortality increase.”

The virus, which erupted late last year, now counts more than 80,000 cases and 2,700 deaths, the majority of them in China.

A study published Monday in *The Journal of the American Medical Association*that examined the first 45,000 cases in China found that 80% of the reported cases appear to be mild. The other 20% of those diagnosed had moderate, severe, or critical symptoms, including a hard time breathing, pneumonia, and organ failure. About 2.3% of overall infections have been lethal. Severe acute respiratory syndrome (SARS), a similar virus that started in China in 2002, also hit people over 60 the hardest. More than 8,000

people contracted the virus over 8 months, nearly 10% of whom died.



With COVID-19, so far children ages 1-9 account for just 1% of all Chinese infections, and none of the deaths, according to the *JAMA* study. Another 1% were ages 10-19.

Of people in their 70s who got the virus, 8% died, the study found, along with nearly 15% of those 80 and older. “Someone in their 80s has a pretty high risk of not leaving the hospital” if treated for COVID-19, Mina says.

Early data suggested that men were more vulnerable, as they accounted for just more than half the cases, according to the Chinese Center for Disease Control and Prevention. Infected men died twice as often as infected women. Mina says men might account for more cases because they were tested more often, but the “evidence is not strong to make any good conclusions.”

It’s possible, several experts told *The New York Times*, that because Chinese men are more likely than women to be smokers, they could be hit harder than women. A World Health Organization study from 2019 found that 47.6% of Chinese men smoke, compared to only 1.8% of Chinese women. Women also generally mount stronger immune responses than men.

People with heart problems, diabetes, or lung issues like COPD are also at a higher risk for severe disease and death, says Jeanne Marrazzo, MD, director of the Division of Infectious Diseases at the University of Alabama at Birmingham School of Medicine. She compared COVID-19 to viral pneumonias, which tend to have a worse effect on people who already have a weakened immune system.

Protection for Babies

Pregnant women do not seem to be impacted by this infection, though only a few have been carefully tracked so far. One study published recently in *The Lancet* found that nine women who became infected with COVID-19 did not pass the virus on to their babies, and Mina says that newborns seem to be spared the worst of the disease. “I think the numbers of young babies who have died have been extraordinarily small, compared to the number that have probably been exposed,” he says. “We’re just not seeing clinical illness.”

Scientists don't know why children seem to be protected, even though as any parent knows, they are usually a carrier for disease. It could be that children’s bodies are better able to handle the effects of the virus, Mina says, or perhaps they have immunity from a previous, related viral infection, or the virus doesn’t replicate as well in them for some reason.

Health care workers also appear to be at particular risk. At least 1,700 have become infected while treating patients in China, most in Hubei province where the outbreak began. Overall, nearly 15% of cases among health workers were classified as severe or critical, and five have died, including Li Wenliang, a 34-year-old Chinese ophthalmologist who tried to raise an early warning about the disease.

Trying to Help, Getting Sick

Health care workers are likely to be particularly vulnerable, according to Mina, either because they did not realize the person they treated was infectious, did not wear protective gear perfectly with every one of the dozens of patients they treated, or because they were exposed when they thought they were safe, such as in dormitories where they slept. Being run-down from the fight didn't help, he says.

Marrazzo says she’s particularly concerned about the previously healthy health care workers who are falling ill and dying. It’s possible they are sicker than average people because they have been exposed to patients with extremely high viral loads, she says, adding that she is concerned that the data from China may not be telling the full story about these workers.

To be prepared, Marrazzo says, people should keep up with news about where the virus is spreading and take the usual precautions to keep themselves as healthy as possible: getting enough rest, exercising, eating well, and getting the flu vaccine.

“Also, to be sure you’re in good shape to withstand an infection is even more important now,” she says. “We know that people who are generally healthier -- not smoking, getting their vaccines, etc. -- the boring preventive health stuff -- those are the people who do best when they go to the hospital for surgery; they recover the quickest from surgery.”

> Rather than focusing so much on trying to quarantine and prevent this from spreading -- it’s going to spread -- all effort needs to be on what can we do to best prepare.
>
> Michael Mina, MD, assistant professor of epidemiology, Harvard T.H. Chan School of Public Health.

Mina says that if he were 65 or older, he wouldn’t do any foreign travel that wasn’t absolutely needed right now “out of a pure abundance of caution,” saying that “if it’s totally just for fun, it’s not a horrible idea” to cancel or postpone a foreign trip.

He says it’s also better for people who aren’t feeling well to stay home from work, self-quarantining themselves to avoid passing illness on to others.

Mina says he agrees with the U.S. CDC that the COVID-19 virus is likely to hit this country more heavily than it has, and spread through the community.

It may, in fact, already be here, he says. The CDC has been relying on its flu detection system to pick up any cases of COVID-19, but he’s not convinced that works well enough.

Knowing who is most vulnerable to disease can help communities respond better if and when the virus arrives, Mina says. For instance, an 80-year-old with a lung condition should be treated aggressively from the start if they come down with the virus, rather than waiting until their condition worsens.

Mina says he would like to see a home-based test, like a pregnancy test, where people can tell if they’re infected without going to a hospital or clinic and risk spreading COVID-19 further.

He says he’s also concerned that the U.S. hasn’t prepared enough for the virus to spread across the country, as he expects it to do at some point. “Rather than focusing so much on trying to quarantine and prevent this from spreading -- it’s going to spread -- all effort needs to be on what can we do to best prepare,” he says.

Stay Up-to-Date on COVID-19
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Editorial

Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19)

Samuel James Brake [1], Kathryn Barnsley [2], Wenying Lu [1], Kielan Darcy McAlinden [1], Mathew Suji Eapen [1] and Sukhwinder Singh Sohal [1,*]

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Abstract: The epicenter of the original outbreak in China has high male smoking rates of around 50%, and early reported death rates have an emphasis on older males, therefore the likelihood of smokers being overrepresented in fatalities is high. In Iran, China, Italy, and South Korea, female smoking rates are much lower than males. Fewer females have contracted the virus. If this analysis is correct, then Indonesia would be expected to begin experiencing high rates of Covid-19 because its male smoking rate is over 60% (Tobacco Atlas). Smokers are vulnerable to respiratory viruses. Smoking can upregulate angiotensin-converting enzyme-2 (ACE2) receptor, the known receptor for both the severe acute respiratory syndrome (SARS)-coronavirus (SARS-CoV) and the human respiratory coronavirus NL638. This could also be true for new electronic smoking devices such as electronic cigarettes and "heat-not-burn" IQOS devices. ACE2 could be a novel adhesion molecule for SARS-CoV-2 causing Covid-19 and a potential therapeutic target for the prevention of fatal microbial infections, and therefore it should be fast tracked and prioritized for research and investigation. Data on smoking status should be collected on all identified cases of Covid-19.

Keywords: ACE2 receptor; SARS-CoV-2; Covid-19; Smoking; COPD; Electronic cigarettes; Vaping; Heat-Not-Burn; IQOS

Little attention has been given to the role of smoking in either the transmission of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, actual virus) or mortality rate of Covid-19 (name of the disease caused). Smokers contract more respiratory ailments, including colds (commonly rhinoviruses, but also coronaviruses) than non-smokers. Smokers also show double the influenza rate and increased rates of bacterial pneumonia and tuberculosis [1–5]. The damage caused to the lungs by smoking makes patients more susceptible to pulmonary infections, both bacterial and viral [6]. Smokers are 34% more likely than non-smokers to contract the flu [6]. Han and colleagues conclude that literature evidence showed that smoking was consistently associated with a higher risk of hospital admissions after influenza infection [7]. Smoking is the primary etiological factor behind chronic obstructive pulmonary disease (COPD) in the developed world, but environmental pollution and degrading air quality are also responsible in developing countries. It is now the fourth leading cause of death in the world [8]. Vaccination against influenza is strongly recommended for patients with COPD, as the frequency and progression of exacerbations are strongly linked to respiratory viruses

in 30% of cases [1]. Rubin et al. found that COPD patients who were prone to viral infections had higher exacerbation rates, more inflammation, and loss of lung function compared to those with existing exacerbating disease conditions [9]. Symptomatology and mortality in influenza-infected smokers were also enhanced [9]. According to the WHO, comorbidities are associated with a high percentage of Covid-19 related deaths [10,11]. In conjunction with the complications arising from comorbidities in patients who smoke [12], we put forth the question of whether smoking, smoking-induced health conditions, and comorbidities, in combination, is culminating in a high risk demographic for both contraction of the virus and the severe presentation of Covid-19.

China has a high male smoking rate at around 50% in rural areas and is estimated to be about 44.8% overall [13]. Most of the deaths identified from the epicenter of the Covid-19 outbreak were in men from older age groups and those with underlying conditions such as chronic respiratory disease, cancer, hypertension, diabetes, or cardiovascular disease. The initial age distribution of Covid-19 cases was skewed towards older age groups with a median age of 45 years (IQR 33–56) for patients who were alive or who had an unknown outcome at the time of reporting. The median age of patients who had died at the time of reporting was 70 years (IQR 65–81) as reported by Sun and colleagues [14]. This data was also supported by an early epidemiological study of 99 Covid-19 cases from Wuhan, China [14].

Fatality rates are given as the percentage of the defined group with confirmed Covid-19 that died, and therefore will not add up to 100%. The Table 1 was adapted from Coronavirus Disease (Covid-19) Research and Statistics [15].

Table 1. Risk factor-based fatality rates of Covid-19 from early data in China.

Age group	Fatality rates
0–9 years	0%
10–19 years	0.2%
20–29 years	0.2%
30–39 years	0.2%
40 - 49 years	0.4%
50–59 years	1.3%
60–69 years	3.6%
70–79 years	8%
80 years and above	14.8%
Underlying health conditions	
Cardiovascular disease	10.5%
Diabetes	7.3%
Chronic respiratory disease	6.3%
Hypertension	6%
Cancer	5.6%
No underlying health conditions	0.9%

The term “coronaviruses” arose from their crown-like appearance when imaged, the Latin for crown being corona. The distinguishing crown-like feature of coronaviruses is attributed to the presence of large type 1 transmembrane spike (S) glycoproteins. This heavily glycosylated cell surface protein contains two distinct functional domains (S1 and S2) which are thought to mediate host cell entry by the virus. The S1 domain contains the angiotensin-converting enzyme-2 (ACE2) receptor-binding domain and is responsible for first stage host cell entry [16]. The S2 domain facilitates fusion between cell and virus membrane, required for cellular infiltration [17]. S proteins are enzymatically modified, exposing the fusion site for cellular adhesion. This is achieved through cleavage by cellular proteases, mediated by protein convertase called “furin” [17,18]. Furin is expressed significantly in the lungs, and respiratory viruses also utilize this system to convert their surface proteins [17]. Although the S protein cleavage site is less observed in coronavirus with similar genomic sequence [17], it is essential to note that more pathogenic influenza viruses share similar cleavage sites [19].

The ACE2 receptor provides a human cell-binding site for the S protein for the SARS-coronavirus (SARS-CoV) [20–22] (a virus that was first identified in 2003 in a southern province of China [23–25]), the coronavirus NL63 [20,26], and now SARS-CoV-2 [27]. Recent studies have found that the modified S protein of SARS-CoV-2 has a significantly higher affinity for ACE2 and is 10- to 20-fold more likely to bind to ACE2 in human cells than the S protein of the previous SARS-CoV [28,29]. This increase in affinity may enable easier person-to-person spread of the virus and thus contribute to a higher estimated R0 for SARS-CoV-2 than the previous SARS virus. The ACE2 protein is expressed on the surface of lung type-2 pneumocytes [30]. It could thus act as a novel adhesion molecule for Covid-19 and be a potential therapeutic target for the prevention of fatal microbial infections in the community.

An early suggestion is that ACE2 is upregulated on the airway epithelium of smokers. Guoshuai Cai recently reported higher ACE2 gene expression in smoker samples compared to never-smokers. Zhao et al. observed that ACE2 is expressed explicitly in type-2 pneumocytes, in which genes regulating viral reproduction and transmission are highly expressed [31]. This indicates that smokers may be more susceptible to infection by SARS-CoV-2, and possibly Covid-19. We recently identified enhanced ACE2 expression in resected lung tissue from patients with COPD and healthy lung function smokers, albeit comparably less in the latter, while entirely absent in heathy non-smoking individuals (Figure 1). ACE2 expression was quite evident in the type-2 pneumocytes, alveolar macrophages, and the apical end of the small airway epithelium. COPD patients showed significantly higher levels of ACE2, suggesting that COPD further exaggerates ACE2 and potential SARS-CoV-2 adhesion site. ACE2 expression could also be true for patients with another chronic lung disease such as idiopathic pulmonary fibrosis [32]. The attachment of the virus to cell surface ACE2 protects them from immune surveillance mechanisms, leaving them tagged to the host for relatively longer periods, thus making them an efficient carrier and vulnerable host for future infections and spread. The eventual engulfment of ACE2 further provides the virus access to the host cells system, thus providing a flourishing environment, not just to sustain and proliferate but also to mutate and modify host evasion mechanisms. Previous observations using in vivo knockout mice models suggest that SARS-CoV-2 adhesion on ACE2 could also downmodulate the expression of ACE2 itself. This, in turn, increases the production and activation of other related ACE enzymes. This differential modulation and the drastic reduction in ACE2 results in severe acute respiratory failure [33,34].

Wang et al. also noted an ACE2 connection to smoking and Covid-19 [35]. The increases seen in smokers further raises the question of whether this is also true for people engaged in waterpipe smoking [36] and those switching over to the more recent alternatives such as electronic cigarettes and "heat-not-burn" IQOS devices. It is essential to recognize that these devices are not "safer", they are still a tobacco product that produces vapor or smoke and similarly could cause infectious lung damage as we see with traditional cigarettes [37–39].

Further research on these products and their influence on the virulence of coronaviruses is urgently needed. Following the outbreak in New York City, Mayor Bill de Blasio announced that "If you are a smoker or a vaper that does make you more vulnerable," urging that now is the perfect time to quit [40]. Smokers, as a vulnerable group, must be supported to quit and should be advised to avoid areas where they may be liable to be exposed to Covid-19, especially smokers with pre-existing respiratory health concerns. Smokers should be prioritized for vaccination when a vaccine is developed, particularly if it is found they are a key transmission source.

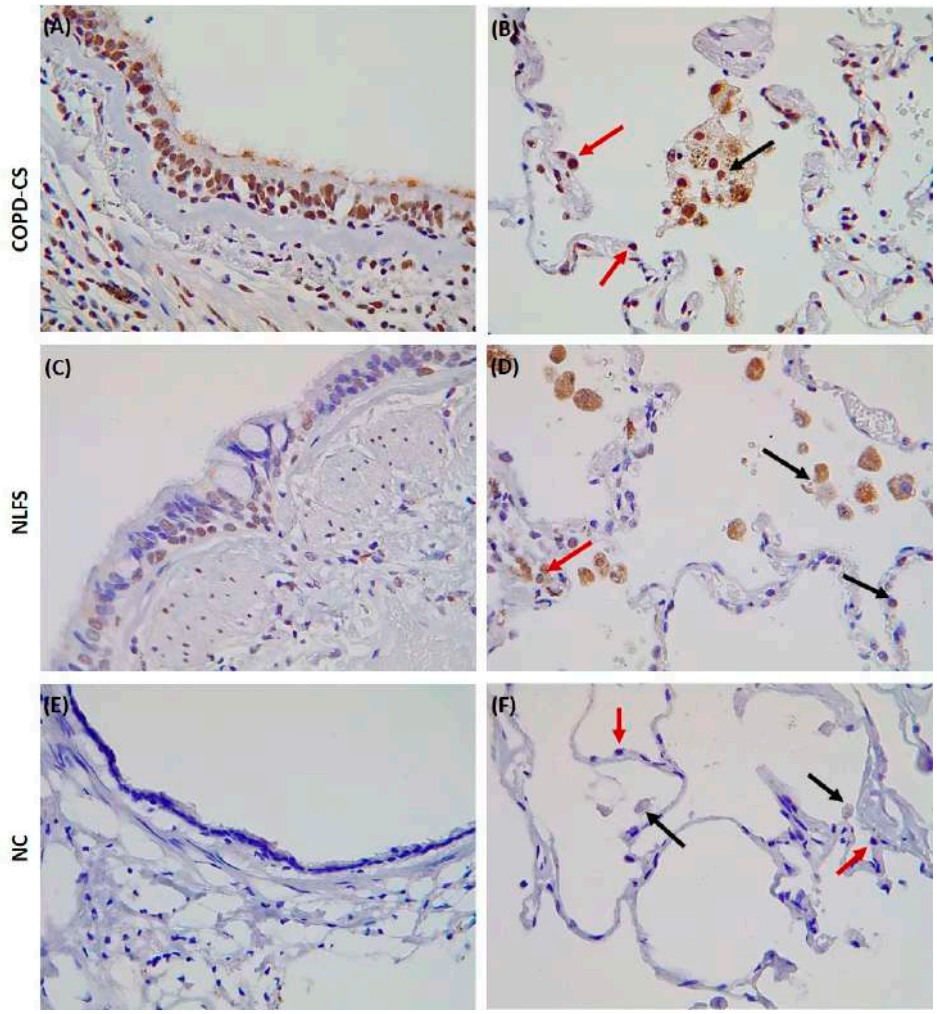

Figure 1. Surgically resected lung tissue stained for the angiotensin-converting enzyme-2 (ACE2) receptor. Current smoker with chronic obstructive pulmonary disease (COPD-CS), (**A**) showing positive staining in the small airway epithelium but also apical including cilia (**B**) red arrows indicating positive staining in type-2 pneumocytes and black arrows showing alveolar macrophages positive for the ACE2 receptor. Normal lung function smoker (NLFS), (**C**) and (**D**) showing similar pattern for COPD-CS although a little less staining is observed. Normal controls (NC), (**E**) and (**F**) no staining observed in any of the areas. **This is the first immunohistochemical human lung evidence for ACE2 receptor expression in smokers and patients with COPD.**

Research on smoking and potential exacerbations of Covid-19 transmission and mortality should include waterpipes, electronic smoking devices, and "heat-not-burn" devices, such as IQOS devices. Further compounding this link between smoking and Covid-19 vulnerability are the comorbidities that have been identified as a significant increased risk factor for severe and fatal Covid-19. The link between smoking and comorbidities, such as diabetes and cardiovascular disease, have long been established [12]. As a research community, we must ask the questions:

(1) Are COPD and other smoking-related illnesses associated with fatal Covid-19 cases?
(2) Are smokers more likely to contract and transmit SARS-CoV-2 than non-smokers?
(3) Are demographics with high smoking rates more vulnerable to Covid-19 outbreaks?

WHO and all countries should ensure that the smoking status of patients identified with Covid-19, including deaths, is recorded and incorporated in data sets, so the smoker's relationship to Covid-19 can be determined.

Status data collection could be simple in four categories,

1. active smoker,
2. passive smoker (those living in households with smokers or working in smoky environments),
3. former smoker (12 months or longer abstinence),
4. non-smoker.

Governments should act to reduce smoking rates in all countries in accordance with the WHO Framework Convention on Tobacco Control (FCTC), and initiate a stimulus package for health, as they have done for business, at the time of this outbreak/pandemic including all communicable pulmonary diseases and Covid-19, as it is possible that smoking exacerbates contraction, transmission, and mortality. It appears that smoking has the potential to upregulate the ACE2 receptor, making smokers and COPD patients more vulnerable to Covid-19. The new electronic smoking devices also do not seem to be safer options. ACE2 thus could be a potential therapeutic target for SARS-CoV-2 and should be prioritized for further research.

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Covid-19: The role of smoking cessation during respiratory virus epidemics

blogs.bmj.com/bmj/2020/03/20/covid-19-the-role-of-smoking-cessation-during-respiratory-virus-epidemics

March 20, 2020

The growing epidemic of the respiratory virus covid-19 has been accompanied by public health messages focusing on how to best reduce the spread of the causative agent, SARS-CoV-2. So far, public health efforts have tended to emphasise key health behaviours such as covering one's mouth when coughing, hand washing, social distancing, and reduced hand-to-hand contact. However, the role of tobacco smoking in the spread and exacerbation of covid-19 has received little attention to-date.

Covid-19 is predominantly a disease of the respiratory tract, with emerging evidence indicating that cellular entry, viral replication and virion shedding occurs within the respiratory tract. [1] The virus has been shown to enter cells using the ACE-2 receptor, which is abundant in mucosal epithelial cells and the lung alveolar tissue. [2] Research on a similar respiratory virus, respiratory syncytial virus, has shown that inhaled tobacco smoke increases the rate of transmission and severity of viral respiratory tract infections. [3] Hence, it has been argued that smokers are at increased risk of contracting covid-19. Notably, smoking involves repetitive hand-to-face movements, which provide a route of entry for viral capsules. Smoking rates in countries that report sizable outbreaks of covid-19 (e.g. China, South Korea, Italy) remain high at approximately 19-27% of the population. [4]

Definitive evidence on whether current smokers are at increased risk of disease, morbidity and mortality from covid-19 are, to our best knowledge, not yet available. An article reporting disease outcomes in 1,099 laboratory confirmed cases of covid-19 reported that 12.4% (17/137) of current smokers died, required intensive care unit admission or mechanical ventilation compared with 4.7% (44/927) among never smokers. [5] Smoking prevalence among men in China is approximately 48% but only 3% in women; this is coupled with findings from the WHO-China Joint Mission on Coronavirus Disease 2019, which reports a higher case fatality rate among males compared with females (4.7% vs. 2.8%). [6,7] It is plausible that rates are even higher in subgroups of the population in which high mortality from SARS-CoV-2 infection is observed (e.g. those with extant cardiovascular and respiratory conditions such as chronic obstructive pulmonary disease). This needs to be further examined.

In the meantime, we strongly recommend that public health messages focused on how to curb the spread of SARS-CoV-2 also include country specific, evidence-based smoking cessation advice (e.g. https://quitnow.smokefree.nhs.uk/). Smoking has many negative effects on heart function and circulation and there is high quality evidence that preoperative smoking cessation interventions can lead to significant health benefits. [8] Smoking cessation at any time represents a huge opportunity for public health, with

smokers tending to lose at least ten years of life. [9] It is likely that the current concern about the covid-19 epidemic provides a “teachable moment” in which smokers may be uniquely receptive to stop smoking advice. Smoking cessation mass media campaigns are ordinarily cost-effective, but budgets in England have been heavily reduced in recent years.

In addition to the health benefits of stopping smoking, it is plausible that a spike in quit rates could help reduce community transmission of SARS-CoV-2. During viral epidemics, evidence suggests that multipronged approaches involving both pharmacological and behavioural interventions (e.g. travel restrictions, school closures, vaccination) are best able to bring the reproductive number below 1. [10] We hence believe that high quality smoking cessation advice should form part of public health efforts during epidemics of respiratory viruses such as covid-19.

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Conflicts of interest

DS and OP have no conflicts of interest to declare. JB has received unrestricted research funding from Pfizer to study smoking cessation.

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News Update

Smoking may increase the risks of COVID-19

2020.03.13

Spreading to over 110 countries, coronavirus disease 2019 (COVID-19) has aroused panic across the globe. The World Health Organization (WHO) raised the global risk of COVID-19 to “very high” on 28 February 2020 and declared COVID-19 as a pandemic on 11 March 2020. While limited is known about the novel coronavirus, rumors are going around. WHO has already clarified that the fake statement “smoking could help prevent COVID-19” is false and misleading. Scientific evidence has also emerged to show that smoking may increase the risk of the infection.

Researchers from China and the United States examined the background characteristics of the first 8,866 COVID-19 cases in China. Consistent with the cases of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), men and elderly are more likely to be infected, and suffer from severe pneumonia and die upon infection. Given the higher susceptibility to respiratory illness in smokers and the much higher smoking prevalence in Chinese males than females (52.1% vs 2.7%, WHO Report on the Global Tobacco Epidemic 2019), experts suspect that smokers may have higher risk of COVID-19.

Latest laboratory studies have shed light on the potential links between smoking and COVID-19. Angiotensin-converting enzyme 2 (ACE2) is a receptor of the novel coronavirus. Although whether it is the only or major receptor of the virus is still unknown, it is noteworthy that significantly higher ACE2 gene expression was observed in lung tissue of smokers compared with non-smokers. Researchers also found active ACE2 expression at different locations of the lungs in smokers and non-smokers. These findings suggest that smokers may have higher susceptibility to COVID-19 and infection paths different from non-smokers.

While further investigations on the links between smoking and COVID-19 are necessary, everyone in the society should do their utmost to minimize their risk of COVID-19. In addition to maintaining personal hygiene, COSH strongly advises the public not to initiate smoking and go smoke-free in order to reduce the susceptibility to respiratory illness.

Source: Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China (2020); Tobacco-Use Disparity in Gene Expression of ACE2, the Receptor of 2019-nCov (2020); Bulk and Single-Cell Transcriptomics Identify Tobacco-Use Disparity in Lung Gene Expression of ACE2, the Receptor of 2019-nCov (2020)

BACK

 doi:10.20944/preprints202002.0051.v1

Tobacco-use disparity in gene expression of ACE2, the receptor of 2019-nCov

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Abstract

In current severe global emergency situation of 2019-nCov outbreak, it is imperative to identify vulnerable and susceptible groups for effective protection and care. Recently, studies found that 2019-nCov and SARS-nCov share the same receptor, ACE2. In this study, we analyzed four large-scale datasets of normal lung tissue to investigate the disparities related to race, age, gender and smoking status in ACE2 gene expression. No significant disparities in ACE2 gene expression were found between racial groups (Asian vs Caucasian), age groups (>60 vs <60) or gender groups (male vs female). However, we observed significantly higher ACE2 gene expression in smoker samples compared to non-smoker samples. This indicates the smokers may be more susceptible to 2019-nCov and thus smoking history should be considered in identifying susceptible population and standardizing treatment regimen.

Key words

Wuhan 2019-nCov, ACE2, expression, susceptibility, race, age, gender, smoking

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Introduction

In the past two decades, pathogenic coronaviruses (CoVs) have cause pandemic infections, including the server acute respiratory syndrome (SARS)-CoV outbreak in 2003, the Middle East respiratory syndrome (MERS) outbreak in 2012 and the current novel Wuhan 2019-nCov outbreak. We have learned from SARS-Cov and MERS-Cov that human populations showed disparities in susceptibility to these viruses. For example, epidemiology studies found that males had higher incidence and mortality rates than females.[1,2] We believe that the susceptibility to the novel 2019-nCov is also different among population groups. In current severe global emergency situation of 2019-nCov outbreak, it is imperative to identify vulnerable and susceptible groups for effective protection and care.

Recently, Xu et.al. computationally modelled protein interactions and identified a putative cell entry receptor of 2019-nCov, angiotensin-converting enzyme 2 (ACE2), which is also a receptor for SARS-nCov.[3] Zhou et.al. further confirmed this virus receptor in the HELA cell line.[4] Interestingly, Zhao et al. found ACE2 is specifically expressed in a subset of type II alveolar cells (AT2), in which genes regulating viral reproduction and transmission are highly expressed.[5] They also found that an Asian male has much higher ACE2-expressing cell ratio than other seven white and African American donors, which may indicate the higher susceptibility of Asian. However, the sample size was too small to draw conclusion on this racial disparity. Here, we analyzed four large-scale datasets of normal lung tissue to investigate the disparities related to race, age, gender and smoking status in ACE2 gene expression.

Methods

Two RNA-seq datasets and two DNA microarray datasets from lung cancer patients were analyzed in this study, including a Caucasian RNA-seq dataset from TCGA (https://www.cancer.gov/tcga), an Asian RNA-seq dataset from Gene Expression Omnibus (GEO) with the accession number GSE40419[6], an Asian microarray dataset from GEO with the accession number GSE19804[7] and a Caucasian microarray dataset from GEO with the accession number GSE10072[8]. Both RNA-seq datasets were generated with the Illumina

HiSeq platform and both microarray datasets were generated with the Affymetrix GeneChip Human Genome U133 Array. The details and processing of data were described in our previous study[9]. All datasets contain samples from tumor and normal pairs and we only use the normal samples in this study. In total, 54 samples in the TCGA dataset, 77 samples in the GSE40419 dataset, 60 samples in the GSE19804 dataset and 33 samples in the GSE10072 dataset were analyzed. We studied the Reads per kilobase per million mapped reads (RPKM) values for RNA-seq data and Robust Multi-Array Average (RMA)[10] values for microarray data. All data were log2 transformed to improve normality. The data means across samples in each dataset from the same platform were highly correlated (Pearson correlation coefficient r=0.9 for microarray datasets and r=0.97 for RNA-seq datasets, Fig. S1), indicating no significant system variation in datasets from the same platform.

Simple linear regressions were used to test the association of ACE2 gene expression with each single variable of age, gender, race and smoking status. Also, multiple linear regression was used to test the association of ACE2 expression with multiple factors (age, gender, race, smoking status and data platform). All data management, statistical analyses and visualizations were accomplished using R 3.6.1.

Results

Racial Disparity

Inconsistent with the study of Zhao et al.[5], we observed no significant difference in ACE2 expression in Caucasian lung tissue samples compared to Asian lung tissue samples in the RNAseq datasets (*p*-value=0.45, Fig 1A). In the microarray datasets, a higher ACE2 expression was observed in Caucasian samples compared to Asian samples (*p*-value=0.03, Fig 1A). Given that the GSE19804 RNA-seq study focused on female non-smokers while the TCGA dataset includes samples from both males and females and both smokers and non-smokers, we believe that the observed disparity may be due to other factors other than race, such as smoking, gender and unknown factors. Therefore, we performed multiple linear

regression on multiple independent variables (age, gender, race, smoking status and platform) and found no significant difference between racial groups (*p*-value=0.36, Fig. 1E).

Tobacco-related disparity

We found a significant higher ACE2 gene expression in smoker samples compared to non-smoker samples in the TCGA (*p*-value=0.05) and GSE40419 datasets (*p*-value=0.008, Fig. 1B). Smokers in GSE10072 showed a higher mean of ACE2 gene expression than non-smokers. The difference is not significant (*p*-value=0.18), which may be due to its small sample size (n=33) with insufficient power to detect the difference. The GSE19804 data with only smoker samples available was not included into the analysis. Adjusted by other factors (age, gender, race and platforms) in multivariate analysis, smoking still shows a significant disparity in ACE2 gene expression (*p*-value=0.008, Fig. 1E).

Age and Gender

We didn't observe a disparity between age groups (>60 vs <60) or gender groups (male vs female) in ACE2 gene expression in each available study (Fig. 1C, D). Consistently, multivariate analysis didn't reject the null hypothesis that there is no difference between groups of age or gender after other variables (age/gender, race, smoking status and platforms) were adjusted (*p*-value=0.90 for age, *p*-value=0.35 for gender, Fig. 1E). We also consistently found no difference between male and female healthy lung tissue samples from GTEx[12] (Fig. S2).

Discussion

In this study, we investigated the disparities related to race, age, gender and smoking status in ACE2 gene expression and found significantly higher ACE2 gene expression in lung tissue of smokers compared to that of non-smokers. This may explain the reason why more males (56% of 425 cases) were found in a recent epidemiology report of 2019-nCov early transmission by China CDC[11]. We didn't observe significant disparities in ACE2 gene expression between racial groups (Asian vs Caucasian), age groups (>60 vs <60) or gender groups (male vs female).

This study has several limitations. First, the data analysed in this study were from the normal lung tissue of patients with lung adenocarcinoma, which may be different with the lung tissue of healthy people. Although we observed no difference between male and female healthy samples from GTEx, further validation studies are required for other factors. Second, our analysis was based on the average expression from bulk tissue. This may lead to a power loss in detecting the expression from particular cell types such as the AT2 cells in which ACE2 are specifically highly expressed.

Whether ACE2 is the only or major receptor of 2019-nCov is unknown. The reason(s) for the tobacco-related disparity in ACE2 expression is unknown. Despites current limited knowledge, this study indicates the smokers may be more susceptible to 2019-nCov and thus smoking history should be considered in identifying susceptible population and standardizing treatment regimen. Wuhan, stay strong.

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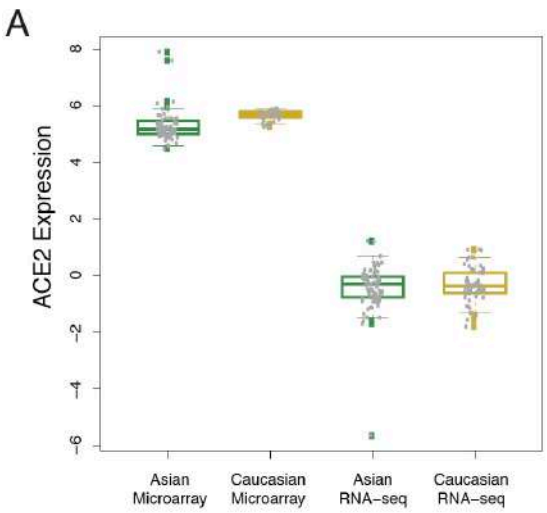
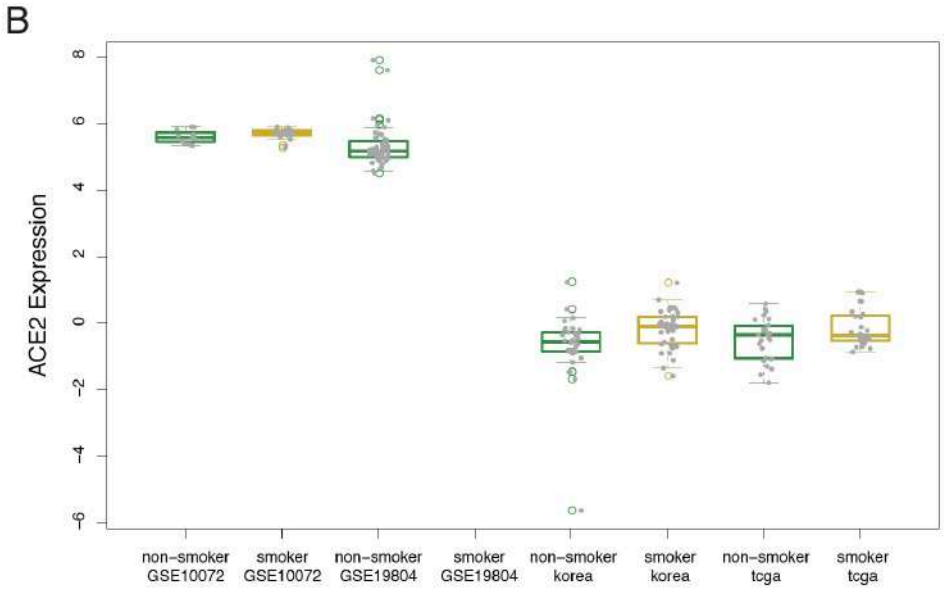
Figure



E

Variable	Beta	P-value
Platform: RNA-seq	-5.940	<2e-16
Race: Caucasian	0.088	0.359
Age: >60	-0.012	0.900
Gender: Male	0.105	0.352
Smoking: Smoker	0.313	**0.008**



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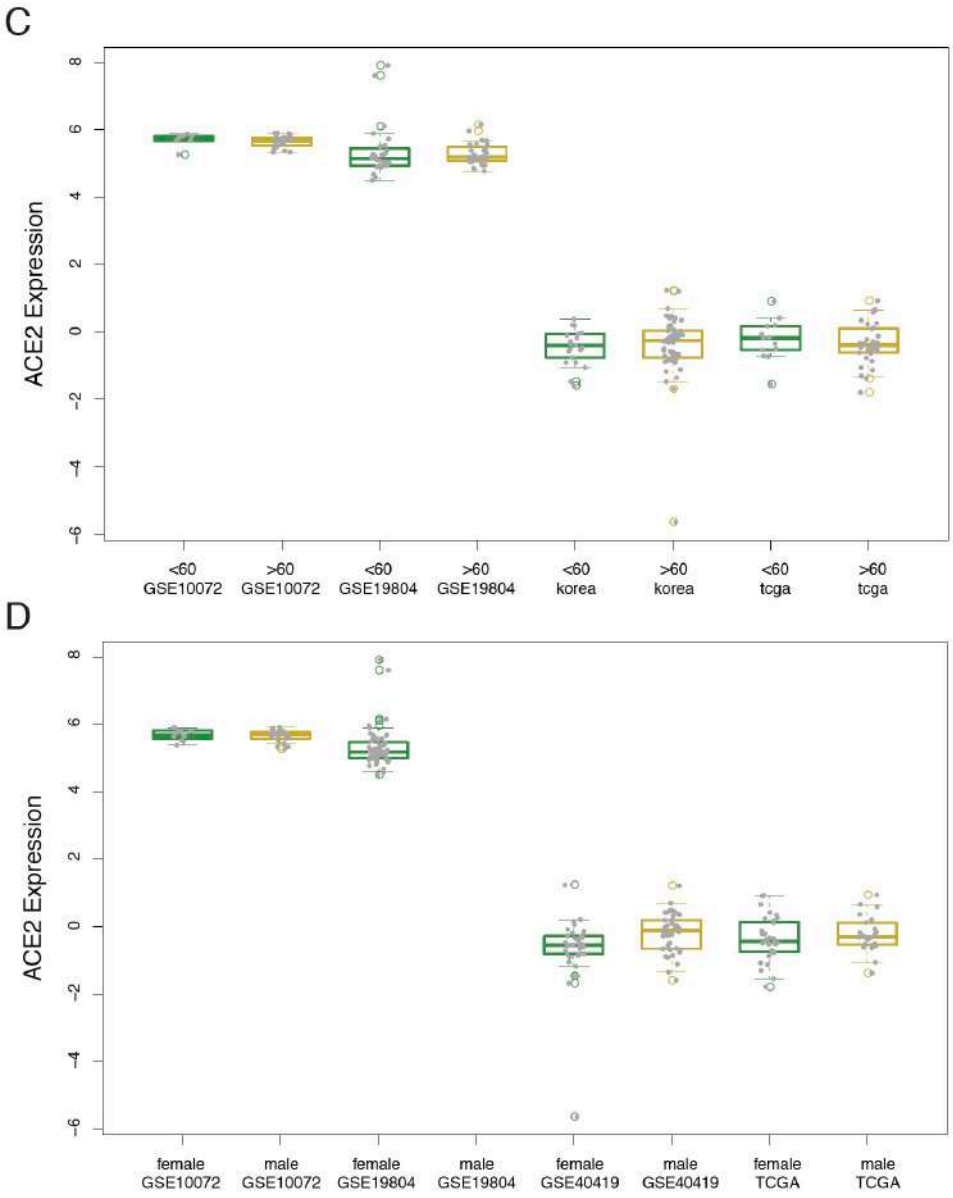

Figure 1. ACE2 gene expression profiling in groups.
A-D shows groups in race (Caucasian vs Asian), smoking (smoker vs non-smoker), age (>60 vs <60) and gender (male vs female). E shows the result from multivariate analysis with all factors including age, gender, race, smoking and platforms.

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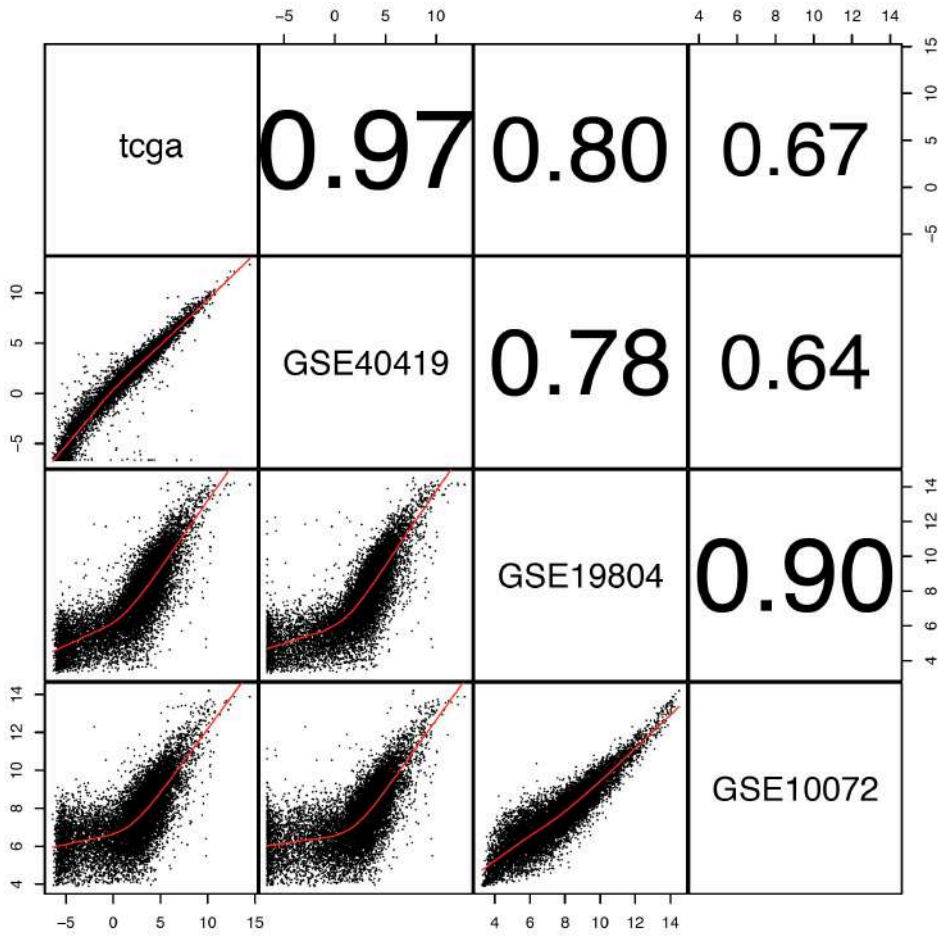


Figure S1. Correlation of four datasets.
Lower panel shows pairwise scatter plots of data mean across samples in each dataset.

Upper panel shows their corresponding Pearson correlation coefficients.

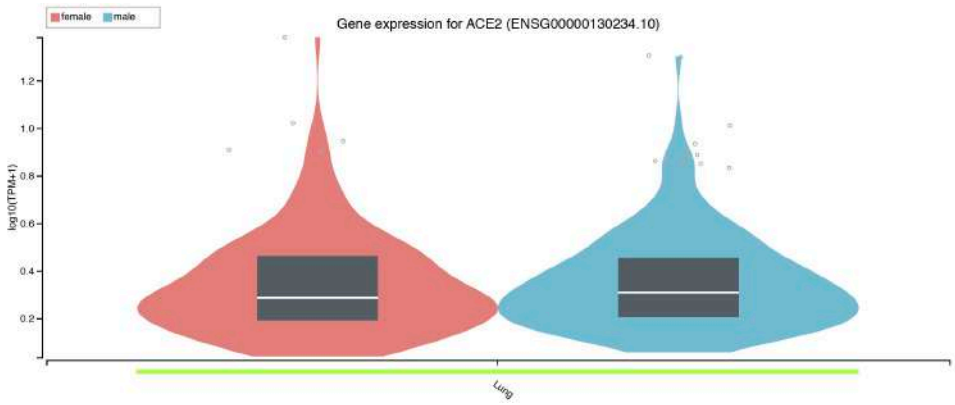


Figure S2. ACE2 gene expression in GTEx female and male lung tissues.
y-axix shows the log10 scaled RNA-seq Transcript Per Million (TPM) values.

More than 70% of coronavirus deaths in Italy are men

dailymail.co.uk/news/article-8135211/More-70-coronavirus-deaths-Italy-men.html

March 20, 2020

- **Italy reports that fewer than 30 per cent of its coronavirus victims are women**
- **Men are also more likely to pick up the infection in the first place, experts found**
- **Data from China has also found that men make up the majority of fatalities**
- **Do you have a coronavirus story? Email vanessa.chalmers@mailonline.co.uk**
- **Coronavirus symptoms: what are they and should you see a doctor?**

More than 70 per cent of Italy's coronavirus deaths have been among men but scientists there admit they are mystified by the gender gap.

At least 3,400 people in Italy have died of the devastating disease - it yesterday announced it had a higher death toll than China - but less than 1,000 of them have been women.

Men are also more likely to pick up the infection in the first place and account for 60 per cent of confirmed cases, according to Italy's public health research agency.

An earlier analysis found the figures were even higher - that 80 per cent of the deaths were in men and just 20 per cent were in women - but the gap has narrowed over time.

Research in China, where the pandemic started and outbreaks are now petering out, shows that at least two thirds of patients who died were male.

A reliable male to female ratio is not clear in the UK because the epidemic is still in its early stages and the death toll is considerably lower than in other nations.

Scientists say they don't know why women seem less likely to die, but have suggested that women naturally tend to have stronger immune systems and are less likely to have long-term health conditions which make patients more vulnerable.

In China, researchers pointed the finger at men being more likely to smoke and drink, but this was a cultural factor which may be different in other countries.

It may be necessary for men to be more careful than women about avoiding the coronavirus, experts said.

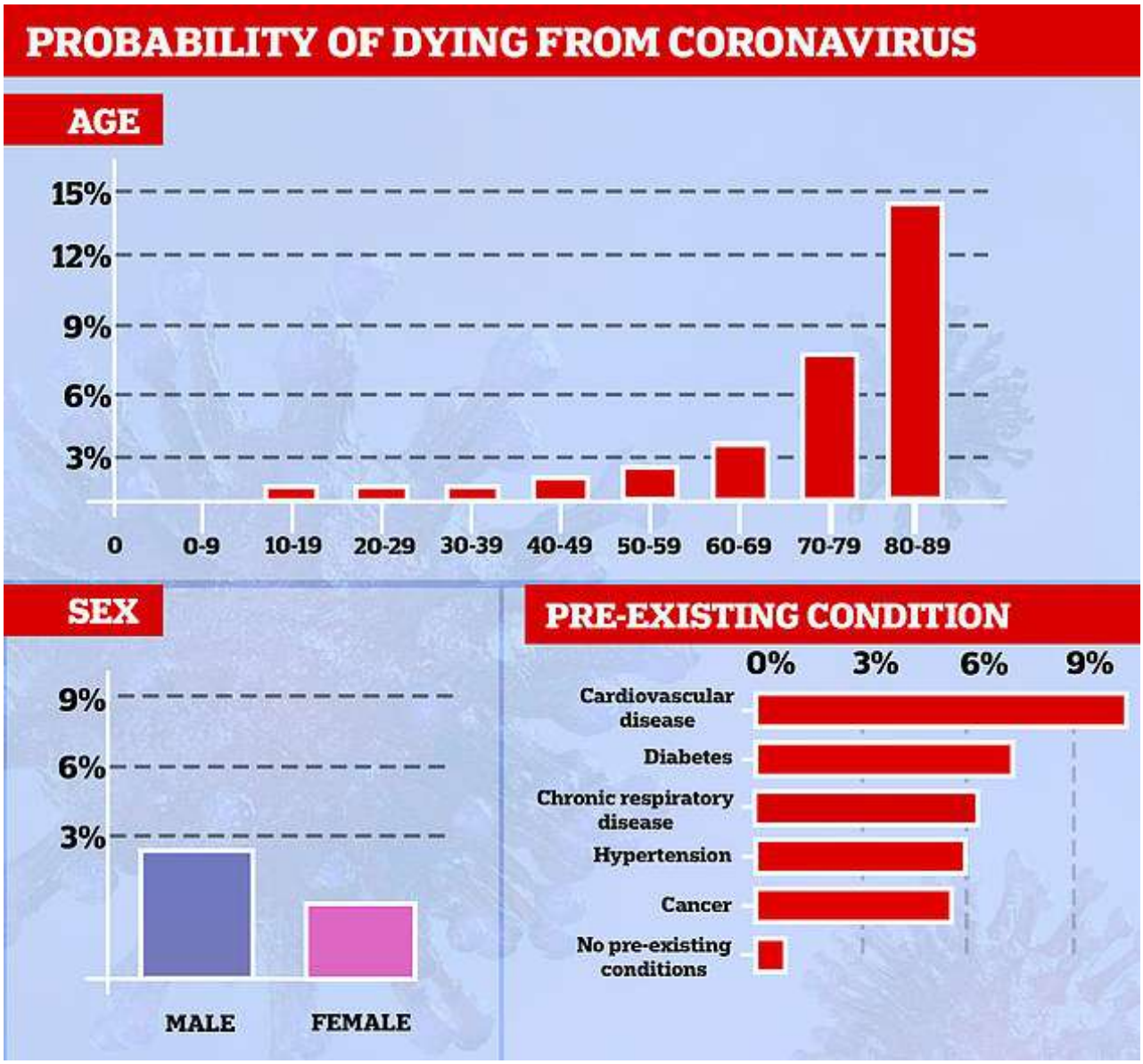
+6

More than 70 per cent of coronavirus deaths in Italy are men but scientists admit they are 'mystified'. Pictured, a patient in intensive care in Cremona, Italy

+6

Men are 65 per cent more likely than women to die from coronavirus, according to

statistics from The World Health Organization. Pictured, a man in London wearing a face mask



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Figures from the World Health Organization and Chinese scientists has revealed that 1.7 per cent of women who catch the virus would die compared to 2.8 per cent of men. Long-term health conditions also dramatically raise the risk of death

There are now more than 254,000 coronavirus cases worldwide and at least 10,440 people have died.

Data coming from countries which have been worst hit in the pandemic, like China and Italy, is being brought together by scientists around the world so they can look at trends and patterns which emerge as the virus spreads.

From the early days of its epidemic, China was reporting that almost all of those who died of COVID-19 were already dealing with a serious health condition.

Those with heart disease, diabetes or asthma, for example, already have weakened bodies that may struggle to fight off another coronavirus if it becomes serious.

WHAT DO PATIENT FATALITIES LOOK LIKE IN THE UK AND US?

NHS England said it would not be releasing a breakdown of age, gender, or health conditions in UK deaths.

MailOnline looked at the first 50 deaths reported by hospital trusts in the UK, 33 of which revealed the victims' genders.

We found that 23 were men (69 per cent) and ten were women (31 per cent), in line with data from Italy.

Of the 50 first deaths, 38 of which the hospital trusts reported the ages of the victims.

These were as follows:

60s: 15.7% (six)

70s: 23.6% (nine)

80s: 42.1% (16)

90s: 13.1% (five)

Two of the 50 deaths were reported as 'elderly', therefore it is not clear if they were in their 80s or 90s.

More detailed data is expected to emerge in the coming days and weeks of exactly who in the UK is catching and dying of the disease.

The Centers for Disease Control and Prevention (CDC) published a preliminary description of outcomes among patients with COVID-19 in the US on March 18.

It broke down ages, but not gender.

CASES

Of 2,449 patients with a known age:

0-19 years: 5%

20-44 years: 29%

45-64 years: 18%

65-84 years: 25%

Over 85: 6%

CASES ADMITTED TO INTENSIVE CARE

Of 121 known patients admitted to ICU:

0-19 years: 0%

20-44 years: 12%

45-64 years: 36%

65-84 years: 46%

Over 85: 7%

DEATHS

Among 44 cases with known outcome:

20-64 years: 20%

65-84 years: 46%

Over 85: 34%

But another trend – that more men are dying than women – has been less well understood.

'The honest truth is that today we don't know why covid-19 is more severe for men than women or why the magnitude of the difference is greater in Italy than China,' Professor Sabra Klein, at Johns Hopkins' University in Baltimore, Maryland, told the Washington Post.

'What we do know is that in addition to older age, being male is a risk factor for severe outcome and the public should be made aware.'

According to Carlos del Rio, chair of the department of global health at Emory University in Atlanta, Georgia, exactly what makes a group vulnerable has experts 'mystified'.

'This difference in mortality is creating a lot of anxiety,' he said.

When looking at the death rates in men compared to women, researchers have produced slightly different results – but they are always in the same ballpark.

Across the first 1,697 coronavirus deaths in Italy, 71 percent (1,197) were men and 29 per cent (493) were women, data from Italy's top health research agency Istituto Superiore di Sanità showed.

And a study of more than 72,000 patients from China's Center for Disease Control found that 64 per cent of fatalities there were men.

More researchers from Italy, who published their findings in the prestigious British medical journal, The Lancet, last week, found the male to female ratio of 827 deaths in Italy was 80 per cent men to 20 per cent women.

The World Health Organization and Chinese scientists revealed in early March that the overall fatality rate - the total of proportion of people who died - was 1.7 per cent of women, compared to 2.8 per cent of men.

This gave men a 65 per cent higher chance of succumbing to the virus if they caught it.

But the reasons for this aren't clear.

Some experts believe the gender disparity relates to higher rates of smoking or alcohol problems among men, both of which are habits which weaken the immune system.

For example, in Italy, smoking is much more common among men than women – 25 per cent compared with 15 per cent, according to figures from the WHO.

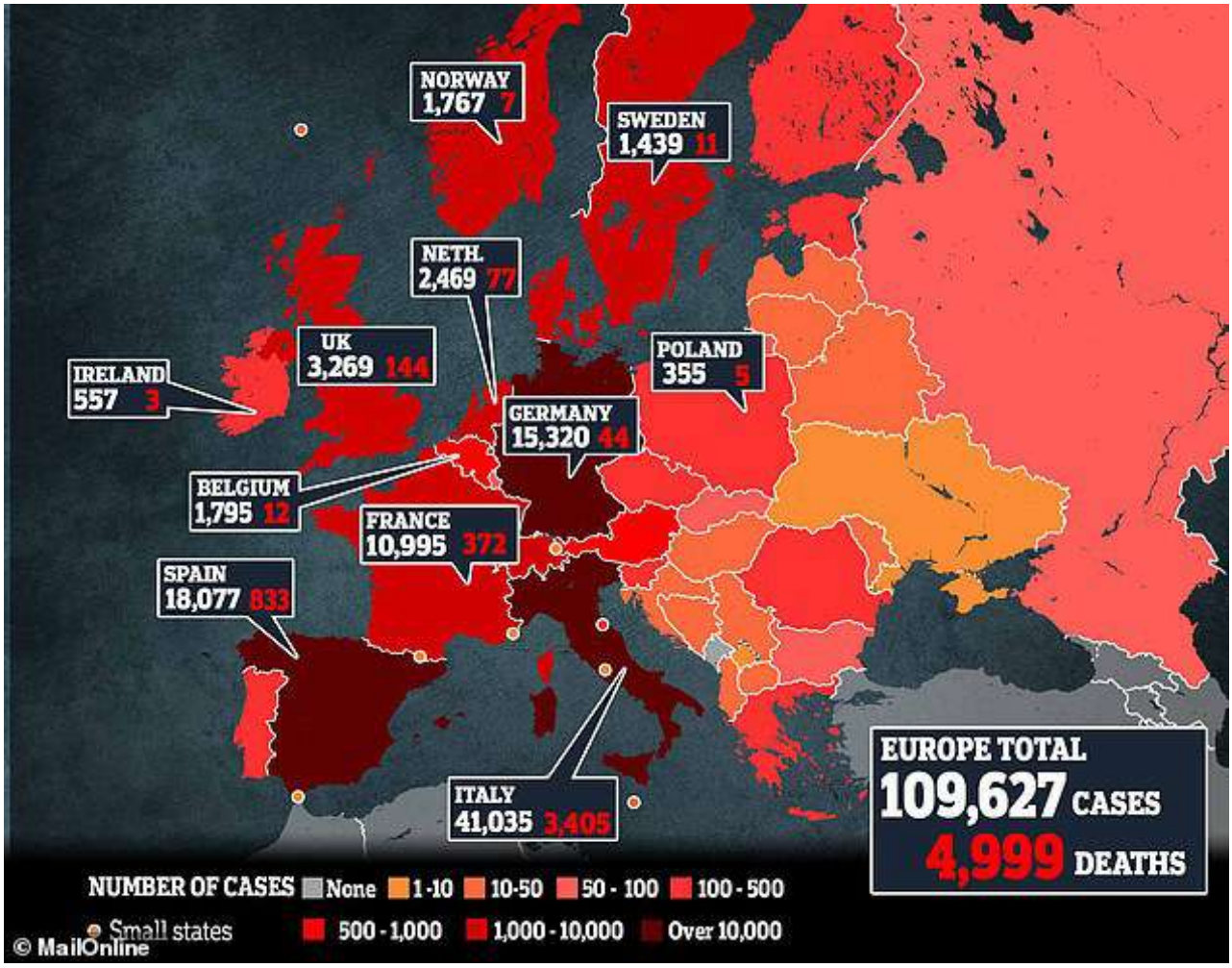
Others say men are more likely to have underlying health conditions such as heart disease and diabetes, with figures showing this would put them in a more vulnerable position.

Paul Hunter, professor of medicine at the University of East Anglia, believes women have better immune systems to fight infection.

There is also historical evidence that women are biologically better at fighting stress on the body, such as famine, which is due to genetic differences.

Professor Hunter told The Telegraph: 'Women are intrinsically different to men in their immune response.

'Sometimes that works in women's favour. Women seem to have more powerful immune systems, which means they suffer more from autoimmune disease like rheumatoid arthritis, when the immune system responds over-aggressively and ends up attacking the body.



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Italy is by far the worst hit area of Europe. The continent now accounts for almost half of all the world's coronavirus cases

+6

Some experts believe the gender disparity relates to a higher prevalence of smoking or chronic alcohol use among men, which weakens the immune system. Pictured: Medical staff collect a patient from an ambulance in Rome, Italy

+6

When it comes to infection rates, it's not clear if men are more likely to catch the deadly disease in the first place. Pictured, men in a hospital in Italy

WHAT IS THE MORTALITY RATE BY AGE AND HEALTH CONDITION?

Chinese Centre for Disease Control and Prevention researchers looked at 72,314 confirmed, suspected, clinically diagnosed, and asymptomatic cases of COVID-19 illness across China as of February 11.

They found the mortality rate for the following:

Conditions:

Heart disease: 10.5%

Diabetes: 7.3%

Chronic respiratory disease: 6.3%

High blood pressure: 6%

Cancer: 5.6%

None: 0.9%

Ages:

0-9 years: N/A

10-19 years: 0.2%

20-29 years: 0.2%

30-39 years: 0.2%

40-49 years: 0.4%

50-59 years: 1.3%

60-69 years: 3.6%

70-79 years: 8%

Over 80 years: 14.8%

'This happens in men far less frequently, but it appears to be a good thing for a number of infections and particularly influenza, and there is evidence women produce better antibody responses to the influenza vaccine than men.'

Men were also disproportionately likely to die during the SARS and MERS outbreaks, which were caused by extremely similar coronaviruses in China and Saudi Arabia.

When it comes to infection rates, it's not clear whether men are more likely to catch the disease in the first place.

Research by the WHO finds that neither sex is more likely to catch it.

But an early study of 99 patients at a hospital in Wuhan, China, where the virus originated, found that men made up two-thirds of COVID-19 patients.

Nearly 60 per cent of diagnoses in Italy have been in men, according to the Istituto Superiore di Sanità.

This is supported by an infographic published by scientists in JAMA this week, which showed that of 22,512 patients in Italy, 60 per cent were male and 40 per cent were female.

Based on current figures from Italy, 8.2 per cent of people infected in the country have died. That's almost one in ten people.

It's more than double the global figure estimated by the World Health Organization, of 3.4 per cent.

Italy's aging population is probably particularly susceptible to the disease, researchers say.

Of all age groups, the elderly are at risk of becoming the most severely ill, although the young are not exempt.

Italians over the age of 70 represent more than 87 per cent of deaths there, according to the country's main health agency.

Data from the European Health Interview Survey (EHIS) report that around five per cent of Italians live with asthma, more than 20 per cent live with high blood pressure and around 6.5 per cent have diabetes.

ITALY'S GENERATIONAL MIXING 'HAS FUELLED THE FIRE OF ITS CORONAVIRUS CRISIS'

Italy's coronavirus outbreak may be so devastating because it has such an old population and the elderly come into frequent contact with the young.

A study by the University of Oxford has suggested that multiple generations living under the same roofs 'accelerated' the spread of the virus in rural Italy.

More than 41,000 people have been diagnosed with the virus in the crisis-hit country and at least 3,400 people have died – the worst death rate in the world.

The country has the world's second oldest population after Japan – 22 per cent of people are over 65 – and people in that group are known to be more likely to die if infected.

But it could be the movements of young people which triggered the disaster.

It's common for young adults in rural areas to live with their parents and grandparents but to commute into cities, such as Milan, to work and socialise.

They may have been picking up the virus while travelling and brought it home without realising they were ill, the Oxford researchers said.

Another study published this week suggested that 86 per cent of patients may have no idea they're ill in the early stages of a country's epidemic, raising the risk of this deadly spread going unnoticed.

The whole country is in lockdown and all citizens have been banned from travelling and urged from going outside – all tourists have been sent home.

In their study, published in the journal Demographic Science, the researchers wrote: 'Even relatively few connections between communities can lead to a stark reduction in average network distances; the so-called small world phenomenon.

'Such community "connecting" individuals might be those young people around Milan that work in the city but reside in the most hard-hit villages in the surrounding with their parents and grandparents.

'Thus, intergenerational co-residence may have accelerated the outbreak by creating intercommunity connections that increase the proximity of elderly to the initial cases, an area for further study.'

The danger of the lifestyle described in the study is that the city-goers interact with a lot of people, visit busy places and work or travel in more cramped conditions.

They risk picking up the virus and spreading it without realising, either because they get such a mild illness, or because it is transmitted before they get sick.

And through this route, the virus could make its way out of a city like Milan – where travellers will have brought it in – into smaller villages in the countryside.

Italy: number of smokers 2018, by age and gender

In 2018, 1,265 Italian men and 942 women aged 45 to 54 years were smokers. This was the age group with the greatest incidence of smokers, even though the number of male smokers aged 35 to 44 years was almost as high as the number of smokers aged up to 54 years. Overall, smoking was more common among males than females no matter how old they were.

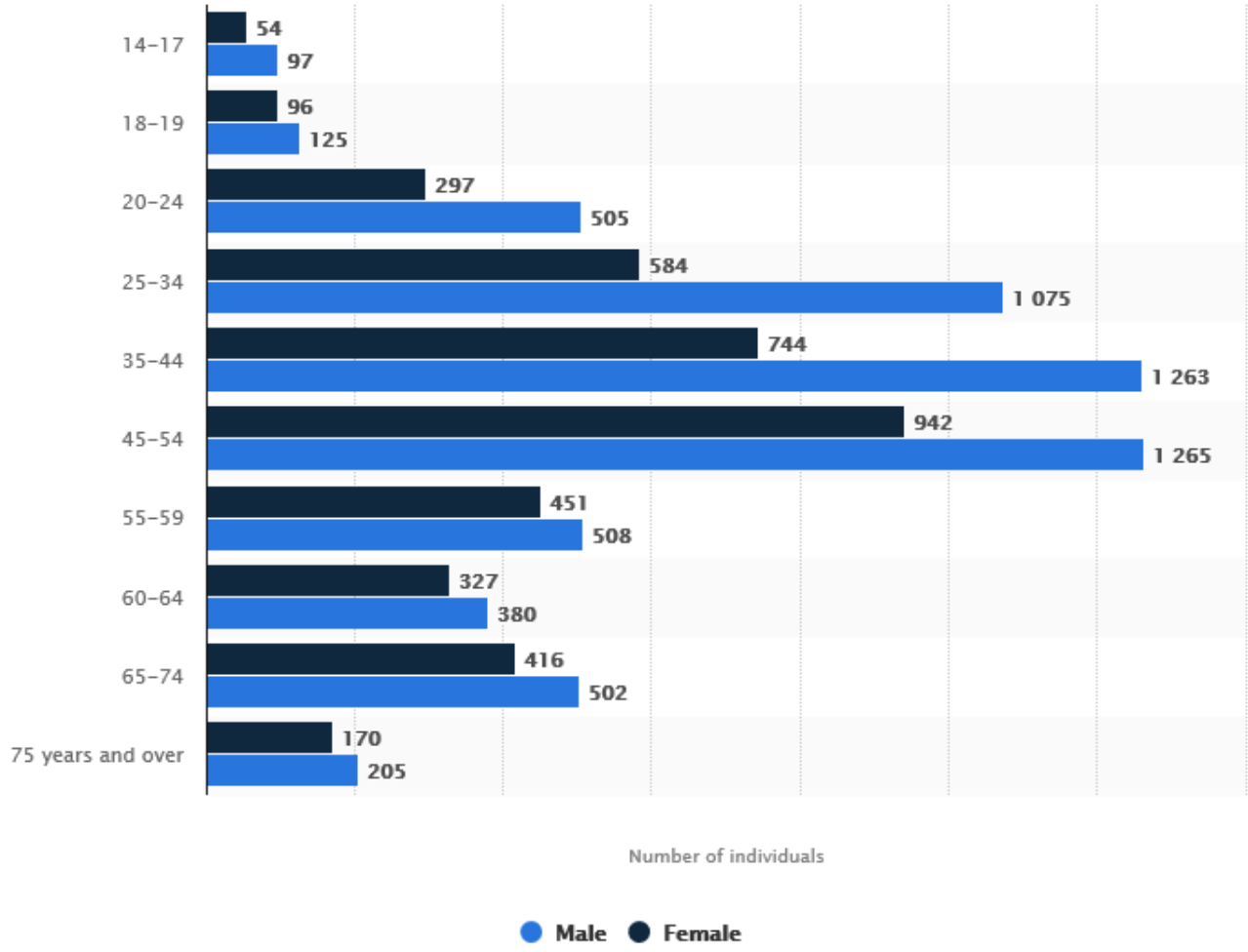
Cigarette consumption

In 2019, 42.8 percent of Italian smokers declared to consume on average ten to 19 cigarettes per day . Between 2015 and 2019, the share of individuals smoking ten to 19 cigarettes per day decreased, while it increased the percentage of smokers stating to consume no more than nine cigarettes daily. During the same period, also the share of heavy smokers – people smoking more than 20 cigarettes per day – decreased.

E-cigarette

According to a survey conducted in 2017 by the European Commission, more than one third of Italian respondents declared that e-cigarettes were harmful to the health of those who used them. E-cigarettes were not very popular among Italians, given that 90 percent of respondents stated that they had never tried or used them.

Number of individuals who smoke in Italy in 2018, by age and gender



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35-44

• Female	744
• Male	1 263

$59 / Month *

Cigarette consumer habits

Cigarette brand products

Hand rolling tobacco products

Cigar products