



Are smoking, environmental pollution, and weather conditions risk factors for COVID-19?

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is probably systemic, has a major respiratory component, and is transmitted by person-to-person contact, via airborne droplets or aerosols. In the respiratory tract, the virus begins to replicate within cells, after which the host starts shedding the virus. The individuals recognized as being at risk for an unfavorable COVID-19 outcome are those > 60 years of age, those with chronic diseases such as diabetes mellitus, those with hypertension, and those with chronic lung diseases, as well as those using chemotherapy, corticosteroids, or biological agents. Some studies have suggested that infection with SARS-CoV-2 is associated with other risk factors, such as smoking, external environmental pollution, and certain climatic conditions. The purpose of this narrative review was to perform a critical assessment of the relationship between COVID-19 and these potential risk factors.

Keywords: Coronavirus infections; COVID-19; Air pollution; Smoking; Tobacco use disorder.

INTRODUCTION

In recent decades, life-threatening viral epidemics have emerged in various regions of the world. Serious outbreaks of Ebola virus disease, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle Eastern respiratory syndrome coronavirus (MERS-CoV), as well as outbreaks of influenza, particularly more severe types of influenza, such as H1N1.⁽¹⁾

Because of the severity and worldwide dissemination of the current outbreak of the new coronavirus (designated SARS-CoV-2) infection, the World Health Organization (WHO) has stated that the coronavirus disease 2019 (COVID-19) has become a pandemic. On April 16, 2020, COVID-19 had reached 210 countries and territories, having caused over 100,000 deaths and infected approximately 2 million people, the overall fatality rate being 3.4%. Previous case-fatality rates for SARS-CoV and MERS-CoV epidemics were 10% and 37%, respectively.⁽¹⁾

COVID-19, Caused by a highly contagious virus,⁽²⁾ is probably systemic, has a major respiratory component, and is transmitted by person-to-person contact, via airborne droplets or aerosols. In the respiratory tract, the virus begins to replicate within cells, after which the host starts shedding the virus.^(3,4)

The role of smoking has been little remembered and even less discussed in this current public health situation. Other factors, such as environmental pollution and climatic conditions, also need to be understood better. The purpose of this narrative review was to perform an assessment of the current knowledge about these risk factors and their importance in the COVID-19 pandemic.

SMOKING

Smoking has been associated with unfavorable outcomes in COVID-19.^(5,6) Smokers, who are more vulnerable to respiratory viruses than are nonsmokers, have a greater risk of severe influenza infection and more severe clinical conditions. Therefore, smokers, when compared with nonsmokers, have a higher risk of hospitalization (OR = 1.5; 95% CI: 1.3-1.7) and ICU admission (OR = 2.2; 95% CI: 1.4-3.4) after having influenza infections.⁽⁷⁾ In addition, during the MERS-CoV outbreak, smokers had higher mortality rates than did nonsmokers.^(8,9) The use of electronic cigarettes and heated tobacco devices have also been related to a higher frequency of respiratory infections, especially viral ones.⁽¹⁰⁻¹⁵⁾

The mechanism of this increased susceptibility appears to be multifactorial, including structural changes, such as increased permeability of the bronchial mucosa, impaired mucociliary clearance, greater pathogen adherence, rupture of the respiratory epithelium, peribronchial inflammation, and fibrosis. There is also a decrease in the production of antibodies and defense immune cells.^(10,16) In addition to those mechanisms, the association between SARS-CoV-2 and smoking can be facilitated by the rituals of smoking, involving repeated hand-to-face movements.⁽¹⁷⁾

Studies on respiratory syncytial virus, which has a similar structure to that of SARS-CoV-2, have shown that inhaling tobacco smoke increases the rate of viral transmission and the severity of infections, confirming the association between tobacco smoke and some viral infections and possibly explaining the severity of COVID-19

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in certain groups of individuals. Tobacco use has been considered a risk factor for MERS-CoV.⁽¹⁸⁾

The need for clarification of that association was reinforced by the fact that the highest proportion of deaths from COVID-19 occurred in males in China.⁽¹⁹⁾ These findings might be related to the fact that the number of smokers, as well as their smoking history, is a lot greater among males than among females in that country (288 million vs. 12.6 million in 2018).⁽²⁰⁾ This fact is likely to be at least a cofactor that increases the chance of males to develop pulmonary, heart, and neoplastic diseases. These data are in line with the findings of the WHO-China Joint Mission on Coronavirus Disease 2019, which has reported higher case-fatality rates in men than in women (4.7% vs. 2.8%).^(21,23)

Other studies have also reported a higher prevalence of COVID-19 in men. Guan et al.,⁽²⁴⁾ evaluating 1,099 critical patients with COVID-19 in 552 hospitals in 30 provinces in China, found a proportion of 58.1% of male patients. In addition, Yang et al.⁽²⁵⁾ found that males accounted for 67% of the patients in their sample. Liu et al.⁽²⁶⁾ identified that tobacco use was more frequent in the group of patients with unfavorable outcomes when compared with nonsmokers (27.3% vs. 3.0%, $p = 0.018$). However, Zhang et al.,⁽²⁷⁾ evaluating 140 patients with COVID-19 in China, found no differences regarding gender. In that same publication, the authors reported only 1.4% of male patients as current smokers, although the proportion of cases with COPD included in the sample was much higher. Guan et al.⁽²⁴⁾ showed a greater number of current smokers (12.6%) and former smokers (1.9%) in their study. Nevertheless, the authors could point out that being a current smoker was significantly related to presenting with more severe symptoms. The small proportion of smokers in those two studies,^(24,27) when compared with the high prevalence of smoking in China (50.5%),⁽²²⁾ might indicate a smaller chance of an association of smoking with the incidence and severity of COVID-19.⁽²⁰⁾

Two meta-analyses reached contradictory results. Lippi et al.⁽²⁸⁾ identified no association between smoking and disease severity. However, Vardavas & Nikitara⁽²⁹⁾ showed that current smoking was associated with a risk of developing more severe symptoms 1.4 (95% CI: 0.98-2.00) times greater and a risk of needing mechanical ventilation 2.4 (95% CI: 1.43-4.04) times greater. Mehra et al.⁽³⁰⁾ studied patients with COVID-19 admitted to 169 hospitals in Europe (64.6% of the sample), Asia (18.2% of the sample), and North America (17.2% of the sample). Of those, 2.5% of the cases had COPD, and the proportions of former and current smokers were 16.8% and 5.5%, respectively. The individuals were classified as survivors ($n = 8,395$, 22.5% being current or former smokers) and nonsurvivors ($n = 515$, 25.0% being current or former smokers). The authors concluded that smoking had an OR of 1.79 (95% CI: 1.29-2.47) for in-hospital mortality.⁽³⁰⁾ Additional analyses involving other series of cases adjusted for other factors are necessary in

order to clarify the association between the severity of COVID-19 and current smoking.

The possibility of this association has been investigated regarding biological aspects. The angiotensin-converting enzyme 2 (ACE2) is likely to be related to the severity of symptoms and unfavorable outcomes of COVID-19. SARS-CoV-2 penetrates human cells by binding to the extracellular domain of the ACE2 receptor.^(31,32) This enzyme acts on the renin-angiotensin system, fragmenting the molecule of angiotensin 2, a potent inflammatory and vasoconstrictor agent, and producing angiotensin-(1-7), which has a significant anti-inflammatory action.^(33,34) Therefore, anti-ACE2 antibodies or the blockade of their receptor prevent the virus from binding, contributing to a greater severity of the disease in the elderly, as well as in those with diabetes or hypertension.⁽³⁵⁾ In those groups of patients, there is a clear decrease in the expression of ACE2, making it difficult to form degradation products, which have anti-inflammatory action, whereas there would be greater amounts of ACE2, which is an inflammatory agent. These two mechanisms could partially explain the greater severity of the clinical course of the disease. Younger patients have a higher expression of angiotensin-(1-7), which has anti-inflammatory action, and tend to present with less severe disease, although much more frequently.^(35,36)

Smith & Sheltzer⁽³⁷⁾ found that samples of lung tissue collected from smokers had 40-50% more ACE2 receptors than did those collected from nonsmokers, even when the analysis was controlled for age, sex, race, and body mass index. Smokers with a history of > 80 pack-years showed a 100% increase in ACE2 receptors when compared with smokers with a history of < 20 pack-years. In that same study,⁽³⁷⁾ the authors found that smoking cessation led to decreased levels of ACE2 in the lungs, i.e., the increase in the expression of ACE2 was shown to be potentially reversible. This type of upregulation of ACE2 was also found in patients with idiopathic pulmonary fibrosis, but not in those with asthma, sarcoidosis, or cystic fibrosis, which reinforces the association of smoking with the upregulation of ACE2, but this association does not occur in other respiratory diseases.⁽³⁸⁾

The greater amount of ACE2 receptors in the lungs of smokers, possibly induced by nicotine itself, would bring more opportunities for the virus to enter the cells. This might at least partially explain why those individuals are more likely to develop severe forms of COVID-19.⁽³⁹⁾ In addition, since smoking cessation is associated with a decreased expression of ACE2, it can be speculated that there would also be a reduction in susceptibility to severe forms of COVID-19.^(40,41)

Literature reviews have shown that smoking conventional cigarettes or using electronic cigarettes or heated tobacco devices is associated with a greater expression (upregulation) of ACE2, and there is also a clear dose-dependent relationship in this effect.^(23,41,42)

The low prevalences of smoking and of COPD in COVID-19 reports are noteworthy, especially when we consider that most studies are from China, where the prevalence of smoking is very high; however, when such frequencies have been assessed in other countries, these prevalences have also been low.^(30,42) Preliminary data from an American case series show that the prevalences of chronic lung disease and of current smoking, respectively, are 9.2% and 1.3%.⁽⁴³⁾

In contrast to the mechanisms described, another hypothesis is beginning to be raised. Tobacco use could attenuate the normal response of the immune system, through which the body would be more tolerant and less reactive to the aggression caused by the virus. Nonsmokers would maintain the ability to respond immediately to this type of insult through the cytokine release syndrome, i.e., immunocompetent individuals would more readily respond to the aggression, explaining their greater severity and high mortality due to COVID-19.⁽⁴⁴⁾

Clinical and epidemiological data mainly from Chinese cohorts, but also from other countries, when analyzed separately or by means of meta-analyses, are controversial regarding the role of smoking as a risk factor and as a risk of greater severity of the disease. However, experimental and clinical studies point to a greater expression of ACE2 in smokers, acting as a possible link between smoking and COVID-19, although such mechanisms are yet to be fully understood. Since this association remains unclear, the WHO strongly advises smokers to quit smoking to minimize the direct and indirect (passive smokers in the household) risks.⁽⁴⁵⁾ The current COVID-19 pandemic is an opportune time to divulge those messages to users of any form of tobacco, who are probably very concerned about their health.

We can infer that the increase in smoking cessation rates might impact on community transmission of SARS-CoV-2. In previous viral epidemics, there was evidence that multifaceted approaches to smoking cessation, by means of behavioral and pharmacological interventions, could play a significant role in both situations, i.e., viral epidemic and smoking.⁽⁴⁶⁾ Overtime, smoking cessation normalizes part of the architecture of the respiratory epithelium, with a decrease in hyperplasia and downregulation of ACE2 levels.⁽⁴⁷⁾

Since much remains to be clarified about this relationship, cohort and experimental studies from other countries are necessary. Nevertheless, considering the innumerable damages caused by smoking to human health, especially to the respiratory tract, smoking cessation during the COVID-19 pandemic might contribute to a better evolution of the disease, a decreased risk of death, and smaller contamination rates.^(48,49)

ENVIRONMENTAL POLLUTION

Air pollution is well recognized as a cause of prolonged systemic inflammation affecting the innate immune

system, especially in the respiratory tract. Despite this knowledge, few studies have identified air pollution as a potential factor for the spread of SARS-CoV-2 and, eventually, as a cofactor that influences lethality related to the current COVID-19 pandemic.⁽⁴⁹⁻⁵²⁾

The Italian Society of Environmental Medicine, in one of the few notes in the literature, showed that air pollution might have played a significant role in the spread of the COVID-19 outbreak in northern Italy, but they reported no evidence that, by worsening the health of individuals, it could also have interfered with SARS-CoV-2-related case fatality.⁽⁵⁰⁾ That region is considered one of the most polluted in Europe according to the European Environment Agency.⁽⁴⁸⁾

Therefore, in addition to the already known routes of transmission by droplets and aerosols, it is possible that the inhalation of particulate matter (PM) has some role in the spread of COVID-19, since infectious diseases might be related to the inhalation of viral agents adsorbed to PM, especially those with a diameter between 2.5 and 10 μm (coarse PM), < 2.5 μm (fine PM), and ≤ 0.1 μm (ultrafine PM).⁽⁴⁹⁻⁵¹⁾ Ultrafine PM might transport coronavirus from tracheobronchial regions to the most peripheral areas of the lungs.⁽⁵²⁾ This mechanism might have greater implications in countries and cities with high rates of environmental pollution, such as China and Milan. Polluting agents with oxidative potential might reduce the immune defense against the virus, exacerbating the COVID-19 infection.⁽⁴⁹⁾

Animal and human studies have confirmed that the inhalation of coarse and fine PM induces systemic inflammation by means of increased expressions of various agents, such as IL-1, IL-4, IL-6, TNF- α , and TGF- β 1, which is directly related to longer periods of exposure. This phase is called the cytokine-storm syndrome.^(51,53) These mechanisms might at least partially explain the relevant number of COVID-19 cases, with greater case fatality rates in regions with high environmental pollution rates. However, the clear plunge in air pollution rates as a result of social distancing might have also influenced the decrease in the severity of the outbreak in various cities and regions.⁽⁵¹⁾

In the near future, SARS-CoV-2 is likely to become a seasonal infectious agent. Therefore, knowledge of its frequency, survival conditions in the more diverse environments, contamination mechanisms, its pathophysiological cascade, and its virulence need to be clarified in detail.⁽⁵⁴⁾

CLIMATIC CONDITIONS

Although the relationship between SARS-CoV and climatic conditions has already been demonstrated, a more severe phase occurring during cold weather,^(55,56) this variable has yet to be fully studied in relation to SARS-CoV-2. However, it is very likely that climatic conditions are related to various parameters of COVID-19.

The increase in the incidence of influenza is known to be associated with low temperatures, low humidity, and greater temperature changes.⁽⁵⁷⁾ Those climatic factors are also related to a higher frequency of deaths from respiratory diseases.⁽⁵⁸⁾ Breathing dry air causes damage to the respiratory mucosa and reduces the effectiveness of mucociliary clearance, making the individual more susceptible to viral infections. However, droplets exhaled in high humidity environments tend to be heavier and float for less time, reducing contamination, and the opposite occurs in low humidity environments. Although these factors have yet to be studied regarding the COVID-19 pandemic, it is very likely that they are also valid for the current coronavirus outbreak.⁽⁵⁹⁾

The few studies available relating COVID-19 and climate conditions have found an increase in the doubling time of COVID-10 cases when there is an increase in daily temperature, but no relationship was found with an increase in temperature regarding mortality rates.^(54,60) Wu et al.⁽⁶¹⁾ reported that a 1°C increase in temperature was associated with a 3.08% (95% CI: 1.53-4.63%) reduction in new daily cases and a 1.19% (95% CI: 0.44-1.95%) reduction in the number of deaths. The same authors stated that a 1% increase in relative air humidity was related to a daily decrease in new cases of 0.85% (95% CI: 0.51-1.19%) and a decrease of new deaths of 0.51% (95% CI: 0.34-0.67%).

Ma et al.⁽⁶²⁾ analyzed 2,299 deaths from COVID-19 between January 20 and February 29, 2020, in Wuhan, China, against meteorological and pollution parameters. The authors found an association between the decrease in death rates from COVID-19 and the increase in humidity. Inhaling dry air causes epithelial damage and reduced mucociliary clearance, making the individual more susceptible to viral respiratory infections. These findings are in accordance with previous publications relating the increase in deaths from respiratory diseases to the decrease in temperature,⁽⁶³⁾ particularly when there is very intense cold and low humidity.⁽⁶⁴⁾

Other factors that might influence the assessments of any outbreak should be considered, such as government

interventions, availability of human resources and materials to treat the population, availability of hospital beds, among others. The outbreak of influenza in Japan, concurrently with COVID-19, has been less intense than in previous years. This might have occurred due to the lesser virulence of the agent, but also due to SARS-CoV-2-related restrictive measures, especially those of social distancing, such as closing schools and prohibiting large events and agglomerations. The search for medical care related to influenza might have also been altered by the severity of the COVID-19 epidemic.⁽⁶⁵⁾

FINAL CONSIDERATIONS

Pandemics pose major challenges for individuals and health care systems. Those that are more prepared or consider such difficult times as windows of opportunity to prepare for future outbreaks will have better results. Different types of measures have a marked influence on the spread of the virus and the resulting diseases.

This article reviews the influence of smoking, environmental pollution, and climatic conditions on the incidence and severity of COVID-19. As for environmental pollution and climate, it is urgent that the global outcry result in objective actions from various government bodies and society so that everyone can do their part. As for smoking, we are facing the opportunity and challenge to stop tobacco use in order to reduce the risk of acquiring or having more severe forms of COVID-19 and of other diseases. Even though the relationship between smoking and COVID-19 needs to be further clarified, there is no doubt that among the major risk factors for presenting with severe forms of the disease are smoking itself and smoking-related diseases.

AUTHOR CONTRIBUTIONS

JMC: review of the literature, preparation of the text, and approval of the final version. IG: critical review of the literature and participation in the preparation of the manuscript.

REFERENCES

- World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2020 May 1]. Coronavirus. Available from: https://www.who.int/health-topics/coronavirustab=tab_1
- Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China [published correction appears in *Nature*. 2020 Apr;580(7803):E7]. *Nature*. 2020;579(7798):265-269. <https://doi.org/10.1038/s41586-020-2008-3>
- Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020;382(12):1177-1179. <https://doi.org/10.1056/NEJMc2001737>
- Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;109:102433. <https://doi.org/10.1016/j.jaut.2020.102433>
- Qi D, Yan X, Tang X, Peng J, Yu Q, Feng L, et al. Epidemiological and clinical features of 2019-nCoV acute respiratory disease cases in Chongqing municipality, China: a retrospective, descriptive, multiple-center study. *medRxiv* 2020.03.01.20029397. <https://doi.org/10.1101/2020.03.01.20029397>
- World Health Organization. Regional Office for the Eastern Mediterranean [homepage on the Internet]. Geneva: World Health Organization [cited 2020 May 1]. Tobacco and waterpipe use increases the risk of COVID-19. Available from: <http://www.emro.who.int/tfi/know-the-truth/tobacco-and-waterpipe-users-are-at-increased-risk-of-covid-19-infection.html>
- Han L, Ran J, Mak YW, Suen LK, Lee PH, Peiris JSM, et al. Smoking and Influenza-associated Morbidity and Mortality: A Systematic Review and Meta-analysis. *Epidemiology*. 2019;30(3):405-417. <https://doi.org/10.1097/EDE.0000000000000984>
- Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med*. 2004;164(20):2206-2216. <https://doi.org/10.1001/archinte.164.20.2206>
- Park JE, Jung S, Kim A, Park JE. MERS transmission and risk factors:

- a systematic review. *BMC Public Health*. 2018;18(1):574. <https://doi.org/10.1186/s12889-018-5484-8>
10. Groskreutz DJ, Monick MM, Babor EC, Nyunoya T, Varga SM, Look DC, et al. Cigarette smoke alters respiratory syncytial virus-induced apoptosis and replication. *Am J Respir Cell Mol Biol*. 2009;41(2):189-198. <https://doi.org/10.1165/rncmb.2008-0131OC>
 11. Moazed F, Chun L, Matthey MA, Calfee CS, Gotts J. Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. *Tob Control*. 2018;27(Suppl 1):s20-s25. <https://doi.org/10.1136/tobaccocontrol-2018-054296>
 12. Maedel C, Kainz K, Frischer T, Reinweber M, Zacharasiewicz A. Increased severity of respiratory syncytial virus airway infection due to passive smoke exposure. *Pediatr Pulmonol*. 2018;53(9):1299-1306. <https://doi.org/10.1002/ppul.24137>
 13. Sohal SS, Eapen MS, Naidu VGM, Sharma P. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. *ERJ Open Res*. 2019;5(1):00159-2018. <https://doi.org/10.1183/23120541.00159-2018>
 14. Miyashita L, Suri R, Dearing E, Mudway I, Dove RE, Neill DR, et al. E-cigarette vapour enhances pneumococcal adherence to airway epithelial cells. *Eur Respir J*. 2018;51(2):1701592. <https://doi.org/10.1183/13993003.01592-2017>
 15. McAlinden KD, Sohal SS, Sharma P. There can be smoke without fire: warranted caution in promoting electronic cigarettes and heat not burn devices as a safer alternative to cigarette smoking. *ERJ Open Res*. 2019;5(3):00114-2019. <https://doi.org/10.1183/23120541.00114-2019>
 16. Sopori ML, Kozak W. Immunomodulatory effects of cigarette smoke. *J Neuroimmunol*. 1998;83(1-2):148-156. [https://doi.org/10.1016/S0165-5728\(97\)00231-2](https://doi.org/10.1016/S0165-5728(97)00231-2)
 17. Berlin I, Thomas D, Le Faou AL, Cornuz J. COVID-19 and smoking [published online ahead of print, 2020 Apr 3]. *Nicotine Tob Res*. 2020;ntaa059. <https://doi.org/10.1093/ntr/ntaa059>
 18. Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk Factors for Primary Middle East Respiratory Syndrome Coronavirus Illness in Humans, Saudi Arabia, 2014. *Emerg Infect Dis*. 2016;22(11):49-55. <https://doi.org/10.3201/eid2201.151340>
 19. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7)
 20. Cai H. Sex difference and smoking predisposition in patients with COVID-19 [published correction appears in *Lancet Respir Med*. 2020 Apr;8(4):e26]. *Lancet Respir Med*. 2020;8(4):e20. [https://doi.org/10.1016/S2213-2600\(20\)30117-X](https://doi.org/10.1016/S2213-2600(20)30117-X)
 21. Wang M, Luo X, Xu S, Liu W, Ding F, Zhang X, et al. Trends in smoking prevalence and implication for chronic diseases in China: serial national cross-sectional surveys from 2003 to 2013. *Lancet Respir Med*. 2019;7(1):35-45. [https://doi.org/10.1016/S2213-2600\(18\)30432-6](https://doi.org/10.1016/S2213-2600(18)30432-6)
 22. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [updated 2020 Feb 28 cited 2020 May 1]. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Available from: [https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-\(covid-19\)](https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19))
 23. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7]. *JAMA*. 2020;323(11):1061-1069. <https://doi.org/10.1001/jama.2020.1585>
 24. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. <https://doi.org/10.1056/NEJMoa2002032>
 25. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study [published correction appears in *Lancet Respir Med*. 2020 Apr;8(4):e26]. *Lancet Respir Med*. 2020;8(5):475-481. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5)
 26. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)*. 2020;133(9):1032-1038. <https://doi.org/10.1097/CM9.0000000000000775>
 27. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print, 2020 Feb 19]. *Allergy*. 2020;10.1111/all.14238. <https://doi.org/10.1111/all.14238>
 28. Lippi G, Sanchis-Gomar F, Henry BM. Active smoking and COVID-19: a double-edged sword [published online ahead of print, 2020 May 1]. *Eur J Intern Med*. 2020;S0953-6205(20)30182-5. <https://doi.org/10.1016/j.ejim.2020.04.060>
 29. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis*. 2020;18:20. <https://doi.org/10.18332/tid/119324>
 30. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19 [published online ahead of print, 2020 May 1]. *N Engl J Med*. 2020;NEJMoa2007621. <https://doi.org/10.1056/NEJMoa2007621>
 31. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
 32. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol*. 2020;94(7):e00127-20. <https://doi.org/10.1128/JVI.00127-20>
 33. Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang Q, et al. Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. *Nat Rev Cardiol*. 2014;11(7):413-426. <https://doi.org/10.1038/nrcardio.2014.59>
 34. AlGhatrif M, Cingolani O, Lakatta EG. The Dilemma of Coronavirus Disease 2019, Aging, and Cardiovascular Disease: Insights From Cardiovascular Aging Science [published online ahead of print, 2020 Apr 3]. *JAMA Cardiol*. 2020;10.1001/jamacardio.2020.1329. <https://doi.org/10.1001/jamacardio.2020.1329>
 35. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-879. <https://doi.org/10.1038/nm1267>
 36. Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL, Simoes-E-Silva AC. The Anti-Inflammatory Potential of ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Evidence from Basic and Clinical Research. *Curr Drug Targets*. 2017;18(11):1301-1313. <https://doi.org/10.2174/1389450117666160727142401>
 37. Smith JC, Sheltzer JM. Cigarette smoke triggers the expansion of a subpopulation of respiratory epithelial cells that express the SARS-CoV-2 receptor ACE2. *bioRxiv* 2020.03.28.013672. <https://doi.org/10.1101/2020.03.28.013672>
 38. Olds JL, Kabbani N. Is nicotine exposure linked to cardiopulmonary vulnerability to COVID-19 in the general population? [published online ahead of print, 2020 Mar 18]. *FEBS J*. 2020;10.1111/febs.15303. <https://doi.org/10.1111/febs.15303>
 39. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). *J Clin Med*. 2020;9(3):841. <https://doi.org/10.3390/jcm9030841>
 40. Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCoV. *medRxiv* 2020.02.05.20020107. <https://doi.org/10.20944/preprints202002.0051.v2>
 41. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol*. 2018;315(5):R895-R906. <https://doi.org/10.1152/ajpregu.00099.2018>
 42. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med*. 2020;8(1):e35.
 43. CDC COVID-19 Response Team. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(13):382-386. <https://doi.org/10.15585/mmwr.mm6913e2>
 44. Garufi G, Carbognin L, Orlandi A, Tortora G, Bria E. Smoking habit and hospitalization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related pneumonia: The unsolved paradox behind the evidence [published online ahead of print, 2020 Apr 23]. *Eur J Intern Med*. 2020;S0953-6205(20)30163-1. <https://doi.org/10.1016/j.ejim.2020.04.060>

- ejim.2020.04.042
45. Cochrane Library [homepage on the Internet]. Special Collections; [updated 2020 May 11; cited 2020 May 11]. Coronavirus (Covid-19): effective options for quitting smoking during the pandemic 2020 Available from: <https://www.cochranelibrary.com/collections/doi/SC000042/full>
 46. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. *Nature*. 2006;442(7101):448-452. <https://doi.org/10.1038/nature04795>
 47. Setti L, Passarini F, Genaro G, Gilio A, Palmisani J, Buono P, et al. Evaluation of the potential relationship between Particulate Matter (PM) pollution and COVID-19 infection spread in Italy [monograph on the Internet]. Milan: Società Italiana di Medicina Ambientale; 2020 [cited 2020 May 1]. Available from: http://www.simaonlus.it/wpsima/wp-content/uploads/2020/03/COVID_19_position-paper_ENG.pdf
 48. European Environment Agency [homepage on the Internet]. European Air Quality Index. Available from: <https://airindex.eea.europa.eu/>
 49. Qu G, Li X, Hu L, Jiang G. An Imperative Need for Research on the Role of Environmental Factors in Transmission of Novel Coronavirus (COVID-19). *Environ Sci Technol*. 2020;54(7):3730-3732. <https://doi.org/10.1021/acs.est.0c01102>
 50. Conticini E, Frediani B, Caro D. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?. *Environ Pollut*. 2020;261:114465. <https://doi.org/10.1016/j.envpol.2020.114465>
 51. Tsai DH, Riediker M, Berchet A, Paccaud F, Waeber G, Vollenweider P, et al. Effects of short- and long-term exposures to particulate matter on inflammatory marker levels in the general population. *Environ Sci Pollut Res Int*. 2019;26(19):19697-19704. <https://doi.org/10.1007/s11356-019-05194-y>
 52. Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. *Sci Total Environ*. 2020;727:138704. <https://doi.org/10.1016/j.scitotenv.2020.138704>
 53. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China [published correction appears in *Intensive Care Med*. 2020 Apr 6;:]. *Intensive Care Med*. 2020;46(5):846-848. <https://doi.org/10.1007/s00134-020-05991-x>
 54. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern [published correction appears in *Lancet*. 2020 Jan 29]. *Lancet*. 2020;395(10223):470-473. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)
 55. Wallis P, Nerlich B. Disease metaphors in new epidemics: the UK media framing of the 2003 SARS epidemic. *Soc Sci Med*. 2005;60(11):2629-2639. <https://doi.org/10.1016/j.socscimed.2004.11.031>
 56. Tan J, Mu L, Huang J, Yu S, Chen B, Yin J. An initial investigation of the association between the SARS outbreak and weather: with the view of the environmental temperature and its variation. *J Epidemiol Community Health*. 2005;59(3):186-192. <https://doi.org/10.1136/jech.2004.020180>
 57. Park JE, Son WS, Ryu Y, Choi SB, Kwon O, Ahn I. Effects of temperature, humidity, and diurnal temperature range on influenza incidence in a temperate region. *Influenza Other Respir Viruses*. 2020;14(1):11-18. <https://doi.org/10.1111/irv.12682>
 58. Pinheiro Sde L, Saldiva PH, Schwartz J, Zanobetti A. Isolated and synergistic effects of PM10 and average temperature on cardiovascular and respiratory mortality. *Rev Saude Publica*. 2014;48(6):881-888. <https://doi.org/10.1590/S0034-8910.2014048005218>
 59. Steel J, Staeheli P, Mubareka S, Garcia-Sastre A, Palese P, Lowen AC. Transmission of pandemic H1N1 influenza virus and impact of prior exposure to seasonal strains or interferon treatment. *J Virol*. 2010;84(1):21-26. <https://doi.org/10.1128/JVI.01732-09>
 60. Wang M, Jiang A, Gong L, Luo L, Guo W, Li C, et al. Temperature significant change COVID-19 transmission in 429 cities. *medRxiv* 2020.02.22.20025791. <https://doi.org/10.1101/2020.02.22.20025791>
 61. Wu Y, Jing W, Liu J, Ma Q, Yuan J, Wang Y, et al. Effects of temperature and humidity on the daily new cases and new deaths of COVID-19 in 166 countries. *Sci Total Environ*. 2020;729:139051. <https://doi.org/10.1016/j.scitotenv.2020.139051>
 62. Ma Y, Zhao Y, Liu J, He X, Wang B, Fu S, et al. Effects of temperature variation and humidity on the death of COVID-19 in Wuhan, China. *Sci Total Environ*. 2020;724:138226. <https://doi.org/10.1016/j.scitotenv.2020.138226>
 63. Fallah Ghalhari G, Mayvaneh F. Effect of Air Temperature and Universal Thermal Climate Index on Respiratory Diseases Mortality in Mashhad, Iran. *Arch Iran Med*. 2016;19(9):618-624.
 64. Dadbakhsh M, Khanjani N, Bahrampour A, Haghighi PS. Death from respiratory diseases and temperature in Shiraz, Iran (2006-2011). *Int J Biometeorol*. 2017;61(2):239-246. <https://doi.org/10.1007/s00484-016-1206-z>
 65. Sakamoto H, Ishikane M, Ueda P. Seasonal Influenza Activity During the SARS-CoV-2 Outbreak in Japan [published online ahead of print, 2020 Apr 10]. *JAMA*. 2020;323(19):1969-1971. <https://doi.org/10.1001/jama.2020.6173>