Is there an association between the level of ambient air pollution and COVID-19?

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Wang B, Chen H, Chan YL, Oliver BG. Is there an association between the level of ambient air pollution and COVID-19? Am J Physiol Lung Cell Mol Physiol 319: L416–L421, 2020. First published July 22, 2020; doi:10.1152/ajplung.00244.2020.—Epidemiological studies suggest that environmental factors (e.g., air pollution) can influence the spread and infectivity of coronavirus disease 2019 (COVID-19); however, very few papers have investigated or discussed the mechanism behind the phenomenon. Given the fact that pollution will increase as social distancing rules are relaxed, we summarized the current understanding of how air pollution may affect COVID-19 transmission and discussed several possible mechanisms. Air pollution exposure can dysregulate the human immune response and make people more susceptible to infections, and affect infectivity. For example, in response to exposure to air pollution, angiotensin-converting enzyme 2 will increase, which is the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This may increase the efficiency of viral infection. It is also possible that air pollution can facilitate SARS-CoV-2 spread by increasing the transmission, and potentially, SARS-CoV-2 can also survive longer when attached to a pollutant.

ACE2; infection; SARS-CoV-2; transmission

INTRODUCTION

In December 2019, the first confirmed case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, Hubei Province of China (15). Then, it caused a rapid outbreak in the rest of China despite the tough regional lockdown at the end of January 2020. Now, 6 months after the first reported case in China, COVID-19 has emerged in more than 180 countries in six continents (9), with more than 11.5 million people infected and more than 500,000 deaths.

In addition to close personal contact, environmental factors may also play a critical role in accelerating the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which is responsible for COVID-19. Patients with COVID-19 showed a similar cluster of symptoms to severe acute respiratory syndrome (SARS) caused by SARS-CoV, which initiated in the Guangzhou province of China in 2003. Both viruses are coronaviruses, which are thought to originate in bats. As SARS-CoV-2 is novel, it is understandable that people would refer to SARS-CoV as a reference point for transmission, pathogenesis, and treatments.

EPIDEMIOLOGY

An epidemiological study suggested a positive correlation between the amount of particulate matter (PM) (measured by the air pollution index, API) and the fatality rate of SARS in 2003 (14). The death rate was increased by 100% and 84% in those patients in high and moderate API regions, respectively, compared with those in regions with low API. This finding is echoed by another study that demonstrated that each increment of 10 μg/m3 PM10 over a 5-day period results in a 1.06 (1.00–1.12) increased risk of daily mortality (26).

If air pollution plays an important role during the new coronavirus, i.e., SARS-CoV-2, infection, there should be a positive relationship between the number of COVID-19 cases and measures of pollution, for example, the PM concentration. Globally, the highest population-weighted mean PM2.5 (50–60 μg/m3) is in eastern and southern Asia (52). Hubei is one of the most polluted provinces in the winter in China and the epicenter of COVID-19 (34). According to the European Environment Agency (EEA) reports, the Lombardia and Emilia Romagna are the most polluted areas in Italy and one of the more polluted regions in Europe (10). In fact, Lombardy became the COVID-19 epicenter in Italy, with the highest confirmed cases and death rate, with more than 78,000 confirmed cases and 14,000 deaths when the manuscript was prepared.

The relationship between PM level and the COVID-19 fatality rate was investigated in a recent epidemiological study of a Wuhan cohort. It found a positive correlation between PM10 and PM2.5 concentrations and the COVID-19 fatality rate (56). A further nationwide study in China, including 49 cities outside and 15 cities inside Hubei province, demonstrated that short-term PM10 and PM2.5 exposure have a strong association...
with COVID-19 death rates (57). The European Public Health Alliance recently reported that people living in polluted cities face greater COVID-19 threat (17), which was confirmed by later research in Italy. Studies from Italy demonstrated high PM10 concentration in northern Italy promoted the spreading of SARS-CoV-2, and another study confirmed the significant correlation between PM10 distribution in 110 Italian provinces and SARS-CoV-2 infection rates (47). Data in those studies showed that there were only three positive cases every 100,000 residents in the less polluted provinces, while in highly polluted provinces, there were around nine times higher positive cases of COVID-19 (23a, 48). A nationwide study from the United States showed that every 1 μg/cm³ increment in PM2.5 exposure in the long term results in 8% increase in COVID-19 death rate (53). A similar observation in the Netherlands was made, which concluded that PM2.5 exposure has a close association with COVID-19 confirmed cases, where a 20% increase in the pollution doubled the COVID-19 case number (3).

POSSIBLE MECHANISMS

There are many plausible reasons why there might be a relationship between air pollution and COVID-19. It is important here to recognize that short-term effects of air pollution are generally proinflammatory, while chronic exposure can cause immune dysregulation and other diseases. Here, we will discuss several possible mechanisms.

Air Pollutants Impair the Immune Function, Making People More Susceptible to the Infection

It is well accepted that air pollution is detrimental to health, not only damaging the lung, which is exposed to the air directly, but also inducing pathological changes in other organ systems through excessive mitochondrial-produced oxidative stress. Interestingly, the enzyme that produces reactive oxygen species, NOX2, has been shown to be critical for PM-induced NADPH-oxidase activation and systemic vascular dysfunction (25, 33). In the context of respiratory viral infection, NOX2 oxidase activation suppresses antiviral and humoral signaling networks (51); therefore, PM may increase NOX2 activity through producing a suppressed antiviral response prior to SARS-CoV-2 infection. The respiratory mucosa is the first line of defense against all of the inhaled pollutants and toxicants with the help of alveolar epithelial cells, alveolar macrophages (AM), dendritic cells (DC), and adaptive T and B lymphocytes. Air pollution could affect the function of this mucosal barrier, as depicted in Fig. 1. These changes caused by air pollution could dysregulate the antiviral immune response (19). Both SARS-CoV-2 and PM activate cells via mechanisms, including Toll-like receptors (TLRs) and their downstream signaling cascades (5); however, PM signals via TLRs 2 and 4, which are important in bacterial infections, and SARS-CoV-2 is recognized by the “viral” TLRs 3, 7, and 8. Studies have shown that alveolar macrophages from people living in highly polluted cities have a reduced innate immune capacity, which is proportional to the amount of phagocytosed PM (20). Experimental studies in mice have found that PM exposure reduces activity at the interferon (INF)-β gene promoter, and subsequent INF-β transcription, and enchanted influenza replication (37). As innate immunity, in general, and in particular INF-β, a key antiviral cytokine, is reduced by PM, it is likely that these mechanisms would enhance SARS-CoV-2 pathogenicity. Epidemiological studies demonstrated that even short-term PM2.5 exposure could increase the risk of infectious diseases, such as influenza, pneumonia, and other lower respiratory infections (12, 23). Experiments using mouse models also demonstrated that PM exposure could create an inflammatory environment and promote respiratory syncytial virus infection (28, 29). In fact, PM exposure has been shown to induce or exacerbate respiratory diseases, such as chronic obstructive pulmonary disease (COPD) through dysregulated immune response (16, 30). A recent systematic review of 2,002 COVID-19 cases concluded that COPD patients experienced a four-fold higher

![Fig. 1. Exposure to air pollution may increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection through dysregulating immune response. DCs, dendritic cells; Mac, macrophages; Th, T helper cell.](image-url)
infection risk and worse progress and outcome of COVID-19 (61). This suggested an impaired immune response against SARS-CoV-2 infection and dysregulated inflammatory responses after the infection.

These mechanisms of immune dysregulation are synonymous with chronic diseases, which may also occur as a result of exposure to air pollution. These include, but are not limited to COPD, cardiovascular disease, diabetes, and cancers. As exemplified above, these diseases can independently confer an increased risk of adverse outcomes following SARS-CoV-2 infection.

**PM Exposure Could Deteriorate COVID-19 Symptoms Through Damaging Surfactant Homeostasis**

Surfactant is synthesized, stored, and secreted by type II pneumocytes. The primary function of surfactant is to reduce surface tension at the air-liquid interface of the lung and prevent alveoli from collapsing at the end of expiration. In adults, abnormal surfactant production can occur after critical insults such as trauma or sepsis, and this lack of surfactant will result in acute respiratory distress syndrome (ARDS) (24). Patients with severe COVID-19 also have ARDS, which histologically manifests as diffuse alveolar damage, including type II pneumocyte hyperplasia and dysfunctional alveolar barrier (18, 60). This suggests that the pulmonary surfactant system may be compromised by SARS-CoV-2 infection. As surfactant covers the entire air-liquid interface of the lung, it is vulnerable to attack from inhaled toxicants (38). In particular, experimental studies have shown that physical interaction between small PM and surfactant occur that can change the biomechanical function of surfactant (27), and in mice, PM can cause alveolar collapse (44). Therefore, it is possible that people exposed to PM have dysfunctional surfactant. When combined with infection of alveolar epithelial cells with SARS-CoV-2, the combined insult to the lungs may accelerate the development of ARDS (23a).

**PM Could Increase Angiotensin-Converting Enzyme 2 Expression Level and Facilitate COVID-19 Infection**

The entry of COVID-19 into the cell depends on the spike protein (S), which can bind to angiotensin-converting enzyme 2 (ACE2) receptor on the cellular membranes (22). However, whether this means the ACE2 expression level can determine the viral load of SARS-CoV-2 infection has yet to be investigated. There is abundant ACE2 in a transient secretory cell type in subsegmental bronchial branches (49). In a murine model of PM exposure, ACE2 expression is increased in the lung tissue at 2 and 5 days after installation of PM (31). This indicates PM may facilitate SARS-CoV-2 infection through upregulating ACE2 expression (Fig. 2).

Fig. 2. Air pollution could increase angiotensin-converting enzyme 2 (ACE2) level in patients with respiratory diseases.

**PM Exposure Could Contribute to the Cytokine Storm Induced by COVID-19**

When SARS-CoV-2 infection progresses from pneumonitis to ARDS, patients showed a sustained high level of inflammation with overexpression of proinflammatory cytokines (i.e., TNF-α, IL-6), followed by multiple organ failure, eventually leading to death (36). This highly sustained inflammation is commonly referred to as a “cytokine storm”. Macrophages play an important role in the cytokine storm. During the infection, alveolar macrophages are quickly mobilized by signals released by the SARS-CoV-2-infected cells to defend COVID-19 invasion through the phagocytosis and secreting proinflammatory cytokines to attract more immune cells (including monocytes, macrophages, and T cells) to the infected sites. However, this results in a positive feedback loop leading to hyperinflammation and vascular hyperpermeability (50). In turn, this leads to pulmonary and interstitial tissue damage, excessive fluid in the lungs reducing gas exchange, and unfortunately death (58).

PMs have been regarded as toxic pollutants inducing prolonged inflammation and hyperactivation of the innate immune system, even at a low dose. In our murine model of low-dose PM exposure (5 µg/day per mouse), subchronic exposure for 3 weeks significantly increased macrophage number in the bronchoalveolar fluid and IL-1β level in the lung tissue (7). A similar phenomenon was found in another murine model of PM exposure for 3 months, where TNF-α level and macro-
phage number were significantly increased (55). A clinical study also confirmed the findings with overexpression of TNF-α and IL-6 in the healthy subjects after PM10 and PM2.5 exposure (42). Those cytokines induced by short-term and long-term PM exposure are the same types in the cytokine storm in patients with COVID-19. This suggests that PM exposure may boost the development of a cytokine storm in a SARS-CoV-2 infection.

**PM Could Increase the Transmission Distance of SARS-CoV-2**

PM fractions (PM10 and PM2.5) can float in the air for a long time and disperse over long distances (35). During their formation, black carbon can absorb various chemical and biological components on the surface. Thus, PMs can act as a carrier to transport viruses over longer distances than that would otherwise occur (48). The SARS-CoV-2 diameter is around 100 nm. Similar to other respiratory viruses, SARS-CoV-2 can travel through the air in droplets known as Flügge droplets (Fig. 3). The large droplets (>5 μm) from a cough or sneeze can only travel <1–1.5 meters because of the resistance of the air and their mass, and then deposit on surfaces. However, smaller virus-laden particles (<5 μm) could remain in the air for hours and spread over longer distances (11). A previous study demonstrated a positive correlation between virus deposition rate and organic aerosols smaller than 0.7 μm, making viruses stay longer in the air (43). According to the data collected in hospitals from Wuhan, aerosolized SARS-CoV-2 had an aerodynamic diameter size ranging from >2.5 μm to 0.25–1 μm (32).

A number of studies have confirmed that viruses could spread faster through airborne transmission routes beyond close contact with infected people, for example, for viruses such as measles (8, 32, 40, 46). A retrospective cohort study published in 2014 of patients with SARS during the 2003 outbreak in Hong Kong also suggested that the airborne transmission route played an important role in spreading the virus (59).

In a study collecting three types of aerosol samples (total suspended particles, aerodynamic size-segregated particles, and deposited samples) from two hospitals in Wuhan, SARS-CoV-2 was found in the patient’s toilets (19 copies/m3) and Protective Apparel Removal Rooms (PARRs) (18–42 copies/m3). The patients’ breath and excrement may contribute to the high COVID-19 concentration in the toilet. The high COVID-19 concentration in PARRs may be due to the resuspension of the virus-laden aerosol from the personal protective equipment and floor dust aerosol containing virus (32).

Researchers have found that aerosolized PM could facilitate COVID-19 transmission. A study in Italy also showed SARS-CoV-2 RNA in environmental PM samples (3). The high concentration of dust and airflow conditions in northern Italy could promote SARS-CoV-2 viral transmission by forming viral clusters with PMs (48, 49).

Worryingly, studies also found that PM can not only extend transmission distance, but also increase the infectivity in the aerosol. Respiratory syncytial virus was found to be stable for up to 6 months in a solution mixed with PM, and had increased infectivity in vitro (13). Researchers from Italy speculated that PM could induce a “boost effect” on the SARS-CoV-2 viral infectivity after analyzing the PM concentration and death rate in Milan and Rome (48).

**PM Exposure May Weaken COVID-19 Treatment Efficiency**

PM is an oxidative and proinflammatory stimulus in the lungs. In general, most therapeutics would have altered (typically reduced) efficacy when oxidative or inflammatory conditions coexist. In the case of SARS-CoV-2 infection, it is possible that as we have found with rhinovirus infection (6), pollution enhances virus-induced inflammation, which could reduce the efficacy of therapeutics. One plausible mechanism by which this may occur is sequestration and elimination of inhaled therapeutics in mucous (produced as part of the inflammatory response). Interestingly, PM increases lung neutrophil numbers, and therefore affects neutrophil-to-lymphocyte ratios. This may also influence clinical decisions around when to initiate remdesivir treatment (21, 39). Other potential interactions may also occur, for example, systemic clotting is found in patients with late-stage SARS-CoV-2 infection, leading to multiple organ failure. As such, anticoagulation treatment has been used in patients with COVID-19 to increase their survival rate (4). However, PM exposure has been shown to induce venous thrombosis through platelet overactivation (45), which may compromise the efficiency of anticoagulation treatment.

**CONCLUSIONS**

Air pollution is a modifiable environmental factor that will affect the pathogenesis of SARS-CoV-2. PM exposure could weaken and dysregulate immune response, resulting in a failure to defend against virus invasion. PM exposure could cause ACE2 overexpression to increase viral load during invasion (54). Airborne PM can also increase transmission distance of SARS-CoV-2. If the cited studies are correct, this pollution may facilitate a second wave of infection by transmitting the virus from one country to another.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

B.W. and Y.L.C. prepared figures; B.W., H.C., and B.G.O. drafted manuscript; xxx edited and revised manuscript; H.C. and B.G.O. approved final version of manuscript.

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