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Review Article

# Exposure To Ambient Nanoparticles And COVID-19 Infection

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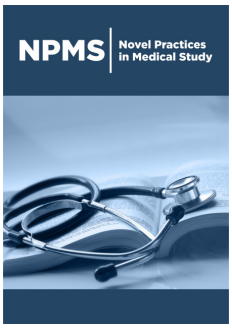
**Abstract**

Epidemiological studies have shown that respiratory viral infections have been associated with air pollutants exposure. So that, the increased incidence of SARS-CoV-2 infection and mortality from COVID-19 is related to exposure to urban air pollution. In addition, changes in meteorological parameters have been involved in air pollution and the incidence and development of COVID-19. Although, the molecular mechanisms by which exposure to air pollutants affects COVID-19 are still unknown and it is not yet clear how the virus is transmitted from one sick person to another and why it is so transmissible. Viruses can be probably transmitted through speech and exhalation aerosols. Findings show that SARS-CoV-2 aerosol transmission is possible. Spike (S) proteins of SARS CoV-2 determine tissue tropism using an angiotensin-converting enzyme receptor type2 (ACE-2) to bind to the cells. This mini-review briefly describes the COVID-19 biology and the viral transmission route and explains the relationship between air pollution exposure and COVID-19, and helps us anticipate the potential role of urban air pollution in the spread of COVID-19.

**Keywords:** COVID-19; Air pollution exposure; Nanoparticles; Airborne Particulate matter

**Abbreviations:** Ang I: Angiotensin I; Ang II: Angiotensin II; Ang II (1-7): Angiotensin-(1-7); ARDS: Acute Respiratory Distress Syndrome; ACE: Angiotensin-Converting Enzyme; ACE2: Angiotensin-Converting Enzyme 2; AT1R: Angiotensin II type 1 receptor; ANE: Acute Necrotizing Encephalopathy; BBB: Blood–Brain Barrier; OB: Olfactory Bulb; HI: Hippocampus; CO: Carbon Monoxide; CNS: Central Nervous System; COVID-19: Coronavirus Disease 2019; ERK: Extracellular signal-Regulated Kinase; IL: Interleukin; $NO_2$: Nitrogen Dioxide; $O_3$: Ozone; PM: Particulate Matter; PM0.1: Particulate Matter<0.1μm (ultrafine particles); PM2.5: Particulate Matter<2.5μm (fine particles); PM10: Particulate Matter with a diameter between 2.5μm and 10μm (coarse particles); RBD: Receptor Binding Domain; ROS: Reactive Oxygen Species; RAS: Renin Angiotensin System; $SO_2$: Sulfur Dioxide; STAT3: Signal Transducer and Activator of Transcription 3; SARS: Severe Acute Respiratory Syndrome; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TNFα: Tumor Necrosis Factor alpha; INFγ: Interferon-gamma; UFPs: Ultra-Fine Particles; US: United States; HCOV: Human Coronavirus

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## Introduction

The mechanisms by which air pollutants exposure, such as ultrafine particulate matters (UFPs; <100nm), can affect respiratory health and includes pulmonary inflammation, which can lung function reduction through contracting bronchi or altering the immune system pulmonary [1,2]. In general, ambient particles include elemental and organic carbon, inorganic components (trace metals, nitrates, sulfates, chloride, and ammonium), biological components (pollens, bacteria, and spores), volatile and semi-disintegrating organic compounds [3]. Furthermore, when the ambient particles are mixed with atmospheric gases (carbon monoxide, sulfur, ozone, and nitric oxides), they can form airborne particles. Environmental particles are commonly characterized by aerodynamic properties and their size and defined as PM2.5 and PM10 with diameters of less than 2.5 and 10μm: PM with an aerodynamic diameter of 2.5 to 10μm (PM10), PM smaller than 2.5μm (PM2.5) and very small PM less than 0.1μm or UFPs. This particles are acceptable fractions from different sources such as agricultural dust, wood combustion, road, vehicles emission, tire wear propagation, construction, mining operations, and demolition work [4,5].

In parallel, exposure to UFPs could significantly exacerbate inflammation by cellular proliferation and reorganization of the extracellular matrix [6], as well as weakening the pulmonary immune response [7]. This mechanism has been described by several toxicological studies [7,8] and a lot of epidemiological evidences corroborate the role of exposure to

chronic and acute air pollutants in the admission of respiratory hospitals, such as exacerbation of asthma [9] or chronic obstructive pulmonary disease [10].

Furthermore, several studies reported that air pollution exposure exacerbates the intensity of various respiratory diseases [11], for example influenza infection [12] and severe acute respiratory syndrome (SARS) or another coronavirus [13]. One study in US indicates that exposure to PM2.5 and ozone was dangerous and increased the risk of SARS among older adults [14]. Based on this presupposition, it is possible that the air pollution exposure will alter the intensity of the COVID-19 symptoms or help explain the differential-spatial patterns of disease prevalence. Recent surveys have reported that people with severe COVID-19 may already have respiratory disease [15-22]. Recent studies on viral respiratory disease (such as influenza) have shown that an infectious virus can be emitted from infected peoples by speaking even breathing, without sneezing or coughing [23,24]. Normal and ordinary speech converts significant amounts of respiratory particles into airborne aerosols. Experimental research has shown that vocalization emits up more aerosols than breathing [25], also, a recent study indicated the louder one speech, the more aerosols are produced [26]. COVID-19 is a severe respiratory infection, and recent studies clearly identified the SARS-CoV-2 presence in a tract of the respiratory system [27]. Therefore, particles derived from breath and speech may contain viruses. These particles may be due in part to the mechanism of "liquid film bursting" in alveoli in the pulmonary, and or through the vibration of the vocal cords during a speech [28]. The findings suggest that particles and aerosols in the air reach the brain and affect CNS health, with changes in the blood-brain barrier (BBB) or leakage and transmission along the olfactory nerve to the olfactory bulb (OB) and active Microglia are the main components [29-32].

## The Relationship Between Air Pollution Exposure and COVID-19

Based on the previous studies, air pollutants exposure is closely related with the respiratory infection due to other microorganisms [8,11]. Also, it was showed that the exposure to a high concentration of PM2.5 was associated with more acute lower respiratory infections [33]. A significant association between exposure to urban air PM and hospitalizations due to respiratory disease was reported using a model of distributed lag nonlinear [34]. In Thailand, time series analysis performed found that PM10, $SO_2$, CO, $O_3$ and $NO_2$ were significantly related to an increased risk of admission to respiratory hospitals [35]. Another review found that the exposure to $NO_2$, $SO_2$, and CO could increase the risk of respiratory diseases and was harmful to health [36]. Another study showed that there was a statistically significant link between exposure to a high level of air pollutants such as PM10, PM2.5, $NO_2$, $O_3$, CO, and COVID-19 infection [22,37].

The COVID-19 is cause by SARS-CoV-2 [37-39], and it was first observed in December 2019 [40,41]. In the following months, it rapidly spreads to all of China and gradually became a pandemic public health problem in the whole world [39,42,43]. Various studies have demonstrated that the risk of COVID-19 infection could increase following human-to-human contacts [42,44,45]. Thus, the mobility of the population has a remarkable effect on the COVID-19 pandemic [46]. Previous findings have shown that the exposure to urban air pollutants by carrying microorganisms is a risk factor for respiratory infections to make the pathogens invasive to the humans and affect the body's immunity to more expose people to pathogens [33,34,47,48]. Because COVID-19 is a severe respiratory disease and the SARS-CoV-2 can survive for hours in an aerosol. The impact of exposure to air pollution needed a careful survey [49], thus, the investigation of effect the air pollution exposure on the COVID-19 infection is very interesting.

## The Concentration of PM2.5 As the Main Stem of Viral Susceptibility

Increases in PM2.5 and PM10 concentrations are associated with an increase in the number of COVID-19 confirmed cases. PM2.5 can penetrate deep into the lungs and deposit into the alveoli. The chronic exposure to air pollutants such as PM2.5, $SO_2$ and $NO_2$ causes to reduce lung function, respiratory disease, and cardiovascular disease [22,50,51]. In addition to causing a persistent inflammatory reaction, air pollutants have been shown to increase risk of viruses targeting the respiratory tract, even in relatively young people [16,17]. PM2.5 penetrates into peripheral lung air spaces [52] and can through interaction with the renin-angiotensin system (RAS) facilitate the viral infection. The pulmonary RAS include the two axes involved in the local inflammatory responses with the opposite functions [53]: the ACE /AngII /AT1R axis that is involved in the release of proinflammatory cytokines (TNF-a and IL-6). The ACE-2/ Ang1-7/Mas axis that culminates in the Mas activation concludes that affects STAT3 and ERK and produces an anti-inflammatory effect. The angiotensin-converting enzyme2 (ACE2) protects against the RAS induced damage through two processes:

a. degradation of AngI and AngII to limit the substrate availability in adverse the receptor axis of ACE /AngII /AT1;

b. production of Ang1-7 to increase capability of the substrate in ACE-2 /Ang1-7 /Mas receiver axis [53].

The ACE-2 knockout mice after the PM2.5 exposure are more prone to lung damage and reduced pulmonary repair compared to controls. This indicates an important role for the ACE-2 in protecting the lungs against the air pollutants [54]. The chronic exposure to PM2.5 leads to upregulation the pulmonary ACE expression and activity in mice that can be the protective response to the chronic harmful injury [54,55]. Also, despite having normal function and structure of the lung, ACE-2 knockout mice compared with the control mice of wild-type, showed very intensive pathology of the acute respiratory distress syndrome (ARDS) [54,56]. Corona virus protein's spike facilitates the viral entry into the target cells by engaging the ACE-2 receptors [57]. ACE-2 is, predominantly expressed at level of the alveolar, and explains viral tropism for the lower airways. In fact, by the interaction between the S1 subunit receptor binding domain (RBD) in viral spike glycoproteins with ecto ACE-2 domain, binding and entry is facilitated of the SARS-CoV and the SARS-CoV-2 into the human cells [58].

Infection and challenge of SARS-CoV with recombinant SARS-Spike protein significantly reduces ACE-2 expression in the lungs and in the cell culture and led to the more severe lung damage [59]. Reduction of viral ACE-2 emerges to be very important in mediating the lung damage [59,60]. We postulate that overexpression of ACE-2 in patients are chronic exposed to high concentration of PM2.5, can facilitates the viral penetration, resulting in a decrease in ACE-2 leading to more intense forms of the disorder. This may explain the low incidence of sever pneumonia in the children, most of the whom are asymptomatic. Limitations in PM2.5 exposure owing to young age in children may excuse them from overexpression of the ACE-2 receptor. Out of all infected patients in China, less than 1% were under 10 years old children [61] that developed milder disease [62]. Therefore, chronic upregulation of the ACE-2 in the PM 2.5 dose -dependent manner can explain a wide variety of clinical manifestations from the asymptomatic patients to the patients with severe, moderate, or mild disease [62]. According to findings, the average viral load 60 times higher in the SARS-CoV2 severe cases than in the mild cases [63]. While the COVID-19 causes only mild symptoms in most patients, in rare cases it can lead to an extreme-inflammatory response leading to ARDS and death.

In addition to the clear overlap between the COVID-19 -induced ARDS symptoms and prolonged air pollution exposure, there is evidence of an association between COVID-19 cases and ozone and nitrogen oxide concentrations [15]. Another study in northern Italy found that air pollutant concentrations may play a role in increasing COVID-19 mortality in that region [16]. Similar evidence in Italy suggests that PM may actually carry virus and thus directly contribute to its spread [64]. In the Netherlands also, preliminary analysis evidenced a link between the PM2.5 concentrations and COVID-19 cases [65]. Results of the study of the relationship between COVID-19 mortality rate and long-term exposure to the high concentration of PM2.5 in US cities shown that an increase of 1μg/$m^3$ in PM2.5 concentration was associated with the 8% increase in death rate of COVID-19 [66].

## Conclusion

Scientific studies on urban air pollution exposure can help transmit the virus via aerosol, how to use personal protective equipment in personal exposure, source of entry into the receptor pathways, the survival of the virus at different levels, in various environments conditions and meteorological including temperature, ultraviolet radiation, humidity [67]. Extreme heat and or the arrival of the cold season and decreasing air temperature and the occurrence of temperature inversion, especially in crowded cities, can interfere with the dispersion of air pollutants on the ground level and increase the concentration of pollutants and the health damage.

Considering the additional risk that some communities may face with COVID-19 and the extra burden that they face during severe weather events, also the interplay between COVID-19 prevention measures and coping strategies against the severe reduction of air temperature in cold seasons and or extreme heat (for example, restrictions on service centers and shops, respect for social distance, wearing a mask despite the occurrence of respiratory distress, the occurrence of temperature inversion in winter and increasing concentrations of air pollutants, and traffic restrictions in cities, ...), epidemic preparedness strategies are essential for the climate adaptation. In these time-sensitive pandemics, to help inform the targeted interventions and reduce disease prevalence while minimizing socio-economic inequalities and considering the combined risks in the changing environment, especially given a recession predicted economic, practical evidence is needed.

## Declaration of interest

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## Abbreviations

| | |
|---|---|
| Ang I | Angiotensin I |
| Ang II | Angiotensin II |
| Ang II (1-7) | Angiotensin-(1-7) |
| ARDS | Acute Respiratory Distress Syndrome |
| ACE | Angiotensin-Converting Enzyme |
| ACE2 | Angiotensin-Converting Enzyme 2 |
| AT1R | Angiotensin II type 1 receptor |
| ANE | Acute Necrotizing Encephalopathy |
| BBB | Blood–Brain Barrier |
| OB | Olfactory Bulb |
| HI | Hippocampus |
| CO | Carbon Monoxide |
| CNS | Central Nervous System |
| COVID-19 | Coronavirus Disease 2019 |
| ERK | Extracellular signal-Regulated Kinase |
| IL | Interleukin |
| NO2 | Nitrogen Dioxide |
| O3 | Ozone |
| PM | Particulate Matter |
| PM0.1 | Particulate Matter < 0.1 μm (ultrafine particles) |
| PM2.5 | Particulate Matter < 2.5 μm (fine particles) |
| PM10 | Particulate Matter with a diameter between 2.5 μm and 10 μm (coarse particles) |
| RBD | Receptor Binding Domain |

| | |
|---|---|
| ROS | Reactive Oxygen Species |
| RAS | Renin Angiotensin System |
| SO2 | Sulfur Dioxide |
| STAT3 | Signal Transducer and Activator of Transcription 3 |
| SARS | Severe Acute Respiratory Syndrome |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| TNFα | Tumor Necrosis Factor alpha |
| INFγ | Interferon-gamma |
| UFPs | Ultra-Fine Particles |
| US | United States |
| HCOV | Human Coronavirus |

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