Emerging role of air pollution and meteorological parameters in COVID-19

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Abstract
Exposure to air pollutants has been associated with respiratory viral infections. Epidemiological studies have shown that air pollution exposure is related to increased cases of SARS-COV-2 infection and COVID-19-associated mortality. In addition, the changes of meteorological parameters have also been implicated in the occurrence and development of COVID-19. However, the molecular mechanisms by which pollutant exposure and changes of meteorological parameters affects COVID-19 remains unknown. This review summarizes the biology of COVID-19 and the route of viral transmission, and elaborates on the relationship between air pollution and climate indicators and COVID-19. Finally, we envisaged the potential roles of air pollution and meteorological parameters in COVID-19.

KEYWORDS
air pollution, COVID-19, meteorological parameters

1 INTRODUCTION

In late 2019, a group of patients with unexplained pneumonia were related to a seafood wholesale market in China. Since then, a novel coronavirus (SARS-CoV-2), which can cause serious acute respiratory syndrome, has triggered off a pneumonia outbreak in China. The World Health Organization names this disease as coronavirus disease 2019 (COVID-19) in February 2020 and announced COVID-19 has pandemic characteristics in March 11, 2020. As of 26 March 2021, the number of confirmed cases was 124,535,520 and the number of confirmed deaths was 2,738,876 among 223 countries, areas or territories (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).

The incubation period of COVID-19 is typically 3-7 days (range: 1-14). The main clinical manifestations include symptoms of respiratory tract infection (e.g., nasal obstruction, runny nose, sore throat, fever, dry cough, and dyspnea), gastrointestinal issues, neurological impairment, and cutaneous manifestations.1 Multiple system complications (nervous system, respiratory system, cardiovascular system, digestive system, urinary system) tend to occur in patients with severe COVID-19.1 Subjects with chronic diseases, including hypertension, obesity, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease, are at higher risk.1

Solid, liquid, and gas components in air pollution affect biological systems. Impact of air pollution and climatic change on the spread, morbidity, and mortality of the virus has been increasingly studied. In this review, we summarize the impacts of particulate matter (PM), carbon monoxide (CO), nitrogen dioxide (NO$_2$), ozone (O$_3$), and sulfur dioxide (SO$_2$) on COVID-19 infection. Previous results showed significant heterogeneity across countries. For example, Liu et al selected data from 9...
countries covering Asia, North America, and Europe, and found greater influence of PM2.5 and PM10 on COVID-19 infection in European countries, but greater impact of O3 and PM2.5 on COVID-19 infection in North American countries. For Asian countries, PM10, CO, and PM2.5 were more strongly correlated with infection in China; O3 and PM2.5 were more strongly linked with infection in Japan, whereas SO2 and PM2.5 were more strongly related to infection in Korea.

This review first summarizes the biology of SARS-CoV-2 and its route of transmission, and then discusses the results of major epidemiological studies on the influences of air pollution and climate indicators on COVID-19. We then envisage the possible roles of air pollution and meteorological parameters in COVID-19.

2  |  CORONAVIRUS BIOLOGY

Coronaviruses (COVs) is a highly diverse family of enveloped positive sense single-stranded RNA viruses. According to the phylogenetic relationship and genomic structure, the viruses are classified into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. The genome size of coronavirus ranges from 26 000-32 000 bases, including an variable number of open reading frames. COVID-19 is 99.4% homologous to SARS-COV, indicating that the two viruses belong to the same SARS-CoV. SARS-COV genome structure follows other known coronavirus characteristic gene sequences. It is blocked at the 5' end, has a 3' poly (a) tail and a short 5' and 3' UTR sequence. Coded proteins include S, envelope (E), membrane (M) and N proteins. Among these proteins, spinous proteins are essential for the binding of virus to host, and mediate the entry of virus into host cells. The spinous process of coronavirus consists of three fractions: a large outer domain, a one-way transmembrane anchor, and a short intracellular tail. The outer domain is composed of receptor binding subunit S1 and membrane fusion subunit S2. Entry of coronaviruses into host cells is a two-step process mediated by the virion spike proteins that modify the virus particles. S1 domain is in charge of receptor binding, S2 domain is in charge of membrane fusion. COVs replication and transcription occur in the cytoplasm of invaded cells and are mediated by replication transcript (RTC). In COVs genome replication, continuous negative RNA synthesis is designed to produce full-length complementary templates, which are then replicated into multiple positive offspring genomes.

3  |  EFFECT OF CORONAVIRUS ON IMMUNE SYSTEM

SARS-CoV-2 infection activates innate and adaptive immune responses, which can lead to immune system damage, such as lymphopenia, lymphocyte activation and dysfunction, abnormal granulocyte and monocyte, high cytokine level and high antibody level.

Innate immune cells trigger a series of inflammation. The interaction between SARS-CoV-2 and hosts is initiated by the single stranded RNA (ssRNA) and double-stranded RNA (dsRNA) of SARS-COV-2 through the cytoplasmic RIG pattern recognition receptors. PRR senses the viral replication process and forms abnormal RNA structure, and activates IRFs and NF-κB. Activated PRR triggers cytokine secretion via downstream signal transduction cascades. A large body of clinical evidences suggested critical roles of a wide range of cytokines in the nosogenesis of COVID-19. It has been confirmed that there is an uncontrolled "cytokine storm" in patients with poor prognosis, which is characterized by local and systemic pro-inflammatory factors, including interleukin (IL)–6, tumor necrosis factor-α (TNF-α), and IL-1β.

The adaptive immune system is mainly composed of B cells, CD4+ T cells (helper T cells) and CD8+ T cells (cytotoxic or killer cells), which react to pathogens in an antigen-specific way and produce protective immunity. Acute respiratory distress syndrome (ARDS) is an important manifestation of COVID-19. Macrophages participate in epithelial injury during ARDS. When recognizing damage associated molecular pattern (DAMP) or pathogen associated molecular pattern (PAMP) in the process of COVID-19, macrophages are activated via TLRs, NLRP3/inflammasome or triggering cytoplasmic DNA sensors. Subsequent signal transduction stimulates the secretion of cytokines and activates the antiviral gene expression program in adjacent cells.

4  |  COVID-19 PATHOGENESIS

The average incubation period of COVID-19 is 6.4 days and could range from 2.1 to 11.1 days. The pathogenesis of SARS-CoV-2 infection is akin to that of SARS-COV infection. Nasal epithelial cells are the primary site of SARS-CoV-2 infection; lower respiratory tract infection may be caused by inhalation-mediated virus seeding into the lung. Patients infected with SARS coronavirus initially show fever, sore throat, cough, and dyspnea. In addition to respiratory symptoms, some infected patients also have gastrointestinal symptoms, such as stomachache, diarrhea, inappetence, nausea, and vomiting. The gastrointestinal tropism of SARS-CoV-2 coronavirus has also been confirmed by biopsy specimens and fecal virus test. SARS-CoV-2 could combine with the viral receptor angiotesin converting enzyme (ACE2), and the overexpression of ACE2 mRNA in the gastrointestinal system may explain the gastrointestinal symptoms. General symptoms including myalgia, headache, and loss of taste and smell.

Patients with severe COVID-19 are characterized by profound hypoxemia but no proportional signs of respiratory distress and rapid deterioration. In addition, the immune system releases a large amount of cytokines during virus infection and secondary infection, which can lead to sepsis. In these patients, uncontrolled inflammation can result in multiple organ damage, including the heart, liver, and kidneys. Most patients who developed renal failure after SARS-CoV-2 infection eventually die.

Epidemiological data showed that the most common mode of transmission is face-to-face contact (talking, coughing, or sneezing). Contact transmission is another feasible mode of transmission. Aerosols may also mediate transmission.
5  |  EPIDEMIOLOGICAL STUDY BETWEEN AIR POLLUTANTS AND COVID-19

Studies have analyzed the association between COVID-19 and air quality index (AQI), and found that there were significant relationships between air quality and daily new cases, total cases, and mortality\(^{42-48}\) (Table 1).

### 5.1  |  Particulate matters and COVID-19

PM\(_{2.5}\) can invade deeply into the lungs and deposit into alveoli. Elevated concentration of PM\(_{2.5}\) and PM\(_{10}\) has been associated with increased numbers of confirmed COVID-19 cases.\(^{49}\) After adjusting for confounding and spatial autocorrelation, each 1 \(\mu\)g/m\(^3\) increase in the PM\(_{2.5}\) exposure is associated with 1.4% (95% CI: −2.1%−5.1%) increase in COVID-19 mortality risk.\(^{50}\) A study in India using machine learning verified a causal relationship between PM\(_{2.5}\) and COVID-19 deaths.\(^{51}\) Similarly, many studies have shown positive correlations between PM\(_{2.5}\), PM\(_{10}\) and daily new COVID-19 cases and mortality,\(^{24,44,46-48,52-69}\) indicating that air pollution increases susceptibility to COVID-19.

There are significant inconsistencies among different results. For example, Bonetempi et al failed to find a correlation between PM\(_{10}\) and the diffusion of the COVID-19 virus. Specifically, cities with the most severe event of PM\(_{10}\) pollution had low number of cases, whereas cities where PM\(_{10}\) concentration exceeded the higher limit only occasionally had the highest number of cases.\(^{67}\) Liang et al also failed to observe a significant association.\(^{70}\) Jiang et al suggested that COVID-19 deaths are positively associated with PM\(_{2.5}\) but negatively with PM\(_{10}\).\(^{46}\) Another study in the United States showed that as the moving average of PM\(_{2.5}\) (\(\mu\)g/m\(^3\)) increased by one unit, the number of daily new COVID-19 cases decreased by 33.11% (Table 2).

### 5.2  |  NO\(_2\) and COVID-19

Many studies have examined the association between NO\(_2\) and COVID-19.\(^{66,10-74}\) NO\(_2\), an endogenously generated oxidant, has a potential impact on COVID-19 transmission.\(^{75}\) NO\(_2\) has been positively associated with COVID-19 infectivity, positive cases, incidence and deaths.\(^{64,56,63,64}\) After adjustment for relative humidity and temperature, transmission ability of the 11 Cities in Hubei Province (except Xianning City) was positively related to NO\(_2\) concentration (with 12-day time lag), indicating that NO\(_2\) may increase underlying risk of infection during COVID-19 transmission.\(^{76}\) Magazino et al demonstrated a causal effect of NO\(_2\) on mortality, namely, the ability of NO\(_2\) to accelerate COVID-19 mortality.\(^{69}\) Ogen et al showed that out of the 4 443 fatality cases, 3 487 (78%) were in five regions with the highest NO\(_2\) concentrations.\(^{77}\) A recent study found a 0.5% (95% CI: −0.2%, 1.2%) increase in COVID-19 mortality risk for every 1 \(\mu\)g/m\(^3\) increase in NO\(_2\), after adjusting for confounding and spatial autocorrelation.\(^{50}\) Liu et al found that aggravating effect of NO\(_2\) on COVID-19 infection in Canada and France.\(^2\) A 10 \(\mu\)g/m\(^3\) increase (lag 0-14) in NO\(_2\) was associated with a 6.94% (95% CI: 2.38-11.51) increase in the daily counts of confirmed cases.\(^{49}\) The causal links between NO\(_2\) and COVID-19 deaths were also verified in India by a study using machine learning method.\(^{51}\) However, two other studies showed that ground level NO\(_2\) was inversely correlated with COVID-19 infections and the basic reproductive ratio (R\(_0\)).\(^{71,78}\) In an ML experiment by Mele et al, when NO\(_2\) exceeded the threshold level, the number of deaths from COVID-19 increased.\(^{75}\) Overall, NO\(_2\) renders the respiratory system more susceptible to COVID-19.\(^{75}\) (Table 3).

### 5.3  |  O\(_3\) and COVID-19

A 10 \(\mu\)g/m\(^3\) increase (lag 0-14) in O\(_3\) was associated with a 4.76% increase in the daily counts of confirmed cases.\(^{59}\) Liu et al evaluated the
| Author          | Country                | Period                  | Analysis method                                                                 | Quantified results                                                                                                                                                                                                 |
|-----------------|------------------------|-------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Liu et al       | 9 countries            | 21 Jan to 20 May 2020   | Discontinuous linear regression                                                  | PM$_{10}$ plays a stronger role in accelerating the spread of COVID-19 infection in China, England, Germany, and France.                                                                                             |
| Zoran et al     | Italy (Milan)          | 1 Jan to 30 Apr 2020    | NA                                                                              | Daily maximum PM$_{2.5}$ and PM$_{10}$ were positively associated with daily new COVID-19 cases.                                                                                                                     |
| Li et al        | China (Wuhan and Xiaogan) | 26 Jan to 29 Feb 2020   | Linear regression model                                                          | PM$_{2.5}$ was prominently correlated with COVID-19 incidence.                                                                                                                                                         |
| Jiang et al     | Wuhan in China         | 25 Jan to 7 Apr 2020    | The Pearson’s and Poisson’s regression models                                   | PM$_{2.5}$ was positively associated (relative risk [RR] = 1.079, 95%CI 1.071-1.086, $P < 0.01$) with COVID-19 deaths.                                                                                               |
| Jiang et al     | Wuhan in China         | 25 Jan to 7 Apr 2020    | The Pearson’s and Poisson’s regression models                                   | PM$_{10}$ was inversely associated with COVID-19 deaths.                                                                                                                                                              |
| Wang et al      | 337 prefecture-level cities in China | NA                     | Spearman’s rank correlation analysis and multiple linear regression         | PM$_{2.5}$, PM$_{10}$ were positively correlated with newly confirmed COVID-19 cases.                                                                                                                               |
| Pei et al       | 325 cities in China    | Up to 27 May 2020       | Geographically weighted regression                                               | PM$_{2.5}$ and PM$_{10}$ had significantly positive impacts on COVID-19.                                                                                                                                         |
| Zhu et al       | China (120 cities)     | 23 Jan to 29 Feb 2020   | Generalized additive model                                                       | 10 mg/m$^3$ increase in PM$_{2.5}$ was positively associated with 2.24% (95% CI: 1.02-3.46) increase in the daily counts of confirmed cases; 10 mg/m$^3$ increase in PM$_{10}$ was positively associated with 1.76% (95% CI: 0.89-2.63) increase in the daily counts of confirmed cases. |
| Konstantinoudis et al | England               | Up to 30 June 2020     | Bayesian hierarchical models                                                     | Every 1 $\mu$g/m$^3$ increase in PM$_{2.5}$ was associated with a 1.4% (95% CI: −2.1%-5.1%) increase in COVID-19 mortality risk.                                                                                      |
| Frontera et al  | Italy                  | Updated to 31 March 2020| Pearson’s correlation analyses                                                   | Mean PM$_{2.5}$ was positively associated with COVID-19 total number cases, ICU admissions per day, deaths, and hospitalized cases.                                                                                 |
| Frontera et al  | Italy                  | 1 Feb to 31 Mar 2020    | Correlation analyses                                                            | PM$_{2.5}$ was positively associated with total number of COVID-19 cases.                                                                                                                                          |
| Frontera et al  | Europe (47 regional Euro-pean capitals and 107 major Italian cities) | 10 Feb to 10 Apr 2020   | Binary classifier based on an artificial neural network                          | PM$_{2.5}$ and PM$_{10}$ were positively associated with number of COVID-19 cases.                                                                                                                                   |
| Setti et al     | Italy (northern 110 Italian provinces) | 7 Feb to 15 Mar 2020   | Correlation analyses                                                            | The average number of exceedances of PM$_{10}$ daily limit value was positively associated with the number of COVID-19 cases in each province.                                                                        |
| Wang et al      | China (63 cities)      | 1 Jan to 2 Mar 2020.    | Generalized additive models (GAM) with a quasi-Poisson’s distribution           | A 10 $\mu$g/m$^3$ increase in the concentration of PM$_{10}$ and PM$_{2.5}$ were positively associated with the confirmed cases of COVID-19, and the estimated strongest RRs (both at lag 7) were 1.05 (95% CIs: 1.04-1.07) and 1.06 (95% CIs: 1.04-1.07), respectively. |
| Travaglio et al | UK Biobank data sources | 2018-2019              | Generalized linear models, negative binomial regression analyses                | An increase of 1 m$^3$ in the long-term average of PM$_{2.5}$ was associated with a 12% increase in COVID-19 cases.                                                                                                     |
| Author                  | Country                   | Period                      | Analysis method                                      | Quantified results                                                                 |
|-------------------------|---------------------------|-----------------------------|------------------------------------------------------|------------------------------------------------------------------------------------|
| Travaglio et al         | UK Biobank data sources   | 2018-2019                   | Generalized linear models, negative binomial regression analyses | A one-unit increase in PM$_{2.5}$ was associated with approximately 8% more COVID-19 cases in the UK biobank. |
| Pozzer et al            | Worldwide                 | Up to June 2020             | Global atmospheric chemistry general circulation model (EMAC) | PM$_{2.5}$ contributed 15% (95%CI: 7%-33%) to COVID-19 mortality worldwide.         |
| Yao et al               | Wuhan in China            | 19 Jan to 15 Mar 2020       | Time series analysis                                 | PM$_{2.5}$ and PM$_{10}$ were positively associated with the case fatality rate of COVID-19 (CFR). |
| Magazzino et al         | Paris, Lyon, and Marseille | NA                          | Artificial Neural Networks (ANNs) experiments Machine Learning (ML) methodology | PM$_{2.5}$ and PM$_{10}$ showed a direct relationship with COVID-19 fatality.        |
| Coker et al             | Northern Italy            | 1 Jan to 30 Apr 2020        | Negative binomial regression                        | A one-unit increase in PM$_{2.5}$ concentration (µg/m$^3$) was associated with a 9% (95% CI: 6%-12%) increase in COVID-19 related mortality. |
| Vasquez-Apestegui et al | 20 districts in Lima (Peru) | As of 12 June 2020          | Ecological study, linear regression                  | Higher PM$_{2.5}$ levels were associated with higher number of cases and deaths of COVID-19. |
| Hendryx et al           | USA                       | As of 31 May 2020           | Mixed model linear multiple regression analyses     | Greater diesel particulate matter (DPM) were significantly associated with COVID-19 prevalence and mortality rates. |
| Landoni et al           | 33 European countries     | NA                          | Pearson’s correlation analysis                      | PM$_{2.5}$ was positively correlated with positive COVID-19 cases and deaths.       |
| Jiang et al             | China (Wuhan, Xiaogan and Huanggang) | 25 Jan to 29 Feb 2020       | Multivariate Poisson’s regression                   | PM$_{2.5}$ was positively associated with daily COVID-19 incidence in Wuhan (1.036, 95% CI: 1.032-1.039), Xiaogan (1.059, 95% CI: 1.046-1.072), and Huanggang (1.144, 95% CI: 1.12-1.169). |
| Jiang et al             | China (Wuhan, Xiaogan, and Huanggang) | 25 Jan to 29 Feb 2020       | Multivariate Poisson’s regression                   | PM$_{10}$ was negatively associated with daily COVID-19 incidence in Wuhan (0.964, 95% CI: 0.961-0.967), Xiaogan (0.961, 95% CI: 0.95-0.972), and Huanggang (0.915, 95% CI: 0.896-0.934). |
| Wu et al                | USA (3000 counties)       | Up to 22 April 2020         | Binomial mixed models                               | 1 mg/m$^3$ increase in PM$_{2.5}$ was positively associated with 8% increase in the COVID-19 death rate (95% CI: 2%-15%). |
| Fattorini et al         | Italy (71 provinces)      | Updated 27 April 2020       | NA                                                    | PM$_{2.5}$ and PM$_{10}$ were favorable for the spread of virulence of the SARS-CoV-2. |
| Bontempi et al          | Italy (Piedmont, Lombardy, 12 cities) | 10 Feb to 27 Mar 2020      | Correlation analyses                                | No evidence of correlations between the presence of high quantities of PM$_{10}$ and COVID-19 cases. |
| Amoatey et al           | Middle Eastern countries  | NA                          | NA                                                    | Facilitate transmission of SARS-CoV-2 virus droplets and PM in indoor environments. |
| Magazzino et al         | New York state            | NA                          | Machine Learning experiments                        | PM$_{2.5}$ accelerated COVID-19 death.                                               |
| Liang et al             | USA (3 122 US counties)   | 22 Jan to 29 Apr 2020       | Zero-inflated negative binomial models              | No significant association was observed between PM$_{2.5}$ and COVID-19.             |
| Adhikari et al          | USA (Queens, NY)          | 1 Mar to 20 Apr 2020        | Negative binomial regression model                  | A one-unit increase in the moving average of PM$_{2.5}$ (µg/m$^3$) was associated with a 33.11% (95% CI: 31.04-35.22) decrease in the daily new COVID-19 cases. |
| Author       | Country                                                                 | Period              | Analysis method                                                                 | Quantified results                                                                                                                                 |
|--------------|--------------------------------------------------------------------------|---------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Li et al     | Wuhan and Xiaogan, China                                                | 26 Jan to 29 Feb 2020 | Linear regression model                                                          | NO$_2$ was prominently correlated with COVID-19 incidence.                                                                                         |
| Jiang et al  | Wuhan, Xiaogan, and Huanggang, China                                     | 25 Jan to 29 Feb 2020 | Multivariate Poisson's regression                                                | NO$_2$ was positively correlated with daily COVID-19 incidence in Wuhan (1.056, 95% CI: 1.053-1.059) and Xiaogan (1.115, 95% CI: 1.095-1.136).    |
| Yao et al    | 11 Hubei cities                                                         | 1 Jan to 8 Feb 2020  | Multiple linear regression, residual analysis, principal component analysis, meta-analysis method | NO$_2$ concentration (with 12-day time lag) was positively related to transmission ability (basic reproductive number) of the 11 Hubei cities (except Xianning City). |
| Liang et al  | 3 122 US counties                                                       | 22 Jan to 29 Apr 2020 | Zero-inflated negative binomial models                                           | Per interquartile range (IQR) increase in NO$_2$ (4.6 ppb) was associated with an increase of COVID-19 case-fatality rate (7.1%, 95% CI: 1.2%-13.4%) and mortality rate (11.2%, 95% CI: 3.4%-19.5%), respectively. |
| Travaglio et al | England                                                              | 2018-2019           | Generalized linear models, negative binomial regression analyses                | NO$_2$ and NO were positively associated with COVID-19 infectivity, with an odds ratio of approximately 1.03 for both the single-year and multiyear model. |
| Ogen et al   | 66 administrative regions in Italy, Spain, France and Germany          | Jan to Feb 2020      | NA                                                                              | NO$_2$ was positively correlated with COVID-19 fatality cases. Out of the 4443 fatality cases, 3487 (78%) were in five regions (have the highest NO$_2$). |
| Lin et al    | 29 provinces, China                                                     | 21 Jan to 3 Apr 2020 | Chain-binomial model, correlation analyses                                        | NO$_2$ was inversely correlated to the basic reproductive ratio of COVID-19.                                                                 |
| Konstantinoudis et al | England                                | Up to 30 June 2020  | Bayesian hierarchical models                                                    | Every 1 mg/m$^3$ increase in NO$_2$ was associated with a 0.5% (95% CI: −0.2%-1.2%) increase in COVID-19 mortality risk.                            |
| Zoran et al  | Milan, Italy                                                            | 1 Jan to 30 Apr 2020 | Time series analysis                                                            | Ground level NO$_2$ was inversely correlated with COVID-19 infections.                                                                           |
| Liu et al    | 9 countries                                                             | 21 Jan to 20 May 2020 | Discontinuous linear regression                                                  | The aggravating effect of NO$_2$ on COVID-19 infection appears in Canada and France.                                                              |
| Landoni et al| 33 European countries                                                   | NA                  | Pearson's correlation analysis                                                  | NO$_2$ was positively correlated with positive COVID-19 cases and deaths.                                                                           |
| Mele et al   | 3 major French cities                                                   | NA                  | Machine learning                                                                | NO$_2$ levels contribute to COVID-19 deaths and exist threshold values.                                                                              |
| Magazzino et al | 3 French cities            | 18 Mar to 27 Apr 2020 | Machine Learning experiments                                                     | NO$_2$ accelerated COVID-19 deaths.                                                                                                               |
| Zhu et al    | 120 cities, China                                                       | 23 Jan to 29 Feb 2020 | Generalized additive model                                                       | Every 10 mg/m$^3$ increase of NO$_2$ was associated with a 6.94% (95% CI: 2.38-11.51) increase in the daily counts of confirmed COVID-19 cases.  |
| Saez et al   | Catalonia (Spain)                                                       | 25 Feb to 16 May 2020| Spearman's nonparametric correlation                                            | NO$_2$ was significantly correlated with COVID-19 incidence, mortality, and lethality rates.                                                      |
| Fattorini et al | 71 Italian Provinces        | Up to 27 April 2020  | NA                                                                              | NO$_2$ was significantly correlated with cases of COVID-19.                                                                                       |
| Chakraborty et al | 18 Indian States         | 8 Jun to 15 Jun 2020 | Pearson's correlation coefficient and regression analysis                     | NO$_2$ showed strong positive correlation between the absolute number of COVID-19 deaths ($r = 0.79, P < 0.05$) and case fatality rate ($r = 0.74, P < 0.05$). |
| Filippini et al | 28 provinces (Northern Italy)  | 1 Feb to 5 Apr 2020  | Multivariable restricted cubic spline regression model                          | NO$_2$ was significantly correlated with SARS-CoV-2 infection prevalence rate.                                                                   |
TABLE 4  Effect of O$_3$ on COVID-19 cases and mortality

| Author        | Country                     | Period                  | Analysis method                      | Quantified results                                                                 |
|---------------|-----------------------------|-------------------------|--------------------------------------|------------------------------------------------------------------------------------|
| Liu et al$^2$ | 9 countries (China, Japan, Korea, Canada, America, Russia, England, Germany, France) | 21 Jan to 20 May 2020 | Discontinuous linear regression      | O$_3$ presents a more pronounced positive effect on COVID-19 infection in more countries (such as Japan, Canada, America, Russia, France, etc). |
| Zhu et al$^3$ | China (120 cities)          | 23 Jan to 29 Feb 2020   | Generalized additive model           | Per 10 mg/m$^3$ increase in O$_3$ was associated with 4.76% (95% CI: 1.99-7.52) increase in the daily counts of confirmed cases, respectively. |
| Fronza et al$^4$ | Europe (47 regional capitals and 107 major Italian cities) | 10 Feb to 10 Apr 2020 | Artificial neural network            | O$_3$ was negatively associated with number of COVID-19 cases per million ($r = -0.44$). |
| Travaglio et al$^5$ | UK                          | 2018-2019               | Generalized linear models, negative binomial regression analyses | O$_3$ was significantly associated with COVID-19 deaths and cases at the sub regional level. |
| Jiang et al$^6$ | China (Wuhan, Xiaogan, and Huanggang) | 25 Jan to 29 Feb 2020 | Multivariate Poisson’s regression    | O$_3$ was negatively associated with daily COVID-19 incidence in Wuhan (0.99, 95%CI: 0.989-0.991) and Xiaogan (0.991, 95%CI: 0.989-0.993) and positively associated with daily COVID-19 incidence in Huanggang (1.016, 95%CI: 1.012-1.02). |
| Liang et al$^7$ | USA (3 122 US counties)     | 22 Jan to 29 Apr 2020   | Zero-inflated negative binomial models | No significant associations between O$_3$ and COVID-19 cases. |
| Adhikari et al$^8$ | New York, USA               | 1 Mar to 20 Apr 2020    | Negative binomial regression mode    | A one-unit increase in O$_3$ was associated with a 10.51% (95%CI: 7.47-13.63) increase in the daily new COVID-19 cases. |
| Zoran et al$^9$ | Milan, Italy                | 1 Jan to 30 Apr 2020    | Time series analysis                 | COVID-19 infections showed a positive correlation with ground level O$_3$. |

relationship between air pollution and COVID-19 infection in 9 countries, and showed that O$_3$ has a positive effect on COVID-19 infection in many countries across North America, Europe, and Asia.$^2$ However, several other studies reported negative association between O$_3$ and the number of infected individuals. $^{53,55,71,79}$ In a study by Jiang et al, the correlation between O$_3$ and daily incidence was positive in some areas (eg, Huanggang City), but negative in other areas (eg, Wuhan and Xiaogan City).$^{64}$ Liang et al failed to find any significant associations between long-term exposures to O$_3$ and COVID-19 death outcomes. $^{70}$ A metabolomics study showed that long-term exposure to O$_3$ is not correlated to any metabolite change, but short-term exposure is linked to cysteine, a component of cysteine, methionine, taurine, and SAM metabolism.$^{80}$ (Table 4).

5.4 CO and COVID-19

CO and CO$_2$ 24-hour concentrations were positively correlated with R$_0$ and newly confirmed cases.$^{47,78}$ CO increased the propagation speed of COVID-19 infection, especially in Korea and China.$^2$ Similarly, there are inconsistent results. Pei et al explored the effects of environmental and meteorological factors on COVID-19 using the GWR model and found that CO exhibited negative effects.$^{48}$ In a study by Jiang et al,$^{46}$ the correlation between CO and daily incidence was positive in Wuhan City but negative in Xiaogan and Huanggang City,$^{64}$ (Table 5).

5.5 SO$_2$ and COVID-19

Study has shown that SO$_2$ increased the propagation speed of COVID-19 infection, especially in Korea and China.$^2$ SO$_2$ is positively correlated with newly confirmed cases and deaths.$^{47,65}$ However, negative associations have also been found.$^{46}$ In a study by Zhu et al, the number of confirmed COVID-19 cases reduced by 7.79% with every 10-μg/m$^3$ increase in SO$_2$ (lag time: 0-14 days).$^{49}$ In addition, Jiang et al did not find correlation between SO$_2$ and daily incidence.$^{64}$ In conclusion, SO$_2$ may also play an important role in the spread of COVID-19 (Table 6).

5.6 Temperature and COVID-19

Several studies have shown negative correlation between temperature and daily incidence.$^{44,47,48,64}$ However, in a study that analyzed the association between COVID-19 and temperature using Kendall correlation test and Spearman’s test, temperature was positively associated with new cases, total cases, and mortality among New York citizens.$^{43}$ Several studies supported evidence showing that warm season does not stop COVID-19 spreading.$^{71,79}$ Adding to the complexity, Heibati et al did not observe statistically significant association between temperature and COVID-19, possibly due to small number of cases and restricted time period$^{81}$ (Table 7).
TABLE 5  Effect of CO on COVID-19 cases and mortality

| Author    | Country                  | Period              | Analysis method                              | Quantified results                                                                 |
|-----------|--------------------------|---------------------|----------------------------------------------|-----------------------------------------------------------------------------------|
| Liu et al | 9 countries              | 21 Jan to 20 May 2020 | Discontinuous linear regression              | CO will increase the propagation speed of COVID-19 infection, which is significant in Korea and China, respectively. |
| Jiang et al | Wuhan in China          | 25 Jan to 7 Apr 2020 | The Pearson’s and Poisson’s regression models | CO was inversely associated with COVID-19 deaths.                                  |
| Wang et al | 337 prefecture-level cities in China | NA | Spearman’s rank correlation analysis and multiple linear regression | CO was positively correlated with newly confirmed COVID-19 cases. |
| Pei et al | 325 cities in China      | Up to 27 May 2020   | Geographically weighted regression,           | CO had a negative effect on COVID-19 deaths.                                       |
| Jiang et al | China (Wuhan,Xiaogan, and Huanggang) | 25 Jan to 29 Feb 2020 | Multivariate Poisson’s regression            | CO was positively correlated with daily incidence in Wuhan (1.932, 95% CI: 1.763-2.118); but negatively correlated with daily incidence in Xiaogan (0.041, 95%CI: 0.026-0.066) and Huanggang (0.032, 95%CI: 0.017-0.063). |
| Lin et al | 29 Provinces in China    | 21 Jan to 3 Apr 2020 | Chain-binomial model, correlation analyses    | CO was positively correlated with the basic reproductive ratio of COVID-19.         |

TABLE 6  Effect of SO$_2$ on COVID-19 cases and mortality

| Author    | Country                  | Period              | Analysis method                              | Quantified results                                                                 |
|-----------|--------------------------|---------------------|----------------------------------------------|-----------------------------------------------------------------------------------|
| Liu et al | 9 countries              | 21 Jan to 20 May 2020 | Discontinuous linear regression              | SO$_2$ increased the propagation speed of COVID-19 infection, which is significant in Korea and China, respectively. |
| Jiang et al | Wuhan, China            | 25 Jan to 7 Apr 2020 | The Pearson’s and Poisson’s regression models | SO$_2$ was inversely associated with COVID-19 deaths.                                  |
| Wang et al | 337 prefecture-level cities in China | NA | Spearman’s rank correlation analysis and multiple linear regression | SO$_2$ was positively correlated with newly confirmed cases.                                |
| Zhu et al | 120 cities, China        | 23 Jan to 29 Feb 2020 | Generalized additive model                   | 10 μg/m$^3$ increase of SO$_2$ was associated with a 7.79% decrease (95% CI: −14.57 to −1.01) in COVID-19 confirmed cases. |
| Landoni et al | 33 European countries  | NA                  | Pearson’s correlation analysis               | SO$_2$ was positively correlated with positive COVID-19 cases and deaths.               |
| Jiang et al | Wuhan, Xiaogan and Huanggang, China | 25 Jan to 29 Feb 2020 | Multivariate Poisson’s regression            | SO$_2$ was not correlated with daily COVID-19 incidence.                              |

5.7 Humidity, wind speed, cloud and air pressure, and COVID-19

Several studies analyzed the effects of relative humidity on COVID-19, but the results are inconsistent. Three studies showed that relative humidity was positively associated with daily new COVID-19 cases and R$_0$. The other three studies failed to observe the association between relative humidity and COVID-19 (Table 8). Elevated wind speed (m/s) has been associated with increased daily new COVID-19 cases. But several other studies reported opposite findings: mean wind speed was inversely correlated with R$_0$ coronavirus infection, indicating that higher wind speed may decrease the risk of coronavirus infection because of its ability in clearing the fine particles and modulating the dynamics of various vectors and pathogens (Table 8). Increase in the moving average of cloud has also been associated with increased daily new COVID-19 cases. For air pressure, in
TABLE 7  Effect of temperature on COVID-19 cases and mortality

| Author          | Country                  | Period               | Analysis method                        | Quantified results                                                                 |
|-----------------|--------------------------|----------------------|----------------------------------------|--------------------------------------------------------------------------------------|
| Li et al        | China (Wuhan and Xiaogan)| 26 Jan to 29 Feb 2020| Linear regression model                 | Temperature was inversely correlated with COVID-19 incidence (P < 0.05).              |
| Zhang et al     | 219 prefecture cities in China | 24 Jan to 29 Feb 2020| Multivariate regression model           | Maximum temperature and minimum temperature had a significant and negative impact on newly confirmed COVID-19 cases. |
| Wang et al      | 337 prefecture-level cities in China | NA               | Spearman’s rank correlation analysis and multiple linear regression | Temperature was negatively correlated with the newly confirmed cases, indicating that the ambient temperature had a certain inhibitory effect on the transmission of COVID-19. |
| Pei et al       | 325 cities in China      | Up to 27 May 2020    | Geographically weighted regression      | Temperature was negatively correlated with COVID-19 incidence.                      |
| Jiang et al     | China (Wuhan, Xiaogan, and Huanggang) | 25 Jan to 29 Feb 2020| multivariate Poisson’s regression      | Temperature was negatively correlated with daily COVID-19 incidence in Wuhan (0.969, 95%CI: 0.966-0.973), Xiaogan (0.89, 95%CI: 0.871-0.911), and Huanggang (0.738, 95%CI: 0.717-0.75). |
| Zoran et al     | Milan, Italy             | 1 Jan to 30 Apr 2020 | Time series analysis                    | Temperature was positively correlated with COVID-19 incidence, supporting the hypothesis that warm season will not stop COVID-19 spreading. |
| Lin et al       | 29 Provinces in China    | 21 Jan to 3 Apr 2020 | Chain-binomial model, correlation analyses | Daily maximum temperature was inversely correlated with the basic reproductive ratio of COVID-19. |
| Adhikari et al  | New York City, USA       | 1 Mar to 20 Apr 2020 | Negative binomial regression mode       | A one-unit increase in temperature was associated with a 12.87% (95%CI: 10.76-15.02) increase in the daily new COVID-19 cases. |
| Heibati et al   | Finland                  | 1 Jan to 31 May 2020 | Quasi-Poisson’s generalized additional model | Temperature was not related to the COVID-19 incidence.                                |

provinces with medium flow, mean/maximum/minimum air pressure was inversely correlated with $R_0$ (Table 8).

6  EFFECT OF POLLUTANT EXPOSURE ON COVID-19

6.1  PM exposure

Effects of PM on COVID-19 have been associated with: (1) inflammatory effects and immune dysregulation; (2) oxidative stress and cytotoxicity of polycyclic aromatic hydrocarbons (PAHs); (3) dysfunctional surfactants; (4) ACE-2; (5) metabolic pathways.

First, excessive inflammatory response, resulting in a massive release of pro-inflammatory cytokines, also known as “cytokine storms,” has a significant impact on COVID-19. PM$_{2.5}$ is involved in inflammatory pathways, such as toll-like receptor (TLR) signaling that improve systemic pro-oxidant and proinflammatory effects. Gao et al showed that among COPD patients, exposure to air pollution lead to the reduced eotaxin (IL-4 and IL-13), and increased serum levels of IL-2, IL-12, IL-17A, IFNγ, and monocyte displacing protein 1 (MCP-1). Acute exposures were related to lower the forced vital capacity % predicted, possibly due to elevated Th1 and Th17 cytokines and decreased Th2 cytokines. On the other hand, PM may trigger inflammatory state. Long-term residential exposure to PM$_{2.5}$ has been associated with increased IL-6 and IL-10 concentrations in patients evaluated for suspected obstructive sleep apnea. Because of human innate immunity, when PM entered the body, alveolar macrophages would be induced to release cytokines IL-1, IL-6 and TNF-α for reducing the phagocytosis of virus, promoting its proliferation and producing a pro-inflammatory state. PM could increase the severity of COVID-19 through directly damaging the immune response of the lungs to infection or indirectly aggravating respiratory or cardiovascular diseases.

Second, oxidative stress may play important roles. Metal content in fine particles contribute to PM cytotoxicity. It can cause oxidative stress and the formation of reactive oxygen species. Oxidative stress can lead to mitochondrial dysfunction, causing DNA damage, protein adduct formation and cell apoptosis. In addition, oxidative stress can stimulate the activation of redox sensitive pro-inflammatory transcription factors NF-xB, AP-1 as well as Nrf2. PAHs contained in PM is another factor for PM cytotoxicity, and may act as ligands for aryl hydrocarbon receptors (AhR), triggering their nuclear translocation,
**Table 8** Effect of precipitation, cloud, air pressure, wind speed and humidity on COVID-19 cases and mortality

| Author       | Parameter   | Country                  | Period                  | Analysis method                          | Quantified results                                                                 |
|--------------|-------------|--------------------------|-------------------------|------------------------------------------|-------------------------------------------------------------------------------------|
| Zoran et al  | Precipitation| Milan, Italy             | 1 Jan to 30 Apr 2020    | Time series analysis                     | Daily average precipitation rate was inversely correlated with COVID-19 cases.       |
| Adhikari et al| Precipitation| Queens, New York         | 1 Mar to 20 Apr 2020    | Negative binomial regression mode        | A one-unit increase in precipitation associated with a 66.06% (95% CI: 58.33-74.17) increase in the daily new COVID-19 cases. |
| Adhikari et al| Cloud       | Queens, New York         | 1 Mar to 20 Apr 2020    | Negative binomial regression model       | A one-unit increase in cloud was associated with a 2.11% (95% CI: 1.85-2.37) increase in the daily new COVID-19 cases. |
| Lin et al    | Air pressure| 29 Provinces in China    | 21 Jan to 3 Apr 2020    | Chain-binomial model, correlation analyses | Air pressure was inversely correlated with the basic reproductive ratio of COVID-19. |
| Zhang et al  | Wind speed  | 219 prefecture cities in China | 24 Jan to 29 Feb 2020 | Multivariate regression model            | Wind speed was negatively correlated with coronavirus infection.                       |
| Lin et al    | Wind speed  | 29 Provinces in China    | 21 Jan to 3 Apr 2020    | Chain-binomial model, correlation analyses | Mean wind speed was inversely correlated with the basic reproductive ratio of COVID-19. |
| Adhikari et al| Wind speed  | Queens, New York         | 1 Mar to 20 Apr 2020    | Negative binomial regression mode        | A one-unit increase in wind speed was associated with a 3% (95% CI: 1.28-4.73) increase in the daily new COVID-19 cases. |
| Zhang et al  | Relative humidity | 219 prefecture cities in China | 24 Jan to 29 Feb 2020 | Multivariate regression model            | Relative humidity was not significantly related to new COVID-19 cases.               |
| Jiang et al  | Relative humidity | China (Wuhan, Xiaogan, and Huanggang) | 25 Jan to 29 Feb 2020 | multivariate Poisson's regression        | Relative humidity was positively correlated with daily COVID-19 incidence in Wuhan (1.009, 95% CI: 1.007-1.011), Xiaogan (1.013, 95% CI: 1.007-1.019), and Huanggang (1.033, 95% CI: 1.026-1.039). |
| Zoran et al  | Relative humidity | Milan, Italy             | 1 Jan to 30 Apr 2020    | Time series analysis                     | Daily average air relative humidity was inversely correlated with COVID-19 cases.   |
| Adhikari et al| Absolute humidity | Queens, New York         | 1 Mar to 20 Apr 2020    | Negative binomial regression mode        | A 10-unit increase in absolute humidity values was associated with a 4.76% (95% CI: 4.11-5.42) increase in the daily new COVID-19 cases. |
| Adhikari et al| Relative humidity | Queens, New York         | 1 Mar to 20 Apr 2020    | Negative binomial regression mode        | A one-unit increase in relative humidity associated with a 3.54% (95% CI: 3.09-3.99) increase in the daily new COVID-19 cases. |
| Heibati et al| Relative humidity | Finland                  | 1 Jan to 31 May 2020    | Quasi-Poisson's generalized additional model | Relative humidity was not related to the COVID-19 incidence. |
and ultimately increasing the expression of proteins involved in heterologous metabolism, such as cytochrome P450. AHRS can also cross-talk with inflammatory and antioxidant transcription factors (eg, NF-xB, STAT1, and Nrf2).85

Third, surfactants decrease surface tension of lung air-fluid interface and prevent alveolar collapse at the end of expiration.87 Lack of surfactants can lead to ARDS.87 Experimental studies suggested that physical interaction between PM and surfactant can change the biomechanical function of surfactant.88 In mice, PM can cause alveolar collapse.89 On the one hand, PM could compromise the integrity of human respiratory barrier and weaken the host defense.90

Fourth, ACE2 plays a key role in viral entry into respiratory epithelial cells.91 In addition to its physiological function, ACE-2 could serve as a receptor for SARS-COV2. ACE-2 is overexpressed upon chronic exposure to NO2 and PM2.5 in mouse experiments.92 Wide spread presence of ACE2 may help to explain the various symptoms associated with COVID-19. Increased ACE2 expression on epithelial cells promotes viral infection in vitro.93 Impaired tryptophan homeostasis in ACE2-deficient mice decreases antimicrobial peptide generation, resulting in an altered intestinal microbiota.9 This finding may explain the gastrointestinal symptoms in COVID-19 patients. SARS-COV-2 interacts with the renin-angiotensin-aldosterone system through ACE-2; thus, ACE-2 inhibitors have been proposed in the prevention and treatment of COVID-19.95 Moreover, SARS-COV-2 interaction with ACE2 resulted in decreased ACE2 surface expression and impaired cardiopulmonary protection.96 PM may pass through the alveolar capillary membrane and enter the circulatory system, directly altering the blood vessels,97 which may explain the high risk of thrombogenesis in COVID-19 patients.98

Fifth, eight metabolic pathways in glycerophospholipid, propanoate, sphingolipid, and glutathione and sphingolipid and glutathione metabolism have been associated with long-term exposure to PM2.5.80 These pathways are associated with oxidative stress, inflammation, immunity, and nucleic acid damage and repair.80 The above-mentioned mechanisms may work together to enhance the pathogenicity of SARS-COV-2.87,99

6.2 | NO2 exposure

NO2 is associated with increased likelihood of inhalational allergies and poor respiratory health. The main sources of NO2 are emissions from transportation vehicles and fuel combustion. Effects of NO2 levels on COVID-19 have been associated with (1) inflammatory effects and immune dysregulation; (2) increasing pulmonary epithelial permeability; (3) metabolic pathways; and (4) monocyte enrichment.

Many studies have reported the effect of NO2 on immune inflammation. A prospective study in nonsmokers showed that higher exposure to NO2 was associated with IL-17.100 NO2 exposure can promote neutrophil and eosinophil recruitment, and a mixed Th2/Th17 response upon antigen challenge.101 Similarly, NO2 exposure can boost the production of IL-6 and NF-xB activation.102,103 NO2 can function as an adjuvant and induce an antigen-specific Th2 immune response.104 Inhalation of 15 ppm NO2 for just 1 hour can induce MCP-1 within the lungs, indicating that NO2 can promote DC recruitment. After NO2 exposure, CD11c+ pulmonary cells secreted increased amount of IL-1α, IL-1β, IL-12p70, and IL-6, and increased Th2 cell activity.104 In addition, high-level NO2 exposure can induce endothelial dysfunction and oxidative stress disturbances.105 Thus, it is possible that NO2 exposure contributes to inflammation and immune disorders and exacerbate SARS-COV-2–induced lung damage.

High concentrations of NO2 lead to bronchoconstriction and bronchial hyperreactivity and may also result in damage and inflammation of the airway epithelium. Studies have showed that NO2 exposure disrupts tight junctions in the lungs and increases epithelial permeability and human bronchial epithelial cell dysfunction.107,108 In addition, NO2 exposure reduced the ability of alveolar macrophages to inactivate influenza virus.109

Nassan et al found significant associations between long-term exposure to NO2 and 15 blood metabolites using an untargeted metabolomic approach. Short-term exposure to NO2 was related to 100 unique metabolites and four perturbed metabolic pathways (glutathione, glycerophospholipid, beta-alanine, and taurine and hypotaurine metabolisms).10

Monocytes are key white blood cells of the innate immune system and play a central role in inflammasome activation and cardiovascular diseases. Exposure to NO2 was positively associated with monocyte levels and diastolic blood pressure after full adjustment.106 Thus NO2 may promote monocyte enrichment and DNA methylation in monocytes, which subsequently affects diastolic blood pressure and ultimately aggravates COVID-19.

ACE-2 may also play important roles. Study showed about 100-folds higher expression of ACE-2 upon NO2 exposure.110 Study in mice showed a higher risk of ACE mediated respiration disorders when chronically exposed to 5 ppm NO2.111 Therefore, ACE-2 plays a crucial role in COVID-19 since ACE-2 is associated with cardiovascular diseases.

6.3 | O3 exposure

Mounting evidence suggested a link between COVID-19 and O3, CO, and SO2. Studies have shown that O3 can ameliorate inflammation and pain in addition to its bactericidal, virucidal and antiparasitic property.112 O3 forms reactive oxygen species (ROS) and lipid oxidative products (LOP) in the plasma, which in turn serve as messengers to mediate biological functions. O3 and its metabolites could modulate immune system by regulating the release of cytokines113 and the host immune system can produce O3 to develop bactericidal activity.114 A possible explanation for the virucidal property of O3 is the oxidation of glycoproteins in the viral membrane from the reduced form (R-S-H) to the oxidized form (R-S-S-R), which directly prevents the virus from fusing with cells.115 In addition, through the nuclear factor activated T cells (NFAT) and activated protein 1 (AP-1) signaling pathways, O3 can stimulate cellular and humoral immunity.115 These signaling pathways can induce gene expression to release inflammatory cytokines such as IL-2, IL-6, IL-8, TNF-α, and IFN-γ for phagocytosis, thereby killing local
pathogens. At therapeutic concentration, O₃ can regulate the nuclear factor type 2 (Nrf2) and NF-κB signaling pathways and maintain the balance of the antioxidant environment. The imbalance of NF-κB and Nrf2 pathways is related to a variety of diseases, as are the complications of COVID-19. O₃ is capable of reducing C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). Moreover, O₃ therapy can normalize plasma fibrinogen and prothrombin levels in patients with COVID-19 infection, suggesting that O₃ therapy can stabilize liver metabolism. In summary, O₃ is a promising treatment strategy for COVID-19.

6.4 | CO exposure

CO is a gas that is colorless, odorless, tasteless, and hardly soluble in water. At nontoxic concentrations, CO produces vasodilation and anti-inflammatory effects. Previous studies indicated that CO is positively correlated with cumulative cases and cumulative deaths of COVID-19, and the increase in the concentration of CO is capable of exacerbating clinical manifestations. The possible mechanism is that high level of CO damages alveolar-capillary units, resulting in loss of alveolar units and impaired gas exchange. Therefore, low concentration of CO may contribute to the recovery of lung tissue damage due to vasodilation and anti-inflammatory effects, whereas high concentration of CO may aggravate the clinical symptoms of COVID-19 due to damaged alveolar-capillary unit.

6.5 | SO₂ exposure

Excessive SO₂ exposure induces allergies, and could cause varying degrees of damage to the brain and other tissues. Zhang et al examined the association between short-term exposure to ambient air pollutants and the daily number of clinic visits of college students. After controlling for the other pollutants, the effect of SO₂ appeared to be the largest among all pollutants, indicating the important roles of SO₂.

The available evidences of SO₂ and COVID-19 are intricate. Zhu et al demonstrated that an increase in SO₂ concentration by 10 μg/m³ was associated with a 7.79% reduction in confirmed cases of COVID-19. However, Hoang et al showed that SO₂ concentration was positively correlated with daily confirmed cases. Due to the inherent antibacterial properties of SO₂, low concentration of SO₂ may have a protective effect on COVID-19. Nevertheless, high concentrations of SO₂ may damage the respiratory tract and increase host susceptibility.

6.6 | Temperature

Temperature is implicated through a variety of mechanisms. Firstly, immune system function may be repressed under low temperature. Cold stress decreases the phagocytic function of pulmonary alveolar macrophages, secretion of proinflammatory cytokines (e.g., IL-6, IL-8, IL-10, MCP-1), and the number of neutrophil granulocytes, which in turn are required for SARS-COV-2 clearance. Temperature variation could also influence local immune responses. Exposure to cold air leads and subsequent temperature reduction of the respiratory epithelium compromise local immune responses both in upper airway and nasal mucociliary clearance. Second, patients with existing cardiovascular and/or nervous system diseases have higher risk of developing severe COVID-19. Compared to moderate temperature, cold and heat stress can exacerbate the underlying cardiovascular and nervous system diseases due to increased sympathetic activity and circulation regulation as well as the heat-induced dehydration and systemic inflammation. Lung function could also be jeopardized under low temperature. Previous study suggested the forced expiratory volume in one second was declined in cold environment. Breathing cold air can cause bronchoconstriction and mucus hyper-secretion, which in turn increase the susceptibility to pulmonary infection. A positive correlation has been shown between outdoor temperature and serum concentrations of lipoprotein particles as well as some amino acids. Interestingly, lipid metabolism disorders (e.g., decreased apolipoproteins) are frequently found in patients with COVID-19, especially in severe COVID-19 patients. Finally, Zhou et al showed a protective effect of higher body temperature in COVID-19 patients. Studies that simulate molecular dynamics suggested an association between temperature and the combination of SARS-COV-2 to human ACE2. 37°C was the most appropriate temperature for the combination of SARS-COV-2 to human ACE2 and the binding affinity decreased with increasing temperature. These findings might explain why patients typically have low fever after infection with SARS-COV-2. To sum up, it is important to control COVID-19 by environmental interventions. Reducing air pollutants through aggressive policy interventions could help to decrease the susceptibility of the general population to SARS-COV-2, and if indeed infected, follow a milder disease course. Such a task requires the entire community to participate, extensive international and multi-sectoral collaboration.

7 | CONCLUSION

Air pollution and meteorological parameters have critical effects on the rate of propagation and severity of COVID-19 cases. The mechanisms are far from clear, but may include air pollution-mediated comorbidities, airway damage, pulmonary epithelial permeability, inflammatory and immune dysregulation, metabolic pathway and pollution-induced overexpression of ACE-2 receptor. The governments must establish effective pollution monitoring systems to benefit environmental health, thereby reducing the potential impact of pollution and climate change on current and future pandemics.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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46. Jiang Y, Xu J. The association between COVID-19 deaths and short-term ambient air pollution/meteorological condition exposure: a retrospective study from Wuhan, China. Air Quality, Atmosphere & Health. 2021;14(1):1-5. https://doi.org/10.1007/s11869-020-00906-7.

47. Wang Q, Dong W, Yang K, et al. Temporal and spatial analysis of COVID-19 transmission in China and its influencing factors. Int J Infect Dis. 2021;105:675-685.

48. Pei L, Wang X, Guo B, Guo H, Yu Y. Do air pollutants as well as meteorological factors impact Corona Virus Disease 2019 (COVID-19)? Evidence from China based on the geographical perspective. Environmental Science and Pollution Research. 2021; https://doi.org/10.1007/s11356-021-12994-6.

49. 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.

50. Konstantinoudis G, Padellini T, Bennett J, Davies B, Ezzati M, Blangiardo M. Long-term exposure to air-pollution and COVID-19 mortality in England: a hierarchical spatial analysis. Environ Int. 2021;146:106316.

51. Pozzer A, Dominici F, Haines A, Witt C, Münzel T, Lelieveld J. Regional meteorological variables on COVID-19 incidence. Environ Health. 2020;727:138605.

52. Vasquez-Apestegui V, Parras-Garrido E, Tapia V, et al. Association between air pollution and COVID-19 mortality in Italy. Environmental Science and Pollution Research. 2021; https://doi.org/10.1007/s11356-021-12994-6.

53. Fattorini D, Regoli F. Role of the chronic air pollution levels in the Covid-19 outbreak risk in Italy. Environ Pollut. 2020;268:12161.

54. Setti L, Passarini F, De Gennaro G, et al. Potential role of particulate matter in the spreading of COVID-19 in Northern Italy: first observational study based on initial epidemic diffusion. BMJ Open. 2020;10(9):e039338.

55. Wang B, Liu J, Li Y, et al. Airborne particulate matter, population mobility and COVID-19: a multi-city study in China. BMC Public Health [Electr Resour]. 2020;20(1):1585.

56. Fronza R, Lusci M, Schmidt M, Lucic B. Spatial-temporal variations in atmospheric factors contribute to SARS-CoV-2 outbreak. Viruses. 2020;12(6):588.

57. Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. Links between air pollution and COVID-19 in England: a hierarchical spatial analysis. Environ Int. 2021;146:106316.

58. Pozer A, Dominici F, Haines A, Witt C, Münzel T, Lelleveld J. Regional and global contributions of air pollution to risk of death from COVID-19. Cardiovasc Res. 2020;116(14):2247-2253.

59. Yao Y, Pan J, Liu Z, et al. Temporal association between particulate matter pollution and case fatality rate of COVID-19 in Wuhan. Environ Res. 2020;190:109941.

60. Pozzer A, Dominici F, Haines A, Witt C, Münzel T, Lelleveld J. Regional and global contributions of air pollution to risk of death from COVID-19. Environ Health Perspect. 2020;128(11):1663-1667.

61. Amoatey P, Omidvarbora B, Bawain MS, Al-Mamun A. Impact of building ventilation systems and habitual indoor incense burning on SARS-CoV-2 virus transmissions in Middle Eastern countries. Sci Total Environ. 2020;733:139356.

62. Mele M, Magazzino C, Pollution, economic growth, and COVID-19 deaths in India: a machine learning evidence. Environ Sci Pollut Res Int. 2021;28(3):2669-2677.

63. Fronza R, Lusci M, Schmidt M, Lucic B. Spatial-temporal variations in atmospheric factors contribute to SARS-CoV-2 outbreak. Viruses. 2020;12(6):588.

64. Jiang Y, Xu J. The association between COVID-19 deaths and short-term ambient air pollution/meteorological condition exposure: a retrospective study from Wuhan, China. Air Quality, Atmosphere & Health. 2021;14(1):1-5. https://doi.org/10.1007/s11869-020-00906-7.

65. Wu X, Nethery RC, Sabath BM, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States: a nationwide cross-sectional study. medRxiv. 2020, https://doi.org/10.1101/2020.04.05.20054502.

66. Vasquez-Apestegui V, Parras-Garrido E, Tapia V, et al. Association between short-term exposure to air pollution and COVID-19 infection: evidence from China. Sci Total Environ. 2020;727:138704.

67. Konstantinoudis G, Padellini T, Bennett J, Davies B, Ezzati M, Blangiardo M. Long-term exposure to air pollution and COVID-19 mortality in England: a hierarchical spatial analysis. Environ Int. 2021;146:106316.

68. Pozzer A, Dominici F, Haines A, Witt C, Münzel T, Lelleveld J. Regional and global contributions of air pollution to risk of death from COVID-19. Cardiovasc Res. 2020;116(14):2247-2253.

69. Yao Y, Pan J, Liu Z, et al. Temporal association between particulate matter pollution and case fatality rate of COVID-19 in Wuhan. Environ Res. 2020;190:109941.

70. Magazzino C, Mele M, Schneider N. The relationship between air pollution and COVID-19-related deaths: an application to three French cities. Appl Ener. 2020;279:115835.

71. Fattorini D, Regoli F. Role of the chronic air pollution levels as a contributing factor to coronavirus (COVID-19) fatality. Bull Environ Contam Toxicol. 2020;105(2):198-204.

72. Filippini T, Rothman KJ, Goffi A, et al. Satellite-detected tropospheric nitrogen dioxide pollution and spread of SARS-CoV-2 infection in Northern Italy. Sci Total Environ. 2020;739:140278.

73. Mele M, Magazzino C, Schneider N, Strezov V. NO(2) levels as a contributing factor to COVID-19 deaths: the first empirical estimate of threshold values. Environ Res. 2021;194:110663.

74. Yao Y, Pan J, Liu Z, et al. Ambient nitrogen dioxide pollution and spreadability of COVID-19 in Chinese cities. Ecotoxicol. Environ. Saf. 2021;208:111421.

75. Ogen Y. Assessing nitrogen dioxide (NO(2)) levels as a contributing factor to coronavirus (COVID-19) fatality. Sci Total Environ. 2020;726:138605.

76. Lin S, Wei D, Sun Y, et al. Region-specific air pollutants and meteorological parameters influence COVID-19: a study from mainland China. Ecotoxicol. Environ. Saf. 2020;204:111035.

77. Adhikari A, Yin J. Short-term effects of ambient ozone, PM2.5 and meteorological factors on COVID-19 confirmed cases and deaths in Queens, New York. Int J Environ Res Public Health. 2020;17(11):4047.

78. Heibati B, Wang W, Ryti NRI, et al. Weather conditions and COVID-19 incidence in a cold climate: a time-series study in Finland. Front Public Health. 2020;8:605128.

79. Liu C, Ying Z, Harkema J, Sun Q, Rajagopalan S. Epidemiological and experimental links between air pollution and type 2 diabetes. Toxicol Pathol. 2013;41(2):361-373.

80. Gao N, Xu W, Ji J, et al. Lung function and systemic inflammation associated with short-term air pollution exposure in chronic obstructive pulmonary disease patients in Beijing, China. Environ Health. 2020;19(1):12.
84. Laratta C. R, Kondzerska T, Carlsten C, et al. Air pollution and systemic inflammation in patients with suspected OSA living in an urban residential area. Chest. 2020;158(4):1713-1722.

85. Wooldby B, Arnold MM, Valacchi G. SARS-CoV-2 infection, COVID-19 pathogenesis, and exposure to air pollution: what is the connection? Ann N Y Acad Sci. 2021;1468(1):15-38.

86. Lakey PS, Berkemeier T, Tong H, et al. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. Sci Rep. 2016;6:32916.

87. 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 Cellular Mol Physiol. 2020;319(3):L416-L421.

88. Kodama AT, Kuo CC, Boatwright T, Dennin M. Investigating the effect of particle size on pulmonary surfactant phase behavior. Biophys J. 2014;107(7):1573-1581.

89. Riva DR, Magalhães CB, Lopes AA, et al. Low dose of fine particulate matter (PM2.5) can induce acute oxidative stress, inflammation and pulmonary impairment in healthy mice. Inhal Toxicol. 2011;23(5):257-267.

90. Yang L, Li C, Tang X. The impact of PM(2.5) on the host defense of respiratory system. Front Cell Dev Biol. 2020;8:91.

91. Bourdrel T, Annesi-Maesano I, Alahmad B, Maesano CN, Bind MA. The impact of outdoor air pollution on COVID-19: a review of evidence from in vitro, animal, and human studies. Eur Respir Rev. 2021;30(159):200242.

92. Païtal B, Agrawal PK. Air pollution by NO2 and PM2.5 explains COVID-19 infection severity by overexpression of angiotensin-converting enzyme 2 in respiratory cells: a review. Environmental Chemistry Letters. 2021;19(1):25-42. doi:10.1007/s10311-020-01091-w.

93. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of SARS-CoV-2 – a literature review. J Comm Hosp Intern Med Perspect. 2020;10(6):523-528.

94. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382(17):1653-1659.

95. Samavati L, Uhal BD. ACE2, much more than just a receptor for SARS-CoV-2. Front Cell Infect Microbiol. 2020;10:317.

96. Bayram H, Rusznak C, Khair OA, Sapsford RJ, Abdelaziz MM. Effect of ozone and nitrogen dioxide on the permeability of bronchial epithelial cell cultures of non-asthmatic and asthmatic subjects. Clin Exp Aller. 2002;32(9):1285-1292.

97. Frampton MW, Smeglin AM, Roberts NJ Jr., Finkelstein JN, Morrow PE, Utell MJ. Nitrogen dioxide exposure in vivo and human alveolar macrophage inactivation of influenza virus in vitro. Environ Res. 1989;48(2):179-192.

98. Devalia JL, Sapsford RJ, Cundell DR, Rusznak C, Campbell AM, Davies RJ. Human bronchial epithelial cell dysfunction following in vitro exposure to nitrogen dioxide. Euro Respir J. 1993;6(9):1308-1316.

99. Comunian S, Dongo D, Milani C, Palestini P. Air pollution and Covid-19's morbidity and mortality. Am Rev Respir Dis. 1988;137(4):912-917.

100. Fernández-Cuadros ME, Albaladejo-Florín MJ, Peña-Lora D, Alavara-basa S, Pérez-Moro OS. Ozone (O3) and SARS-CoV-2: Physiological bases and their therapeutic possibilities according to COVID-19 evolutionary stage. SN Comprehensive Clinical Medicine. 2020;2(8):1094-1102. https://doi.org/10.1007/s42399-020-00328-7.

101. Alberto PO. Ozone the one and only drug. Acta Neurochirurgica Suppl. 2011;108:143-146.

102. Babior BM, Takeuchi C, Ruedi J, Gutierrez A, Wentworth P, Jr. Investigating antibody-catalyzed ozone generation by human neutrophils. PNAS. 2003(100):3031-3034.

103. Reth M. Hydrogen peroxide as second messenger in lymphocyte activation. Nat Immunol. 2002;3(12):1129-1134.

104. Delgado-Roche L, Riera-Romol M, Mesta F, et al. Medical ozone promotes Nrf2 phosphorylation reducing oxidative stress and pro-inflammatory cytokines in multiple sclerosis patients. Euro J Pharmacol. 2017;811:148-154.

105. Rubio V, García-Pérez A, Iñarrea A, Díez JC. Different roles of Nrf2 and NFKB in the antioxidant imbalance produced by esculetin or quercetin on NB4 leukemia cells. Chem-Biol Interact. 2018;294:158-166.

106. Constantin M, Choi AJ, Cloonan SM, Ryter SW. Therapeutic potential of heme oxygenase-1/carbon monoxide in lung disease. Int J Hypertens. 2012;2012:859235.

107. Meo SA, Abukhalaf AA, Alomar AA, Alessa M, Wildfire and COVID-19 pandemic: effect of environmental pollution PM-2.5 and carbon monoxide on the dynamics of daily cases and deaths due to SARS-CoV-2 infection in San Francisco USA. Euro Rev Med Pharmacol Sci. 2020;24(19):10286-10292.

108. Naqvi HR, Datta M, Mutreja G, Siddiqui MA, Naqvi DF, Naqvi AR. Improved air quality and associated mortalities in India under COVID-19 lockdown. Environ Pollut. 2021;268(Pt A):115691.
121. Zhang F, Zhang H, Wu C, et al. Acute effects of ambient air pollution on clinic visits of college students for upper respiratory tract infection in Wuhan, China. Environ Sci Pollut Res Int. 2021. https://doi.org/10.1007/s11356-021-12828-7 Online ahead of print.

122. Hoang TQ, Tran TTA. Short-term exposure to ambient air pollution in association with COVID-19 of two clusters in South Korea. Trop Med Int Health: Tm & Ih. 2020;26(4):478-491

123. Luo B, Liu J, Fei G, et al. Impact of probable interaction of low temperature and ambient fine particulate matter on the function of rats alveolar macrophages. Environ Toxicol Pharmacol. 2017;49:172-178.

124. Coiffard B, Diallo AB, Mezouar S, Leone M, Mege JL. A tangled threesome: circadian rhythm, body temperature variations, and the immune system. Biology. 2021;10(1):65.

125. Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the immune system. Physiol Res. 2020;69(3):379-388.

126. Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. Acta Oto-Laryngologica. 2002;122(2):183-191.

127. Liu M, Han S, Liao Q, et al. Outcomes and prognostic factors in 70 non-survivors and 595 survivors with COVID-19 in Wuhan, China. Transbound Emerg Dis. 2020. https://doi.org/10.1111/tbed.13969 Online ahead of print.

128. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. Am J Physiol. Heart Circulat Physiol. 2015;309(11):H1793-H1812.

129. Cheshire WP Jr. Thermoregulatory disorders and illness related to heat and cold stress. Autonom Neurosci. 2016;196:91-104.

130. Donaldson GC, Seemungal T, Jeffries DJ, Wedzicha JA. Effect of temperature on lung function and symptoms in chronic obstructive pulmonary disease. Euro Respir J. 1999;13(4):844-849.

131. Koskela HO, Koskela AK, Tukiainen HO. Bronchoconstriction due to cold weather in COPD. The roles of direct airway effects and cutaneous reflex mechanisms. Chest. 1996;110(3):632-636.

132. Li M, Li Q, Yang G, Kolosov VP, Perelman JM, Zhou XD. Cold temperature induces mucin hypersecretion from normal human bronchial epithelial cells in vitro through a transient receptor potential melastatin 8 (TRPM8)-mediated mechanism. J Aller Clin Immunol. 2011;128(3), 626-634.e1–5.

133. Eveleens Maarse BC, Loh NY, Karpe F, et al. Associations between outdoor temperature and bright sunlight with metabolites in two population-based European cohorts. Nutr, Metab Cardiovasc Dis. 2020;30(12):2252-2261.

134. Shen B, Yi X, Sun Y, et al. Proteomic and metabolomic characterization of COVID-19 patient sera. Cell. 2020;182(1):59-72.e15.

135. Zhou Z, Yang Z, Ou J, et al. Temperature dependence of the SARS-CoV-2 affinity to human ACE2 determines COVID-19 progression and clinical outcome. Comput Struct Biotechnol J. 2021;19:161-167.

136. Karan A, Ali K, Teelucksingh S, Sakhamburi S. The impact of air pollution on the incidence and mortality of COVID-19. Glob Health Res Policy. 2020;5:39.

137. Hu G, Qiu W. From guidance to practice: promoting risk communication and community engagement for prevention and control of coronavirus disease (COVID-19) outbreak in China. J Evid Based Med. 2020;13(2):168-172.