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The impact of outdoor air pollution on COVID-19: a review of evidence from *in vitro*, animal, and human studies

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Our review highlights that both short- and long-term exposures to air pollution may be important aggravating factors for SARS-CoV-2 transmission and COVID-19 severity and lethality through multiple mechanisms <https://bit.ly/395aS9w>

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ABSTRACT Studies have pointed out that air pollution may be a contributing factor to the coronavirus disease 2019 (COVID-19) pandemic. However, the specific links between air pollution and severe acute respiratory syndrome-coronavirus-2 infection remain unclear. Here we provide evidence from *in vitro*, animal and human studies from the existing literature. Epidemiological investigations have related various air pollutants to COVID-19 morbidity and mortality at the population level, however, those studies suffer from several limitations. Air pollution may be linked to an increase in COVID-19 severity and lethality through its impact on chronic diseases, such as cardiopulmonary diseases and diabetes. Experimental studies have shown that exposure to air pollution leads to a decreased immune response, thus facilitating viral penetration and replication. Viruses may persist in air through complex interactions with particles and gases depending on: 1) chemical composition; 2) electric charges of particles; and 3) meteorological conditions such as relative humidity, ultraviolet (UV) radiation and temperature. In addition, by reducing UV radiation, air pollutants may promote viral persistence in air and reduce vitamin D synthesis. Further epidemiological studies are needed to better estimate the impact of air pollution on COVID-19. *In vitro* and *in vivo* studies are also strongly needed, in particular to more precisely explore the particle-virus interaction in air.

Introduction

In late 2019, the city of Wuhan, China became the epicenter of a pneumonia epidemic due to a new coronavirus, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which causes a disease given the name coronavirus disease 2019 (COVID-19) in February 2020 by the World Health Organization [1]. COVID-19 infections are not specific, ranging from completely asymptomatic to severe forms which might require mechanical ventilation and/or lead to death. Although older age and comorbidities have consistently been reported as risk factors for unfavourable COVID-19 prognosis, younger patients without known risk factors are also being admitted to intensive care, albeit to a lesser extent and with a different

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range of symptoms. Reported comorbidities include hypertension, obesity, diabetes, cardiovascular disease, COPD, chronic kidney disease and malignancy. Symptomatology, when present, is quite variable reflecting systemic involvement, including symptoms of lower respiratory tract infection (e.g. cough, fever and dyspnoea), neurological impairment, cutaneous manifestations, or gastro-intestinal issues especially in the elderly [2]. Multiple organ failure and cardiopulmonary complications, such as myopericarditis, pulmonary embolism and acute respiratory distress syndrome, represent some of the major complications of severe COVID-19. Some of the severe forms and deaths attributed to SARS-CoV-2 infection are suspected to arise from a disproportionate inflammatory response that leads to a major release of pro-inflammatory cytokines, also referred to as a “cytokine storm” [3].

Emerging epidemiological and experimental data are now suggesting the involvement of air pollution in COVID-19-related outcomes. As suggested by the existing literature on multiple respiratory viruses, air pollution may play a role in COVID-19-related morbidity and mortality according to specific mechanisms.

Air pollution is a complex mixture of gaseous and particulate constituents that vary both spatially and temporally. COVID-19-related epidemiological studies have so far investigated impacts based on particulate matter (PM) of two sizes, e.g. inhalable particles (particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10})) and fine particles (particles with a 50% cut-off aerodynamic diameter of 2.5 μm ($\text{PM}_{2.5}$)). It is also worthwhile mentioning here that both PM_{10} and $\text{PM}_{2.5}$ are a proxy for ultrafine particles (diameter $<0.1 \mu\text{m}$). The size is important in determining the PM transportability and final destination within the respiratory tract or bloodstream. Depending on its source, PM can have different compositions. Carbonaceous PM from coal, fuel or wood combustion is the most harmful and is responsible for many chronic diseases, including cardiopulmonary and metabolic diseases, neurodegenerative conditions, cancer and low birthweight [4, 5]. The gaseous pollutants investigated so far at the population level in relation to COVID-19 and other respiratory viruses include nitrogen oxides (NO_x) and ozone (O_3). NO_2 is a major air pollutant in urban environments, primarily arising from traffic, in particular from diesel cars, and has been associated with asthma, COPD, bronchiolitis and cardiovascular diseases [6]. Tropospheric O_3 levels are dependent on other emitted pollutants, including NO_x and VOCs, as well as on climate parameters, and have been associated with excess cardiorespiratory mortality and morbidity [7].

In this paper, we provide a comprehensive overview and synthesis of key data, bringing in evidence that sheds light on the question of whether or not air pollution and COVID-19 are related.

Methods

We conducted a review of the published literature on the relationship between ambient air pollution and viral respiratory infections with particular emphasis on SARS-CoV-2 using evidence from *in vitro*, animal and human studies. Literature was gathered using available online academic databases such as Pubmed, Science Direct and Google Scholar, with no restrictions on publication dates. We focused our review on outdoor air pollution (including the air pollutants PM, NO_2 and O_3), using MeSH and keywords such as “particulate matter and SARS-CoV-2/COVID-19”, “air pollution and SARS-CoV-2/COVID-19”, “air pollution and viral respiratory disease”, “air pollution and SARS-CoV-1”, “particulate matter and viral respiratory diseases”, “ozone and respiratory viruses”, “nitrogen dioxide and respiratory viruses”, “relative humidity, temperature and respiratory viral diseases”.

In reviewing the epidemiological studies, we considered the STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) checklist of items that should be detailed in reports of observational studies, namely: study design, setting, study participants, variables (*i.e.* exposures, health outcomes and confounding variables), data sources, methods of assessment, statistical methods, main results, sensitivity analyses, limitations, and generalisability [8].

We also included published reviews exploring air pollution and respiratory virus and editorial letters referring to air pollution and COVID-19. However, because the COVID-19 pandemic disease is a current major health issue of urgent concern, we have also included preprint articles. Although environmental tobacco smoke exposure and indoor air pollution are important issues, in this review, we focused on the relationship between outdoor air pollution and SARS-CoV-2/COVID-19 in terms of morbidity-mortality, physicochemical interactions and atmospheric propagation.

First, we present the epidemiological literature on the relationship of outdoor air pollution exposure to respiratory viral infections with particular attention on: COVID-19 morbidity and mortality; the major diseases and organs targeted by both air pollutants and COVID-19; the potential biological mechanisms involved; and the interactions between viruses and air pollutants inside the human body. Secondly, we will review the mode of transport/transmission of SARS-CoV-2, the possible interactions between air pollutants and viruses in ambient air, and discuss whether air pollution plays a role in viral transmission.

Results

Does air pollution exposure increase COVID-19 morbidity and mortality? Evidence from population studies

Air pollution and viral respiratory infections

A century after the Spanish Influenza Pandemic, a study reported that cities that used more coal had tens of thousands of excess flu deaths compared to cities that used less coal, taking into account confounders such as socio-economic and baseline health status [9]. Long-term exposure to air pollution has been associated with increased influenza mortality in the USA [10]. In 2003, a Chinese study on SARS-CoV-1 showed that people living in the most polluted areas had a two-fold increased risk of dying from SARS compared to people living in less polluted areas [11]. In 2015, analysis conducted in 195 countries concluded that air pollution is a significant contributor to the burden of lower respiratory tract infections [12]. As demonstrated for influenza, exposure to air pollution increases the severity of viral respiratory infections [13]. In addition, several studies have demonstrated that increases in air pollutant concentrations were associated with an increased occurrence of respiratory viral diseases among children and adults, in particular when the viral infection was concomitant to a short-term increase in exposure to air pollution. Increases in PM_{2.5} concentrations have been associated with increased rates of viral infection, namely influenza, respiratory syncytial virus (RSV) and measles. In these studies, concentrations of PM_{2.5} were correlated with the number of new cases of respiratory viral infections with a lag time of a few days [14, 15].

Air pollution and COVID-19

Various studies have also reported a link between air pollution exposure and COVID-19 morbidity and mortality in humans (table 1). However, from an epidemiological point of view, several concerns arose from non-randomised studies that have investigated this relationship. First, the values for the number of confirmed COVID-19 cases, including the number of deaths, have been determined without standardised methodologies and tools, and without reliable testing in many cases during the first months of the COVID-19 pandemic, which may have led to an underestimation in the total number of COVID-19 outcomes. Secondly, the studies suffer from air pollution exposure misclassification. Available assessments come from either satellites or local monitoring stations without any detail on individual exposures. Aside from the study by TRAVAGLIO *et al.* [32] with individual level data from the UK Biobank, all epidemiological studies are ecological with aggregated assessments at the population levels (countries, counties and cities); thus, more longitudinal studies with individual level data are needed [36]. Ambient outdoor pollution concentrations can be a general indicator of air quality, but they are not a reliable substitute for the exposure experienced by a given individual. In this context, using exceedance levels established by public authorities is also limiting, although it can be considered as a proxy of chronic exposure to elevated levels of air pollution. Another weakness encountered arises from the fact that both air pollution and infections are autocorrelated both spatially and temporally, which has not been taken into account so far by the existing investigations. Studies lacking a control for spatio-temporal autocorrelations have been shown to bias the estimation of the results. In this context it has to be underlined that COVID-19 cases mainly arise from clusters, *i.e.* at work, that are not taken into account in epidemiological studies [36]. Furthermore, most analyses have not taken into account important confounders, *i.e.* factors related to both air pollution and COVID-19, such as population density [36]. Viral spread may vary considerably across different areas depending on population density, the time of the virus introduction, and the time of infection control measures, such as physical distancing, mask requirements, test policies or stay-at-home directives. All these factors influence the dynamics of the disease that can be estimated through the daily number of new cases or through the calculation of the basic reproductive number (R₀) and effective reproductive number, both depending on transmissibility, contact rates and duration of contagiousness, as well as on virus mutation time. As air pollution may also influence both transmissibility and duration of infectiousness, the analysis of the impact of air pollution on the dynamic of COVID-19 has to take into account confounders such as population density, the time of the virus introduction and the time of introduction of infection control measures [37].

Among the studies addressing short-term effects of air pollution, SETTI *et al.* [16] were the first to observe an association between the number of Italian provinces with daily averaged PM₁₀ concentrations exceeding the European limit values of 50 µg·m⁻³ and the subsequent number of COVID-19. Significant associations were found between mean concentrations of PM_{2.5} during the month of February 2020 and the total number of Italian COVID-19 cases on 31 March 2020 [20]. However, a similar study focusing on the Lombardy and Piedmont regions in Northern Italy from 10 February to 27 March 2020 reported a null association between the number of COVID-19 cases and PM₁₀ concentrations measured several days before the COVID emergency explosion [17]. This study is less robust than the others as it is based only on a visual approach without any statistical tests. A study exploring COVID-19 cases in Italy, France,

TABLE 1 Epidemiological evidence on air pollution exposure and COVID-19 events

First author [ref.]	Study location	Period	Air pollutants exposure	COVID-19 outcome	Findings: quantified results	Comments
Short-term exposure						
SETTI [16]	Italy	7 Feb to 15 March 2020	Daily PM ₁₀ , concentrations higher than the daily limit value (50 µg·m ⁻³) according to the national monitoring system	Daily number of confirmed cases	Positive correlation between the number of cases in each province and the average number of exceedances of PM ₁₀ daily limit value (R ² =0.98)	Only exceedance data and only one air pollutant (PM ₁₀)
BONTEMPI [17]	Italy (Piedmont, Lombardy, 12 cities)	10 Feb to 27 March 2020	Daily PM ₁₀ concentrations according to the national air quality monitoring system	Daily number of confirmed cases	No evidence of correlations between the presence of high quantities of PM ₁₀ and cases on the basis of visual graphs	Lack of statistical test of the correlation
ZORAN [18]	Italy (Milan)	1 Jan to 30 April 2020	Daily average concentrations of O ₃ , NO ₂ according to the national air quality monitoring system	Daily total number of confirmed cases, new positive cases and total deaths	Positive correlation of O ₃ (Pearson coefficient=0.64, 0.50, 0.69) but negative correlation of NO ₂ (Pearson coefficient=-0.55, -0.35, -0.58) with all outcomes	Taking into account humidity, temperature and lockdown (before and after)
ZORAN [19]	Italy (Milan)	1 Jan to 30 April 2020	Daily average concentrations of PM _{2.5} , PM ₁₀ , daily maximum PM ₁₀ according to the national air quality monitoring system and AQI	Daily total number of confirmed cases, new positive cases and total deaths	Positive correlations between daily new cases and daily maximum PM ₁₀ (R ² =0.51), daily average PM _{2.5} (R ² =0.25) and daily AQI (R ² =0.43)	Statistical significance not reported (no p-value)
FRONTERA [20]	Italy	1 Feb to 31 March 2020	PM _{2.5} mean concentration in February (data from Italian Civil Protection Agency)	Total number of cases and deaths	Positive correlation between PM _{2.5} concentration in February and total number of cases (Pearson coefficient=0.64, p<0.0074) and death numbers (Pearson coefficient=0.53, p<0.032) on 31 March 2020	No quantification of the correlation and no adjustment for confounders such as population density
CONTICINI [21]	Italy		AQI based on concentration values for up to five key pollutants, including: PM ₁₀ , PM _{2.5} , O ₃ , SO ₂ and NO ₂	Death rate	Mortality rate in Lombardy and Emilia Romagna (highly polluted by NO ₂) higher than in the rest of Italy (12% versus 4.5%)	AQI as a proxy of exposure. No statistical tests
FRONZA [22]	Europe (47 regional European capitals and 107 major Italian cities)	10 Feb to 10 April 2020	Hourly concentrations of PM _{2.5} , PM ₁₀ , O ₃ and NH ₃ [#]	Daily confirmed cases per province and region	Positive correlation between number of cases per million and PM _{2.5} , PM ₁₀ and NH ₃ (0.58 ≤ r ≤ 0.68) but negative correlation with O ₃ , (r=-0.44).	Introduction of a binary classifier based on an artificial neural network to explain spatial differences

Continued

TABLE 1 Continued

First author [ref.]	Study location	Period	Air pollutants exposure	COVID-19 outcome	Findings: quantified results	Comments
LI [23]	China (Wuhan and Xiao Gan)	26 Jan to 29 Feb 2020	AQI and four ambient air pollutants (PM _{2.5} , PM ₁₀ , NO ₂ and CO) according to the national air quality monitoring system	Daily number of new cases (incidence)	Incidence correlated with: AQI in both Wuhan (R ² =0.13) and Xiao Gan (R ² =0.223); PM _{2.5} and NO ₂ in both cities (R=0.329 for NO ₂ in Wuhan; R ² =0.117 for PM _{2.5} in Xiao Gan); PM ₁₀ (R ² =0.105)	Low values of R ²
JIANG [24]	China (Wuhan, Xiao Gan and Huang Gang)	25 Jan to 29 Feb 2020	Daily data of eight ambient air pollutants (PM _{2.5} , PM ₁₀ , SO ₂ , CO, NO ₂ , and 8-h O ₃) according to the national air quality monitoring system	Daily number of new cases (incidence)	Positive association (RR between PM _{2.5} 1.036 [95% CI 1.032–1.039], 1.059 [1.046–1.072] and 1.144 [1.12–1.169]) and daily incidence in Wuhan, Xiao Gan and Huang Gang	Quantification of the risk
YAO [25]	China (63 cities)	27 Jan to 26 Feb 2020	Hourly NO ₂ data according to the national air quality monitoring system	Number of confirmed cases and basic reproduction number (R0)	Positive association of R0 with NO ₂ in all cities (Chi-squared=10.18, p=0.037) and with 12-day time lag in 11 cities (r>0.51, p<0.005)	Adjustment for temperature and humidity Other confounders that influence R0 (timing of viral introduction, timing of COVID-19 control policies, etc.) not taken into account Only Chi-squared for global test of association
WANG [26]	China (72 cities)	20 Jan to 2 March 2020	Daily concentrations of PM _{2.5} and PM ₁₀ according to the national air quality monitoring system	Daily confirmed cases	Short-term (lag 7 and 14 days) increase of 10 µg·m ⁻³ in PM _{2.5} and PM ₁₀ associated with daily cases (RR 1.64 [95% CI 1.47–1.82] and 1.47 [1.34–1.61])	Quantification of the risk controlled for ambient temperature, absolute humidity and migration scale index
ZHU [27]	China (120 cities)	23 Jan to 29 Feb 2020	Daily concentrations of PM _{2.5} , PM ₁₀ , SO ₂ , CO, NO ₂ and O ₃ according to the national air quality monitoring system	Daily number of confirmed cases	Short-term increase 10-µg·m ⁻³ (lag 0–14) in PM _{2.5} , PM ₁₀ , NO ₂ and O ₃ associated with a 2.24% [95% CI 1.02–3.46], 1.76% [0.89–2.63], 6.94% [2.38–11.51] and 4.76% [1.99–7.52] increase in the daily counts of confirmed cases	Models (GAMs) adjusted for temperature, humidity, wind speed, air pressure and time trend estimating the associations between the moving average (lag 0–7) concentrations of air pollutants Time series analysis allowing to take daily data and lags into account
ADHIKARI [28]	USA (Queens, NY)	1 March to 20 April 2020	Daily maximum 8-h O ₃ , daily average PM _{2.5} according to the national air quality monitoring system	Number of confirmed cases and deaths	Positive association between O ₃ and cases (10.51% increase [95% CI 7.47–13.63] but negative relationship between PM _{2.5} and new cases (a one-unit increase in the moving average of PM _{2.5} associated with a 33.11% [95% CI 31.04–35.22] decrease in the daily new COVID-19 cases)	Adjusted for meteorological factors, day trends and lagged outcome to account for the potential autocorrelation of the time series of new cases (deaths)

Continued

TABLE 1 Continued

First author [ref.]	Study location	Period	Air pollutants exposure	COVID-19 outcome	Findings: quantified results	Comments
Long-term exposure						
FATTORINI [29]	Italy (regions)	2010–2019	Daily data on distribution of NO ₂ , O ₃ , PM _{2.5} and PM ₁₀ and days exceeding regulatory limits during the last 4 years, and during the last decade (2010–2019) with limits exceeded for at least 35 days according to the national air quality monitoring system	Daily number of confirmed cases	Positive correlations in up to 71 provinces between PM _{2.5} , PM ₁₀ , O ₃ , and NO ₂ and cases ($0.23 \leq R^2 \leq 0.34$)	No adjustments for meteorological factors and population density
Wu [30]	USA (all inland counties)	Up to 4 April 2020	County-level long-term average of PM _{2.5} between 2000 and 2016 from prediction models using national air quality monitoring system	COVID-19 death rate	A 1 µg·m ⁻³ increase in PM _{2.5} associated with an 8% increase in the COVID-19 death rate [95% CI 2–15%]	Main analysis adjusted by 20 potential confounding factors including population density, household income, ethnic group and education, median house value, age, sex, BMI, smoking, temperature, relative humidity, number of individuals tested for COVID-19 Possible bias: county-level adjustment factors excluded institutionalised residents
LIANG [31]	USA (3122 US counties)	22 Jan 2020 to 29 April 2020	Long-term (2010–2016) county-level exposures to NO ₂ , PM _{2.5} and O ₃ according to the national air quality monitoring system	COVID-19 case-fatality rate and mortality rate	IQR (~4.6 ppb) increase in NO ₂ associated with increase of 7.1% [95% CI 1.2–13.4%] and 11.2% [95% CI 3.4–19.5%] in COVID-19 case-fatality and mortality rates No significant association for PM _{2.5} and O ₃	Both single and multipollutant models and controlled for spatial trends and a comprehensive set of potential confounders including state-level test positive rate, county-level healthcare capacity, phase-of-epidemic, population mobility, sociodemographic, socioeconomic status, behaviour risk factors and meteorological factors

Continued

TABLE 1 Continued

First author [ref.]	Study location	Period	Air pollutants exposure	COVID-19 outcome	Findings: quantified results	Comments
TRAVAGLIO [32]	UK Biobank data sources	2018 to 2019	Annual average of daily measurements for NO ₂ , NO and O ₃ according to the national air quality monitoring system and higher resolution air pollution estimate (<2 km away from self-reported address)	Number of confirmed cases allowing to compute the infectivity rate and deaths	Association between SO ₂ , PM _{2.5} , PM ₁₀ and infectivity rate (OR 1.316 [95% CI 1.141–1.521], 1.120 [1.036–1.211] and 1.074 [1.017–1.136]) Smaller association for NO ₂ association between SO ₂ , NO ₂ , O ₃ and COVID-19 mortality (OR 1.172 [95% CI 1.005–1.369], 1.200 [1.026–1.414] and 8.503 [2.029–35.626])	Adjusted for population density and individual-level data from UK Biobank
OGEN [33]	Europe (66 administrative regions in four countries: Italy, France, Germany, Spain)	Jan to Feb 2020	Tropospheric concentrations of NO ₂ (Sentinel-5P data) taking into account vertical airflow	Number of deaths collected from each country	Data from the Sentinel-5P showed two main NO ₂ hotspots over Europe: Northern Italy and Madrid metropolitan area, regions in which COVID-19 mortality has been particularly high	Long-term exposure defined as a 2-month period (Jan to Feb 2020)
COLE [34]	The Netherlands (355 municipalities)	Up to 5 June 2020	Annual concentrations of PM _{2.5} , NO ₂ or SO ₂ , averaged over the period 2015–2019	Number of cases, hospital admissions and deaths	A 1 µg·m ⁻³ increase in PM _{2.5} concentrations associated with 9.4 more COVID-19 cases, 3.0 more hospital admissions and 2.3 more deaths	The relationship was observed in rural settings and persisted after controlling for a wide range of explanatory variables and a number of sensitivity and robustness exercises including instrumenting pollution to mitigate potential endogeneity and modelling spatial spill-overs using econometric techniques
POZZER [35]	Worldwide	Up to June 2020	Chronic exposure to PM _{2.5} in the years prior to the COVID-19 outbreak estimated on the basis of satellite observations over the year 2019	Mortality rate ratios attributed to air pollution in the COVID-19 pandemic [34] and the SARS-CoV-1 epidemic [11]	PM _{2.5} contributes 15% [95% CI 7–33%] to COVID-19 mortality worldwide, 27% [95% CI 13–46%] in East Asia, 19% [95% CI 8–41%] in Europe and 17% [95% CI 6–39%] in North America	Relative risk (or hazard ratio) of excess COVID-19 mortality for USA and SARS-CoV-1 in China (assuming that SARS and COVID-19 mortality are similarly affected by long-term exposure to air pollution) from long-term exposure to air pollution using the exposure-response function of the WHO to estimate the attributable fraction

COVID-19: coronavirus disease 2019; PM_x: particles with a 50% cut-off aerodynamic diameter of x µm; AQI: Air Quality Index; SARS-CoV-1: severe acute respiratory syndrome-coronavirus-1; GAM: generalised additive model; R²: coefficient of determination defined as the proportion of the variance in the dependent variable (COVID-19 outcomes) that is predictable from the independent variable(s); IQR: interquartile range; BMI: body mass index; WHO: World Health Organization. #: according to the ENSEMBLE multi-model that combines the values of other seven models: CHIMERE METNorway, EMEP RIUUK, EURADIM KNMI/TNO, LOTOS-EUROS SMHI, MATCH FMI, SILAM Météo-France and MOCAGE UKMET (www.regional.atmosphere.copernicus.eu).

Germany and Spain reported a positive association between PM_{2.5} and PM₁₀ concentrations between February and April 2020 and the number of SARS-CoV-2 infected cases, while a negative association was found for O₃ [33].

In China, city-specific effects of PM₁₀ and PM_{2.5} on daily confirmed COVID-19 cases were examined in more than 70 cities. Short-term lagged (7 and 14 days) increases in PM_{2.5} were associated with daily COVID-19 confirmed cases, and the magnitude of effect was greater for PM_{2.5} compared to PM₁₀ [26]. Another study in China looked at short-term levels of six different pollutants (PM_{2.5}, PM₁₀, SO₂, CO, NO₂ and O₃) in 120 cities to determine their association with daily COVID-19 confirmed cases. The study reported an approximate 2% increase in daily COVID-19 cases for every 2-week lagged 10 µg·m⁻³ increase in PM_{2.5} and PM₁₀ [27]. A pre-print study also reported a positive association between NO₂ levels measured with a 12-day time-lag and the spread of COVID-19 (estimated with the basic reproduction number R₀) in 63 Chinese cities, after adjustment of temperature and humidity [25].

Regarding the role of long-term exposure to air pollution, an Italian study reported that mean levels of NO₂, O₃, PM_{2.5} and PM₁₀ during the past 4 years, as well as the number of days exceeding the limit values established by the European Commission during the past 3 years, were both correlated with the number of COVID-19 cases in Italy [29]. A UK study using individual data from the UK Biobank of 1450 participants, including 669 COVID-19 confirmed cases, that adjusted the models for confounding variables, reported significant positive associations of PM_{2.5} and PM₁₀ with SARS-CoV-2 infectivity [32].

In addition, to explore the link between air pollution and the spread of COVID-19, several studies have analysed the effect of air pollution on the prognosis of COVID-19. Although these studies answer a different question and may also have their own weaknesses, exploring the prognosis of COVID-19 is less influenced by the dynamics of infection and thus leads to less internal validity threats such as unmeasured confounding. In terms of COVID-19 mortality, NO₂ was found to be related to COVID-19 in a study covering Italy, Spain, Germany and France that revealed 83% of COVID-19 fatalities occurred in the regions with the highest NO₂ levels [33]. In an Italian study, COVID-19 mortality on 31 March 2020 was twice as high in the regions with the highest levels of PM_{2.5} compared to that in the regions with the lowest levels of PM_{2.5} [20].

Interpretations of these short- and long-term effects should be made in the context of their respective epidemiologic designs. Since all of the previously mentioned studies were ecological and cross-sectional, individual-level inferential statements cannot be derived. The currently available ecological studies have an inherent internal validity threat, unmeasured confounding bias. Potential confounders such as population density, socioeconomic composition, access to healthcare and social distancing measures could also explain the findings. However, a US study examined the link between long-term ambient fine particulate concentrations and COVID-19 mortality taking these into account. This study, adjusted for multiple county-level confounders, covered more than 3000 US counties and examined whether the COVID-19-related mortality per capita varied by estimated county level PM_{2.5} concentrations across the 2000–2016 period. After adjusting for population density, average body mass index, levels of poverty, smoking rates, average temperature, humidity, and the number of tests performed in each state, the study concluded that a 1 µg·m⁻³ increase in long-term PM_{2.5} concentration was associated with an 8% increase in COVID-19 mortality, which is a factor of 10 higher than all-cause mortality rates in the same counties reported in a previous analysis [30]. By taking into account the time of virus introduction in each county, this study also took into account the dynamic of the disease. Although this study adjusted for potential confounders, it is based on the assumption that previous PM_{2.5} concentrations were still representative of those during 2016–2020. Another limitation comes from the fact that many of the county-level adjustment factors resulted from the Behavioral Risk Factor Survey that excluded institutionalised residents, whereas they represent a large part of COVID-19 deaths [36].

Recently, another large study conducted at the county level in the USA showed a significant relationship between long-term exposure to NO₂ and COVID-19 mortality [31]. This study used both single and multi-pollutant models and controlled for spatial trends and a comprehensive set of potential confounders including state-level test positive rates, county-level healthcare capacity, phase-of-epidemic, population mobility, socio-demographics, socioeconomic status, behaviour risk factors, and meteorological factors. Furthermore, the previously mentioned UK study, adjusted for population density, found that the levels of SO₂ and NO₂ recorded between 2018 and 2019, were positively linked to COVID-19 cases and COVID-19 mortality, while O₃ was negatively correlated [32]. Although population density is important because it can promote both viral spread and air pollution, it fails to explain why some highly populated regions have larger numbers of COVID-19 cases and fatalities, pointing to socioeconomic and racial inequalities, including disparities related to environmental exposure. Recent data from the USA indicate that the number of COVID-19 cases and fatalities experienced by Black citizens were higher (up to 75%) than in

the rest of the population, although they constitute only a small proportion (32% at maximum) of the overall population [38]. Outside conventional epidemiology, comprehensive econometric methods were applied to study the effect of PM_{2.5} and COVID-19 cases, hospitalisations and deaths in all 355 municipalities in the Netherlands [34]. The authors attempted a number of sensitivity analyses to account for unmeasured confounding (or omitted variable bias as commonly known in econometrics), measurement error in the exposure and the outcome and spatial spill-over. They found that a 1 µg·m⁻³ increase in long-term PM_{2.5} is associated with nine additional cases, three additional hospital admissions, and two additional deaths. Interestingly, this study found that the relationships between air pollution and COVID-19 are also observed in rural zones, which suggests that air pollution plays a direct role in impacting COVID-19, independent of an urban setting with all its characteristics, such as density or crowding. In those rural zones, PM_{2.5} mainly arises from agricultural sources and especially from intensive livestock farming that leads to NH₃ release. By interacting with other gaseous pollutants such as NO_x, atmospheric NH₃ leads to PM_{2.5} formation. In Europe, agriculture is one of the main sources of PM_{2.5} [39].

Additional limitations of these observational studies include the fact that most environmental health studies estimate conditional associations between non-randomised environmental exposures and health outcomes by directly regressing observed data without conceptual and design stages [40], an approach that is well documented to not guarantee valid causal inferences in general, especially in air pollution studies in which environmental exposures can be correlated with each other and effects are small [41, 42]. Disentangling independent air pollutant effects has been a challenge for observational studies, but can be achieved if the latter is embedded into a hypothetical multi-pollutant randomised experiment [42]. Moreover, to assess the robustness of epidemiological conclusions, air pollution studies should systematically consider sensitivity analyses that either: 1) vary the magnitude of the relationships between the unmeasured background covariates and both the exposure assignment mechanism and the outcome; or 2) study deviations from the assumed exposure assignment mechanism. Further investigations taking into account these limitations are needed to better understand the relationship of air pollution exposure to COVID-19.

Potential mechanisms explaining the relationship between air pollution and COVID-19 morbidity and mortality

How does air pollution affect COVID-19 comorbidities?

Air pollution and COVID-19 impact the same organs (figure 1). The course of COVID-19 indicates the very important role of the existence of comorbidities, which significantly increase a patient's risk profile.

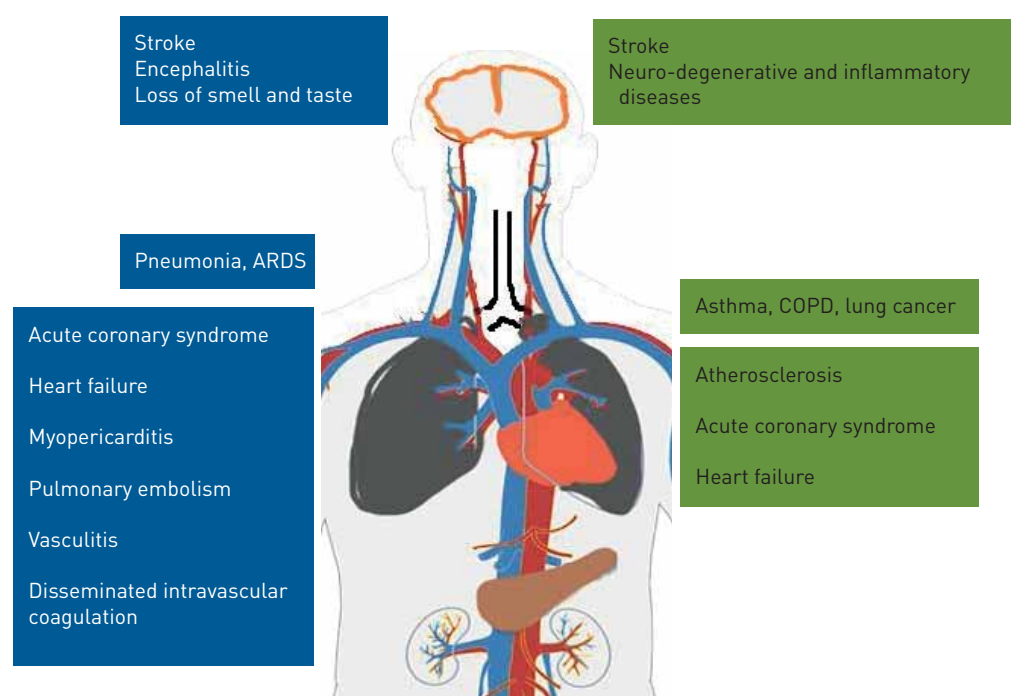


FIGURE 1 Target organs and the main diseases that coronavirus disease 2019 (blue) and air pollution (green) share. ARDS: acute respiratory distress syndrome.

These include many chronic diseases such as cardiopulmonary and metabolic diseases, which air pollution adversely contributes to through both long- and short-term/acute air pollution exposure. This may explain why exposure to air pollution could indirectly predispose people to severe and more lethal forms of COVID-19, as suggested by epidemiological studies. In addition, air pollution may facilitate viral entry into the body *via* several processes. Herein, we review the main physiological systems affected by both air pollutants and SARS-CoV-2 and discuss the underlying mechanisms.

Impact on the respiratory system

Respiratory effects of COVID-19 range from mild illness of the upper airways to severe pneumonia and acute respiratory distress syndrome (ARDS). Air pollution affects the respiratory system through lung inflammation and oxidative stress that lead to short- and long-term effects on obstructive airway diseases such as asthma and COPD, and restrictive lung parenchyma diseases such as fibrosis [43, 44]. By weakening the respiratory system, air pollution could increase the severity of SARS-CoV-2 pneumonia, as suggested by the fact that children exposed to high NO₂ concentrations are more likely to have severe forms of virus-induced asthma [45]. Additionally, it is well-documented that air pollution is correlated with chronic rhinitis and rhinosinusitis, which may increase airway mucosal permeability and allow for an easier penetration of SARS-CoV-2 [46, 47]. Recently, it has been suggested that nasal epithelial cells may be the primary access for SARS-CoV-2 [48]. SARS-CoV-2 uses angiotensin converting enzyme-2 (ACE2) receptors in the nasal and upper airways for cellular entry, which in turn, requires the cleavage of the spike protein by proteases and then, the binding of the spike protein to a specific cellular receptor such as ACE2 [48]. A study reported that inhibitors of proteases could be efficient to block viral entry [49]. As discussed later in this review (see the section *In vitro* studies), air pollution may actually activate proteases and thus facilitate viral entry in the cells. ACE2 receptors are found in several organs targeted by COVID-19, including the cardiovascular system [50].

Impact on the cardiovascular and metabolic system

Long-term exposure to air pollution increases all-cause mortality, particularly cardiovascular mortality. An annual increase of 10 µg·m⁻³ in PM_{2.5} has been associated with an 11% increase in cardiovascular mortality [51]. Similarly, a short-term increase in PM_{2.5} was associated with an increase in acute cardiovascular events [52]. In particular, stroke and ischaemic heart diseases drive the majority of air pollution-related mortality [53, 54]. The underlying mechanisms for the adverse cardiovascular effects of air pollution include oxidative stress and systemic inflammatory reactions that can be measured in the lungs and in the blood, such as increases in interleukin (IL)-1, IL-6, IL-8, IL-18, tumour necrosis factor-α, vascular endothelial growth factor, or intercellular adhesion molecule-1 [4, 55]. Systemic oxidative stress through reactive oxygen and nitrogen species can lead to endothelial dysfunction, characterised by vasoconstriction/vasodilation imbalance, platelet activation, and leukocyte vascular adhesion that finally lead to atherothrombosis, myocardial infarction and stroke [4].

Several studies have reported that serious forms of COVID-19 are also associated with vascular endothelial inflammation and dysfunction [56]. Cardiovascular impairment of COVID-19 includes myopericarditis, acute coronary syndromes and heart failure, as well as vascular thrombotic diseases such as pulmonary embolism, vasculitis and disseminated intravascular coagulation that can lead to multiple organ failure. Severe forms of COVID-19 are also associated with systemic inflammation, and increased pro-thrombotic factors and markers of inflammation such as antiphospholipid antibodies, fibrinogen and D-dimer. Systemic acute inflammation in severe forms of COVID-19 is associated with increased levels of IL-6 and macrophage activation syndrome (also referred to as cytokine storms) that can lead to multiple organ failure [3]. Moreover, systemic inflammation in COVID-19 may play a role in destabilising coronary plaques resulting in acute coronary syndrome [57].

Air pollution is also involved in developing cardiometabolic risk factors like hypertension and insulin resistance [58, 59]. Chinese studies have found that hypertension or coronary heart disease were prevalent in about 38% of COVID-19 patients, whereas diabetes was prevalent in approximately 19% of patients [60]. Additionally, these patients showed higher risk of mortality from COVID-19 [61].

Impact on the neurological system

Neurological impairments in COVID-19, other than cerebrovascular diseases, include loss of smell and taste and encephalitis, and it has been described that SARS-CoV-2 could also be a neurotropic invasive virus that is site specific for the olfactory system [62]. In addition, evidence shows that ultrafine particulate matter can enter the olfactory epithelium then translocate to the olfactory bulb and potentially migrate to the olfactory cortex, thus implicating air pollution in the development of neurodegenerative disorders and neuroinflammatory diseases [63, 64]. However, although ultrafine particles and SARS-CoV-2 share the

same mechanisms of migration through the olfactory nerves, to date, there is actually no evidence that exposure to ultrafine particles increases the risk of neurological impairment by SARS-CoV-2.

How might air pollution interact with SARS-CoV-2 in the human body? Evidence from experimental studies

Aside from the impact of air pollution on COVID-19 comorbidities at the population level, air pollutants may also decrease the immune response and facilitate respiratory virus replication as suggested by experimental studies that have explored the effect of concomitant exposure to air pollutants and respiratory viruses.

Human studies

A study involving 222 children reported that those living close to an electronic waste area with high PM_{2.5} concentrations had significantly decreased levels of salivary agglutinin (one of the primary antimicrobial proteins and peptides) compared to children living in a less polluted area [65]. In a randomised double-blind study in which volunteers were exposed to either ambient air or air with high levels of NO₂, in an environmental chamber, analysis of bronchoalveolar lavage has demonstrated that macrophages were less efficient in inactivating the influenza virus when individuals were previously exposed to NO₂ compared to ambient air [66]. In another randomised double-blind study, nonsmoking volunteers were exposed to wood smoke particles or filtered air before nasal inoculation with a vaccine dose of live attenuated influenza virus. When exposed to smoke particles, nasal lavage revealed reduced levels of interferon- γ -induced protein-10, which may lead to a decrease in immune response to viral infection, as interferon- γ -induced protein-10 is involved in the recruitment of cytotoxic lymphocytes [67]. In another double-blind randomised study including both healthy volunteers and volunteers with allergic rhinitis, nasal inoculation of live attenuated influenza virus was performed after 2 h of exposition to diesel exhaust or clean air and concluded that diesel exposure led to eosinophil activation and increased viral replication in the allergic group, highlighting the fact that diesel exhaust promotes inflammation and reduces virus clearance in allergic patients [68].

In vitro studies

As suggested by human studies, *in vitro* studies have also reported that air pollution may reduce antimicrobial activity through the downregulation of antimicrobial proteins and peptides (e.g. salivary agglutinin and surfactant protein D) in respiratory mucosal fluid [69]. In the epithelial lining fluid of the human respiratory tract, air pollutants, in particular O₃ and PM, induce oxidative stress and the formation of reactive oxygen species that lead to antioxidant and surfactant depletion [70]. A similar experimental study demonstrated that when RSV is associated with ultrafine particles from combustion sources (e.g. those found in diesel exhaust) and then incubated with an epithelial cell culture, the inflammatory response was elevated compared to that from RSV alone [13, 71]. Another *in vitro* study examining human lung epithelial cells infected by the H1N1 virus also showed that *in vitro* exposure to secondary organic aerosols, which are part of combustion-derived particles (e.g. traffic or heating), led to cell apoptosis and increased viral replication [72].

Studies using environmental chambers have investigated the interactions between fine particles and different types of bacteriophage viruses, which were mixed with each other and brought into contact with host bacteria. When the air and virus mixture was previously filtered through a high-efficiency particulate absorbing filter, which removes a large fraction of fine particles, the activity of the viruses on the host bacteria was significantly modified: for some viruses, the presence of fine particles had a potentiating effect on viral infection, whereas for other viruses, fine particles significantly reduced viral replication [73]. This study illustrates the fact that the chemical and electrical characteristics of both particles and viruses play an important role in virus–particulate matter interactions. Regarding NO₂ and O₃ and concomitant exposure to rhinovirus, a major increase in the production of IL-8 in human nasal and bronchial epithelial cells was seen, as well as a decrease in macrophage activity [13]. In human nasal epithelial cells exposed to influenza A, pre-exposure to O₃ increases viral replication due to an increase in cellular protease activity resulting from oxidative stress [74]. Proteases play an essential role in driving the cleavage of the viral membrane protein hemagglutinin and of the spike protein, necessary for viral entry into the host cells [75, 76]. This proteolysis plays an important role in the spread of several respiratory viruses, including both SARS-CoV-1 and SARS-CoV-2 [48, 49].

Animal studies

When mice are exposed to RSV after being exposed to ultrafine particles from combustion sources, studies found a significant decrease in immune response, specifically, a decrease in tumour necrosis factor- α , lymphocytes and interferons in bronchoalveolar lavage fluid, which was followed over the next 7 days, by

an exacerbation of inflammation and infection [13]. In another study, authors observed a significant reduction in the phagocytosis capacity of macrophages when they were previously exposed to ultrafine particles from combustion sources [13]. Similar results were observed when mice were previously exposed to high concentrations of NO₂ for 2 days and then exposed to murine cytomegalovirus [13]. The amount of virus needed in order to become infected was 100 times lower than that for mice exposed to ambient air. O₃ exposure in mice led to different results depending on time and duration of exposure. In particular, when exposure to O₃ occurred at the same time as viral infection, O₃ may have had an antiviral activity [13, 77, 78]. This paradoxical protective effect of O₃ may be explained by its oxidising behaviour, degrading viral macromolecules such as lipids, proteins and nucleic acids. As an example, O₃ has an antimicrobial effect in high concentrations and is used to disinfect waterborne pathogens, *e.g.* ozonated water used in dental medicine and O₃ treatment for sewage water [79, 80]. However, for O₃ to decrease viral suspension in the air, the O₃ must be present in high concentrations, which are not seen by current ambient levels. Thus, we do not expect the overall effect of O₃ to decrease the viral load within humans or animals, but rather to impair immune response.

In rats, exposure to PM, especially ultrafine particles, induces the expression of the renin-angiotensin-aldosterone system (RAAS) and increases the expression of AT1R, a receptor of angiotensin 2, which is involved in lung and heart injuries [81, 82]. RAAS is involved in several diseases: while angiotensin 2 (through AT1 receptors) leads to vasoconstriction and inflammation, ACE2 receptor converts angiotensin 2 into protective angiotensin 1–7 with anti-inflammatory and vasodilating properties [83]. Severe forms of COVID-19, such as ARDS, have been associated with ACE2/AT1R imbalances [83, 84]. Although the exact role of RAAS on the severity of COVID-19 is still unclear, we know that SARS-CoV-2 uses the ACE2 receptor to enter the cells, which may lead to an increase in bioavailability and toxicity of angiotensin 2 through AT1R. In addition to the possible increase of AT1R expression due to PM, previous studies on rats have also reported that NO₂ exposure induces the expression of ACE (angiotensin-converting enzyme that converts angiotensin 1 into angiotensin 2) and increases the liaison of angiotensin 2 to AT1R [85]; however, further studies are needed to explore the exact role of RAAS on the severity of COVID-19 and the possible role of air pollution.

How does air pollution interact with SARS-CoV-2 in the air?

In addition to their interactions with the body, air pollutants and respiratory viruses show complex interactions in ambient air which can influence the persistence of the virus in the air. Of extreme importance in the investigation of the relationship between air pollution and SARS-CoV-2 are: 1) the mode of transport or transmission of SARS-CoV-2; and 2) the possible physicochemical interactions between respiratory viruses and pollutants present in ambient air.

Droplets and aerosols

The physical size of SARS-CoV-2 is approximately 70–130 nm and its transmission mainly arises through the emission of macro droplets of 50–100 µm, *e.g.* through coughing and sneezing. Macro droplets consist of the virus in the centre, surrounded by water molecules and also mucus or cellular debris. These macro droplets are heavy and fall rapidly to the ground, which is why a safety distance of 2 m has been established by the health authorities in order to limit viral transmission. Macro droplets can also be deposited on solid surfaces where viral RNA is still quantifiable several hours later [86]. As has been demonstrated for influenza and measles, and suspected for SARS-CoV-1, recent studies are also considering SARS-CoV-2 transmission by aerosols formed by micro- and nano-droplets, also called droplet nuclei and defined as a suspended system of solid or liquid particles <5 µm in the air [87–90]. Depending on the particle mass, aerosols are able to remain suspended in the air for several hours and studies have found that SARS-CoV-2 RNA is still detected in the air 3 h after being emitted [86]. The role of airborne transmission of SARS-CoV-2 in COVID-19 is getting more recognition now. Some doubt remains about the pathogenicity of SARS-CoV-2 in suspensions because aerosols are smaller than macro droplets, and may contain fewer viable viruses but, in a recent study, increases in viral SARS-CoV-2 RNA during cell culture of the virus from recovered aerosol emitted by patients through breathing or speaking demonstrated the presence of infectious, replicating virions in <1 µm aerosol samples at a significant level (*p*<0.05) [91]. Western blot and transmission electron microscopy analysis of these samples also showed evidence of viral proteins and intact virions. The infectious nature of aerosols collected in this study suggests that airborne transmission of COVID-19 is possible, and that aerosol prevention measures are necessary to effectively stem the spread of SARS-CoV-2. Other studies are needed to support it.

Airborne SARS-CoV-2 and PM and related mechanisms

Regardless of infectivity, SARS-CoV-2 emitted in aerosol form, for example from breathing, should behave like ultrafine particles arising from other sources, such as road traffic and heating. Viruses may mix with

other suspended ultrafine particles, and thus may agglomerate to form particles of various sizes through aggregation condensation of ultrafine particles and nucleation of gaseous precursors [92, 93]. It is also well known that particles may serve as vectors for various substances such as pollen and microorganisms, including bacteria, fungi and viruses [94, 95]. It has previously been demonstrated that viruses are carried by fine particles. For example, a study has shown that the avian influenza virus was transmitted by dust particles between separated chicken groups [96]. SARS-CoV-2 RNA has recently been detected on PM in the Bergamo Province, Northern Italy, collected over a continuous 3 week period by two independent air samplers [97]. However, the presence of viral RNA does not necessarily mean viral infectivity, which depends on viral structural integrity, such as surface glycoproteins and sufficient viral concentration [98].

How do weather-related conditions impact the air pollution–virus interaction?

Meteorological conditions may also play an important role in air pollution–virus interactions. Although, a recent study did not find any evidence of an association between solar UV radiation and COVID-19, several studies have shown that UV radiation has antibacterial and antiviral impacts, both through a direct effect and through the formation of O₃ and reactive oxygen species [99, 100]. Air pollution, especially PM, can reduce UV penetration, as demonstrated by several studies which reported that air pollutants such as PM significantly reduce the amount of UVB received by the body and thus, lead to reduced vitamin D synthesis [101–105]. In high concentrations, O₃ can also filter UVB and can lead to decreased vitamin D levels. Vitamin D has an antioxidant activity, which has protective effects against respiratory viral infections and against oxidative stress due to air pollution [106, 107]. In addition, studies also reported that vitamin D modulates the inflammatory response to viral infections, regulates the RAAS and that reduced levels of vitamin D may play a role in the severity of COVID-19 [108, 109].

Regarding the influence of relative humidity, several studies have reported negative associations with SARS-CoV-2 transmission [110, 111]. As viral droplets contain water, humidity may play a role in

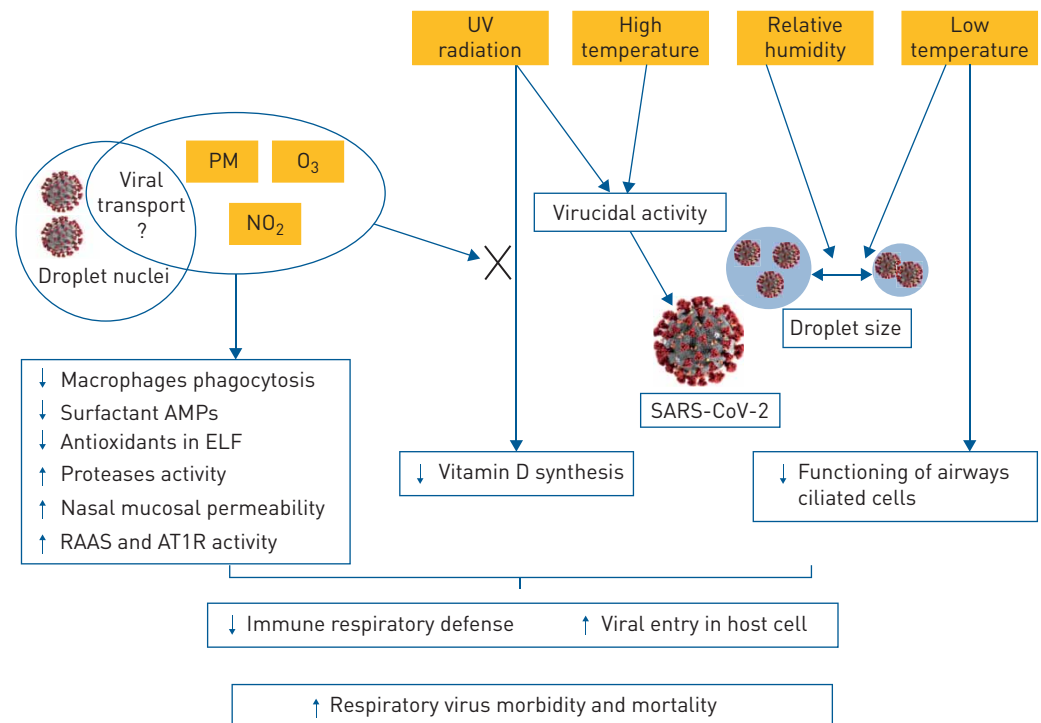


FIGURE 2 Air pollutants/virus interaction according to atmospheric conditions. Relative humidity plays a role in the desiccation or hydration of viral droplet and, thus, influences the size of the droplet and the persistence of respiratory viruses in the air. Solar ultraviolet (UV) radiations have *in vitro* antiviral activity and lead to an increase in vitamin D synthesis. Atmospheric air pollutants may lead to decreased UV penetration leading to reduced vitamin D synthesis. Temperature influences the size of the viral droplet. In addition, low temperatures decrease the functioning of airways ciliated cells, while high temperatures may have antiviral activity. Droplet nuclei refers to viral droplets $\leq 5\mu\text{m}$, it is also called viral airborne or viral aerosol. In addition to the common effect of air pollutants, which lead to a decrease in immune respiratory defence, particulate matter (PM) may be involved in respiratory virus transport. AMP: antimicrobial proteins and peptides; ELF: epithelial lining fluid; RASS: renin-angiotensin-aldosterone system; AT1R: angiotensin 2 receptor type 1.

evaporation and rehydration of viral aerosols, and thus be involved in viral stability, but its actual role in viral transmission and viral activity remains unknown [112]. Although there is as yet no consensus on the subject, it seems likely that a decrease in humidity leads to dehydration of macro droplets into smaller droplets that are able to remain in suspension in the ambient air, while an increase in humidity may lead to increased water content of viral droplets, and thus increased weight, enabling them to fall to the ground faster.

Whereas colder conditions lead to an increase in other respiratory viral transmissions such as influenza, we have found contradictory results on the link between COVID-19 and temperature [113]. Although several studies found that temperature was negatively associated with COVID-19 mortality and transmission, another study did not find any evidence of an association [23, 109, 111]. As recently reported, dry (relative humidity <20%) and cold air affects both immunity and viral spread owing to the fact that dry air may facilitate airborne viral transport, and that cold conditions, in addition to low humidity, may impair the functioning of airways ciliated cells [113]. Relative humidity and temperature also have an influence on ambient air pollution concentrations. In a cold season, the dense cold air causes a temperature inversion, which reduces air mixing and thus, exacerbates existing particulate pollution. The persistence of air pollutants can also be influenced by the lack of wind, preventing dispersion. Finally, atmospheric conditions that promote PM formation and stagnation may also promote SARS-CoV-2 persistence in the air [22]. In contrast, sunny days with hot temperatures and solar UV radiation increase the oxidative potential of the atmosphere, leading to higher O₃ concentrations and may also lead to a reduced viability of SARS-CoV-2 in the air.

Discussion

Interactions between air pollutants and SARS-CoV-2 are summarised in figure 2. Existing literature suggests that PM and gaseous pollutants may act on COVID-19 in several ways. Air pollution may increase COVID-19 morbidity and mortality through its action on associated comorbidities. Experimental studies conducted for other respiratory viruses support the hypothesis that air pollution exposure may facilitate the occurrence of COVID-19 infection through a decrease in immune response. *In vitro*, animal and human studies have reported that exposure to air pollutants leads to increased mucosal permeability and oxidative stress, decreased antioxidants and surfactant antimicrobial proteins, as well as impaired macrophage phagocytosis. In addition, SARS-CoV-2 entry in host cells through ACE 2 requires the cleavage of the viral spike protein by proteases, and such protease activity may be increased by air pollution, as is documented for several other respiratory viruses.

In ambient air, pollutants and respiratory viruses show complex interactions. According to their composition, PM and viruses can interact and modify viral activity as shown by *in vitro* studies. In addition, PM is known to carry microorganisms such as viruses, and SARS-CoV-2 RNA has been identified on PM. It is still unclear, however, how long this virus remains infectious in ambient air and whether the low viral load contained within the aerosol is sufficient to induce infection. Atmospheric interactions between gases and viruses are also complex and depend on meteorological contributing factors such as UV radiation and relative humidity. By reducing UV radiations (which have antiviral activity) air pollutants may promote viral persistence in ambient air and also reduce vitamin D synthesis, and thus may play a role in the immune response against viral infections.

Although there is a need for more specific studies exploring interactions between air pollutants and SARS-CoV-2 in the ambient air and their impact on human health, this review highlights that both short- and long-term exposures to air pollution may be important aggravating factors for SARS-CoV-2 transmission and COVID-19 severity and lethality through multiple mechanisms. Future studies should also examine the role of indoor air pollution, in particular biomass and tobacco smoke, in COVID-19. The fact that both biology and atmospheric chemistry are separately implicated suggests that a more holistic approach to disease management and mitigation is necessary both in addressing the current COVID-19 pandemic and future viral epidemics. We cannot ignore that our surrounding environment may be exacerbating not only chronic disease, but infectious disease as well. In the light of these relationships between air pollution and COVID-19, and by virtue of the precautionary principle, we recommend the reduction of air pollution from all sources, especially that from road traffic and heat generation, through the reinforcement of public health policy.

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