Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A review on the biological, epidemiological, and statistical relevance of COVID-19 paired with air pollution

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ABSTRACT

This narrative review paper is aimed to critically evaluate recent studies of the associations between air pollution and the outcomes in the COVID-19 pandemic. The main air pollutants we have considered are carbon monoxide (CO), nitrogen dioxide (NO_2), ground-level ozone (O_3), particulate matter ($PM_{2.5}$ and PM_{10}), and sulfur dioxide (SO_2). We, specifically, evaluated the influences of these pollutants, both individually and collaboratively, across various geographic areas and exposure windows. We further reviewed the proposed biological mechanisms underlying the association between air pollution and COVID-19. Ultimately, we aim to inform policy and public health practice regarding the implications of COVID-19 and air pollution.

1. Introduction

The global scale of the ongoing pandemic of coronavirus disease 2019 (COVID-19) is unmatched in our lifetime. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the type of coronavirus that causes COVID-19 disease. (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020, Grant et al., 2020) Common symptoms include headache, loss of smell and taste, nasal congestion and rhinorrhea, cough, muscle pain, sore throat, fever, diarrhea, and breathing difficulties. (Clinical characteristics of COVID-19 2022) COVID-19 transmission occurs via person-to-person contact through respiratory droplets and airborne aerosol transmission. (Transmission of COVID-19 2022)

Now in the third year of the COVID-19 pandemic, our knowledge-base regarding risk factors for increased transmission and disease severity has greatly improved. A growing body of evidence has highlighted the important role of environmental factors, including air pollution. Here, we first reviewed the epidemiological and statistical evidence regarding the impact of air pollution on COVID-19 outcomes. We paid specific attention to the geographic variation in these associations, the different types of air pollutants evaluated and the variation in air pollutant exposure window (long-term versus short-term exposure). Second, we evaluated proposed plausible biological mechanisms of interaction between air pollutants and this novel coronavirus.

2. Air pollutants

Air pollution is a leading environmental cause of disease and premature death globally. (GBD 2017 Risk Factor Collaborators 2017) The Environmental Protection Agency has identified six criteria pollutants, namely; carbon monoxide (CO), particulate matter ($PM_{2.5}$ and PM_{10}), ground-level ozone (O_3), nitrogen oxides (NO_2), sulfur oxides (SO_2), and lead. (Air Pollutants | Air | CDC. Published 2021)

CO is the most dangerous product of incomplete fossil fuel combustion. The hemoglobin affinity for CO is even greater than that of oxygen (O_2). Thus, when inhaled by humans, CO can result in decreased peripheral and cerebral oxygenation causing symptoms ranging from headache, confusion, chest pain and dyspnea to loss of consciousness or death. (Manisalidis et al., 2020)

Particulate matter refers to the solid and liquid particles suspended in the air. Fine particulate matter is produced as a byproduct of fossil fuel combustion and is characterized by the diameter of the particle. $PM_{2.5}$ comprises inhalable particles with diameters 2.5 micrometers or smaller, while PM_{10} particles are 10 micrometers or smaller. Inhalation of $PM_{2.5}$ and PM_{10} can cause mechanical trauma to human airways. (Manisalidis et al., 2020)

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Ground level ozone forms as a secondary pollutant from the reaction between nitrogen oxides (NO_x) and volatile organic compounds (VOCs). When inhaled, O_3, can penetrate deep into the lungs causing inflammation. (Manisalidis et al., 2020)

Similarly, NO_2, increases bronchial sensitivity. (Hesterberg et al., 2009) Primarily a traffic-related air pollutant, high atmospheric concentrations are associated with pulmonary edema and immune suppression. Long-term exposure can result in chronic lung disease. (Manisalidis et al., 2020)

Sulfur dioxide is primarily emitted from fossil fuel consumption and industrial activities, as well as natural sources such as fires and phytoplankton. SO_2 exposure increases the risk of respiratory tract infections, causing increased airway resistance. SO_2 can also interfere with airway mucus production. (Hesterberg et al., 2009, Chen et al., 2007)

Lastly, lead is emitted by industrial plants, petrol engines and some aircraft. Accumulating in bones, blood, and soft tissues, lead can have developmental and neurotoxic effects. Notably, little data exists addressing the role of lead exposure in COVID. (Manisalidis et al., 2020)

Researchers delineate the unique effects of each pollutant on human health, but, in reality, communities and individuals are exposed to sources (e.g. air pollution, heavy industry) that emit a mixture of all these pollutants. Although we will discuss research specifically addressing each criteria pollutant in turn, each pollutant should be conceptualized as more of a marker of a complex set of exposures, rather than an individual exposure itself.

3. Search methodology

We conducted a literature search of the National Library of Medicine's PubMed database (National Institutes of Health et al.). The search date was on November 23, 2021 and searched for the last one year. The "Air pollution" and "COVID-19" were used as the keywords for the searches, along with their synonyms, including "$PM_{2.5}$," "NO_2," "ozone," "O_3," etc., for air pollution, and "coronavirus," "SARS-CoV-2," etc., for COVID-19. Other key words included were "biological", "epidemiological", "Full text", "Classical Article", "Clinical Study", "Meta-Analysis", "Randomized Controlled Trial", "Review", "Systematic Review", and "English". We updated the search using the same strategy on April 1, 2022.

4. Epidemiological evidence on the impact of air pollution on COVID-19 mortality and infectivity

In this section, we surveyed epidemiological evidence on the impact of various air pollutants on COVID-19 mortality and infectivity. We further characterized the results by exposure window and geographic variation.

We identified literature evaluating the impact of all criteria pollutants on COVID outcomes except lead (Table 1). $PM_{2.5}$, NO_2 and O_3 were all frequently identified as culprits implicated in exacerbations of COVID-19 incidence and mortality. At the population level, positive associations between high air pollution levels and worse COVID-19 outcomes were identified despite significant variation in study design. Study approaches varied in methodologies of air pollution measurement, COVID-19 data collection (documented new cases, Emergency Department [ED] visits, deaths, etc.) and modeling strategy. Some authors evaluated bivariate correlations while others accounted for potential environmental and regional confounders. Despite this variation, the sum of existing evidence suggests that $PM_{2.5}$ and NO_2 likely exacerbate COVID-19. (Pansini and Fornacca, 2020, Lavigne et al., 2022, Sarkodie and Owusu, 2021, Zoran et al., 2020, Filippini et al., 2021) Using data extrapolated from the US and China, one group found the effect of $PM_{2.5}$ to be so significant as to contribute 15% to the overall COVID mortality burden. (Pozzer et al., 2020) Although a handful of studies failed to detect an effect for NO_2 or $PM_{2.5}$, (Liang et al., 2020, Xu et al., 2021) no studies found a protective effect from either.

On the other hand, evidence regarding ground-level ozone was mixed. Studies drawing on data directly from the US, China and Canada found no effect from O_3 on mortality ED visits. (Sarkodie and Owusu, 2021, Hendryx and Luo, 2020, Fattorini and Regoli, 2020, Zhu et al., 2020) Yet, several global studies and regional work in Italy and China identified a positive association between O_3 and COVID incidence. (Sarkodie and Owusu, 2021, Xu et al., 2021, Fattorini and Regoli, 2020, Zhu et al., 2020) Overall, such data suggest O_3 may increase vulnerability to COVID transmission without exacerbating the severity of disease.

Only one study identified any protective effects associated with air pollution exposure. Specifically, Zhu et al (2020) found SO_2 exposure within the preceding two weeks to be protective against COVID-19 incidence. (Zhu et al., 2020) The authors noted that these findings conflicted with work in other respiratory disease processes, where SO_2 exposure has been associated with worse outcomes. They proposed that SO_2 may have virucidal properties but emphasize the need for further investigation.

4.1. Geographic variation

Both air pollution and COVID-19 exposure vary significantly by topography and community. The studies we reviewed incorporated data from across the globe. However, Italy, the US and China were relatively over-represented compared to other nations. Such emphasis likely reflects the national capacity for tracking both COVID-19 and air pollution.

Overall, high-income countries were disproportionately represented in the literature we reviewed. China and Iran were the only middle-income countries evaluated, although some global studies incorporated data from cities of a wide variety of income levels around the world. However, even these more globally focused studies note the underrepresentation from low-income countries and the notable effect of this lack of data on confidence in results for these countries. (Pozzer et al., 2020) These differences likely greatly impact the amount and types of air pollution to which communities are exposed and the national public health infrastructure available to respond to the pandemic.

Studies in the US mostly found positive correlations to COVID-19 measures. One study that examined only $PM_{2.5}$ found a positive correlation with death rate. (21) Liang et al used county-level long-term pollutant exposure data in the US and showed mixed results; NO_2 correlated with COVID-19 case-fatality and mortality rates, while $PM_{2.5}$ and O_3 did not. (Liang et al., 2020) In Pansini and Formacca's multi-country study, the US data suggested that CO, NO_2, PM_{10}, $PM_{2.5}$ all were associated with exacerbated infection rates, death rates, and mortality rates. (Pansini and Fornacca, 2020)

For China, Zhu et al used a generalized additive model to find short-term $PM_{2.5}$, PM_{10}, CO, NO_2, and O_3 all were positively correlated with daily confirmed COVID-19 cases and SO_2 was negatively correlated. (Zhu et al., 2020) Pansini and Formacca reported CO, NO_2, $PM_{2.5}$, and PM_{10} all were positively associated with death rate and morality versus O_3 had no correlation. (Pansini and Fornacca, 2020)

Positive associations between air pollutant exposure and exacerbation of the COVID-19 pandemic were most consistently demonstrated in Italy. These positive correlations included short-term $PM_{2.5}$ and PM_{10} to number of new cases daily; (Zoran et al., 2020) long-term NO_2, O_3, $PM_{2.5}$, and PM_{10} and confirmed cases; (Fattorini and Regoli, 2020) short-term NO_2 and mortality; (Filippini et al., 2021) long-term NO_2, $PM_{2.5}$, PM_{10} with death and infection rates. (Pansini and Fornacca, 2020)

Rather than focusing on a specific region, some authors aggregated data on air pollution and COVID globally. Inherent in this study approach is the assumption that geography does not modify the effect of pollution exposure on COVID. While this assumption may be debated, these studies do provide broader guidance for global policymaking and pandemic readiness. In these studies, most findings were positive

Table 1
Epidemiologic Studies on COVID-19 and Air Pollution.

Title	Authors	Year	Journal	Geography	Pollutant (s)	Exposure Duration	Direction of Outcome	Outcome
Role of the chronic air pollution levels in the COVID-19 outbreak risk in Italy	Fattorini D & Regoli F	2020	Environ Pollution	Italy	NO_2 O_3 $PM_{2.5}$ PM_{10}	Long-term	Exacerbated COVID *incidence*	Pearson correlations across 71 Italian provinces were significant for the following exposure measures and outcomes; - Incidence of Covid-19 cases vs levels of A) NO_2, B) $PM_{2.5}$ and C) PM_{10} (four years means) - Incidence of Covid-19 cases vs number of days per year exceeding regulatory limits of D) O_3 and E) PM_{10} (three years means)
COVID-19 prevalence and fatality rates in association with air pollution emission concentrations and emission sources	Hendryx M & Luo J	2020	Environ Pollution	United States	O_3 $PM_{2.5}$	Long-term	No effect on COVID *prevalence* or *mortality*	When accounting for diesel particulate matter (DPM), neither O_3 nor $PM_{2.5}$ were found to have a significant association with COVID-19 prevalence or mortality in mixed linear multiple regression models.
Urban Air Pollution May Enhance COVID-19 Case-Fatality and Mortality Rates in the United States	Liang D, Shi L, Zhao J, Liu P, Sarnat JA, Gao S, Schwartz J, Liu Y, Ebelt ST, Scovronick N, Chang HH	2020	Innova-tion	United States	NO_2 O_3 $PM_{2.5}$	Long-Term	NO_2 exacerbated COVID *case-fatality* and *mortality rate* O_3 & $PM_{2.5}$ had no effect	County-level average NO_2 concentrations were positively associated with both COVID-19 case-fatality rate and mortality rate in single-, bi-, and tri-pollutant models (p-values$<$0.05). Concluded that long-term exposure to NO_2, which largely arises from urban combustion sources such as traffic, may enhance susceptibility to severe COVID-19 outcomes, independent of long-term $PM_{2.5}$ and O_3 exposure.
Regional and global contributions of air pollution to risk of death from COVID-19	Pozzer A, Dominici F, Haines A, Witt C, Münzel T, Lelieveld J	2020	Cardio Res	US China (estimate worldwide effects)	$PM_{2.5}$	Long-term	Exacerbated COVID *mortality*	Applied the global atmospheric chemistry general circulation model (EMAC) to estimate that particulate air pollution contributed 15% to mortality (95% confidence interval 7–33%) to COVID-19 mortality worldwide (27% (13 – 46%) in East Asia, 19% (8–41%) in Europe, and 17% (6–39%) in North America).
Exposure to Air Pollution and COVID-19 Mortality in the United States	Wu X, Nethery RC, Sabath MB, Braun D, Dominici F	2020	Science Advance	United States	$PM_{2.5}$	Long-term	Exacerbated COVID *mortality*	Developed a binomial mixed model and found that the association between long term $PM_{2.5}$ exposure and the COVID mortality rate ratio (MRR) which was 1.08 (1.02-1.15)for a 1mcg/m3 increase in $PM_{2.5}$
Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China	Zhu Y, Xie J, Huang F, Cao L	2020	Total Environ	China	CO NO_2 O_3 $PM_{2.5}$ PM_{10} SO_2	Short-term	All exacerbated COVID *incidence*, except SO_2 reduced COVID *incidence*	Used a generalized additive model to determine the Spearman correlation coefficients with new confirmed COVID-19 cases, incorporating lag effects. Across multiple lags (0-21 days), $PM_{2.5}$, PM_{10}, NO_2, O_3 and CO were all associated with increased daily counts of COVID-19 cases. SO_2 was negatively associated with COVID-19 confirmed cases across lag 0-14 days.

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Table 1 (*continued*)

Title	Authors	Year	Journal	Geography	Pollutant (s)	Exposure Duration	Direction of Outcome	Outcome
Assessing the relationship between surface levels of $PM_{2.5}$ and PM_{10} particulate matter impact on COVID-19 in Milan, Italy	Zoran MA, Savastru RS, Savastru DM, Tautan MN	2020	Sci Total Environ	Italy	$PM_{2.5}$ PM_{10}	Short-term	Both exacerbated COVID *incidence*	Identified a significant positive association between confirmed daily new cases and air pollution, PM_{10} & $PM_{2.5}$.
Associations between mortality from COVID-19 in two Italian regions and outdoor air pollution as assessed through tropospheric nitrogen dioxide	Filippini T, Rothman KJ, Cocchio S, Narne E, Mantoan D, Saia M, Goffi A, Ferrari F, Maffeis G, Orsini N, Baldo V, Vinceti M	2021	Sci Total Environ	Italy	NO_2	Short-term	Exacerbated COVID *mortality*	Ecological study utilizing negative binomial regression model identified positive, non-linear associations between high NO_2 trophospheric levels shortly before COVID 2020 lockdowns in several Italian provinces and mortality lagged at 14, 28 and 42 days.
Early Spread of COVID-19 in the Air-Polluted Regions of Eight Severely Affected Countries	Pansini R & Fornacca D	2021	Atmosphere	China United States Italy Iran France Spain Germany United Kingdom	$PM_{2.5}$ PM_{10} NO_2 CO O_3	Long-Term	China - CO, NO_2, $PM_{2.5}$ & PM_{10} exacerbated COVID *mortality* & *case-fatality*; O_3 had no effect United States - CO, NO_2, $PM_{2.5}$ & PM_{10} exacerbated COVID *incidence, mortality* & *case-fatality rates* Italy - NO_2, $PM_{2.5}$ & PM_{10} exacerbated COVID *incidence* & *case-fatality rate* Iran - NO_2 exacerbated COVID *incidence*; $PM_{2.5}$ had no effect France - NO_2 & $PM_{2.5}$ exacerbated COVID *case-fatality* Spain - NO_2 & $PM_{2.5}$ had no effect Germany - $PM_{2.5}$ reduced COVID *incidence* but exacerbated *case-fatality rate*; NO_2 had no effect United Kingdom - $PM_{2.5}$ & NO_2 had no effect on COVID *incidence* but exacerbated *case-fatality rate*	Assessed bivariable Kendall correlations for aggregated long-term air quality estimates with COVID incidence rates (per 100,000 inhabitants), COVID mortality rates (per 100,000 inhabitants) and case-fatality rates (deaths per infections).
Global effect of city-to-city air pollution, health conditions, climatic & socio-economic factors on COVID-19 pandemic	Sarkodie SA & Owusu PA	2021	Sci Total Environment	615 cities globally	NO_2 O_3 $PM_{2.5}$	Long-Term	All exacerbated COVID *incidence*	Aggregated city-level COVID data and aligned it with World Air Quality Index project data to develop ln-transformed linear models estimating the effect of air pollutants on incident COVID cases.
Weather, air pollution, and SARS-CoV-2 transmission: a global analysis	Xu R, Rahmandad H, Gupta M, DiGennaro C, Ghaffarzadegan N, Amini H, Jalali MS	2021	Lancet Planetary Health	211 countries globally	NO_2 O_3 $PM_{2.5}$ SO_2	Short-term	O_3 & SO_2 exacerbated COVID *reproduction number* $PM_{2.5}$ & NO_2 had no effect	Developed a linear model predicting the reproduction number utilizing daily documented infections and previously defined methods for estimating viral reproduction.
Short-term exposure to ambient air pollution and individual emergency department	Lavigne E, Ryti N, Gasparrini A, Sera F, Weichenthal S, Chen H, To T, Evans GJ, Sun L,	2022	Thorax	Canada	NO_2 O_3 $PM_{2.5}$	Short-Term	$PM_{2.5}$ & NO_2 exacerbated *COVID-19 ED visits* O_3 had no effect	Applied conditional logistic regression to a case-crossover study of 78,000 emergency department

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Table 1 (*continued*)

Title	Authors	Year	Journal	Geography	Pollutant (s)	Exposure Duration	Direction of Outcome	Outcome
visits for COVID-19: a case-crossover study in Canada	Dheri A, Lemogo L, Kotchi SO, Stieb D							(ED) visits in two Canadian provinces finding that ED visits were highest 3 days following elevated NO_2 and $PM_{2.5}$ ambient concentrations.

correlations. Sarkodie and Owusu investigated the effects of long-term exposure to $PM_{2.5}$, O_3, and NO_2 on aggregated city-level COVID-19 incidence and found a positive association. (Sarkodie and Owusu, 2021) Xu et al noted positive correlations for O_3 and SO_2 but no effect for $PM_{2.5}$ and NO_2. (Xu et al., 2021) Although Xu's study relied on many modeling assumptions and imputations for missing data, the model was robust to multiple iterations of simulated epidemiologic conditions. (Xu et al., 2021) Finally, Pozzer et al. extrapolated data from the USA and China to estimate that particulate air pollution contributed approximately 15% to COVID-19 mortality worldwide. (Pozzer et al., 2020)

Lastly, Pansini and Formacca's evaluated air pollution and COVID in 8 countries without aggregating the underlying data, enabling practical comparisons across national borders. (Pansini and Fornacca, 2020) In both Italy and Iran, air pollution independent of population density correlated with the distribution pattern of the virus for each country. $PM_{2.5}$ had no effect in Iran, the country whose initial COVID-19 data was most limited. No correlations between pollutants and COVID-19 were found in Spain, and this was attributed to fairly even distribution of high air quality levels nationally with minimal differences between provinces. Germany's mixed findings, alternatively, were attributed to the fairly even spread of high pollution levels throughout the country's districts. In the United Kingdom (UK), $PM_{2.5}$ and NO_2 had no effect on infection rates but positively correlated to death and mortality rates, a country noted to enforce containment measures much later compared to other countries. For China and the US, pollutants were found to correlate positively with infection, death, and morality rates except for no correlation of O_3 in China. (Pansini and Fornacca, 2020)

Consistently across these studies, population density was highlighted as a potential geographic confounder of the relationship between air pollution and COVID-19 disease burden. Dense population could drive both disease transmission and anthropogenic pollution. Both Pansini et al. and Sarkodie et al. specifically highlight this potential limitation. (Pansini and Fornacca, 2020, Sarkodie and Owusu, 2021) More specifically, in Liang's US study the authors could not exclude the possibility that NO_2, a traffic-related air pollutant, might simply be a proxy of urbanicity. (Liang et al., 2020)

4.2. Exposure windows

We classified studies into short-term and long-term pollution exposure groups. Short-term exposure studies evaluated the impact of near-simultaneous air pollutant exposure at the time of COVID-19 transmission. Short-term air pollution levels could theoretically be impacted by acute changes in human activity, such as reduced productivity as witnessed during pandemic lockdowns. The long-term exposure window was measured in years and reflected the chronic level of air pollution in a given region, less affected by day-to-day changes in human activity.

In general, short-term air pollution exposure exacerbated COVID-19 outcomes. In one study, $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 levels in China were correlated to daily COVID-19 confirmed cases. Only SO_2 had a negative correlation with daily confirmed COVID-19 cases, whereas all other pollution measures were positively correlated with increasing COVID-19 daily cases. (Zhu et al., 2020) Two other short-term studies, one in Canada and one in 211 countries worldwide, showed mixed effects of short-term pollutants on COVID measures. The Canadian showed that $PM_{2.5}$ and NO_2 were correlated with more COVID-19 emergency room visits while O_3 had no effect. (Lavigne et al., 2022) Xu et al estimated COVID-19 reproduction numbers for 211 countries worldwide and determined higher O_3 and SO_2 exposure related to greater COVID-19 reproduction number, while $PM_{2.5}$ and NO_2 were found to have no relation to COVID-19 reproduction number. (Xu et al., 2021) Lastly, a study in Italy determined that short-term $PM_{2.5}$ and PM_{10} levels correlated to greater transmission of disease represented by daily COVID-19 case number. (Zoran et al., 2020)

The majority of studies examining long-term pollution measures accounting for chronic exposures found that pollution was positively correlated with COVID transmission and mortality. In Sarkodie and Owusu's study, they used aggregated city-level COVID-data for 615 cities globally and World Air Quality Index data to determine that $PM_{2.5}$, O_3, NO_2 were associated with exacerbated COVID-19 incidence. (Sarkodie and Owusu, 2021) Another multi-country paper correlated various aggregated air quality estimates with COVID-19 incidence rates, death rates, and mortality rates and found a mix of mostly positive and no correlations, except for in Germany where they found that $PM_{2.5}$ was associated with improved COVID-19 infection rates but a worse death rate. (Pansini and Fornacca, 2020) Conversely in Germany, NO_2 had no association with COVID-19. (Pansini and Fornacca, 2020) Liang's cross-sectional US study on NO_2, $PM_{2.5}$, O_3 long-term exposures and correlation to COVID-19 case-fatality and mortality rates also showed mixed effects: NO_2 positive associations to both, $PM_{2.5}$ marginal positive for mortality rate, and O_3 no association to either. (Liang et al., 2020) Also in the US and then more globally, two studies investigating the long-term exposure to $PM_{2.5}$ on COVID-19 reported positive correlations. (Pozzer et al., 2020, 21) Fattorini's study focused on long-term NO_2, O_3, $PM_{2.5}$, and PM_{10} exposure in Italy found all positive correlations to COVID-19. (Fattorini and Regoli, 2020)

Overall, both long- and short-term exposure window studies demonstrated mostly positive associations to COVID-19 transmission and outcomes. The lack of consistent findings between the studies for which measures had positive, negative, or null correlations to COVID-19 measures, highlights the complex nature of the relationship between pollution measures, population density, and COVID-19 transmission versus outcome measures. However, when comparing the short- and long-term exposure window studies, there was fairly consistent variation between both groups suggesting that both short- and long-term exposure to pollution may be useful and valid measures for future studies.

5. Biological mechanisms: air pollution and COVID-19

Beyond identifying epidemiologic trends in associations between air pollutants and COVID-19 outcomes, we sought to better elucidate the proposed mechanisms by which these pollutants exert health effects in the COVID-19 disease pathway. We reviewed literature highlighting the role of air pollutants in COVID lung infection, clotting complications and neurologic symptoms (Table 2). While a wide variety of air pollutants were evaluated for epidemiologic associations with COVID-19, mechanistic proposals focused on NO_2 and $PM_{2.5}$.

5.1. Air pollution and COVID lung infection

Angiotensin-converting enzyme-2 (ACE-2) is a transmembrane

Table 2
Studies of Biological Mechanisms of Air Pollution Exacerbating COVID-19.

Lead Author	Year	Mechanism	Findings
Ni	2020	Lung	ACE-2 serves as the transmembrane protein that facilitates SARS-CoV-2 cellular entry
Frontera	2020	Lung	Correlated $PM_{2.5}$ & NO_2 with COVID 19 cases and ICU admissions in Italy Proposed ACE-2 as the receptor responsible for SARS-CoV-2 cellular entry Suggested $PM_{2.5}$ & NO_2 must up-regulate ACE-2
Borro	2020	Lung	Correlated $PM_{2.5}$ & COVID rates in Italy Identified consensus motifs for the transcription factor AhR in the regulative region of the ACE-2 gene Highlighted that AhR is stimulated by air pollutants, including PM
Watzky	2021	Lung	Investigated chemicals that modify the expression of ACE-2, TMPRSS2, FURIN, and CATHEPSINs (all previously linked to COVID cell entry)
Liu	2020	Lung	Compared heart and lung expression of other proteins potentially involved in SARS-CoV-2 cell entry including TMPRSS2, FURIN, CTSL, S protein Found proteins more over-expressed in lung tissue
Li	2021	Lung	Elucidated the pathway that PM further up-regulates ACE2 and TMPRSS2 via IL-8 Used murine models with bleomycin-induced pulmonary fibrosis
Zhang	2020	Thrombosis	Identified SARS-CoV-2 viral particles within platelets Identified ACE-2 expression on murine and human platelets
Hottz	2020	Thrombosis	Found high circulating levels of CRP and fibrinogen in COVID-19 patients correlated with markers of platelet activation/aggregation Monocyte TF was over-expressed in COVID-19 Platelet aggregation was mediated by platelet P-selectin and integrin AII/b3
Zaid	2020	Thrombosis	Identified SARS-CoV-2 viral particles within platelets
Manne	2020	Thrombosis	Identified SARS-CoV-2 viral particles within platelets
Reyes	2020	Neurologic	Reviewed two potential mechanisms for SARS-CoV-19 to access the brain: 1. Via neuronal spread across the olfactory membrane 2. Via hematologic spread across the blood-brain barrier
Nalleballe	2020	Neurologic	Epidemiologic review of neurologic symptoms in COVID-19 patients globally in the TriNetX database
Guerrero	2021	Neurologic	Identified SARS-CoV-2 in the CSF of a minority of COVID-19 patients with neurologic symptoms
Solomon	2020	Neurologic	Found no immunohistochemical evidence of SARS-CoV-19 in brain tissue at 18 serial autopsies All brains demonstrated hypoxic changes
Liu	2021	Neurologic	Reviewed two potential mechanisms for SARS-CoV-19 to access the brain: 1. Via neuronal spread across the olfactory membrane 2. Via hematologic spread across the blood-brain barrier
Heusinkveld	2016	Neurologic	Proposed that PM could enter brain tissue via intranasal canal neuronal passage via the olfactory bulb or through the cerebrovascular circulation
	2020	Neurologic	
Calderon-Garciduenas			Described accelerated neurodegenerative change in young COVID-19 patients in a highly polluted community (Mexico City) who experienced accelerated neurodegeneration in Alzheimer's and Parkinson's disease
Borisova	2021	Neurologic	Proposed that the viral lipid membrane of SARS-CoV-2 could bind to water-suspended PM PM would act as a carrier for the virus, both trans-membrane in neuronal cells and via environmental distribution

protein expressed in most human tissues, but highly expressed in the lungs. The spike glycoprotein on the SARS-CoV-2 viral envelope binds to one of the sub-domains on ACE-2, enabling cellular entry (Fig. 1). (Ni et al., 2020)

Chronic exposure to $PM_{2.5}$ and NO_2 has been associated with over-expression of ACE-2in the lung. (Frontera et al., 2020) In a bioinformatic analysis, Borro et al (2020) defined consensus motifs for the aryl hydrocarbon receptor (AhR) in the regulative region of ACE-2. (Borro et al., 2020) Airway exposure to $PM_{2.5}$, among other toxicants, promotes an inflammatory milieu, which promotes up-regulation of ACE-2 via AhR stimulation. (Borro et al., 2020, Watzky et al., 2021) It is through this over-expression of ACE-2 that air pollution is believed to exacerbate COVID-19 lung infection.

However, ACE-2 expression is higher in heart than lung tissue. The higher prevalence in the lungs of other transmembrane proteins that support viral uptake are believed to explain the predominantly respiratory complications of COVID-19. Transmembrane protease serine 2 (TMPRSS2) primes the viral spike protein for uptake while a disintegrin metallopeptidase domain 17 (ADAM17) cleaves ectodomains of ACE-2 further promote cellular entry. Both the greater prevalence of these associated proteases in lung tissue and the primary method of COVID transmission via airborne particles likely account for the respiratory predominance of the disease process. (Liu et al., 2020, Zhang et al., 2020, Li et al., 2021)

5.2. *Air pollution and COVID thrombotic complications*

Both epidemiologic and biologic evidence for an association between air pollutant exposure and COVID-associated thrombosis is sparse relative to respiratory manifestations. However, two previously proposed pathways via which COVID-19 exerts effects on platelet function could be vulnerable to air pollution.

First, the pro-inflammatory state promoted by SARS-CoV-2 infection has been associated with platelet hyperactivity and aggregation. (Zhang et al., 2020, Manne et al., 2020, Hottz et al., 2020) High circulating plasma levels of CRP and fibrinogen have been correlated with platelet activation, while No consensus exists on the exact pathway by which COVID-19 promotes these effects, but several pathways have been suggested. Generally, COVID-19 patients have high circulating plasma levels of CRP and fibrinogen, which correlate with platelet activation. (Hottz et al., 2020) Further, SARS-CoV-2 may promote over-expression of monocyte TF, precipitating increased monocyte-platelet aggregation mediated by platelet P-selectin and integrin aIIb/b3. (Hottz et al., 2020) Air pollution is known to induce similar inflammatory states and could therefore further promote the same pro-thrombotic pathways during COVID-19 infection.

Second, a handful of studies have identified SARS-CoV-2 within platelets. (Zhang et al., 2020, Manne et al., 2020, Zaid et al., 2020) However, only Zhang et al (2020) definitively identified ACE-2 expression on platelets in both mice and humans. (Zhang et al., 2020) These discordant findings highlight the need for further analysis. But if at least

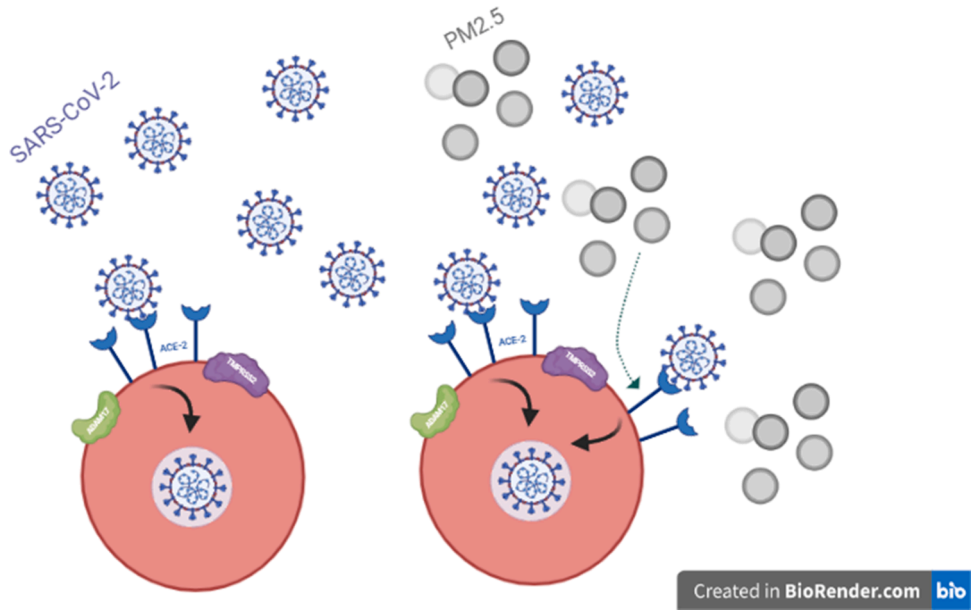

Fig. 1. Air pollution and COVID-19 cellular entry.

some proportion of the global population have platelet ACE-2 expression, upregulation of this receptor with air pollutant exposure could theoretically exacerbate thrombotic outcomes.

5.3. *Air pollution & neurologic COVID-19 complications*

Recent work suggests exposure to particulate matter, such as $PM_{2.5}$ and PM_{10} could influence and augment the neurological impacts of COVID-19. (Reyes and Medina, 2020) Neurological symptoms caused by COVID-19 in patients, range from mild headaches and dizziness to seizures and encephalopathy. (Nalleballe et al., 2020) These symptoms may be a result of a neuroinflammatory response of the Central Nervous System (CNS) to a SARS-CoV-2 infection. (Reyes and Medina, 2020) Because sampling brain tissue is challenging, consensus has not been reached on whether SAS-Cov-2 regularly penetrates brain tissue. One systematic review detected viral particles in the cerebrospinal fluid (CSF) of a minority of COVID-19 patients with neurologic symptoms. (Guerrero et al., 2021) Another histopathologic analysis of 18 consecutive patients who died of COVID-19 identified hypoxic changes to the brain tissue but could not definitively identify the virus in brain tissue via immunohistochemical analysis at autopsy. (Solomon et al., 2020)

If SARS-CoV-2 does reach the CNS, two main mechanisms of transport have been proposed; either through the cerebrovascular circulation by crossing through the capillary endothelium, or by passage from the intranasal canal through the olfactory bulb via a trans-synaptic neuronal route. The latter pathway could explain the anosmia associated with COVID-19. (Reyes and Medina, 2020) Prior work suggests particulate matter accesses the brain by both of these proposed mechanisms. (Heusinkveld et al., 2016) The presence of both viral particles and particulate matter may synergistically promote intra-cerebral inflammation. Clinicians in Mexico City have suggested that this synergy could explain the acceleration of neurodegenerative diseases such as Alzheimer's and Parkinson's Diseases they witnessed in young COVID-19. (Calderón-Garcidueñas et al., 2020)

Further, SARS-CoV-2 is an enveloped virus with a lipid membrane, which supports its passage through a host's cellular membrane. PM can also interact with the lipid components of cell membranes to facilitate entry. Therefore, Borisova and Komisarenko (2021) hypothesized that PM dissolved in airborne water particles could serve as a carrier for SARS-Cov-2, both in the environment and across the olfactory membrane. (Borisova and Komisarenko, 2021)

6. Discussion

Our review suggests that threat of the SARS-CoV-2 virus increases when paired with air pollutant exposure. In different countries around the world, associations and correlations have been drawn between increased concentrations of $PM_{2.5}$, PM_{10}, and NO_2 and other types of pollutants and increased mortality rates and infectivity of COVID-19. Analyzing the overall significance of air pollutants is important in modelling and forecasting future mortality and infection rates, as policymakers plan for future waves of infection. While researchers specifically evaluated associations between COVID outcomes and unique criteria pollutants, policymakers should consider these individual findings as markers of a more complex amalgamated group of air pollutant exposures when considering the comprehensive effects of air pollution in this pandemic. Further, understanding the underlying biological pathways by which air pollution exacerbates COVID-19 infectivity and severity can inform both policy initiatives and clinical management of disease.

In sum, our review suggests air pollution, in both the long- and short-term, is an important and modifiable environmental risk factor for COVID-19. Any public health response seeking to reduce air pollution would result in additional benefits for COVID incidence and severity. Prior work has highlighted the disparate impact of air pollution on poor communities, which further supports an imperative to reduce air pollution as a component of COVID management to reduce socioeconomic health disparities.

This study has some limitations. As with any review, our evaluation of the current literature is affected by publication bias, which may inflate the perceived strength and reproducibility of the associations between air pollutants and COVID-19. The relationship between air pollution and COVID-19 is also likely more nuanced than is captured with our search strategy. Governments often imposed lockdowns in areas where COVID rates were especially high, which would likely reduce the local short-term burden of air pollution. Although the reduction of air pollution during the COVID pandemic is beyond the scope of this review, work is currently ongoing to better understand this dichotomy. Finally, regarding the biologic mechanism studies, the rapidly evolving nature of the virus, may render current bioinformatic studies and their results inaccurate in the near future.

Conclusion

We collected state-of-the-science evidence when assessing the influence of air pollutants on mortality and infectivity. Indications of an association between increased air pollutants and COVID-19 mortality are largely consistent in studies around the world, providing promising but informative insights into how reduction of air pollution can result in lowering mortality rates worldwide.

Author contributions statement

E.Y., K.Z. and T.D. devised the project, the main conceptual ideas, conceived of the presented idea. E.Y., K.Z., A.N., C. F., and T.D. designed the idea. E.Y., K.Z., A.N., and C. F. took the lead in the writing of the manuscript. All authors discussed the results and commented on the manuscript. E.Y., X.W and T.D. supervised the project and were in charge of overall direction and planning.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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