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Toxicological Sciences, 2023, **192(1)**, 3–14
https://doi.org/10.1093/toxsci/kfad003
Advance Access Publication Date: 9 January 2023
In-Depth Reviews

Air pollution and respiratory infections: the past, present, and future

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Abstract

Air pollution levels across the globe continue to rise despite government regulations. The increase in global air pollution levels drives detrimental human health effects, including 7 million premature deaths every year. Many of these deaths are attributable to increased incidence of respiratory infections. Considering the COVID-19 pandemic, an unprecedented public health crisis that has claimed the lives of over 6.5 million people globally, respiratory infections as a driver of human mortality is a pressing concern. Therefore, it is more important than ever to understand the relationship between air pollution and respiratory infections so that public health measures can be implemented to ameliorate further morbidity and mortality. This article aims to review the current epidemiologic and basic science research on interactions between air pollution exposure and respiratory infections. The first section will present epidemiologic studies organized by pathogen, followed by a review of basic science research investigating the mechanisms of infection, and then conclude with a discussion of areas that require future investigation.

Keywords: lung; inflammation; COVID-19; pneumonia; air pollution

Ambient levels of criteria air pollutants continue to rise despite regulations by organizations like the United States Environmental Protection Agency (EPA) (EPA, 2022) and the European Environment Agency (EEA, 2022). According to the World Health Organization (WHO), 9 out of 10 individuals currently live in areas with ambient air pollution that exceeds the current local regulations (WHO, 2022). These elevated air pollution levels have important health consequences and continue to be a significant global public health concern. Air pollution is associated with more than 7 million premature deaths globally every year (IQAir, 2020; WHO, 2022). Beyond mortality, air pollution exposure can exacerbate chronic cardiopulmonary diseases, and can increase susceptibility to respiratory infections (WHO, 2022). As air pollution levels continue to rise despite global regulations on air quality, human morbidity and mortality are also expected to increase. Therefore, concurrent with efforts to improve air quality, research is required to better understand mechanisms driving adverse health effects from air pollution exposure that can be the focus of intervention strategies. The recent COVID-19 pandemic has again brought attention to respiratory infections, particularly the association and mechanisms between air pollution and enhanced infection risk/severity. Associations between air pollution exposure and enhanced respiratory infection severity have been well established in population and laboratory mechanistic studies. The earliest observation was in 1937 where an autopsy study noted evidence of alveolar carbon pigmentation, consistent with air pollution exposure, in individuals who died from pneumonia (Haythorn and Meller, 1938). Consistent with this observation, studies from the Great Smog of London event in 1952 demonstrated a direct correlation between increased ambient particulate matter (PM) and the incidence of pneumonia with an 80% increase in mortality when compared with the previous year and approximately 3500–4000 additional deaths in the 5 years following the event (Bell *et al.*, 2004; Greater London Authority, 2002). Similar associations are being observed with the COVID-19 pandemic (Aggarwal *et al.*, 2021; Bashir *et al.*, 2020; Bianconi *et al.*, 2020; Bilal *et al.*, 2020; Bowe *et al.*, 2021; Chakrabarty *et al.*, 2021; Coker *et al.*, 2020; Cole *et al.*, 2020; De Angelis *et al.*, 2021; Dragone *et al.*, 2021; Fang *et al.*, 2021; Fattorini and Regoli, 2020; Fiasca *et al.*, 2020; Hendryx and Luo, 2020; Jiang *et al.*, 2020; Konstantinoudis *et al.*, 2021; Lembo *et al.*, 2021; Liang *et al.*, 2020; Lin *et al.*, 2020; Liu *et al.*, 2021), suggesting broad implications of air pollution exposure and respiratory infections. Now, more than ever, it is important to understand both the epidemiologic and mechanistic relationships between air pollution and respiratory infection to ameliorate future morbidity and mortality from respiratory infections.

This article will aim to provide a review of the literature regarding air pollution and pulmonary infections. The first section will highlight recent epidemiologic research, primarily focusing on the impact of the criteria air pollutants (O_3, CO, $PM_{2.5}$, NO_2, SO_2, and Pb) on pneumonia. Studies will be classified by pathogen

and will focuse on data related to bacterial, fungal, and viral infections. We will provide a comprehensive review of both epidemiological and laboratory studies as well as an overview of the current mechanisms by which air pollution affects the immune response critical for clearing infections. This article will also highlight the emerging studies of criteria air pollutants and the incidence of SARS-CoV-2 infection, the respiratory virus responsible for the current COVID-19 pandemic. Lastly, we will attempt to identify areas that require further investigation on mechanisms driving susceptibility and severity of respiratory infections from air pollution.

Epidemiological findings of air pollution and infection

Acute respiratory infections are one of the top 5 leading causes of all-causes of global mortality (WHO, 2022). According to the WHO, 17% of deaths from acute lower respiratory infections (ie, pneumonia) are attributable to ambient air pollution (WHO, 2022). Pneumonia may be caused by several organisms including viruses, bacteria, and fungi. A diagnosis of pneumonia is made clinically by the examination of patient symptoms, a physical exam, and radiographic evidence. Because of this, the causative organism is often not identified. Several studies have defined associations between pneumonia diagnosis and ambient air pollutants concentrations. For example, increased $PM_{2.5}$ concentrations were associated with increased emergency department (ED) visits and admissions for 'pneumonia' in New York state (Croft *et al.*, 2019). A similar study was conducted in Utah, where elevated $PM_{2.5}$ was associated with more ED visits, hospitalizations, and mortality from pneumonia (Pirozzi *et al.*, 2018). Similar observations have been defined in national studies. Dominici *et al.* observed that an increase of $PM_{2.5}$ by 10 $\mu g/m^3$ was associated with a 5.4% increase in the rate of respiratory tract infections (Dominici *et al.*, 2006). These associations are not unique to $PM_{2.5}$ as they have been noted with other criteria air pollutants. For example, for every 1 ppb increase in O_3, there was a 0.41% increase in admissions for pneumonia in the United States (Medina-Ramon *et al.*, 2006). There also have been multiple epidemiological studies conducted in populations in Asia and Europe where NO_2, O_3, and PM_{10} have been associated with increased risk of diagnosis and hospital admission for pneumonia (Ciencewicki and Jaspers, 2007; MacIntyre *et al.*, 2014; Qiu *et al.*, 2021). These studies, as well as others (Croft *et al.*, 2020; MacIntyre *et al.*, 2014; Zhang *et al.*, 2019), clearly demonstrate that changes in air pollution levels lead to a greater incidence of morbidity and mortality from pneumonia.

Influenza and respiratory syncytial virus infections

Although pneumonia is a diagnosis that is nonspecific for a causative pathogen, epidemiological data support that changes in air quality increase incidence of viral-specific respiratory infections like influenza and respiratory syncytial virus (RSV). For example, an increase of one standard deviation in the EPA's air quality index results in over 4000 additional hospitalizations for influenza in the U.S. every year (Croft *et al.*, 2020). When examining the effects of specific criteria air pollutants, increases in $PM_{2.5}$ in New York City were associated with a 6% excess rate of influenza-related ED visits (Croft *et al.*, 2020). Similar trends have been seen with other criteria air pollutants. In Brazil, China, and Australia, increased O_3 levels were associated with an increased risk of influenza and ED visits (Ali *et al.*, 2018; Martins *et al.*, 2002; Wong *et al.*, 2009). Song *et al.* (2021) observed a correlation between SO_2, CO, NO_2, $PM_{2.5}$, and PM_{10} levels and influenza diagnoses across China between 2004 and 2017. Similar trends have been reported with RSV, a virus known to cause severe lower respiratory infections in young children. Among the criteria air pollutants, increases in PM_{10}, $PM_{2.5}$, NO_2, CO, and SO_2 levels correlated with RSV diagnosis and ED visits for RSV in Korea, China, and Israel (Pompilio and Di Bonaventura, 2020; Croft *et al.*, 2019; Yitshak-Sade *et al.*, 2017). Taken together, these data indicate that changes in ambient levels of multiple criteria air pollutants influence the incidence and severity of respiratory viral infections.

Bacterial pneumonias

Unlike the incidence of viral pneumonia and/or respiratory virus infections, the association between bacterial pneumonia and air pollution levels has not been as extensively studied. However, there are some sentinel studies suggesting similar associations. For example, in China, levels of O_3, PM_{10}, NO_2, and $PM_{2.5}$, SO_2 are independently associated with an increased risk of infection and admission for pneumonia secondary to *Mycoplasma pneumoniae* (Bono *et al.*, 2016; Chen *et al.*, 2020; Zhang *et al.*, 2019). Similarly, in the United States, SO_2 was associated with increased rates of pneumococcal disease that spread to the bloodstream, caused by the bacteria *Streptococcus pneumoniae* (Kim *et al.*, 1996). The lack of population studies associating air pollution with bacterial pneumonia is likely due to the clinical difficulty in identifying a causative organism. While diagnoses of viral infections often rely on PCR testing that can be easily obtained via nasal swab or rapid blood test, bacterial pneumonias are often diagnosed via culture of respiratory sputum. Sputum samples are often difficult to collect; as patients must either be able to expectorate productively or undergo invasive sampling with bronchoscopy (BAL). Lastly, diagnoses of the specific causative organism are done by assays that are not high throughput and can sometimes take days to obtain results. Despite these challenges, data reported thus far indicate that air pollutants increase the incidence of bacterial pneumonias.

The association between air pollution and tuberculosis (TB; caused by infection from the bacteria *Mycobacterium tuberculosis*) is particularly important in developing countries where TB infections contribute to millions of deaths annually (IQAir, 2020). Many developing countries have both a high incidence of TB as well as high levels of air pollutants. However, a large meta-analysis by Popovic *et al.* (2019) found a correlation between TB and air pollution levels across Asia, Europe, and North America. Although this article demonstrated the strongest correlation between TB outcomes and $PM_{2.5}$, other studies have shown associations with PM_{10}, $PM_{2.5}$, NO_2, and SO_2 (Hwang *et al.*, 2014; Lai *et al.*, 2016). Interestingly, levels of criteria air pollutants are not only associated with an increased risk of TB but also with an increased risk of drug-resistant infection. In Shandong province, China, 725 culture-positive cases of TB were examined and compared with ambient levels of $PM_{2.5}$, PM_{10}, O_3, and CO. $PM_{2.5}$, PM_{10}, and CO were all associated with an increased incidence of multidrug-resistant TB infection (Yao *et al.*, 2019). However, the biological mechanisms by which this occurs are still unknown.

Fungal pneumonias

Fungal pneumonias are rare when compared with bacterial and viral pneumonia but have high morbidity and mortality compared to these more common pneumonias. Air pollution can also impact the severity of fungal pneumonias. *Aspergillus*, a fungi

readily found both indoors and outdoors on surfaces ranging from soil to starchy foods, can cause pulmonary disease in humans, the most severe of which is invasive aspergillosis (Liu *et al.*, 2018). In a study of a large Taiwanese database, Liu *et al.* (2018) demonstrated an association between $PM_{2.5}$ levels and incidence of invasive aspergillosis, suggesting that air pollution exposure may augment the severity of fungal pneumonias. However, these fungal pneumonias often occur in patients who are immunosuppressed. This includes individuals with HIV who are at risk for severe respiratory infections from the fungus *Pneumocystis jirovecii* (PJP). In HIV-positive patients with low CD4 counts, elevated ambient levels of NO_2, SO_2, PM_{10}, and O_3 are associated with increased PJP hospital admission rates (Alvaro-Meca *et al.*, 2015; Djawe *et al.*, 2013). Knowing that air pollution can increase the severity of fungal infections in these susceptible populations indicates that more studies are needed to understand why this association occurs.

SARS-CoV-2 infection

The COVID-19 pandemic is one of the greatest public health crises of modern times and, according to the WHO, it has caused more than 615 million infections and 65 million deaths across the globe as of October 2022 (WHO, 2022). In an effort to stop the spread of the virus, many countries implemented lockdown policies. As people were confined to their homes, most ambient levels of criteria air pollutants were significantly reduced (Venter *et al.*, 2020). Regardless of this reduction in air pollutants, the incidence and mortality of COVID-19 continued to correlate with air pollution levels (Wu *et al.*, 2020). This association has been outlined in Table 1. A nationwide cross-sectional study comparing county-wide, long-term $PM_{2.5}$ levels with mortality from COVID-19 concluded that a 1-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with an 8% increase in mortality (Liang *et al.*, 2020). In the United Kingdom, increased $PM_{2.5}$ levels were associated with a 12% increase in new COVID-19 cases (Travaglio *et al.*, 2021). These findings have been noted in other countries as well as with other air pollutants (ie, NO_2, O_3, $PM_{2.5}$, and PM_{10}) (Cole *et al.*, 2020; Fattorini and Regoli, 2020). For example, in Wuhan China, levels of PM (both $PM_{2.5}$ and PM_{10}) were temporally associated with COVID-19 mortality (Yao *et al.*, 2020a). Thus far, these population-based studies demonstrate associations between air pollutants and COVID-19 incidence and mortality; however, as the pandemic continues and new SARS-CoV2 strains emerge, more studies are required to assess whether these associations will continue and how they are modified by new variants. Additionally, the source of these pollutants (eg, industrial, vehicles, and biomass) may vary among the different areas examined and could potentially alter the pollutant and pathogen interactions in these population studies.

Despite the strengths and number of studies reporting the associations between air pollution and respiratory infections, there are confounders for these datasets that can influence the interpretation of the data. For instance, most of these studies examine large and diverse populations that include patients from a variety of different socioeconomic statuses, demographics, medical comorbidities, and housing and work conditions. This population diversity can make statistical analysis difficult; particularly when accounting for covariates that could be effect modifiers. Additionally, most of the epidemiological studies focus on specific susceptible populations, including the elderly or children, thus raising the question of whether they are broadly applicable to all age groups. A final consideration, as noted above, is that diagnosis of pneumonia and specific pathogens can be challenging due to misdiagnosis and inherent difficulties in obtaining specimens for testing as well as different assay methods. Despite these barriers, the available data support strong associations between elevated air pollution exposure and increased incidence and severity of pulmonary infections.

Laboratory studies defining associations between air pollution and respiratory infections

Laboratory studies have been conducted to uncover the causal relationships between air pollution and respiratory infections; each with inherent strengths and weaknesses. These studies have used a number of different study designs to investigate relationships. The first of these are *in vivo* human modeling. In these studies, human volunteers are exposed to a low, controlled level of the air pollutant and lung or nasal cells are harvested via bronchoalveolar lavage, nasal lavage, or nasopharyngeal brushings. After the cells have been isolated, they can be exposed to a pathogen of interest. Effects have been defined in human alveolar macrophages and respiratory epithelial cells using this method. These methods have demonstrated mechanisms by which air pollutants alter cellular responses to respiratory infection (Becker *et al.*, 2002; Jaspers *et al.*, 2005). However, this type of study design does have limitations, including single pollutant evaluation, examining cells outside of the microenvironment that can influence biological responses, as well as eliminating systemic immune responses to pathogen. To address some of these concerns, investigators have also used rodent exposure models. Rodent models have a number of benefits including allowing for a broader range of exposure concentrations and durations than in humans, and enabling direct infection with pathogens, assessments over a variety of time points, and evaluation of whole-organism responses including systemic translocation of infection. The major limitations of rodent models are that they are generally performed on a single genetic strain that lacks the genetic diversity of human populations. In addition, they have different fractional deposition of pollutants throughout the upper and lower airways than human models, rodent studies are typically performed on young healthy mice without preexisting respiratory disease, and until recently, most rodent studies were performed on a single sex. In contrast, the majority of people who suffer from pneumonia tend to have underlying medical conditions such as chronic cardiac or lung diseases or are at the extremes of age (eg, children or the elderly). This can lead to difficulty in translating observations between rodent models and humans, though they remain an important model for defining causal relationships. A final study design is the use of *in vitro* human cells. This typically involves the use of either a transformed cell line or primary cells isolated from human volunteers that are exposed *in vitro* to a combination of air pollutants and pathogens. This method can facilitate mechanistic research on how that cell type responds to a pollutant and pathogen but has some of the same drawbacks as the cells used from *in vivo* human exposure models.

Using these various study designs, several mechanisms have been defined for how air pollution impacts respiratory infections. This review focuses on 4 principal mechanisms including (1) augmented inflammation within the lining of the respiratory tract disrupting normal innate barrier defenses; (2) disruption of macrophage pathogen clearance functions; (3) alterations in the expression of cellular receptors used by pathogens to cause infection; and (4) modulation of the commensal bacteria in the lung

Table 1. Epidemiological studies of air pollution and COVID-19 outcomes

Pollutant(s) studied	Results	Study location(s)	Reference
$PM_{2.5}$ and PM_{10}	$PM_{2.5}$ and/or PM_{10} are positively associated with COVID-19 mortality and/or case fatality.	Afghanistan, Bangladesh, Chile, China, France, India, Indonesia, Italy, Mexico, Nepal, Netherlands, Pakistan, Sri Lanka, United Kingdom, United States	(Aggarwal *et al.*, 2021; Bashir *et al.*, 2020; Berg *et al.*, 2021; Bianconi *et al.*, 2020; Borro *et al.*, 2020; Coker *et al.*, 2020; Cole *et al.*, 2020; De Angelis *et al.*, 2021; Fang *et al.*, 2021; Gupta *et al.*, 2021; Hendryx and Luo, 2020; Hou *et al.*, 2021; Jain *et al.*, 2021; Jiang and Xu, 2021; Kolluru *et al.*, 2021; Konstantinoudis *et al.*, 2021; Liang *et al.*, 2020; Lopez-Feldman *et al.*, 2021; Magazzino *et al.*, 2020; Mele and Magazzino, 2021; Meo *et al.*, 2021a, b, c; Sahoo, 2021; Valdes Salgado *et al.*, 2021; Yao *et al.*, 2020a, b; Zhou *et al.*, 2021)
	$PM_{2.5}$ and/or PM_{10} are positively associated with COVID-19 incidence.	Canada, Chile, China, India, Italy, Netherlands, Saudi Arabia, United Kingdom, United States	(Bashir *et al.*, 2020; Bianconi *et al.*, 2020; Borro *et al.*, 2020; Cole *et al.*, 2020; De Angelis *et al.*, 2021; Fang *et al.*, 2021; Fattorini and Regoli, 2020; Hadei *et al.*, 2021; Hendryx and Luo, 2020; Jiang *et al.*, 2020; Kolluru *et al.*, 2021; Li *et al.*, 2020; Ma *et al.*, 2021; Meo *et al.*, 2021a, b, c, d; Pei *et al.*, 2021; Pozzer *et al.*, 2020; Stieb *et al.*, 2020; Travaglio *et al.*, 2021; Valdes Salgado *et al.*, 2021; Xu *et al.*, 2022; Zhang *et al.*, 2021; Zhou *et al.*, 2021; Zhu *et al.*, 2020; Zoran *et al.*, 2020b)
	$PM_{2.5}$ and/or PM_{10} are positively associated with COVID-19 prevalence.	Italy	(Petroni *et al.*, 2020)
	$PM_{2.5}$ and/or PM_{10} levels are positively associated with COVID-19 hospitalizations.	Malaysia, United States	(Bowe *et al.*, 2021; Mendy *et al.*, 2021; Nor *et al.*, 2021)
	$PM_{2.5}$ and/or PM_{10} levels are positively associated with COVID-19 epidemic growth rate or transmission.	Italy, Spain, United States	(Chakrabarty *et al.*, 2021; Lolli *et al.*, 2020; Saez *et al.*, 2020; Setti *et al.*, 2020)
	No significant association between $PM_{2.5}$ and/or PM_{10} and epidemic growth rate.	Japan	(Azuma *et al.*, 2020)
	No significant association between $PM_{2.5}$ and COVID-19 mortality.	United States	(Liang *et al.*, 2020)
	$PM_{2.5}$ is negatively associated with COVID-19 incidence.	Germany	(Ogen, 2020)
NO_2	NO_2 is positively associated with COVID-19 mortality and/or case fatality.	France, Germany, India, Italy, Netherlands, Spain, United Kingdom, United States	(Bashir *et al.*, 2020; Cole *et al.*, 2020; Frontera *et al.*, 2020; Liang *et al.*, 2020; Mele and Magazzino, 2021; Meo *et al.*, 2021a; Ogen, 2020; Travaglio *et al.*, 2021)
	NO_2 is positively associated with COVID-19 incidence.	China, Iran, Italy, United Kingdom, United States	(Fattorini and Regoli, 2020; Fiasca *et al.*, 2020; Jiang *et al.*, 2020; Li *et al.*, 2020; Ma *et al.*, 2021; Pozzer *et al.*, 2020; Sahoo, 2021) (Bashir *et al.*, 2020; Hadei *et al.*, 2021; Meo *et al.*, 2021a; Travaglio *et al.*, 2021; Zhang *et al.*, 2021; Zhu *et al.*, 2020)
	NO_2 is positively associated with COVID-19 epidemic growth rate.	Spain	(Saez *et al.*, 2020)
	No significant association between NO_2 and COVID-19 mortality and/or case fatality.	China, United States	(Adhikari and Yin, 2020; Hou *et al.*, 2021)
	No significant association between NO_2 and COVID-19 incidence.	Saudi Arabia	(Adhikari and Yin, 2020; Meo *et al.*, 2021d)
	No significant association between NO_2 and COVID-19 prevalence.	Italy	(Filippini *et al.*, 2020)
	No significant association between NO_2 and COVID-19 epidemic growth rate.	Japan	(Azuma *et al.*, 2020)
	NO_2 is negatively associated with COVID-19 mortality.	Italy	(De Angelis *et al.*, 2021)
	NO_2 is negatively associated with COVID-19 incidence.	Italy	(De Angelis *et al.*, 2021; Zoran *et al.*, 2020a)
CO and CO_2	CO and/or CO_2 are positively associated with COVID-19 mortality.	China, India, United Kingdom, United States	(Kolluru *et al.*, 2021; Mele and Magazzino, 2021; Meo *et al.*, 2021a, b, c)

(continued)

Table 1. (continued)

Pollutant(s) studied	Results	Study location(s)	Reference
	CO and/or CO_2 are positively associated with COVID-19 incidence.	China, Italy, Saudi Arabia, United Kingdom, United States	(Jiang *et al.*, 2020; Kolluru *et al.*, 2021; Li *et al.*, 2017, 2020; Meo *et al.*, 2021a, b; Pozzer *et al.*, 2020; Zhu *et al.*, 2020)
	CO and/or CO_2 are negatively associated with COVID-19 mortality.	China	(Jiang and Xu, 2021)
O_3	O_3 is positively associated with COVID-19 mortality.	India, Italy, United Kingdom, United States	(Kolluru *et al.*, 2021; Meo *et al.*, 2021a, b, c; Travaglio *et al.*, 2021; Tripepi *et al.*, 2021)
	O_3 is positively associated with COVID-19 incidence.	China, India, Iran, Italy, Saudi Arabia, United Kingdom, United States	(Adhikari and Yin, 2020; Fattorini and Regoli, 2020; Hadei *et al.*, 2021; Jiang *et al.*, 2020; Kolluru *et al.*, 2021; Meo *et al.*, 2021a, b, c, d; Tripepi *et al.*, 2021; Xu *et al.*, 2022; Zhu *et al.*, 2020; Zoran *et al.*, 2020a)
	O_3 is positively associated with COVID-19 prevalence.	Italy	(Petroni *et al.*, 2020)
	No significant association between O_3 and COVID-19 mortality and/or case fatality rate.	China, United States	(Adhikari and Yin, 2020; Hou *et al.*, 2021; Liang *et al.*, 2020)
	No significant association between O_3 and COVID-19 incidence.	China	(Zhang *et al.*, 2021)
	O_3 is negatively associated with COVID-19 incidence.	Italy	(Pozzer *et al.*, 2020)
SO_2	SO_2 is positively associated with COVID-19 mortality.	Netherlands, United States	(Bashir *et al.*, 2020; Cole *et al.*, 2020)
	SO_2 is positively associated with COVID-19 incidence.	China, United States	(Bashir *et al.*, 2020; Jiang *et al.*, 2020; Ma *et al.*, 2021)
	No significant association between SO_2 and mortality and/or case fatality rate.	China	(Hou *et al.*, 2021)
	SO_2 is negatively associated with COVID-19 mortality.	China	(Jiang and Xu, 2021)
	SO_2 is negatively associated with COVID-19 incidence.	India	(Sahoo, 2021)
NH_3	NH_3 is positively associated with COVID-19 incidence.	Italy	(Pozzer *et al.*, 2020)

Original epidemiological studies found through searches of Google Scholar and PubMed were included. Review articles, articles examining only conglomerate measures of air pollution, and articles in preprint at the time of search were excluded.

leading to a favorable environment for pathogenic infections. Below, we review the current laboratory findings of these 4 mechanisms of air pollution and their association with increased susceptibility and/or severity of respiratory infection. Additionally, a graphical description of these proposed mechanisms can be found in Figure 1.

Air pollution disruption of barrier functions

Inflammation of the respiratory tract can disrupt a number of innate protective barriers that normally limit or prevent infection. One of these barriers is the epithelial lining fluid (ELF), a protective layer of fluid that physically traps pathogens and contains a number of resident immune cells and compounds important in host defense and anti-oxidant responses including mucins, surfactant/surfactant proteins, glutathione, uric acid, superoxide dismutase, and ascorbate (Cross *et al.*, 1994; Kelly, 2003; Kelly *et al.*, 1996). A number of air pollutants ($PM_{2.5}$, O_3, and NO_2) have been shown to induce oxidative stress and thereby decrease host defense responses (Chauhan and Johnston, 2003; Ciencewicki and Jaspers, 2007; Dellinger *et al.*, 2001; Kelly, 2003). This appears to result in depletion of host defense and anti-oxidant components in ELF as has been observed in samples isolated from human and rodent airspaces (Behndig *et al.*, 2009; Kelly, 2003; Kelly and Tetley, 1997). Depletion of ELF factors such as surfactant proteins, defensins, and/or club cell secretory protein (CCSP) has also been noted in models of air pollution to enhance susceptibility to respiratory infections. For example, diesel exhaust and O_3 exposure deplete the lung of important host defense molecules including CCSP, surfactant protein A (SP-A), and surfactant protein D (SP-D), which directly impact susceptibility to respiratory infection (Ciencewicki *et al.*, 2007; Gowdy *et al.*, 2008). Another lung innate defense function altered by air pollution exposure is mucociliary clearance. Respiratory cilia move debris and potential pathogens trapped in mucus from the lower respiratory tract into the oropharynx where they can be swallowed or expectorated. Not only do cilia have reduced motion following air pollution exposure, but mucous becomes less viscous, significantly decreasing mucociliary clearance and increasing susceptibility to infection (Grose *et al.*, 1980; Pedersen, 1990; Saldiva *et al.*, 1992; Xiao *et al.*, 2013). Air pollutants can also affect the integrity of the epithelial barrier. When exposed to PM, the tight junctions of the alveolar epithelium are disrupted by reactive oxygen-mediated destruction of zona occludens-1 (ZO-1) and occludin proteins (Caraballo *et al.*, 2011; Wang *et al.*, 2012). Disruption of tight junctions impacts the integrity of the alveolar-epithelial barrier, potentially facilitating the entry of pathogens into the respiratory interstitium.

Air pollution alters macrophage functions

The second mechanism by which air pollution may lead to increased susceptibility to respiratory infections is by causing

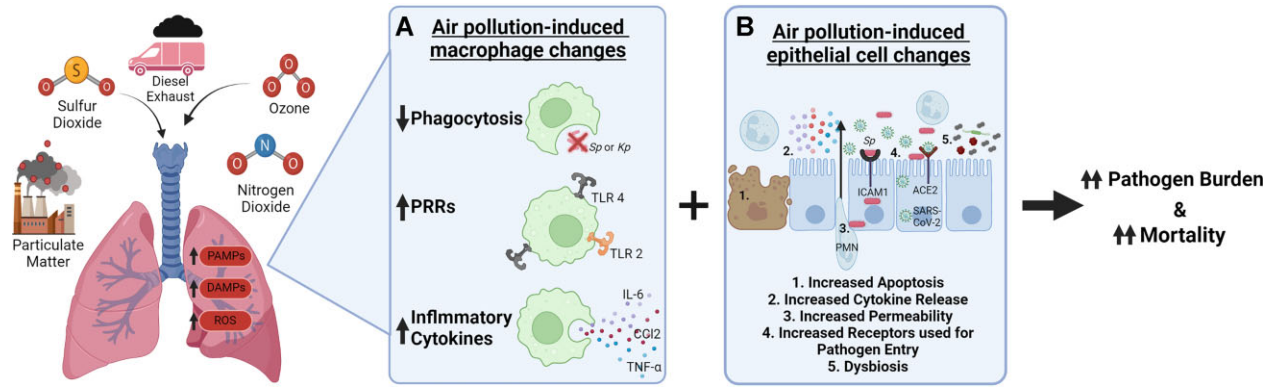

Figure 1. Molecular mechanisms by which air pollution increases susceptibility to respiratory infections. Pollutants that have been shown to increase susceptibility or exacerbate pulmonary infections include PM, sulfur dioxide, diesel exhaust, ozone, and nitrogen dioxide. It is thought that inhalation of these pollutants increases the amount of PAMPs, danger associated molecular patterns (DAMPs), and reactive oxygen species which can alter function and responses of the resident lung cells including the alveolar macrophage and epithelial cells. (**A**) Known air pollution-induced alterations in the alveolar macrophage include (1) decreased phagocytosis; (2) increased expression of PRRs; and increased production of proinflammatory cytokines. (**B**) Known air pollution-induced alterations in epithelial cells include (1) increased cell death; (2) augmented inflammatory cyto/chemokine production; (3) disruption of normal innate barrier defenses; (4) alterations in the expression of cellular receptors used by pathogens to cause infection; and (5) modulation of the commensal bacteria in the lung leading to a favorable environment for pathogenic infections. These air pollution-induced changes to the lung can lead to increased pathogen burden and mortality associated with infection. Created with BioRender.com.

macrophage dysfunction. Macrophage functions are critical to pulmonary host defense. These include phagocytosing pathogens, facilitating antigen presentation, and pathogen destruction via oxygen-dependent pathways. In addition, macrophages produce cyto/chemokines that recruit other important host-defense immune cells (Becker *et al.*, 2005). To identify pathogens, macrophages use pathogen-associated molecular patterns (PAMPs) on microbes that are recognized by pattern recognition receptors (PRRs) including toll-like receptors 2 and 4 (TLR2 and TLR4). Air pollution can regulate the expression of PRRs as evidenced by the downregulation of TLR4 in human alveolar macrophages exposed to PM (Morrow, 1988). This impact on PRRs can then decrease the ability of macrophages to recognize invading pathogens. In addition to having a decreased ability to recognize pathogens, macrophages have decreased motility, altered phagocytosis, and augmented cytokine and chemokine production following air pollutant exposure (Becker and Soukup, 1999; Chauhan and Johnston, 2003; Kienast *et al.*, 1996; Rylance *et al.*, 2015). Although the majority of research has shown that exposure to air pollutants leads to decreased pathogen clearance by macrophages, a recent study by Vose *et al.* (2021) reported that exposure to wood smoke particles altered macrophage phenotypes leading to increased clearance of influenza infection and decreased markers of clinical severity. This suggests that different types of lung macrophages or exposures may result in different effects on respiratory infections. Despite this, macrophages are a principal target of air pollutants impacting lung infection, and more studies are needed to understand the underlying mechanisms.

Immune response alterations following air pollution exposure

Air pollution modifies cellular receptors used by pathogens to cause infection. Diesel exhaust, NO_2, and O_3 have been shown to increase the surface expression of intercellular adhesion molecule 1 (ICAM-1) (Ciencewicki *et al.*, 2007; Pathmanathan *et al.*, 2003; Spannhake *et al.*, 2002; Takahashi *et al.*, 1995). ICAM-1 is the primary cellular attachment for a number of viruses, including rhinovirus (Greve *et al.*, 1989). Similarly, *S. pneumoniae* binds to host epithelial cells via platelet-activating factor receptor (PAFR) and exposure to PM_{10} has been shown to increase PAFR levels and bacterial attachment (Mushtaq *et al.*, 2011). Similarly, both NO_2 and $PM_{2.5}$ have been shown to increase the expression of angiotensin converting enzyme-2 (ACE-2) in the respiratory epithelium, which is a cellular receptor for SARS-CoV-2 (Aztatzi-Aguilar *et al.*, 2015; Hamming *et al.*, 2004; Hoffmann *et al.*, 2020; Lin *et al.*, 2018; Paital and Agrawal, 2021). Despite this, a direct causal relationship between air pollution and SARS-CoV-2 infection in laboratory models has yet to be demonstrated.

In addition to increasing the expression of cellular receptors that pathogens use to gain access to cells, air pollutants can also augment the immune response leading to greater lung inflammation/injury which can perpetuate the systemic dissemination of pathogens. For example, respiratory epithelial cells recognize pathogens through a number of receptors, including toll-like receptors. When rodents are exposed to diesel exhaust prior to influenza infection, the preexposure to air pollution upregulated pulmonary expression of toll-like receptor-3 (TLR3) and increased airspace levels of IL-6, IFN-γ, and TNF-α (Ciencewicki *et al.*, 2007). In most biological models of infection, an augmented immune response is beneficial to the host defense response by promoting pathogen clearance; however, in the context of air pollution, the increased inflammation is mostly coupled with increased pathogen burden. However, it is unclear why this paradox following air pollution exposure happens and few studies have addressed this. It has been shown that this augmented inflammatory response by air pollutants can lead to a disruption of the balance of proteases/antiproteases, allowing for a direct increase in viral entry into cells and/or host susceptibility (Kesic *et al.*, 2012). However, emerging literature has also reported that air pollution exposure can modulate the adaptive immune responses by changing T cell polarization (ie, decreased regulatory T cells and Th22 polarization, increased Th17 and/or Th2 skewing) which results in prolonged inflammation and pathogen load in the lung (Deiuliis *et al.*, 2012; Jaligama *et al.*, 2018, 2017; Kumar *et al.*, 2021; Li *et al.*, 2022). Whether these adaptive immune changes are driven by increased pulmonary inflammation or direct effects on the adaptive immune response still remains unknown.

Air pollution disruption of the microbiome

The 4th mechanism of pollution-mediated respiratory infections is an alteration of the microenvironment within the airways promoting a more hospitable environment for pathogens to survive/proliferate. An important aspect of this is the formation of biofilm, which is clinically important due to its ability to confer antibiotic resistance (Hussey *et al.*, 2017; Woo *et al.*, 2018). When *S. pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* are directly exposed to PM *in vivo* and *in vitro*, there is a significant increase in both biofilm thickness and complexity (Hussey *et al.*, 2017; Li *et al.*, 2017; Woo *et al.*, 2018). Specifically, when *Pseudomonas* was exposed to PM, the biofilm it established had increased cellular adhesion to respiratory cells (Woo *et al.*, 2018). This increased adhesion allows for increased pathogen uptake and/or entry and subsequent infection. In addition, when *Streptococcus* bacteria is exposed to PM, the bacteria had a higher rate of dissemination from the nasopharynx to the lungs, where it may lead to pneumonia (Yadav *et al.*, 2020). Additionally, following air pollution exposure, there is not only a change in the 16S rRNA in the lung, with bacterial diversity decreasing, but also a significant increase in *Proteobacteria* in the lungs (Li *et al.*, 2017). This dysbiosis of the lung microbiome with a decrease in commensal bacterial diversity as well as an increase in bacterial species is known to be pathogenic (Li *et al.*, 2017; Wang *et al.*, 2019; Yu *et al.*, 2016).

Limitations

Though the laboratory research and mechanisms discussed above support the epidemiological findings of pollution-associated respiratory infections, there are still areas where further investigations are warranted. Currently, most human and rodent models used to evaluate the interaction of air pollution and infection are from young and otherwise healthy subjects/specimens. These healthy subjects are mostly used for both financial reasons and safety concerns. In contradiction to these commonly used models, most epidemiological findings report that susceptible populations (children and >65 years of age) are most at risk for air pollution-induced health effects. Furthermore, many of these current controlled human laboratory studies that are performed rely on collecting cellular samples (ie, BAL) which are difficult and complicated to collect and can confer an increased risk for complications. Due to these constraints, majority of the research models used for the study of pollution-associated respiratory infections are relatively limited in mechanism and may not accurately reflect the populations that are most susceptible. Lastly, most laboratory studies only examine a single air pollutant whereas epidemiological studies include exposure to a wide array of environmental exposures. Recent studies have reported that these exposures interact with each other, affecting the immune response in a way that is difficult to replicate in a controlled setting (Hathaway *et al.*, 2021; Majumder *et al.*, 2021a, b). Additionally, there may be interactions with criteria air pollutants and unregulated air toxins (ie, ultrafine particles, acrolein, and biomass). Many of these unregulated toxins have been implicated in pathogen susceptibility in laboratory studies (Brocke *et al.*, 2022; Jaligama *et al.*, 2017; Kumar *et al.*, 2021; Rebuli *et al.*, 2019) but very few are considered in population-based studies. Therefore, evaluating coexposures in the context of susceptibility to infection may yield differential results to the data that are already available. In conclusion, although current data support pollution-mediated damage to innate immune barriers, macrophages, and cellular receptors, the research community has just begun to understand the mechanisms behind pollution-associated respiratory infections and there is a need for more studies to better understand this interaction.

Conclusion and future directions

As highlighted by the current COVID-19 pandemic, respiratory infections are an important cause of human morbidity and mortality and a significant public health threat. Addressing these pandemic and future events will require a detailed understanding of factors that regulate infection risk and severity. Highlighted in this review, air pollution is an important factor impacting respiratory infection risk and severity. This is supported both by population associations in epidemiologic studies and causal mechanistic studies. Despite these observations, there remain gaps in our understanding. Resolving these gaps will be critical as the prevalence and severity of respiratory infections are expected to increase air pollution levels, despite regulations will continue to rise. Addressing this will require collaborations between different environmental health disciplines that will address interactions between respiratory infection and the environment. In addition, more transdisciplinary research is needed that leverages the strengths and weaknesses of population-based research with basic mechanistic studies to identify novel mechanisms by which air pollution alters respiratory infections, risk factors for these effects, and intervention strategies that target this risk. Ultimately, these measures would improve public health and limit morbidity and mortality associated with respiratory infection.

Declaration of conflicting interests

Dr. Brita Kilburg-Basnyat is currently employed by Arcus Biosciences, Inc but completed the majority of her contributions (concept and intellectual contributions) during her postdoctoral scholar position at East Carolina University. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

National Institute of Environmental Health Sciences (R01ES028829 to K.M.G., R01ES027574 to R.M.T.).

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