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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Review

Association of COVID-19 transmission with high levels of ambient pollutants: Initiation and impact of the inflammatory response on cardiopulmonary disease

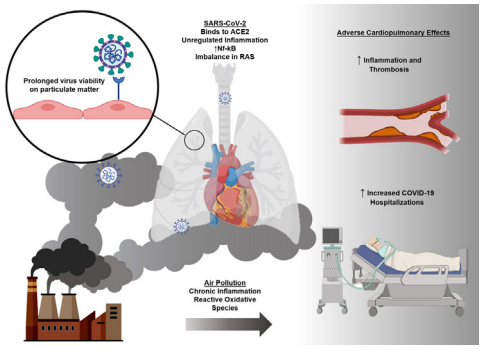
Angela Lai [a], Megan L. Chang [a], Ryan P. O'Donnell [a], Changcheng Zhou [c], Jennifer A. Sumner [d], Tzung K. Hsiai [a,b,e,*]

[a] Division of Cardiology, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, CA, United States of America
[b] Department of Medicine, Greater Los Angeles VA Healthcare System, Los Angeles, CA, United States of America
[c] Division of Biomedical Sciences, School of Medicine, University of California, Riverside, CA, United States of America
[d] Department of Psychology, College of Life Sciences, University of California, Los Angeles, United States of America
[e] Department of Bioengineering, Henry Samueli School of Engineering & Applied Science, University of California, Los Angeles, CA, United States of America

HIGHLIGHTS

- Literature review on the impact of air pollution and COVID-19 on the cardiopulmonary system shows
- Effects from Direct Physical Impact of Air Pollutants and COVID-19 on the Cardiopulmonary System
- Activation of Key Inflammatory Mechanisms from Chronic Air Pollution Exposure and COVID-19
- Air Pollution Exposure-Mediated Transmission of COVID-19
- Suggests a relationship between air pollution exposure and increased susceptibility to severe COVID-19

GRAPHICAL ABSTRACT



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ABSTRACT

Ambient air pollution contributes to 7 million premature deaths annually. Concurrently, the ongoing coronavirus disease 2019 (COVID-19) pandemic, complicated with S-protein mutations and other variants, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in over 2.5 million deaths globally. Chronic air pollution-mediated cardiopulmonary diseases have been associated with an increased incidence of hospitalization and mechanical ventilation following COVID-19 transmission. While the underlying mechanisms responsible for this association remain elusive, air pollutant-induced vascular oxidative stress and inflammatory responses have been implicated in amplifying COVID-19-mediated cytokine release and vascular thrombosis. In addition, prolonged exposure to certain types of particulate matter ($PM_{2.5}$, $d < 2.5$ μm) has also been correlated with increased lung epithelial and vascular endothelial expression of the angiotensin-converting enzyme-2 (ACE2) receptors to which the SARS-CoV-2 spike glycoproteins (S) bind for fusion and internalization into host cells. Emerging literature has linked high rates of SARS-CoV-2 infection to regions with elevated levels of $PM_{2.5}$, suggesting that COVID-19 lockdowns have been implicated in regional reductions in air pollutant-mediated cardiopulmonary effects. Taken together, an increased incidence of SARS-CoV-2-mediated cardiopulmonary diseases seems to overlap with highly polluted regions. To this end, we will review the redox-active components of air pollutants, the pathophysiology of SARS-CoV-2 transmission, and the key oxidative mechanisms and ACE2 overexpression underlying air pollution-exacerbated SARS-CoV-2 transmission.

* Corresponding author at: Department of Medicine and Bioengineering, UCLA, Los Angeles, CA 90095-1679, United States of America.
E-mail address: THsiai@mednet.ucla.edu (T.K. Hsiai).

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Contents

1. Introduction

Ambient air pollution affects millions of people daily as one of the leading causes of morbidity and mortality worldwide (Rajagopalan et al., 2018) (Table 1). In parallel, the coronavirus disease 2019 (COVID-19) represents the worst infectious outbreak of the century, infecting cardiovascular, pulmonary, and other organ systems with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global death toll from COVID-19 infection has risen beyond 2.5 million, as reported by the World Health Organization (WHO) ("Coronavirus Disease (COVID-19)", 2021).

Industrial regions with the highest levels of pollutants are experiencing particularly high mortality rates from SARS-CoV-2 transmission (X. Wu et al., 2020; Ali and Islam, 2020; Comunian et al., 2020; Mukherjee et al., 2021). The first case of COVID-19 in Wuhan City in China and subsequently, in the Po Valley in Italy, are examples of the geographical link with SARS-CoV-2 infection (Fig. 1) (Conticini et al., 2020; Hui et al., 2020; Jiang et al., 2020; Remuzzi and Remuzzi, 2020; Coccia, 2021a, 2021b, 2021c). The Po Valley spans the cities of Lodi, Cremora, Bergamo, and Brescia, known as the four Italian cities with the highest pollution levels (Frontera et al., 2020a). These highly industrialized regions were found to have a two-fold higher mortality rate from COVID-19. However, in other regions of Italy with low pollution, 40–50% of the population had positive COVID-19 swabs but were asymptomatic. Thus, there seems to be a correlation between COVID-19 patients having more severe symptoms and living in an area with higher air pollution (X. Wu et al., 2020).

While ambient particulate matter is widely recognized as a contributor to the underlying cardiopulmonary diseases, recent epidemiological findings support the emerging association between elevated levels of air pollution and COVID-19 outbreaks and mortality (Martelletti and Martelletti, 2020; Petroni et al., 2020). Patients with pre-existing diseases that are correlated with chronic exposure to air pollution, such as atherosclerosis, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diabetes, and obesity, fare worse clinically after contracting SARS-CoV-2. These patients develop an increased risk of death and are in need of mechanical ventilation (Chen et al., 2020a; Colombo et al., 2020; Ji et al., 2020; F. Wu et al., 2020; Mohammad et al., 2021). Emergency department admissions due to exacerbation of COPD or CF have been attributed to 10 $\mu g/m^3$ increases of particulate matter (PM) in the air (Zanobetti and Schwartz, 2005).

Aggressive measures to contain COVID-19 outbreaks through public lockdowns and home quarantines led to a reduction in air pollution from transportation and industrial emissions (Chen et al., 2020b; Huang et al., 2020). In the Yangtze River Delta region, including Shanghai, in China, concentrations of particulate matter with a diameter of 2.5 μm ($PM_{2.5}$) were reduced by 22.9% as compared to pre-lockdown levels (Huang et al., 2020). Daily premature mortality related to $PM_{2.5}$ exposure during the lockdown period was estimated to be 895 (95% confidence interval: 637–1081). This mortality was 43.3% lower than the pre-lockdown period and 46.5% lower than averages for 2017–2019 (Huang et al., 2020). Thus, the substantial health benefits, such as a lowered incidence of premature deaths due to cardiopulmonary diseases in Wuhan, China, suggest an association with the reduced emission levels from reduced human and industrial activities (Chen et al., 2020a; Giani et al., 2020; Han and Hong, 2020; Xu et al., 2020).

Despite the rising mortality rates in the highly polluted regions, the relationship between air pollutant-mediated cardiopulmonary diseases and exacerbation of COVID-19-associated comorbidities has yet to be determined (Giani et al., 2020). High rates of hospitalization from COVID-19 outbreaks have occurred in regions with elevated levels of pollutants (Benmarhnia, 2020; Bianconi et al., 2020; Bontempi, 2020; Frontera et al., 2020b; Giani et al., 2020). To further study the overlapping relationship between the impact of air pollution and COVID-19 on the cardiopulmonary system, we hereby conducted this critical review. This emerging domain of study covers the intersection of COVID-19 and the environmental impacts on the heart, lungs, and vasculature, thereby providing an epidemiological basis for future basic and clinical research. Our review highlights the inflammatory responses, and overexpression of angiotensin-converting enzyme 2 (ACE2) receptors underlying the cumulative effects of ambient $PM_{2.5}$-exposure and SARS-CoV-2 transmission on exacerbating cardiopulmonary outcomes.

2. Research methodology

We conducted a literature search on the PubMed database for keywords ("COVID-19" OR "SARS-CoV-2") AND ("air pollution" OR "environment") AND ("cardiovascular" OR "cardiopulmonary") to identify articles that were relevant to COVID-19 and the intersection between cardiopulmonary effects and air pollution. These articles were manually selected for further comparison. Each article was inserted into a Microsoft Excel document where the title, year, keywords,

Table 1
Size and composition of air pollutants.

Pollutant	Source	US Levels	US Air Quality Standard	Reference
$PM_{2.5}$	Combustion sources (e.g. vehicle emissions and industrial processes) Natural causes (e.g. wildfires)	10.40 μg/m^3 (2000–2019) 8.57 μg/m^3 (2010–2019)	12 μg/m^3 (annual mean) 25 μg/m^3 (24-hour mean)	Brandt et al. (2020) Health effects of particulate matter (2013)
PM_{10}	Atmospheric photochemical reactions with gaseous pollutants such as NO_x, O_3, SO_2, CO, and VOCs	79.49 μg/m^3 (2000–2019) 75.13 μg/m^3 (2010–2019)	No annual mean 150 μg/m^3 (24-hour mean)	Brandt et al. (2020) California Air Resources Board (2020)
$PM_{0.1}$ (UFPs)		4730 particles/cm^3	10,760 particles/cm^3	Brandt et al. (2020) Morawska et al. (2008)
NO_2 and other NO_x	Combustion sources Conversion from NO by atmospheric O_3	44.45 ppb (2000–2019) 37.29 ppb (2010–2019)	40 μg/m^3 (annual mean) 200 μg/m^3 (1-hour mean)	"Basic Information about NO2" (2016) Brook et al. (2004) U.S. Environmental Protection Agency (2016)
O_3	Atmospheric photochemical reactions with oxygen, NO_x, and reactive hydrocarbons in sunlight	0.074 ppm (2000–2019) 0.068 ppm (2010–2019)	100 μg/m^3 (8-hour mean)	U.S. Environmental Protection Agency (2015)
CO	Vehicle emissions Incomplete combustion of organic fuels (e.g. gasoline, oil, and coal from vehicles and other fossil fuel combustion sources)	1.88 ppm (2000–2019) 1.26 ppm (2010–2019)	9 ppm (8-hr mean)	"Carbon Monoxide Trends" (2016) U.S. Environmental Protection Agency (2016)
SO_2	Burning of fuel containing sulfur (e.g. coal and oil in power plants, vehicles, and volcanoes) Reacts with water to form sulfuric acid	47.33 ppb (2000–2019) 25.84 ppb (2010–2019)	20 μg/m^3 (annual mean) 500 μg/m^3 (10-minute mean)	U.S. Environmental Protection Agency (2016)
VOC (e.g. formaldehyde and benzene)	Mostly indoor burning of fuels, organic chemicals in household products	0.1–1 ppb	N/A	Pankow et al. (2003)

Only the most representative citations are given. (PM, particulate matter; $PM_{2.5}$, particles with a diameter ≤ 2.5 μm; PM_{10}, particles with a diameter ≤ 10 μm; $PM_{0.1}$, particles with a diameter ≤ 2.5 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; CO, carbon monoxide; SO_2, sulfur dioxide; VOC, volatile organic compounds; μg/m^3, micrograms per meter cubed; ppm, parts per million; ppb, parts per billion.)

methodology, key findings, authors, and journal names were documented. Through an iterative process, the articles were coded into different themes, followed by classification into three categories in the ensuing Results section. The articles under each category were analyzed for critical reflection and future research directions.

3. Results

Cumulative effects from the exposure to air pollution and COVID-19 on the cardiopulmonary system are not fully understood. From our literature search, we identified three overarching research categories that relate the cumulative effects of COVID-19 and air pollution on the cardiopulmonary systems that require future studies: (1) the direct physical impact of air pollution and COVID-19 on cardiopulmonary organs and tissues, (2) subsequent activation of immune system and imbalance in inflammatory responses, and (3) the indirect and direct effects of air pollution on the transmission of SARS-CoV-2.

3.1. Cumulative effects from direct physical impact of air pollutants and COVID-19 on the cardiopulmonary system

Air pollutants and COVID-19 both enter the human body via inhalation through the lungs, and the cumulated effects may accentuate COVID-19-mediated transmission and symptoms. Patients with existing cardiopulmonary comorbidities are predisposed to cytokine storms and subsequent need for mechanical ventilation following COVID-19 infection (Ejaz et al., 2020; Sanyaolu et al., 2020; Vaughan et al., 2021; Silverio et al., 2021). This may be due to the direct physical impact that both air pollution and COVID-19 impart on the cells at the respiratory interface and the cardiovascular level. The primary ingestion of air pollutant particles is through the lungs, where small gaseous air pollutants and soluble PM deposit (Rao et al., 2018). Some atmospheric ultrafine particles (UFP, d < 0.1–0.2 μm) are reported to enter the digestive system via inhalation (Li et al., 2015). Larger particles, including PM_{10}, tend to deposit in the upper airways, whereas smaller particles, including $PM_{2.5}$ and UFP, have the potential to reach the depths of the alveolar sacs where these particles cross the alveolar epithelial and capillary endothelial tight junctions into the bloodstream (Daigle et al., 2003; Nemmar et al., 2002). A chronic, low-grade inflammatory response due to ineffective mucociliary clearance of the particles is also implicated in the increased risk of cardiopulmonary disease (Lawal, 2017) (Table 2).

The disease at large, COVID-19, is a respiratory infection with systemic effects. As upper airway epithelial cells are the first to be infected, they further contribute to viral shedding and consequently, transmission, as observed during the early phase of infection, when patients' symptoms resemble a routine upper respiratory infection (Wölfel et al., 2020).

3.1.1. Particulate matter and ultrafine particles

Atmospheric pollutants, including components within PM, are well-recognized to induce a systemic inflammatory response and oxidative stress. The compositions and seasonal variations in air pollutants further modulate the overexpression of inflammatory cytokines (Kumarathasan et al., 2018) (Table 2). A host of data supports that exposure to PM promotes cardiomyocyte injury, cardiac sodium channel dysfunction, and decreased cardiomyocyte mitochondrial function (Liu et al., 2015; Nichols et al., 2015; Wang et al., 2012).

$PM_{2.5}$ exposure has been associated with acceleration of atherosclerosis and subsequent vascular calcification, as well as exacerbation of chronic respiratory diseases (Dominici et al., 2006; Kaufman et al., 2016; Rajagopalan et al., 2018; Sun et al., 2005). Recently, studies have shown that inhalation of ambient air particles, especially those from combustion-related sources, imparts far-reaching cardiopulmonary sequelae and mortality in humans. These types of PM consist of a combination of organic and inorganic components in the form of solid and liquid particles of varying sizes and chemical compositions. The PM are categorized in terms of size: (1) PM_{10} particles are less than 10 μm, (2) $PM_{2.5}$ particles are less than 2.5 μm, and (3) $PM_{0.1}$ particles, or ultrafine particles (UFPs), are less than 0.1–0.2 μm in diameter (Conticini et al., 2020).

Due to their small size, $PM_{2.5}$ particles are widely studied epigenetic factors for cardiovascular morbidity and mortality (Kaufman et al., 2016). Compared to PM_{10}, these particles harbor a higher probability of evading the mucociliary clearance to reach the alveoli, accentuating the severity of cardiopulmonary diseases (Sun et al., 2010). Other

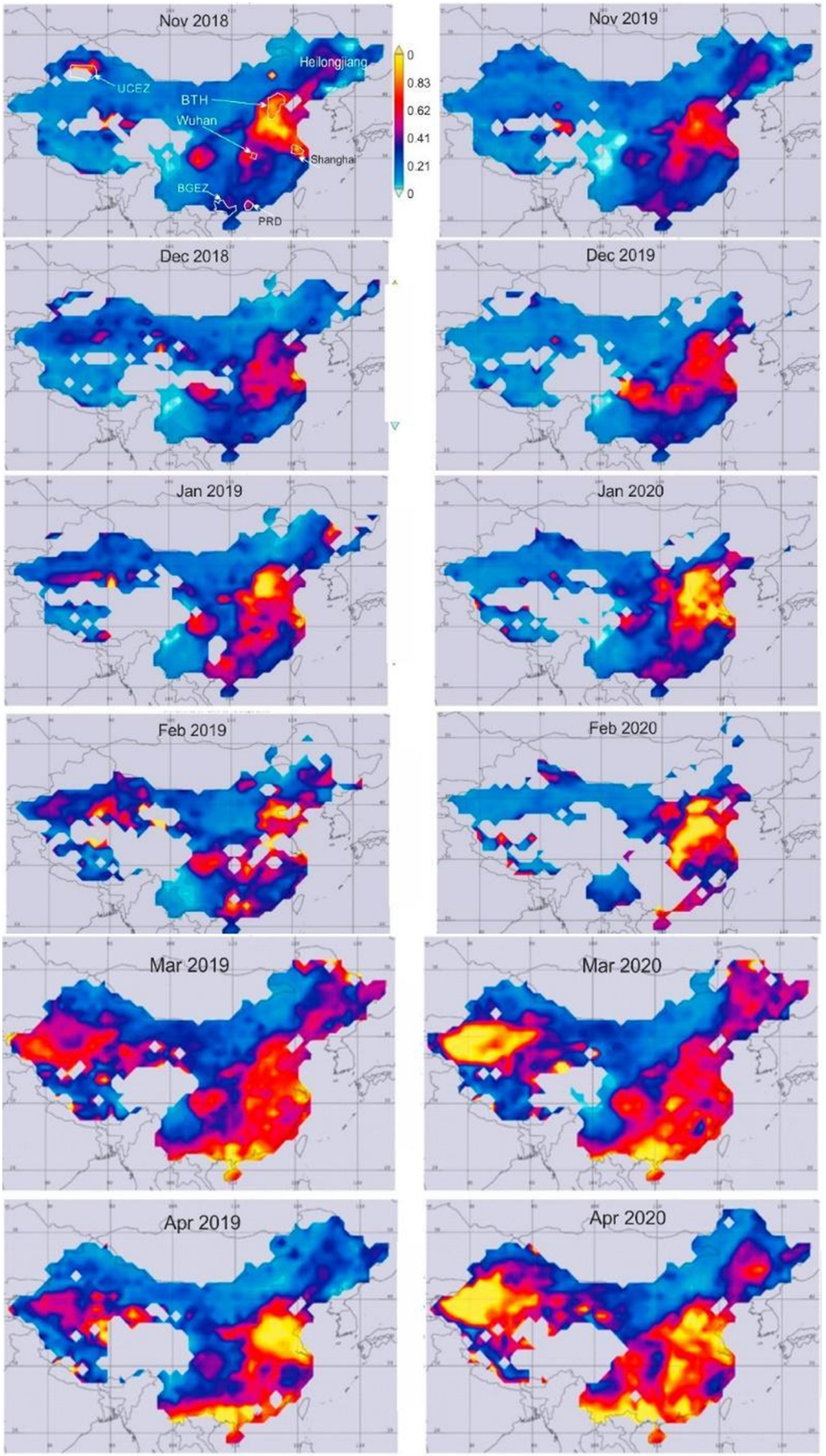

Fig. 1. Maps of the geographical distribution of Aerosol Optical Depth (AOD) across China, which represents tropospheric particulate concentrations. COVID-19 cases and air pollution concentrations were concentrated in industrial regions. Wuhan, China is one of these regions. Figure from Nichol et al. in *Remote Sens.* 2020 under the Creative Commons license (Nichol et al., 2020).

Table 2
Redox mechanisms of air pollutants and cardiopulmonary diseases.

Pollutant	Mechanisms	Physiological outcomes	Reference
$PM_{2.5}$, $PM_{10,}$ & $PM_{0.1}$ (UFPs)	Enters bloodstream Promotion of atherosclerotic progression Oxidative stress Acute conduit artery vasoconstriction	Increased presence of hypertension, blood coagulation, and reactive hyperemia Increased risk for exacerbations of congestive heart failure and respiratory diseases	Briet et al. (2007) Brook et al. (2004) California Air Resources Board. (2020) Gold et al. (2000) Lucking et al. (2008) Morawska et al. (2008) Mutlu et al. (2007) Peters et al. (2001) Suwa et al. (2002) Wellenius et al. (2005)
NO_2 and other NO_x	Oxidative Stress ROS production causing lung tissue damage Inflammation Disrupts endothelial function	Exacerbation of respiratory diseases (e.g. COPD) Trigger/aggravator of cardiovascular conditions (e.g. acute coronary episodes, arrhythmia)	Briet et al. (2007) Brook et al. (2004) Peters et al. (2001)
O_3	Airway inflammation Disrupts endothelial function Oxidative stress Acute conduit artery vasoconstriction	Increased presence of hypertension and blood packet activation, increasing risk for CVD Aggravates CVD (e.g. coronary artery disease, stroke)	Briet et al. (2007) Rajagopalan et al. (2018)
CO	Body cell and tissue hypoxia by binding to hemoglobin Disrupts endothelial function	Damage to heart and lung tissue Worsens respiratory and cardiac function Increased embolisms and thrombotic changes	Blumenthal (2001) Briet et al. (2007) Hoek et al. (2001)
SO_2	Oxidative stress Produced sulfuric acid causes irritation to eyes, mucous membranes, and skin	Disrupts respiratory function and exacerbates pre-existing respiratory conditions Increased morbidity and mortality of CVD (heart failure, arrythmia) Increased hypertension and thrombotic events	Hoek et al. (2001) Ibald-Mulli et al. (2001) Lipsett (2001)
VOC	May combine to form harmful pollutants (tropospheric ozone and smog) May increase CRP plasma levels	Damage to heart and lung tissue Worsens respiratory and cardiac function Increased embolisms and thrombotic changes	Pankow et al. (2003) U.S. Environmental Protection Agency (2014)

Only the most representative citations are given. (PM, particulate matter; $PM_{2.5}$, particles with a diameter ≤ 2.5 μm; PM_{10}, particles with a diameter ≤ 10 μm; $PM_{0.1}$, particles with a diameter ≤ 2.5 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; CO, carbon monoxide; SO_2, sulfur dioxide; VOC, volatile organic compounds; μg/m^3, micrograms per meter cubed; ppm, parts per million; CVD, cardiovascular disease; ROS, reactive oxygen species; CRP, C-reactive protein.)

inhaled smaller particles, such as UFP, may further induce NF-κB-mediated vascular oxidative stress and inflammatory responses, alter the diversity of gut microbiota, and elevate circulating lipid metabolites (Li et al., 2010, 2015, 2017; Salim et al., 2014) (Table 2).

3.1.2. Gaseous pollutants

The gaseous pollutants in the atmosphere, including nitrogen oxides (NO_x), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), volatile organic compounds (VOCs), and polycyclic aromatic hydrocarbons, are considered redox-active (Manisalidis et al., 2020). Akin to PM pollution, these gaseous pollutants gain entry into the circulatory system primarily via inhalation. They can also be absorbed through the skin, causing direct damage in other organ systems (Ghorani-Azam et al., 2016) (Table 2). The relatively low concentration of ambient SO_2 reacts with water to form sulfuric acid (Lipsett, 2001). Due to hemoglobin having a higher affinity for CO rather than for oxygen, CO binds to hemoglobin upon inhalation, resulting in reduced oxygen perfusion to tissues and organs (Blumenthal, 2001). Some VOCs such as formaldehyde and benzene are highly redox-active, undergoing photochemical reaction with other atmospheric gases. This can adversely affect the cardiopulmonary system upon inhalation. However, VOC concentrations tend to be so low that they impart little or no adversarial effects on human health ("Volatile Organic Compounds' Impact on Indoor Air Quality", 2014).

3.1.3. Air pollutants and COVID-19: histology and tissue deterioration

The findings in lung histology of COVID-19 patients resemble those of injured microscopic structures in air pollutant exposure. A histological study of admitted COVID-19 patients revealed viral penetration of liver and small intestine endothelial cells, as well as endothelial inflammation in the small intestine, vascular, lung, heart, liver, and kidney cells. These are all organ systems that are also affected by chronic air pollution (Varga et al., 2020). Although preliminary, animal models exposed to chronic $PM_{2.5}$ report increased fibrosis in the alveolar walls (Sun et al., 2005). Current histological findings of COVID-19 patients reveal diffuse infiltration of alveolar walls by lymphocytes and edema, and patients with severe symptoms developed extensive intra-alveolar fibrin deposits in association with inflammatory or deteriorating hyaline membranes, suggestive of early onset acute respiratory distress syndrome (ARDS) (Bezzio et al., 2020). Tissue biopsies revealed extravasation of red blood cells in both the lung and skin issues such as the mid-dermis (Jimenez-Cauhe et al., 2020; Mayor-Ibarguren et al., 2020). Vascular injury was also a prominent feature in association with endothelial dysfunction, micro-thrombus formation, and cellular inflammation (Fig. 2). Furthermore, a study in Germany found that lung histology from COVID-19 patients showed consistent diffuse alveolar injury in association with activated pneumocytes, protein-enriched edema, and microvascular thromboemboli (Wichmann et al., 2020). Heart tissue biopsies further revealed interstitial mononuclear inflammatory infiltrates consistent with an elevated level of serum troponin and cardiac arrhythmias; however, the molecular mechanisms remain undefined (Lindner et al., 2020). In addition to cardiopulmonary injury, gastrointestinal involvement is reported in up to 26% of patients (Z. Zhou et al., 2020). These COVID-19-infected tissues run in parallel with the organ systems as reported in populations living in areas with high air pollutant concentrations.

3.1.4. Future directions

While air pollution-mediated inflammatory effects often start in the pulmonary system, subsequent effects cascade throughout the circulatory system to induce oxidative stress and deterioration in the heart, lungs, and vasculature. In recent decades, exposure to $PM_{2.5}$ pollution has been associated with increased hospitalization and mortality, especially in patients with congestive heart failure or arrhythmia (Dominici et al., 2006; Mann et al., 2002; Pope et al., 2002). Statistics on COVID-19 mortality corroborate that comorbidities, including coronary artery diseases, hypertension, diabetes, and congestive heart disease, worsen the severity of symptoms and patient outcomes (Harrison et al., 2020; Ssentongo et al., 2020). In the face of increased COVID-19 cases in air

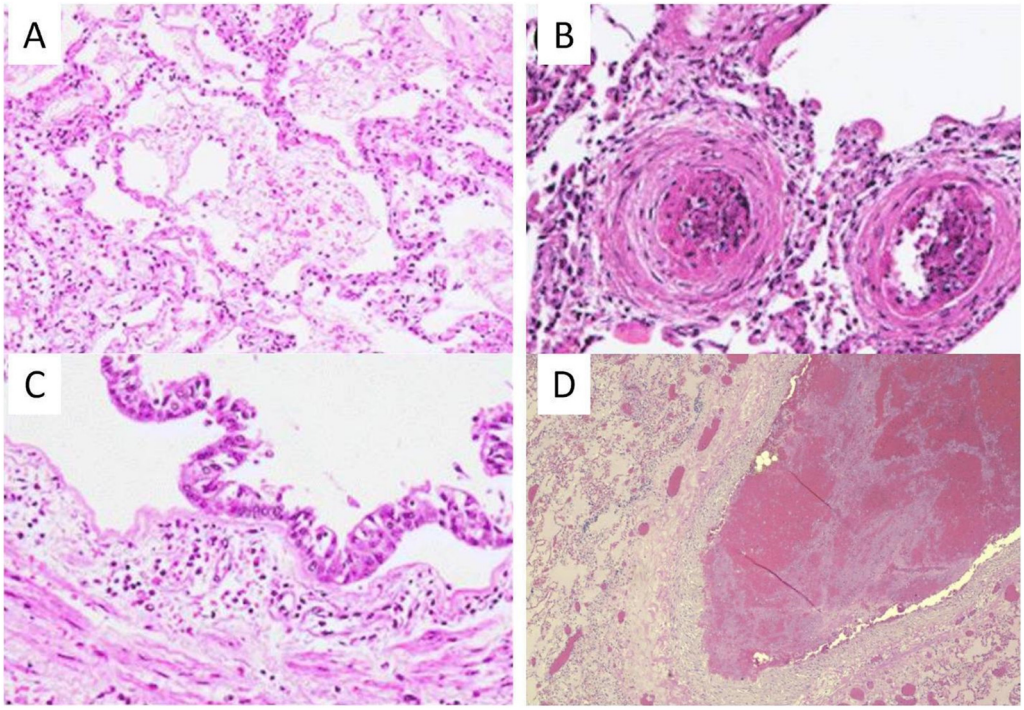

Fig. 2. Histopathologic images from COVID-19 patients showing endothelial injury and thrombus, which is similar to the histopathology seen in populations living in regions with high air pollution. (A) Histopathologic findings from COVID-19 patients show acute lung injury with hyaline membrane in the alveolar space. (B) Vascular damage with microthrombi in lung small vessels. (C) Cases show, airway inflammation in trachea sections with polymorphous inflammatory infiltrate of submucosal layers. (D) Pulmonary thromboembolus is also seen in many COVID-19 patients. Photos A–C from Calabrese et al. in *Virchows Arch.* 2020 and D from Vasquez-Bonilla et al. in *Hum. Pathol.* 2020 under the Creative Commons license (Calabrese et al., 2020; Vasquez-Bonilla et al., 2020).

pollutant-affected regions, epidemiological data supports chronic air pollution-induced oxidative stress and inflammatory response, mediating the direct impact on the cardiopulmonary system from chronic air pollution exposure.

Additionally, industrial and urban regions harbor higher $PM_{2.5}$ and PM_{10} concentrations compared to rural areas. For example, rural locations in the Midwestern United States exhibited lower $PM_{2.5}$ concentrations (8.4–10.4 μg/m^3) as compared to urban locations (9.5–11.6 μg/m^3) (Kundu and Stone, 2014). Thus, investigating the local impact of industrial areas on cardiopulmonary health is essential to elucidate the subsequent impact on the severity of COVID-19 infections.

3.2. Activation of multiple inflammatory mechanisms in response to both chronic air pollution exposure and COVID-19 infection

Populations exposed to long-term high concentrations of PM and gaseous pollutants develop chronic inflammation in association with the pathogenesis of cardiopulmonary diseases. Similarly, a severe immune response has been reported in approximately 15% of COVID-19 patients that present with intravascular cytokine release, and, in more severe cases, microvascular thrombosis (Lippi et al., 2020). One such response is the cytokine release syndrome (CRS) as characterized by the systemic release of cytokines, specifically, interleukin-6 (IL-6) (P.P. Liu et al., 2020; Hirawat et al., 2021). The pro-thrombotic properties of cytokines promote both microvascular and macrovascular thrombosis (P.P. Liu et al., 2020). In combination with raised baseline inflammation levels of populations living in areas of high air pollution concentration, the additive inflammation caused by COVID-19 further magnifies the rate of COVID-19-associated acute respiratory distress syndrome (ARDS), myocarditis, cardiac arrhythmia, and heart failure (P.P. Liu et al., 2020). If left unchecked, these conditions lead to inflammatory infiltration and destruction of alveolar septae and cardiac injury, largely being responsible for patient death due to lung and heart failure (Wichmann et al., 2020). As outlined by this section, the effects of short- and long-term exposure to air pollution create a heightened inflammatory state with symptoms that mirror those of COVID-19 patients. These consequences may be additive and exacerbate cardiopulmonary symptoms in COVID-19 patients, increasing their risk of mortality.

3.2.1. Cardiopulmonary inflammation due to exposure to pollutants increases susceptibility to respiratory infections

Effects of pollutants include pulmonary and systemic oxidative stress that alter vascular homeostasis (Roy et al., 2014). These oxidative effects come through pollutants affecting the lipids and proteins or indirectly through the activation of intracellular oxidant pathways (Daellenbach et al., 2020; Lodovici and Bigagli, 2011). At the molecular level, exposure to pollutants may activate cell signaling membrane receptors, intracellular phosphatases and kinases, and transcription factors that regulate inflammatory responses (Glencross et al., 2020).

Exposure to common air pollutants is well-recognized to alter host immunity to viral respiratory infections by suppression of the host's defenses (Ciencewicki and Jaspers, 2007). Long-term exposure to air pollution is linked to elevated blood pressure, ventricular diastolic dysfunction, reduced coronary flow reserve, and myocardial fibrosis (Rao et al., 2018; Wold et al., 2012). In addition, an altered cardiac autonomic nervous system, including increased mean heart rate and heart rate variability, develop in response to prolonged exposure to air pollution (Park et al., 2005, 2008). However, short-term exposure to $PM_{2.5}$ mediates vascular endothelial dysfunction and increased blood viscosity and circulating fibrinogen to promote a hypercoagulable state, predisposing patients to hypertension, acute coronary events, heart failure, and stroke (Donaldson et al., 2001; Peters et al., 2000; Ghio et al., 2000; Nelin et al., 2012; Rajagopalan et al., 2018). These conditions are implicated in the cumulative effects of COVID-19-patients in whom cardiac injury is evidenced by elevated serum troponin and cytokine levels in association with cardiac arrhythmia, myocarditis, and contractile dysfunction (Bonow et al., 2020; Driggin et al., 2020; Yang and Jin, 2020).

3.2.2. The role of ubiquitous ACE2 receptor and inflammation

Chronic exposure to air pollution has been associated with the expression of ACE2 in lung endothelial cells (Aztatzi-Aguilar et al., 2015; Paital and Agrawal, 2020). ACE2 is the receptor for the SARS-CoV-2 spike protein for virus internalization into the host (Lv et al., 2020). In mammalian models, chronic exposure to $PM_{2.5}$ has also been known to increase epithelial and endothelial ACE2 expression (Lindner et al., 2020). In addition to binding to the ACE2 receptor, transmembrane protease serine 2 (TMPRSS2) and potentially another common protease, furin, participate in the internalization of SARS-CoV-2 to the alveolar type 2 cells in the lung (Ackermann et al., 2020; Walls et al., 2020; Sajuthi et al., 2020). Thus, COVID-19 infection may be correlated with air pollution-mediated ACE2 expression (Hamouche et al., 2020).

ACE2 is a key part of the lung renin-angiotensin system (RAS), an inflammatory response balancing act. ACE2 cleaves Angiotensin II (Ang-II) to form [Ang(1-7)] which binds to the Mas receptor. The ACE2/Ang1-7/Mas receptor axis activation is a response to $PM_{2.5}$ exposure. Mas activation occurs as a result and suppresses STAT3 and ERK, exerting an anti-inflammatory response. The other axis is the ACE/Ang-II/AT1R axis that leads to the release of proinflammatory cytokines (Chamsi-Pasha et al., 2014). When the SARS-CoV-2 virus binds to ACE2 receptors of epithelial cells, there is an increase in Ang-II in the systemic circulation which primes the ACE/Ang-II/AT1R axis activation (Fig. 3). ACE2 and TMPRSS2 are ubiquitous in lung alveolar type 2 cells where their upregulation can lead to increased susceptibility to SARS-CoV-2 binding.

3.2.3. Inflammation and predisposition to cytokine storm

Atmospheric contaminants modulate the host inflammatory response, leading to overexpression of inflammatory cytokines and chemokines. The cytokine storm that is present in severely ill COVID-19 patients may also be worse in populations exposed to chronic air pollution.

The recently coined "cytokine storm" is a symptom seen in patients with severe COVID-19 infection and is characterized by the release of inflammatory cytokines (Hu et al., 2020; P. Zhou et al., 2020). Interleukin-6 (IL-6), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) are dominant cytokines released by lung epithelium upon interaction with PM (Pope et al., 2016). When the inflammatory response "spills over" into systemic circulation, a cellular inflammatory response and platelet activation are implicated in the abundant microthrombi found in COVID-19 patients (Brook and Rajagopalan, 2010). Another major route of inflammation is through the subsequent activation of the NF-κB pathway (Deng et al., 2018). NF-κB activation after coronavirus infection occurs via pattern recognition receptors in the MyD88 pathway, resulting in cytokine induction (DeDiego et al., 2014). Furthermore, receptor CD40, expressed by both immune and non-immune cells, binds to ligand CD40L, temporarily expressed on T cells and is involved with recruitment of TNF-α receptor-associated factors (Kawabe et al., 2011). This interaction further leads to the release of inflammatory cytokines (Bai and Sun, 2016). IL-6 is also a major marker of cellular senescence, supporting the notion of susceptibility to COVID-19 infection and complication from the age-dependent increase in IL-6 (Hirano and Murakami, 2020; Moccia et al., 2020). Taken together, both ambient PM exposure and COVID-19 infection prime the host inflammatory state via the NF-κB signaling pathway in association with elevated IL-6 levels, and COVID-19 infection further potentiates the progression to cytokine storms (Kim et al., 2016).

3.2.4. Future directions

The precise mechanism underlying air pollution-mediated inflammation and COVID-19-mediated cardiovascular diseases remains elusive. A potential mechanism is the ACE2 receptor and disrupted activation of the RAS in the myocardium in association with the pathogenesis of cardiovascular disease (Kuba et al., 2010). As shown by a murine model, the first generation of the SARS virus affected the pulmonary system, triggering an ACE2 dependent myocardial infarction (Kassiri et al., 2009). Additional cellular injury due to elevated IL-6, D-dimer, ferritin, other inflammatory cytokines, and hypoxia-induced excessive intracellular calcium are also implicated in cardiac myocyte apoptosis. However, the precise mechanisms must be investigated further (Clerkin et al., 2020).

Viral entry to the host cell occurs by binding between the S1 region of the virus spike (S) protein to the ACE2 receptor on the cell surface (Lv et al., 2020). SARS-CoV-2 binds to ACE2 for entry, and TMPRSS2 and endosomal cysteine proteases cathepsin B and L (CatB/L) prime the S

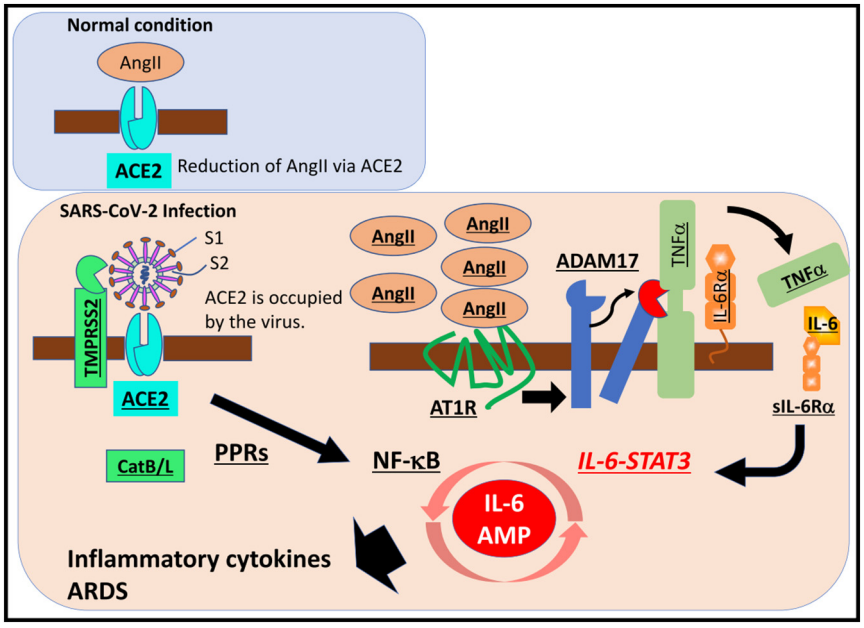

Fig. 3. ACE2 receptor binding to the SARS-CoV-2 spike protein leads to an imbalance of the RAS system and a subsequent inflammatory response. SARS-CoV-2 binding to ACE2 receptors on the surface of endothelial cells leads to the activation of multiple pathways that ultimately result in massive cytokine release. Figure from Hirano and Murakami in *Immunity*. 2020 under the Creative Commons license (Hirano and Murakami, 2020).

protein (Hoffmann et al., 2020b). Interestingly, SARS-CoV-2 also harbors a multibasic cleavage site at the S1/S2 boundary that is absent in SARS-CoV and other closely related animal coronaviruses (Walls et al., 2020). This unique cleavage site can be recognized by furin, essential for SARS-CoV-2 infection of human cells (Hoffmann et al., 2020a). While TMPRSS2 is highly expressed in the lungs, furin is expressed in many other organs, which may contribute to SARS-CoV-2's deleterious effects on multiple organs. In this context, developing inhibitors for both TMPRSS2 and furin may represent a promising therapeutic approach targeting SARS-CoV-2 in the setting of exposure to air pollution (Barile et al., 2020).

3.3. Air pollution exposure-mediated transmission of COVID-19 and overlap

SARS-CoV-2 is the seventh documented coronavirus to infect humans, targeting the ACE-2 receptor for entry into the host cell (Andersen et al., 2020). While SARS-CoV-2 may not be as lethal as previous coronavirus outbreaks, its transmission rate is higher, with R_0 being between 3.6 and 4 (Chen et al., 2020a, 2020b). Respiratory viruses, including SARS-CoV-2, have been understood to undergo transmission via direct contact (person to person) and droplet (bodily fluid to person) routes (Shiu et al., 2019). Controversy remains regarding the spread of viral particles suspended in the atmosphere, otherwise known as aerosol spread (Tellier et al., 2019). Furthermore, other routes of viral transmission relevant to the current pandemic, such as wastewater, have been implicated in its spread (D. Liu et al., 2020).

Air pollution and weather patterns have been recently studied for their physical contribution to the transmission of SARS-CoV-2. Similarly, components of air pollution, which are distributed by weather patterns, may act as viral distributors by acting as a surface to prolong viral survival. SARS-CoV-2 also survives for a longer period of time on dry surfaces than in an aerosol form (van Doremalen et al., 2020). One study analyzing air particles in two Wuhan hospitals found SARS-CoV-2 genetic material in sampled PM in the 0.25 to 1.0 μm range (Y. Liu et al., 2020). This may point to $PM_{2.5}$ and smaller particles acting as transporters for SARS-CoV-2 particles. These PM-virus aggregates can be more easily distributed in the alveoli and upper respiratory tract and facilitate delivery and virus binding to the pulmonary epithelium (Farhangrazi et al., 2020).

Additionally, as with other viruses, the coronaviruses have been observed to survive outside host cells for longer periods at lower temperatures and humidity (Farhangrazi et al., 2020). However, the impact of meteorological conditions on virus transmission remains less understood. One study conducted in a tropical climate revealed that higher temperatures and increased solar radiation limited the effect on COVID-19 transmission (Rosario et al., 2020). A similar study conducted in Italy, a Mediterranean climate, reported that temperature and humidity were negatively correlated with COVID-19 transmission (Lolli et al., 2020). Lastly, a more-comprehensive study using spatial and temporal models found that weather had a non-influential effect on COVID-19 transmission when compared with other factors such as homestay and urban density (Jamshidi et al., 2020). While meteorological factors such as temperature and wind speed have been shown to potentiate the ability of coronavirus to survive outside of a host, they are unlikely to be the singular reason for the extreme variability in COVID-19 infection rates across political borders (Coccia, 2021a, 2021b, 2021c).

3.3.1. Future directions

The precise mechanism whereby the environment modulates SARS-CoV-2 transmission warrants further investigation. Several studies have noted the seasonal relationship between various respiratory virus infections and meteorological variables, including temperature and humidity (Moriyama et al., 2020; Srivastava, 2021). Furthermore, simulated sunlight deactivates SARS-CoV-2 in minutes (Schuit et al., 2020). While PM pollution is a contributor to atmospheric haze, its impact on SARS-CoV-2 transmissibility warrants further study. Whether $PM_{2.5}$ and smaller particles have the capacity to transport SARS-CoV-2 remains to be explored. A previous outdoor study comprehensively isolated and categorized viral and microbial genetic material from PM (Cao et al., 2014), suggesting some viral material was able to associate with the pollution particles. The three most-represented samples were DNA-based viruses; however, SARS-CoV-2 is an RNA virus, and its RNA is unstable under most extracellular conditions. Thus, whether the mere presence of viral RNA indicates infectivity also requires further validation. In addition, volcano ash emission, along with the heavy metals, may contribute to SARS-CoV-2 transmission and/or atmospheric persistence of the viral particle. Both the Po Valley and Wuhan City are relatively close to active volcanoes and vents, possibly providing a link to the severe infection and adverse clinical outcomes observed in those areas (Raciti and Calabrò, 2020).

4. Discussion: pre-existing cardiopulmonary diseases mediated by air pollution and COVID-19 infection

Increasing evidence suggests that chronic exposure to air pollution leads to exacerbation and hospitalization of patients with COVID-19. As explained in the aforementioned redox-active mechanisms (Table 2), PM and air pollutants deposited in the lung reach the deep alveolar spaces to induce cytokine release and oxidative stress. These redox-active reactions are implicated in the exacerbation of COVID-19 infection and hospitalizations. A study in Italy supported the correlation between the Po Valley regions with 4-year exposure to high levels of NO_2, $PM_{2.5}$ and PM_{10} and the regions with the most hospitalizations of COVID-19 patients (Fattorini and Regoli, 2020). The northern regions of Italy, in particular, reflected up to 80 days of exceedance per year of the regulatory limits (Fattorini and Regoli, 2020). These same areas are regions in Italy that have experienced a high number of COVID-19 cases.

In the SARS-CoV-2 predecessors, SARS and MERS, the pre-existing cardiovascular diseases (CVDs) were reported to increase the risk of death, similar to the COVID-19 patients (Badawi and Ryoo, 2016; Booth et al., 2003; Chan et al., 2003). In Wuhan City, where there are high levels of air pollutants, hospitalizations were significantly prevalent among the COVID-19 patients with cardiopulmonary diseases (F. Zhou et al., 2020). In particular, these Wuhan residents with coronary heart disease, congestive heart failure, hypertension, and/or diabetes develop increased susceptibility to the severity of COVID-19 infection and death (Gold et al., 2000; Mutlu et al., 2007). Thus, patients living in polluted regions with pre-existing cardiopulmonary conditions, which may arise from exposure to air pollution, were likely to develop high rates of hospitalization when saddled with a COVID-19 infection (Hamouche et al., 2020).

The relationship between COVID-19 and underlying cardiopulmonary diseases and impact of air pollution is an emerging topic. More studies and comprehensive reviews are necessary to further determine the interrelationships between the deleterious effects of air pollution exposure and the severity of COVID-19 infections.

5. Conclusion

This review presented overarching themes found in current literature that suggest exposure to pollution increases susceptibility to COVID-19 infection, creating a pre-inflammatory state in patients. Populations that are more at-risk for pollution-related CVDs, such as the elderly living in urban areas, may also be more at-risk to COVID-19 (Dockery et al., 1993). Inhalation of PM has been associated with respiratory and cardiovascular events. Therefore, as air pollutants affect respiratory and cardiovascular health, COVID-19 prognosis and mortality are impacted by the presence of respiratory and cardiovascular comorbidities. Air pollution may also negatively impact COVID-19 outcomes.

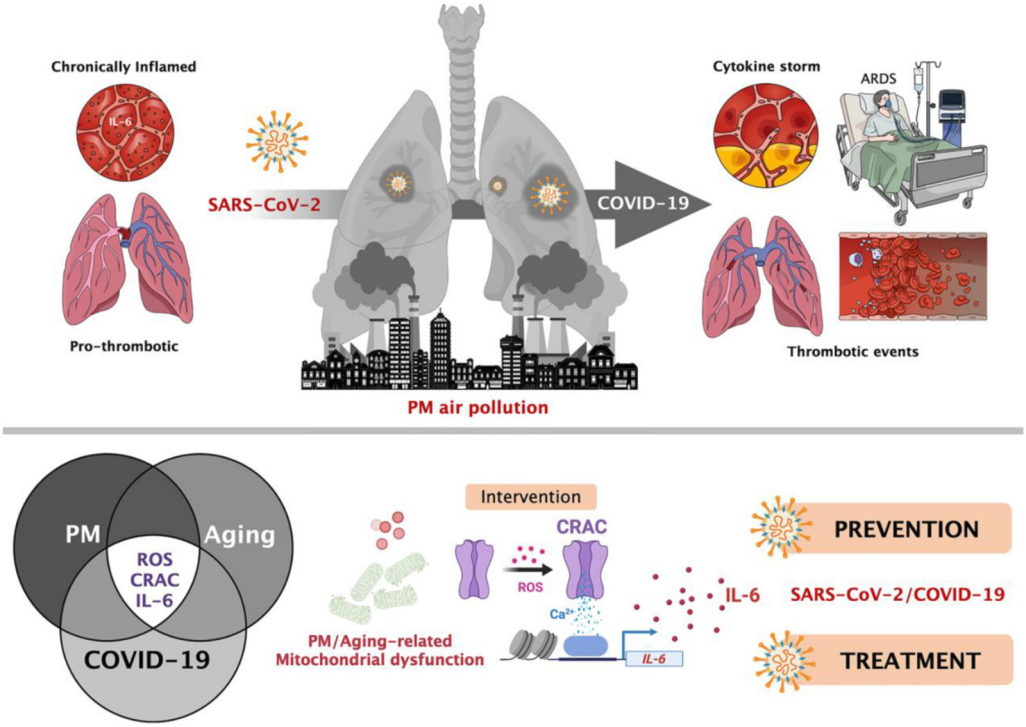

Fig. 4. Relationship between particulate matter (PM) air pollution, SARS-CoV-2 infection, and COVID-19 prognosis and a potential therapy for the prevention and treatment of disease. PM air pollution largely targets the lung, triggering signaling pathways that have also been found to be caused by SARS-CoV-2. These signals include the release of inflammatory cytokines including IL-6, reactive oxygen species (ROS), and calcium-release activation calcium (CRAC) channels and a consequent rise in thrombotic events. Patients who already experience this response may be at risk for a higher severity of COVID-19 disease and increased risk of mortality. Figure from Menendez in *Aging*. 2020 under the Creative Commons license (Menendez, 2020).

Current literature broadly finds that chronic exposure to air pollution results in patients with higher compensatory ACE2 receptor expression, which may also lead to a lower barrier to entry for the SARS-CoV-2 virus. Targeting this pathway alongside pharmaceutical agents to reduce inflammation may ultimately mitigate the severity of symptoms in patients from areas of high air pollution. Furthermore, considering the environmental factors surrounding a COVID-19 patient is essential for effective intervention and prevention.

Ambient pollutants are increasingly recognized as the epigenetic co-factors in the current COVID-19 pandemic and inform potential intervention and prevention (Fig. 4). Chronic exposure to air pollution increases inflammation in populations that are thus more susceptible to contracting the virus. The signaling pathways underlying inflammatory responses can potentially be therapeutic targets to attenuate the cardiopulmonary manifestation from SARS-CoV-2 infection. The RECOVERY Trial is assessing whether existing drugs can be repurposed to treat COVID-19 by enrolling 104 patients for a relatively low dose of 6 mg of dexamethasone, a steroid for inflammation, for 10 days (RECOVERY Collaborative Group et al., 2020). The RECOVERY trial is also evaluating several experimental COVID-19 therapies, including the HIV drug combination Kaletra, convalescent plasma, and the controversial antimalarial drug hydroxychloroquine.

Targeting endothelial inflammation and using anti-inflammatory drugs already proven in clinical use could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction (Varga et al., 2020). Additionally, medicine targeting ACE2 receptors may also reduce viral entry into the alveolar space. Despite concerns that CVD patients taking ACE inhibitors and angiotensin receptor blockers (ARBs) may be more-susceptible to COVID-19, due to resulting ACE2R up-regulation, a global observational study with 169 sites and 8910 patients found no increased risk of in-hospital death (Mehra and Ruschitzka, 2020). In addition, mitigating the long-term cardiopulmonary effects of air pollution would require concerted public health actions to help protect residents in highly polluted regions. While urban air pollution seems to have decreased in the United States during the COVID-19 pandemic, more efforts must be made to maintain lower levels even after business returns to normal (Berman and Ebisu, 2020).

CRediT authorship contribution statement

AL, RO, and MC contributed equally to this review by conducting a literature review and writing the manuscript. JAS and CZ contributed to editing. TKH conceived the review paper and edited the manuscript.

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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