The plausible pathway of air pollutants and the respiratory system among COVID-19 patients: a systematic literature review

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Article Info

ABSTRACT

Studies evidence links air pollution to increased risk of COVID-19 infection and severity during the pandemic. Nonetheless, those studies are unable to discuss specific pollutants, such as particulate matter, Sox, and NOx. This systematic literature review aimed to summarize the most recent studies on the links between pollutants and their effects on the respiratory system, in this case, mostly on COVID-19 patients. We searched using electronic databases (PubMed, Springer, ScienceDirect, and Sage) in May 2023. The keywords chosen were connected to respiratory diseases and air pollution. All relevant studies published in peer-reviewed journals between 2020 and 2023 and written in English were considered. We excluded letters and non-original articles. Relevant keywords were used to select papers. A total of 11 articles are eligible to be included in the present review study. It was reported that countries with a high prevalence of COVID-19 also have greater concentrations of surface air particles (PM_{10} and $PM_{2.5}$) due to vehicle exhaust and industrial pollution. PM-virus aggregates spread easier across the lungs and the top respiratory system, facilitating viral attachment to the lung epithelium. This study found that tiny particles with an aerodynamic dimension fewer than 2.5 μm ($PM_{2.5}$) or ten μm (PM_{10}) have the most significant potential influence on the respiratory system compared to other pollutants.

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1. INTRODUCTION

The COVID-19 pandemic induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a wide-ranging effect on many parts of life since it produces significant infections of the lungs [1], [2]. The rapid transmission from person to person through close contact causes the disease to spread quickly and in a short period. Its high transmissibility has made COVID-19 the third major pandemic in history and become the most significant health concern. Almost every country has been impacted by this pandemic, which has led to a remarkable case of mortalities.

Recent studies highlighted the importance of the environment in impacting the high incidence of confirmed COVID-19 cases. Environmental variables such as excessive air pollution and aerosols in hospitals can get contaminated, increasing the risk of infection and causing asthma, chronic obstructive pulmonary disease, bronchitis, and other respiratory disorders [3]. Contaminated aerosols are linked to an increase in COVID-19 cases since they cause angiotensin converting enzyme 2 (ACE-2) overexpression, which is the attachment receptors of the SARS-CoV-2 rise protein and thus enhances the likelihood of getting

infected and the extent of human respiratory disease. Ironically, the virus in aerosols can survive for up to three hours, resulting in more severe COVID-19 instances [4]. Those findings evidence the role of air pollution, which is part of environmental issues, in causing extreme conditions for the prognosis of COVID-19.

In addition, air pollution affects the worsened health outcomes of residents living in areas with high air pollution. This was also experienced during the COVID-19 pandemic. A previous study comparing COVID-19 cases according to the spatial distribution in Italy identified 39 most polluted regions significantly associated with the elevated number of COVID-19. In 15 samples, the polymerase chain reaction (PCR) method revealed the E gene and a high RdRP gene specific for SARS-CoV-2 [5]. The findings indicate that SARS-CoV-2 RNA may be discovered in urban atmospheric PM_{10}. The SARS-CoV-2 virus is incorporated into the PM by coagulation, increasing the virus's concentration in the lungs [6], [7].

Previous studies reported that long-term contact with air pollution is a primary cause of COVID-19-related death [8]. Particulate matter, both PM_{10} and $PM_{2.5}$, aids the transportation of viral particles; hence, massive COVID-19 transmission through carriers occurred [9]. These conditions may elevate the susceptibility and severity of COVID-19 and the contribution of chronic diseases. Furthermore, fuel is an environmental issue. An estimated 4.2 and 3.8 million fatalities per year are linked to dirty atmospheric air caused by substantial traffic volumes and high manufacturing activity, respectively, as well as residential exposure to smoke from filthy fuel sources [5], [10]–[14]. Indeed, industrial regions with high pollution levels have been demonstrated to have increased hospitalization rates and mortality rates owing to SARS-CoV-2 transmission [15]–[20].

Several studies examine the link between pollutants in the air and the increase in the prevalence of confirmed COVID-19 cases; however, the pathways of outdoor contaminants to COVID-19 transmission and severity remain unclear. $PM_{2.5}$, PM_{10}, NO_2, and SO_2 mechanisms related to ACE-2 overexpression will be discussed in this study to increase understanding, and it is hoped that it will become a reference for further research and that public health service programs will prioritize air quality improvement.

2. METHOD
2.1. Databases and search strategy
This systematic review was written based on the preferred reporting items for systematic reviews standard. We reviewed the published relevant literature exploring how air pollution impacts COVID-19. This study's demographic and sample criteria were patients exposed to air pollution during a pandemic, with no regard for race or ethnicity. While conducting a trial search and reviewing retrieved papers, we enhanced the search term by identifying other relevant words within each concept. We used the following descriptors: "intervention or observational" [Publication Type] OR "intervention or observational as topic" [MeSH terms] OR "intervention or observational" [All Fields]. Based on the information gathered, we have formulated the final search term for PubMed. The details are presented in Table 1.

Table 1. Keywords of searching strategy

Search term	Keywords
AND	"COVID-19" OR "SARS-COV-2" OR "Air Pollution" OR "Air Pollutant" OR "Respiratory System"
AND	"Particulate matter" OR "PM" OR "NOx" OR "nitrogen oxide" OR "NO_2" OR "nitrogen dioxide" OR "SOx" OR "sulfur monoxide" OR "SO_2" OR "sulfur dioxide",
AND	"COVID-19 Pandemic" OR "Effect of Air Pollution" OR "Nitrogen, Sulfur, and Particulate Matter"

2.2. Inclusion criteria
All sources fit the inclusion criteria: i) all relevant studies, ii) papers published in peer-reviewed journals between 2020 and 2023, and iii) written in English. We excluded letters or studies other than the original article type. The papers were then chosen based on their relevance to the historical period and the keywords relevant to COVID-19 and air pollution. As part of the article selection process, we extensively searched relevant articles by examining the references of the included studies. All authors reviewed and evaluated the titles and abstracts of the articles. Then, we carefully assessed the full text of all studies that seemed potentially eligible for inclusion in our research. We discussed and deliberated whether each article was relevant to the present study regarding its topic, outcome, and study design.

2.3. Data extraction and bias assessment
The reviewers extracted data independently for each text using a pilot data extraction form. The systematic review adhered to the PRISMA guidelines for identifying, screening, and collecting primary articles. The authors manually selected papers based on their research goals, using specific inclusion criteria. After

selecting the papers, relevant information was retrieved, such as author, year, title, aims, study design, analysis method, research findings related to the effect of ambient air pollutants on the respiratory system, and notes or critical comments toward the study. This information was then presented in a table for easy reference.

Conducting a biased assessment that aligns with the gold standard of systematic reviews of interventions - the Cochrane Handbook is imperative [21]. The bias domains measured included selection of participants, interventions, outcome data, measurement of outcome, and reported findings. Overall, risk-of-bias judgment was categorized as low bias, some concerns, and a high risk of bias [22]. The authors addressed the issue of discrepancies in research studies, which arise due to differences in review objectives, the types of primary studies included, and the method of qualitative data synthesis. They aimed to minimize potential bias due to subjective judgment while selecting articles for review.

3.   RESULTS AND DISCUSSION

Among the 2,689 studies screened, 58 papers were collected from the four databases (14 from PubMed, 13 from Springer, 19 from ScienceDirect, and 12 from Sage) after the first selection procedure. The 58 papers were then re-selected based on their relevance to the study's aims and the titles and abstracts of each article from the four databases, yielding 11 publications evaluated, see Figure 1. Most studies were conducted in the US, the UK, Italy, China, and Middle Eastern countries (Iran and Saudi Arabia). We also included two extensive studies which analyzed data from several countries. It was also detected that there has been a progressive interest in this topic since the pandemic. Overall, the reviewed studies suggested air pollution, including particulate matter ($PM_{2.5}$ and PM_{10}), SO, and NO correlated to increasing COVID-19-confirmed diseases. The most investigated health outcomes were COVID-19 cases in the general population, see Table 2.
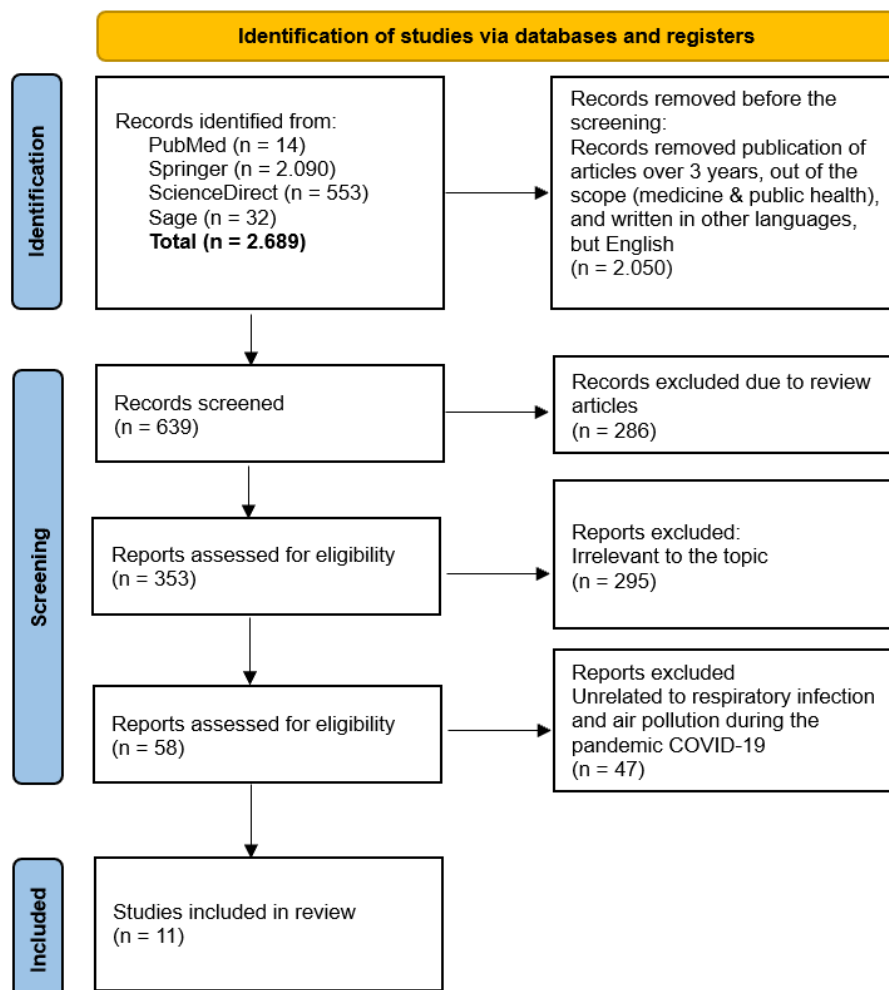

Figure 1. Study selection process

Table 2. Results of a review of studies on the linkage of air pollution to an increase in COVID-19

Author	Study setting	Study design	Analysis method	Variables	The connection between air pollution and the COVID-19 pandemic
[23]	US	Longitudinal study	Generalized additive model	i. Outcome: daily confirmed cases ii. Factors: Air pollutants ($PM_{2.5}$ and O_3)	Increased levels of PM2.5 and O3 in the environment increase the likelihood of infection with COVID-19 by 9.41% and 2.42%, respectively, in daily reported COVID-19 cases between 1 and 14 days.
[24]	UK	Prospective cohort	Logistic regression model	i. Outcome: COVID-19 cases, hospitalizations, and deaths ii. Factors: Air pollutants ($PM_{2.5}$, PM_{10}, and NO_2)	Long-term exposure to PM2.5 and NO2 was linked to a positive COVID-19 test. Chronic diseases such as diabetes, chronic lung disease, and cardiovascular disease are all risk factors for COVID-19 infection.
[25]	UK	Retrospective cohort	Multilevel analysis: regional-level, subregional-level, and individual-level analysis	i. Outcome: COVID-19 cases and deaths ii. Factors: Air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO, and O_3)	A significant statistical link exists between NO and NO_2 ranges and COVID-19 death at the regional and subregional levels. Air pollution from urban traffic raises the probability of a severe COVID-19 result. A 12% rise in UK COVID-19 cases is connected with a 1 m³ increase in long-term average $PM_{2.5}$. A similar impact was shown for PM10, where a one-unit increase was linked with an 8% rise in COVID-19 cases.
[26]	China	Longitudinal study	Time-series analysis	i.Outcome: daily COVID-19 confirmed cases ii.Factors: - Air pollutants ($PM_{2.5}$, PM_{10}, NO_2, CO, SO_2, and O_3) - Meteorological variables (temperature, dew point temperature, and wind speed)	COVID-19 spread is aided by NO_2 exposure. With a 20-day interval, an increase in NO2 concentration per interquartile range of roughly 19% was detected, increasing COVID-19 morbidity. High levels of NO_x in the environment have been linked to protracted exacerbations of viral etiologies, which may enhance susceptibility to infection and contribute to the toxicological consequences of air pollution.
[27]	260 countries	Retrospective, observational, longitudinal study	Spatio-temporal algorithms model	i.Outcome: COVID-19 confirmed cases ii.Factors: - National biodiversity index - Air quality - Pollutants elements (PM_{10}, $PM_{2.5}$, and O_3).	The findings imply a link between biological diversity variables and COVID-19 dissemination. Natural ecological disruption accelerates the transmission of illness from wildlife to people. Also, countries with a high prevalence of COVID-19 have higher amounts of particulate matter in the environment (PM_{10} and $PM_{2.5}$) at ground level due to vehicle exhaust and industry emissions.
[28]	European countries	Retrospective study	Multi-level correlation analysis	i.Outcome: daily reported COVID-19 cases ii.Factors: - Particulate matter ($PM_{2.5}$) - Latitude - Temperature; humidity - Population density - Human development index - Global health security index	Temperature and relative humidity might hasten the transmission of SARS-CoV-2 when $PM_{2.5}$ concentrations are less than 20 mg/m3 due to harmful metal ions and organic debris in $PM_{2.5}$. A single cough or sneeze generates around 710 to 40,000 droplets of SARS-CoV-2, which can interact strongly with $PM_{2.5}$. These aerosol droplets can linger in the air and travel beyond 1 meter.
[29]	Italy	Retrospective cohort study	Multiple generalized linear mixed models with mixed effects logistic regression.	i.Outcome: Daily reported COVID-19 cases ii.Factors: Particulate matter (PM_{10})	Short-term contact with PM_{10} could indicate a risk of developing pneumonia in individuals infected with COVID-19. 1079 (16.6%) of the 6483 COVID-19 patients as probands were diagnosed with pneumonia, where the majority were older, more likely to be male, have poorer health, and have higher individual levels of PM_{10}.
[30]	Iran	Longitudinal study	Time-series correlation analysis	i.Outcome: COVID-19 incidence and positive chest CT scan ii.Factors: - Particulate matter (PM_{10}; $PM_{2.5}$) - Relative humidity - Temperature	Fine PM, having an aerodynamic dimension of fewer than 10 µm (PM_{10}) or 2.5 µm ($PM_{2.5}$), primarily generated by sources such as cars, the energy sector, and dust, has the most severe potential effects on human health. Because daily air temperatures of 10-28 °C and relative humidity of 19-40% are conducive to the spread of the coronavirus in Ahvaz, a positive CT scan of the chest proved this.
[31]	Spain	Retrospective cohort study	A multilevel Poisson regression model	i.Outcome: daily COVID-19 deaths ii.Factors: - $PM_{2.5}$ - NO_2	COVID-19 mortality is associated with high levels of PM2.5 (IRR=1.016, 95% CI: 1.007-1.026), NO2 (IRR=1.066, 95% CI: 1.058-1.075), and rainfall (IRRNO2=0.989, 95% CI: 0.981-0.997). The COVID-19 mortality rate in Spain could be influenced by air pollution.
[32]	China	Longitudinal study	A nonlinear concentration-response analysis	i.Outcome: COVID-19 confirmed cases ii.Factors: - $PM_{2.5}$; PM_{10} - SO_2 - NO_2 - O_3 - CO	At lag4, the parameter increased across the entire range between quarters PM2.5, PM10, SO2, and NO2 corresponded to 1.40 (1.37-1.43), 1.35 (1.32-1.37), 1.01 (1.00-1.02), and 1.08 (1.07-1.010) OR of daily new COVID-19 instances. The ORs for a one °C, 1%, and one m/s rise in wind speed, relative humidity, and temperature are 0.94 (0.92-0.95), 0.96 (0.96-0.97), and 0.97 (0.97-0.98).
[33]	Saudi Arabia	Retrospective cohort study	Linear correlation analysis	i.Outcome: Total COVID-19 confirmed cases ii.Factors: Particulate matters	After evaluating 77 sites, researchers discovered that PM lingered longer in high-altitude air than around the ocean floor. This shows that the connection between PM and COVID-19 transmission might be increased in highland settings.

This study was intended to explore whether pollutant exposures, mainly particulate matter (PM), nitrogen dioxide (NO2), and Sulphur dioxide (SO2), increase the likelihood of the infection of COVID-19 and its mechanism in the human body. Previous findings from different settings and methods support the statement that exposure to those pollutants represents potential factors for developing respiratory issues, including pneumonia among COVID-19 patients [10], [34]. These increased trends were linked to rising exposure to indoor and outdoor pollutants.

WHO defined a threshold value of pollutant level as an annual average of 10 mg/μm^3 and a 24-hour average of 25 μg/m^3 of PM$_{2.5}$, PM$_{10}$ for a yearly average of 20 mg/m^3 and a 24-hour average of 50 μg/m^3, NO$_2$ for an annual average of 40 μg/m^3 and 200 μg/m^3 for an hourly average, and SO$_3$ for an average of 24 hours and 500 μg/m^3 for an average of 24 minutes [35]. The increasing levels of those pollutants may enhance the frequency of COVID-19 outbreaks, notably through increased comorbidities caused by ACE-2 overexpression, which provides SARS-CoV-2 adhesion sites to assault lung cells, see Figure 2 [10], [36]. Concerning the other respiratory diseases, it was found that acute infection in the lower respiratory tract (LST) instances among kids aged 0-4 years, lung cancer and chronic obstructive pulmonary disease in adults aged 30 years, asthma in children aged five years, and TB at age 15 years are all comorbid hazards related to air pollution [10]. This does explain the high fatality rate of air pollutants to the respiratory system, including COVID-19.

Air pollution is well-known to elevate the host susceptibility through chronic exposure, which may weaken the respiratory and immune systems and heighten the risk of comorbidities. Short-term and long-term exposure to air pollution worsens respiratory disease by causing oxidative stress and inflammation throughout the body. For instance, PMs accumulating in the lungs and traveling to extrapulmonary regions via the air-blood barrier produce low-grade systemic inflammation. This low grade of inflammation exacerbates COVID-19 inflammation. It has also been associated with an increased risk of diseases such as cancer, heart disease, stroke, diabetes, asthma, and other comorbidities. As a result, high lung damage may be shown in the COVID-19 symptoms, which also indicates the severity of the disease and increases the risk of death outcome, see Figure 2.
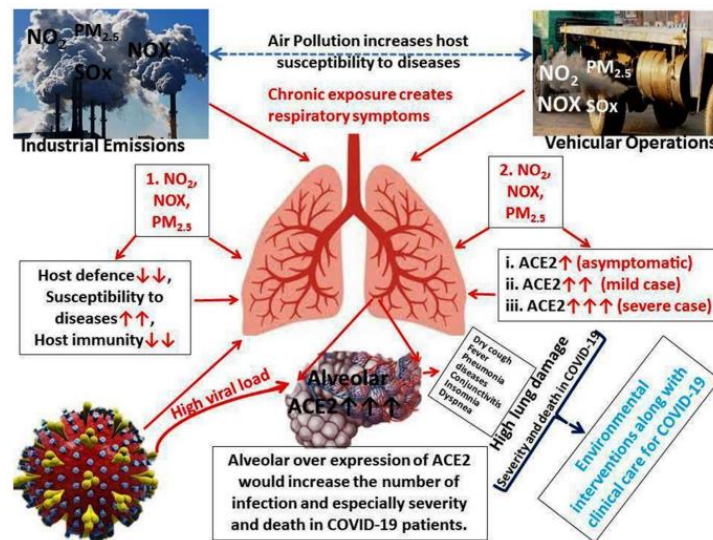

Figure 2. The connection between increased COVID-19 instances and high pollutant levels [10]

Air pollution also causes comorbidities such as the production of ROS, oxidative stress, reactive nitrogen, mitochondrial dysfunction, metabolic reprogramming, smooth muscle cell proliferation, necrosis, apoptosis, neutrophil inflammation, and infiltration. All these comorbidities are influenced by genetic factors that result in abnormal microRNA expression and, ultimately, different physiology worsens as a result of immunological dysregulation, putting it vulnerable to major respiratory disorders, see Figure 3 [37]–[39]. This is linked to the "Cytokine Storm," an overwhelming immune response, because of the large production of systemic inflammatory cytokines, particularly interleukin-6 (IL-6) [11], [40], [41]. When the virus that causes SARS-CoV-2 binds to the receptor for ACE-2 on epithelial cells, Ang-II levels in the blood rise, activating the ACE/Ang-II/AT1R. Overexpression of ACE-2 and transmembrane protease serine 2 TMPRSS2 in type 2 pulmonary alveolar tissue may enhance sensitivity to SARS-CoV-2 binding, see Figure 4 [42].
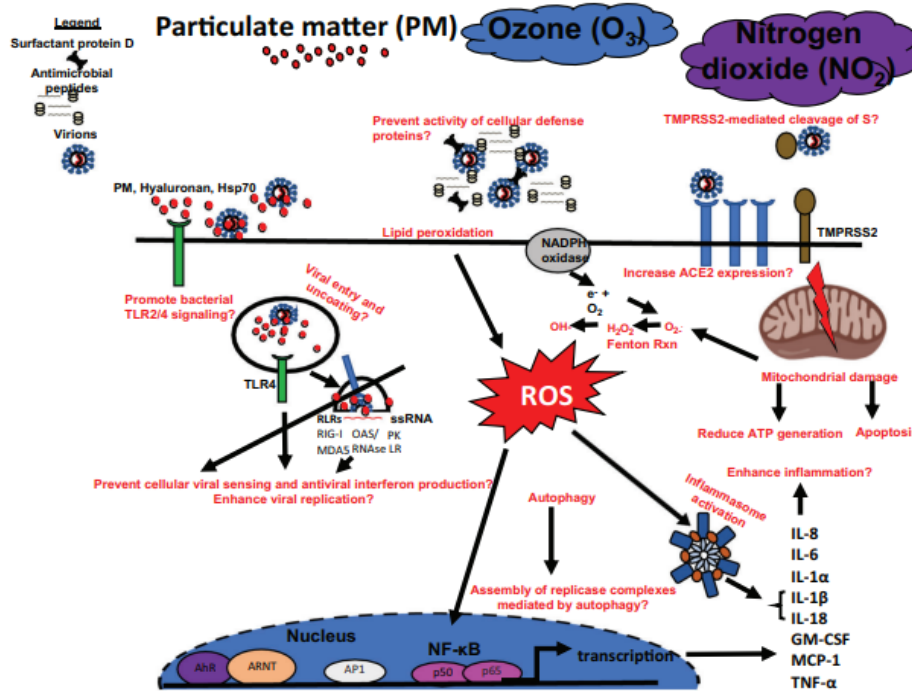
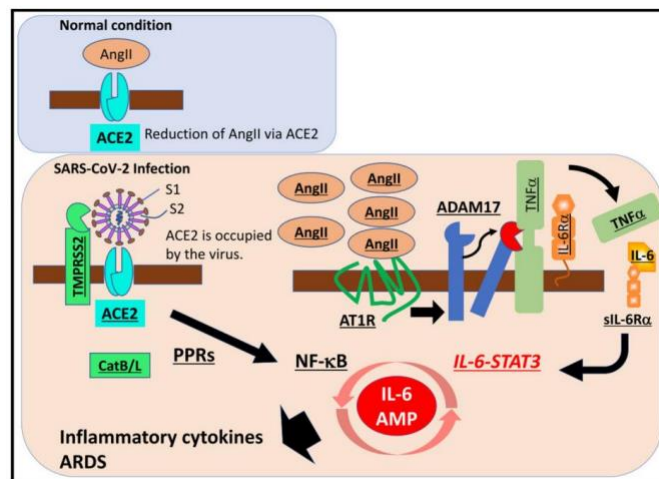Figure 3. Pollutant exposure promotes the activation of inflammation [8]

Figure 4. Inflammatory mechanism [43]

As a result, the body has significant challenges. In a histological analysis of COVID-19 patients, [44] discovered that viral penetration produces endothelial inflammation in small intestine cells, blood vessels, lungs, heart, liver, and kidneys in a histological examination of COVID-19 patients. Vascular injury is commonly associated with endothelial dysfunction, microthrombus formation, and cellular inflammation, see Figure 5. Pollutants induce reactive oxygen species (ROS), activating redox-sensitive transcription factors NF-κB and AP-1, which promote proinflammatory gene transcription. PAHs also start AhRs that interact with NF-κB [8]. SARS-CoV-2 binds to ACE-2 on host cells. The virus spike protein is activated by TMPRSS2 and endosomal cysteine protease cathepsin B and L (CatB/L). This triggers the activation of NF-Kb, the AT1R, A disintegrin, and metalloprotease 17 (ADAM-17), leading to inflammation [43]. COVID-19 patients' lung histology findings mimic those of harmed microscopic structures in air pollution exposure. A histological examination of COVID-19 patients indicated viral penetration of endothelial cells in the liver and small intestine and endothelial inflammation in the small intestine, vascular, lung, heart, liver, and kidney cells [41]. All of these organ systems are impacted by chronic air pollution.
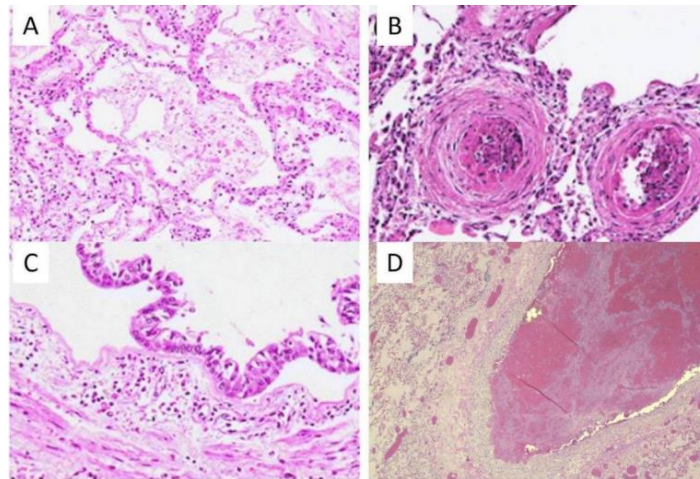
Figure 5. COVID-19 histopathological pictures from a population living in high-pollution locations,
(a) Histopathological signs of acute lung damage with alveolar hyaline membranes, (b) Microthrombi in the
pulmonary vessels cause vascular injury, (c) Tracheal airway inflammation with submucosal inflammation,
(d) Thromboembolism of the lungs [45], [46]

In addition to acute respiratory distress syndrome (ARDS), pollution causes cardiac arrhythmias, atopic disease, myocarditis, chronic cardiopulmonary illness, ischemic heart disease, heart failure, and neurological issues. Even its clinical sequelae have been linked to dementia, chronic renal disease, pediatric leukemia, organ failure, and hypertension [47], [48]. If left untreated, this illness produces severe inflammation, loss of alveolar septa, and heart damage, which can lead to death in people suffering from pulmonary and heart failure, see Figure 6 [49], [50] This is connected to PM, which has been demonstrated to promote ACE-2 expression in the lungs, providing the primary adhesion for SARS-CoV-2. The PM-virus aggregation spreads more quickly and disseminates throughout the lungs and the top of the respiratory tract, making viral attachment to the lung epithelium easier [8]–[10], [36], [39], [51]–[53]. Furthermore, ACE-2 can accelerate the splitting of angiotensin-I and angiotensin-II groups 1 through 7, which operate as a vasodilator and have the potential to produce hypertension [54]. COVID-19 severity is increased by severe air pollution due to poor ACE-2 overexpression [55].
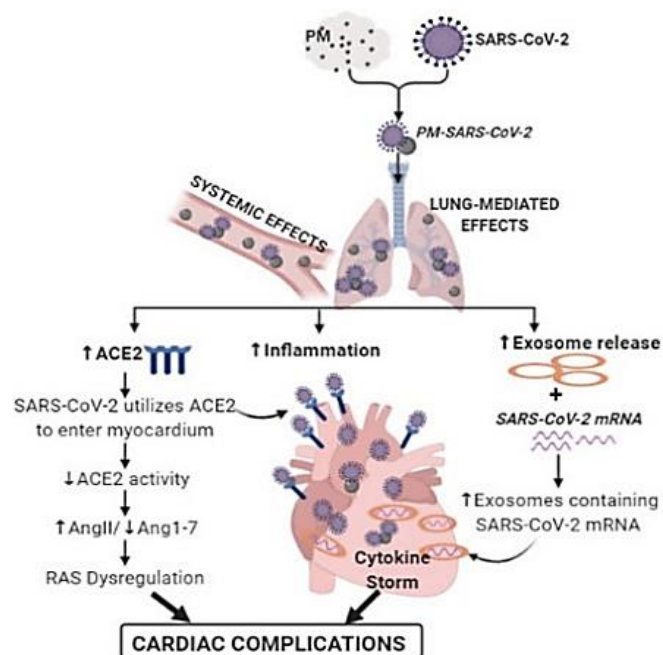

Figure 6. The method through which the SARS-CoV-2 virus causes lung and cardiac damage [49]

As a result of the significant increase in COVID-19 cases, it is critical to determine host susceptibilities due to high outdoor air pollutants, including $PM_{2.5}$, PM_{10}, NOx, and SOx. The existing findings proved that a high concentration of particulate matter significantly affects the prevalence of chronic respiratory diseases, including COVID-19 [56], [57]. Moreover, it is also noted that exposure to $PM_{2.5}$ is correlated with a longer recovery time. This pollutant decreases the pulmonary diffusing capacity in lung function, elevates airway inflammation and hyperresponsiveness, and worsens the respiratory system [58]. The mechanism has been examined, beginning with the organic components of PM producing body harm, which may increase free radical formation and oxidize lung cells. Excessive formation of free radicals or ROS causes an imbalance in intracellular calcium homeostasis, which reduces the antioxidant capacity of cells. Furthermore, particulate matter has been linked to inflammatory cytokines by stimulating the overexpression of transcription factor genes and inflammation-related cytokine genes, resulting in inflammatory damage [57].

While particulate matter and the respiratory-related outcome are explained, NOx and Sox have caused a similar effect. High intensity and ambient NOx and SOx exposure contributed to respiratory tract infections. A strong association has been reported between pollutants (SO_2 and NO_2), a significant decline in small airway function, and an increase in airway oxidative stress among children with asthma [59]. NO_2 is demonstrated in increasing leukotriene production, which may cause a significant trigger for asthma exacerbations [60]. Those findings suggest outdoor air pollutants, including particulate matter, NOx, and SOx, plausibly explain the effects on the respiratory system of both healthy and pulmonary patients.

Despite the COVID-19 pandemic subsiding, the danger of air pollution should not be ignored. This study does not solely focus on COVID-19 but instead uses it as an example of a respiratory-based disease discussed in this study. Previous research has already indicated that chronic exposure to air pollutants not only exacerbates pre-existing conditions but also increases the number of new cases of asthma, chronic obstructive pulmonary disease (COPD), and lung cancer, even in rural areas [61]–[63]. This means that COVID-19 is not the only disease caused by high levels of air pollution. This study highlights that air pollution and its health implications remain a significant global issue even after the pandemic. The pollutants discussed in this review pose a widespread health threat, causing chronic and acute respiratory complications. This is particularly true in developing countries where biomass fuels and coal are commonly used for home heating and cooking [64]. It is crucial for all levels of government, industry, and the private sector to work together to reduce the burden of air pollution and provide better respiratory health protection for everyone.

Although comprehensive recent findings related to the relationship between pollutants and respiratory diseases, such as COVID-19, are constantly being developed, we acknowledge the existing literature has limitations. The mechanism of contaminants affecting the respiratory system is generally described; however, no single study focuses on specific pollutants. It should be noted that while all reviewed studies assumed the use of reliable air quality data from official monitoring stations, it is challenging to generalize the validation of data sources across different countries. This is because some countries may have a reliable reporting system, while others may not. As a result, the robustness of the association between air pollutants and COVID-19 may be confounded by uncontrolled bias due to the data sources. Nevertheless, this study examines recent peer-reviewed investigations to ensure accurate conclusions from professionally executed studies. In addition, all the studies suggest a similar decision: areas with high levels of pollutants have a higher transmission rate of COVID-19 cases. These findings could have implications for the prevention of respiratory systems-based diseases. Further extensive study to understand the specific mechanism of pollutants and human defense may lead to broad knowledge. It will be necessary to conduct more longitudinal or cohort studies to obtain better respiratory function measurements in infants and biomarkers of impact. This will facilitate tracking the link between exposure to air pollution and the development of respiratory diseases.

4. CONCLUSION

This study found a link between air pollutants, including particulate matter, NOx, SOx, and NO, and respiratory diseases, mainly focusing on COVID-19 cases. Fine particles that have an aerodynamic dimension of fewer than 2.5 µm ($PM_{2.5}$) or 10 µm (PM_{10}) from vehicles, the energy industry, and dust have the most prominent possible effect on the prevalence of human respiratory disease, according to pollutant levels analyzed for their association with COVID-19. This situation implies that air pollutants raise the risk of respiratory illnesses via increasing ACE-2 expression.

ACKNOWLEDGEMENTS

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