Journal of Air Pollution and Health (Autumn 2020); 5(4): 243-258

Review Article

Available online at http://japh.tums.ac.ir

A review on the effect of air pollution and exposure to PM, NO_2, O_3, SO_2, CO and heavy metals on viral respiratory infections

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ARTICLE INFORMATION

Article Chronology:
Received 24 October 2020
Revised 28 November 2020
Accepted 30 November 2020
Published 30 December 2020

Keywords:
Air pollution; Upper respiratory infections; Lower respiratory infections; COVID-19; Influenza

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ABSTRACT

The ambient air pollutants that have a major role in causing respiratory diseases are particulate matter, sulfur dioxide, nitrogen dioxide, ozone, carbon monoxide, and heavy metals. In addition, respiratory infections, divided into upper respiratory tract and lower respiratory tract infection, are most commonly caused by viral agents. Thus, in light of the current COVID-19 pandemic, this review has focused on the association between exposure to general air pollution including each of the mentioned air pollutants and viral respiratory infections. The gathered evidence from the reviewed studies in this article showed that most of these air pollutants have a positive correlation with mortality, severity, transmission, inflammation, and incidence of different viral respiratory infections. Whereas, some studies found contradictory results such as non-significant and negative connections between exposure to air pollutants and viral respiratory infections, which are further discussed in this text. Therefore, following the SARS-CoV-2 outbreak, these contradictions in the reported correlation between air pollution and different aspects of viral respiratory infections must be thoroughly investigated and cleared.

Review

According to World Health Organization (WHO) data, an estimate of 7 million deaths occurs each year due to both outdoor and indoor air pollution. The main outdoor air pollutants are carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxide (NO_2), particulate matter (PM) such as PM_{10} (with diameters≤10 μm) and $PM_{2.5}$ (with diameters≤2.5 μm), ozone (O_3) and heavy metals [1]. The mentioned air pollutants can jeopardize normal function of the pulmonary system and may cause asthma, respiratory infections, lung cancer, and chronic obstructive pulmonary disease (COPD)., They may also affect the cardiovascular system, immune system, skin and other organs of the human body [2]. One of the most commonly observed clinical manifestations caused by exposure to air pollution is respiratory infection. The most common agents of upper respiratory infections (URIs) are viruses, including influenza, parainfluenza, rhinovirus (RV), coronavirus, respiratory syncytial virus (RSV), and adenoviruses. The other type of respiratory infection is known as lower respiratory tract infections (LRIs) which are bronchitis and pneumonia. To be more specific, bronchitis is an LRI that is usually caused by viruses such as RSV, influenza, parainfluenza, adenovirus [3]. Thus, several

Please cite this article as: Khajeamiri Y, Sharifi S, Moradpour N, Khajeamiri A. A review on the effect of air pollution and exposure to PM, NO_2, O_3, SO_2, CO and heavy metals on viral respiratory infections. Journal of Air Pollution and Health. 2020; 5(4): 243-258.

studies have investigated the potential effects of air pollutants on the transmission and severity of respiratory viral infections. Moreover, considering the recent COVID-19 pandemic, a more clear understanding of the association between respiratory viral infections and air pollution is required. In this review article, the epidemiologic and experimental evidence is gathered from previous studies that analyzed the impact of each major air pollutant on respiratory viral infections.

Association between ambient air pollutants and viral respiratory infections:

In a time-series study conducted by Arbex et al., the impact of air pollution on acute upper respiratory tract infections (URTI) was investigated. The authors recorded the daily air pollution data and the URTI visits to the emergency department (ED) from São Paulo Hospital located in São Paulo, Brazil. In their conclusion, with an emphasis on viral agents being the most common cause of URTI, they suggested that exposure to air pollution in general – including CO and especially PM_{10} – can increase the ED visits for URTI [4]. In another study done by Hajat et al., the effect of air pollution on upper respiratory disease in London, England was explored. This effect was quantified by the number of visits to the family/general practitioner and also considering the air quality data of the time (general air pollution considering all major air pollutants). In the results of this study, an increase in consultations was found with exposure to all air pollutants except for O_3. For ozone, the association between the number of consultations to family doctors and its concentration was consistently negative [5]. In a study done by Li et al., it was shown that the increased concentration of all air pollutants such as $PM_{2.5}$, CO, NO_2, PM_{10}, and SO_2 (except O_3) can lead to more hospitalization for acute URTIs in children aged 0-14 years in Hefei, China [6].

Moreover, a systematic review and meta-analysis of 17 studies were conducted by Nhung et al. to investigate the short-term association between ambient air pollutants (PM_{10}, $PM_{2.5}$, SO_2, O_3 and NO_2) and pediatric pneumonia. Findings of this article reported significant positive correlation between daily concentration of air pollutants and hospital admissions for pneumonia among children [7]. Also, in another study, Nhung et al. investigated short-term association between ambient air pollution and LRI in children. They performed a time-series study for the years 2007–2014 with 57,851 hospital admissions due to bronchitis, pneumonia, and asthma among children under 18 years old in Hanoi, Vietnam. Results of this study demonstrated that all ambient air pollutants were consistently and strongly correlated with hospital admissions for acute respiratory disease and the strongest correlation was seen for NO_2 for pneumonia, bronchitis, and asthma [8]. Wong et al. conducted another study to further understand the effect of four main air pollutants (such as SO_2, NO_2, O_3 and PM_{10}) on the prognosis of influenza in patients who are already infected with the virus in four Asian cities. The results of this study showed that, in comparison to other pollutants, the effects of O_3 might be more pronounced in these patients with regard to both mortality and hospitalization. This pronounced effect is mostly caused by overlapping of the peak season of influenza and level of concentration of other pollutants in the air. To be more specific, patients with pre-existing influenza infection and exposed to O_3 could be seen develop respiratory disease, acute respiratory disease, and COPD. However, with other pollutants (NO_2, PM_{10}, and SO_2) the effects of influenza was only detected in patients with one of the respiratory diseases mentioned earlier [9]. Also, in another study conducted by Su et al. in Jinan, China, the connection between exposure to all air pollutants and the risk of influenza like illness (ILI) was investigated. Their results indicated the risk of ILI can be enhanced by short-term exposure to air pollutants including $PM_{2.5}$, PM_{10}, SO_2, and CO; in contrast, O_3 can decrease the occurrence of ILI in different age groups [10].

Kan et al. conducted a time-series study in Beijing, China, to investigate the correlation between daily SARS mortality, ambient air pollution, and other factors. Findings of this study showed an

increase of 10 μg/m^3 in the average concentration of NO_2, SO_2, and PM_{10} led to 1.22, 0.74, 1.06 and relative risks of daily SARS mortality, respectively. Thus, the authors reported that there is a positive correlation between daily SARS mortality and air pollution [11]. Similar to this study, Cui et al. conducted an ecologic analysis to demonstrate the association between ambient air pollutants and SARS case fatality. They performed this study among 5 regions with 100 or more SARS cases, using an air pollution index (API) taken from the concentrations of PM, SO_2, NO_2, CO, and ground-level O_3. The results showed that SARS patients from regions with moderate APIs had significantly more risk of fatality from SARS in comparison to those from regions with lower APIs [12].

In a study conducted by Marquès et al., the association between exposure to air pollution and transmission and mortality of COVID-19 was investigated. In this study, the number of daily confirmed COVID-19 cases and deaths were recorded along with the air quality data (with regard to the presence of NO_2, O_3, and PM_{10}) of Catalonia, Spain. The results of this study suggested that there is a positive correlation between the exposure to NO_2 and PM_{10} and the incidence of COVID-19 (with only that of NO_2 being significant). Moreover, in the case of chronic exposure to O_3, they found a negative correlation between levels of O_3 and incidence of COVID-19. Similar to its incidence, the mortality of COVID-19 was found to have a statistically non-significant positive correlation with levels of NO_2 and PM_{10}. Whereas, this correlation was found to be a negative and non-significant one in the case of exposure to O_3 [13]. In a similar study performed in China, the association between short-term exposure to air pollutants and COVID-19 infection was investigated. In this study, confirmed new COVID-19 cases of each day were recorded with the air pollution data regarding to levels of SO_2, $PM_{2.5}$, O_3, NO_2, PM_{10}, and CO [14]. The findings of this study showed that $PM_{2.5}$, O_3, NO_2, PM_{10}, and CO are positively correlated, while SO_2 is negatively correlated with the new number of confirmed COVID-19 cases.

Air pollutants can have effects on different immune cell types such as particle-clearing macrophages, dendritic cells, inflammatory neutrophil and various types of lymphocytes. Furthermore, air pollution causes dysfunction of multicellular immune responses that may cause disease and lead microbes to trigger damages of microbial infections more than microbe itself. It can also make wider damages on the immune system by different mechanisms and act as stimulants on proinflammatory immune responses [15]. In conclusion, according to this fact that air pollution may weaken the immune system, it can dysregulate the antiviral immune responses and increase the severity and health risks of infections.

Association between particulate matter and respiratory viral infections

PM concentration is composed of different sizes: coarse (2.5-10 μm), fine (<2.5 μm), and ultrafine (<0.1 μm) which can be in the air including both solid and liquid particles [2]. According to recent research, specific features of ecotoxicity, genotoxicity and oxidative potential of PM can increase the incidence of viral infections [16] The relevance and importance of PM particles is due to its prominent role in causing asthma, respiratory infections, lung cancer, and COPD [17]. For instance, studies have shown that smaller particles can cause more damage by penetrating the lungs and bloodstream [18]. Furthermore, PM particles smaller than 10 μm can lead to the formation of a condensation nuclei for the influenza viruses and increase the spreading of the virus [19]. Also, under a certain climate condition (with regards to humidity and temperature) matter can be a carrier for Coronavirus to transmit and survive under different conditions [20]. Moreover, PM can stay in the air for a long time which enables virus droplets to attach to these particles [21]. For instance, $PM_{2.5}$ consists of elements that can absorb organic pollutants, bacteria, viruses, and toxic heavy metals which might increase its toxicity. Moreover, PM particles with a size of less than or equal to 2.5 μm have been a great concern cone

sidering patients with acute pulmonary disease [22-26].

Also, there are many studies that have shown PM can increase airway epithelial damage and barrier dysfunction that can lead to a temporary immunosuppressive pulmonary environment [27]. A study conducted in Utah, The United States of America, analyzed subjects to examine the connection between the concentration of $PM_{2.5}$ in the air and diagnosis of ALRI. Their findings showed that in a large sample, an increase of 10 μg/m^3 in $PM_{2.5}$ can cause 15-30 % higher cases with ALRI in both children and adults [28]. In a study done by Lin et al., in Toronto, Canada, the association between respiratory infections and a short-term exposure to PM in children was investigated. The authors concluded that a short-term increase in levels of PM led to more hospitalizations of children younger than 15 years old with respiratory infections [29]. These results are consistent with the findings of another study where observations showed that a long exposure to PM can cause respiratory illness in children and infants [30]. Furthermore, in a recent study, Kim et al. observed the correlation between short-term $PM_{2.5}$ exposure and acute upper respiratory infection (AURI) and bronchitis or bronchiolitis among children aged 0–4 years. Their data included $PM_{2.5}$ concentrations on a daily basis, hospital admissions for acute respiratory infections, and climate changes of 15 regions in the Republic of Korea (2013–2015). The findings of this research suggested a 10 μg/m^3 increment in $PM_{2.5}$ levels led to an increased risk of AURIs (relative risk = 1.048) and bronchitis/bronchiolitis (relative risk = 1.083) [31]. According to a study conducted by Boldo et al. which observed the effects of $PM_{2.5}$ levels in 23 European cities, it was estimated that a reduction of up to 15 μg/m^3 in long-term exposure to $PM_{2.5}$ might lead to a decrease of 17,000 premature deaths [32].

In another study, Lambert et al. observed RSV infection in mice that were exposed to carbon black. Although, an early response was observed to RSV infection, the levels of tumor necrosis factor (TNF) and lymphocytes in the bronchoalveolar lavage (BAL) fluid were decreased. Also it continued with a reduction of interferon-inducible protein/CXCL10 and IFN- mRNA in the lung [33]. Moreover, in another study, exposure of alveolar macrophages (AM) obtained from pigs to PM_{10} and its connection to RSV was observed. This study suggests that PM_{10} exposure can interact with the mechanisms of RSV replication and lead to a reduction in the production of cytokines by AM. In short, AM exposure to PM_{10} and RSV showed a reduction of RSV yield and the production of cytokines such as IL-6 and IL-8, while AM increased their production of TNF after their exposure to PM_{10}, RSV, or both [34]. In another study, it was shown that RSV infection severely decreased phagocytic ability of AM [35].

In a case crossover study performed in six urban sites in New York State, authors examined the connection between $PM_{2.5}$ and the rate of hospitalizations for influenza and pneumonia from 2005-2016. They observed that the hospitalization rate for influenza in adult patients (age>18 years old) was associated with the increase in the total $PM_{2.5}$ concentrations that they were exposed to [36]. Similarly, Lall et al. reported that there is a connection between the concentration of $PM_{2.5}$ and rate of hospitalization due to respiratory infection and pneumonia [37]. Moreover, Mishra et al. investigated the impact of PM_{10} on RNA virus infections using Highly Pathogenic Avian Influenza – H5N1 virus. They determined the transcriptomic profile of lung epithelial cell line as it was treated with PM_{10} prior to H5N1 infection. The results of this study demonstrated that PM_{10} regulates virus infectivity to enhance overall pathogenic burden in the lung cells as it increases the severity of respiratory tract viral infection by cell damages. Also, PM_{10} can increase influenza virus replication via modulation of metabolic pathway genes and reduction of antiviral innate immunity [38]. In addition, Landguth et al. explored the associations between $PM_{2.5}$ and influenza counts at the county level in Montana, United States of America. They evaluated $PM_{2.5}$ effects for two different time period groups: $PM_{2.5}$ exposure 1–4 weeks before influ-

enza cases and $PM_{2.5}$ during the wildfire season 1–10 months before influenza cases. The results of this study demonstrated a positive association between daily average $PM_{2.5}$ concentration during wildfire season and influenza rate months later. On the other hand, daily average $PM_{2.5}$ concentration during the winter period had no impact on influenza rate [39]. Another study examined the relationship between source-specific PM and the rate of hospitalizations and ED visits for influenza or culture-negative pneumonia in New York State adults from 2005 to 2016. The findings of this research showed that short-term increases in $PM_{2.5}$ levels potentiate influenza hospitalizations and ED visits [36].

In a recent investigation done by Zoran et al. in Milan (Lombardy region), Italy, they studied the connection between the mortality of COVID-19 and air pollution –specifically PM particles in two sizes of 10 and 2.5. Moreover, in this paper, they found that during the pre-lockdown period (January- February 2020) and during the lockdown, people were more susceptible to viral infections because of the increasing level of PM during that time. The authors concluded that both air pollutants and climate conditions have their role in spreading COVID-19 [26]. Another study investigated the association between air pollutants (specifically PM_{10} and $PM_{2.5}$) and COVID-19 in 3 major cities in France from March 18th to April 27th 2020. They concluded that PM_{10} and $PM_{2.5}$ threshold values identified by the Artificial Neural Networks were higher than the limits stated by the European Parliament, which can confirm that there is a direct connection between air pollutants and COVID-19 death rates [40]. In a study conducted by Wu et al., the authors investigated the connection between long-term exposure to $PM_{2.5}$ and COVID-19 fatality in the USA until April 22th 2020. They concluded that an increase of 1μg/m^3 in $PM_{2.5}$ concentration is related to an increase of 8% in COVID-19 fatality [41]. In addition, Yongjian et al. studied the association between air pollutants and COVID-19 cases. Analogous to the previous study, the results showed a 10 g/m^3 increase in $PM_{2.5}$ and PM_{10} is connected to an increase of 2.24% and 1.76% in COVID-19 cases, respectively [14].

Association between Nitrogen Dioxide and respiratory viral infections

NO_2 is a common air pollutant outdoors and indoors. Inflammatory responses of the lungs and bronchi, respiratory symptoms including wheezing and coughing are the possible dangers of exposure to NO_2. Moreover, NO_2 causes oxidative stress, produces free radicals that can damage the epithelial cells of the lung, aggravates pulmonary inflammation and injury, triggers asthma symptoms, depletes tissue antioxidant defenses, and weakens macrophage phagocytosis. Also, it can increase the risk of respiratory problems such as asthma and COPD. Different studies have shown that oxidative stress increases the severity of viral infections, as well. Furthermore, investigations have indicated that NO_2 and its chemical products can stay in the lung for a long time [42-45].

Air pollutants considerably can increase the susceptibility to RSV. Several studies suggest that children exposed to NO_2 and living in polluted cities or with smoking parents, are more vulnerable to respiratory viral infections [46, 47]. Li et al. conducted a time-series analysis at Anhui Province Children's Hospital in Hefei, China, from 1 January 2014 to 31 December 2015 using an ecological method to show the association between air pollution and pediatric hospital outpatients with URTI. Authors reported that a 10 mg/m^3 increase in the average levels of NO_2 led to 4.47% increment in the number of hospital outpatients with URTI [6]. Another time-series analysis investigated the daily number of ED admissions in a children's hospital for 883 days in Turin, Northwestern Italy. The results of this study showed that ED admissions for URTI increases by 1.3%, five days after a 10 μg/m^3 increase in NO_2 concentration [48]. To summarize, these studies concluded that NO_2 was found to be the major air pollutant affecting the number of daily hospital outpatients with URTI. In addition to studies focused on URIs, different time-series studies have also investigated the association

between NO_2 concentration and LRIs. The findings of the study conducted by Mehta et al. have shown ALRI admissions were positively correlated to ambient levels of NO_2, in the dry season [49]. The findings of other studies have indicated the significant positive link between NO_2 levels and influenza prevalence. For instance, Frampton et al. explored the ability of human AM to inactivate influenza virus when exposed to NO_2 and air. The researchers observed that AMs obtained by BAL after exposure to continuous levels of NO_2 had fewer effects than cells collected after air exposure to inactive influenza virus in vivo [50]. Another study analyzed the impact of NO_2 exposure on influenza A virus infection in adult volunteers. The subjects exposed to NO_2 the year before became infected (91%) nearly 20% more than those breathing clean air (71%). Thus, the researchers suggested that nitrogen dioxide alone may play an important role in increasing the susceptibility to viral infections in adults, but more studies are needed to prove that [51]. Furthermore, the recent study conducted in mountainous regions of China suggested that excessive exposure to NO_2 can be responsible for about 14% influenza cases [52].

Studies have shown that NO_2 can have a stronger and faster effect on pneumonia and bronchitis than other air pollutants. In one of these studies Nhung et al. examined the short-term connection between air pollution and daily counts of hospitalization due to pneumonia, bronchitis, and asthma among children. They reported the addition of 21.9μg/m^3 in the average level of NO_2 was related to a 6.1% increase in pneumonia hospitalizations [8]. Authors of this study observed that although all ambient air pollutants were positively associated with pneumonia hospitalizations in children under 18 years old, the strongest effect was for NO_2 [8]. Also, according to the observations of another study, Kowalska et al. observed the strongest correlation in the case of NO_2 concentration and bronchitis outpatient visits. Their findings showed that increasing the average concentration of NO_2 even in one day leads to an increased bronchitis risk ratio [42]. Furthermore, previous studies have shown the synergetic effect of NO_2 exposure and RV infection. For example, Spannhake et al. examined the impact of NO_2 exposure and RV infection in human bronchial and nasal epithelial cells (NEC). The results showed that exposure to NO_2 after RV infection can intensify the production of IL-8 and the expression of major groups of RV receptors which are intercellular adhesion molecule1 (ICAM-1) [53, 54]. In addition, a research conducted by Kan et al. on the connection between air pollution and daily SARS mortality reported that an increase of 10 μg/m^3 over a moving average of NO_2 led to 1.22 risk of daily SARS mortality, which were the higher relative risk than PM_{10} and SO_2 [11].

According to a study done by Yongjian et al. in 120 cities in China, there is a significantly positive relationship between short-term exposure to NO_2 and the daily counts of confirmed cases of COVID-19 [14]. In another study, Ogen, examined the relationship between long-term exposure to NO_2 and Coronavirus fatality. Data were collected from 66 administrative regions in Italy, Spain, France, and Germany on NO_2 concentration in the troposphere for a two-month period (January–February 2020) before the outbreak of COVID-19 in Europe. Results of this study showed that 83% of the 4443 Coronavirus fatalities in these countries belonged to regions with above 100 μmol/m^2 maximum NO_2 concentration and only 1.5% were for regions with below 50 μmol/m^2 NO_2 concentration. To be more specific, four of the top five regions with the highest fatalities were in Northern Italy [55]. This finding is consistent with the results found by Filippini et al. as they observed a positive correlation between COVID-19 prevalence and exposure to high levels of NO_2 in Northern Italy [56]. On the other hand, Zoran et al. conducted a time-series analysis of daily average inhalable gaseous pollutants O_3 and NO_2, together with climate variables for January–April 2020 period in Milan, Italy. In this study, data collection for the meteorological factors and COVID-19 data (such as daily new confirmed cases, total cases, and deaths) was done using online platforms. However, the results of

this study have shown a negative association between NO_2 levels and the number of COVID-19 confirmed cases [26].

Association between Ozone and respiratory viral infections

Ozone is a secondary air pollutant that is formed via a set of reactions between nitrogen dioxide and the free radicals and oxygen that are created by volatile organic compounds under the sunlight [57, 58]. Several studies have established the adverse health effects of O_3 on the respiratory system. For instance, an inflammatory response was seen in the lungs of humans and animals who were subjected to an experimental exposure to ozone gas [59-61]. In addition, researchers found a positive correlation between the ambient O_3 concentration and respiratory mortality epidemiological evidence [62, 63]. Thus, further studies and investigation are needed to gain more insight into the link between ambient levels of O_3 and viral respiratory infections.

In another study, Kesic et al. studied the difference in the susceptibility of cells to influenza in cells exposed to O_3 in comparison to the ones that were not [64]. In this study, researchers used two groups of human NECs: one exposed to 0.4 ppm ozone for 4 hours and another one exposed to filtered air before being infected with influenza. The results of this study showed an increase in the levels IL-6 (proinflammatory cytokine) and LDH (marker of cytotoxicity) in NECs previously exposed to ozone. Moreover, observations showed a significant increase in the production of viral hemagglutinin transcript mRNA and an increase in viral titers of cells that were exposed to O_3 prior to infection, compared to the control group. Also, this team examined the effect of exposure to O_3 on the antiviral innate immune response elicited by the cells. This evaluation was done by measuring the amount of mRNA of interferon-β, retinoic acid inducible gene I, interferon-α, Toll-Like receptor-3 produced when NECs were exposed to O_3 and later infected with influenza A. They observed no change in the gene expression of the mentioned elements of immune response in cells that were exposed to O_3, when compared to the control NECs. Thus, the authors concluded that previous exposure to ozone results in a significant increase in viral replication in nasal epithelial cells, but it does not interfere with the antiviral response of the cell. In another study, Wong et al. investigated the association between concentration of ozone and hospital admissions for cardiovascular and respiratory disease [65]. Moreover, the authors found a positive association between admission for influenza and pneumonia and levels of ambient O_3. To be more specific, a relative risk of 1.028 for influenza and pneumonia admissions was achieved with a 0.005 ppm increase in ozone concentration. These results suggested that, especially in the elderly (>65 years), an increase in the susceptibility to influenza and its related diseases occurs following an exposure to the ozone.

In another experiment, Jakab and Hmieleski explored the alterations in influenza virus pathogenesis in the presence of O_3 [66]. In this study, the authors divided female mice into four groups classified as virus-infected, control, ozone-exposed (0.5 ppm ozone), and both virus-infected and ozone-exposed (0.5 ppm ozone). Their results showed that considering the sites of viral replication, the influenza infection post-exposure to O_3 is less widespread. Moreover, they observed less number of B- and T-lymphocytes in the lung tissues they dissected along with a reduced number of serum antibodies. Hence, based on their findings, they suggested that O_3 exposure reduces the severity of viral respiratory infections by redistribution of infection in the lungs and suppression of the inflammatory reactions. In a more recent study, Jakab and Bassett investigated the association between exposure to O_3 gas and influenza virus infection with more focus on fibrogenesis of the lung [67]. To do this, after two groups of mice (one group infected with Influenza A and the other healthy) were exposed to 0.5 ppm O_3 or ambient air, on specific dates, some of them would be sacrificed for a thorough assessment of their lungs. The results of this study showed that up to 15 days post-infection, exposure to ozone

did not change the viral proliferation in the lungs, but it led to a 50% reduction in the virus-induced acute lung injury. Moreover, the authors found that after 30 days of continuous exposure to O_3, the incidence of post-influenza structural changes in the lung tissue and alveolitis increased. Thus, they concluded that exposure to O_3 can increase the potential of residual damage in the lung and reduces the virus-induced lung injury.

In a similar study, Spannhake et al. investigated the effect of concentration of O_3 gas on the inflammatory response in the human bronchial and nasal epithelial cells to RV infection. In this study, the mentioned RV infected epithelial cells were exposed to 0.2 ppm ozone for 3 hours. Spannhake et al. observed a 67% increase in the production of IL-8 in reaction to RV infection after cells were exposed to O_3 compared to the inflammatory response in the absence of this gas. Based on these results, their conclusion suggested a synergistic effect in the enhancement of the inflammatory response elicited by the respiratory system to RV in the presence of ozone [53]. Their observations are consistent with the previous in vivo experiments that have demonstrated that exposure to O_3 leads to significant increases in the levels of inflammatory mediators (such as IL-8, IL-6, and fibronectin) in BAL fluid of healthy subjects [68, 69]. In one of these studies, Devlin et al., examined the BAL fluid of non-smoking male volunteers who did a moderate exercise for 6.6 hours post- exposure to either filtered air, 0.08 ppm O_3, or 0.10 ppm O_3 for proinflammatory cytokines [68]. In addition, in the experiment done by Balmes et al. the BAL fluid and the proximal airway lavage fluid of volunteers were examined for inflammatory mediators after exercising for 4 hours post-exposure to 0.2 ppm ozone [69].

A similar study was done by Henderson et al. to investigate the changes in the response of the cells infected with RV after being exposed to O_3 for a longer time [70]. After inoculation with the rhinovirus, these human cells were subjected to an exposure of 0.3 ppm ozone for 6 h/day for 5 days. The results of this study showed no adjustment in the neutrophil count, interferon levels, or nasal RV titers; thus, suggesting that exposure to O_3 had no impact on the development of RV infections. Considering the contradictory results obtained from these studies, it can be concluded that the effect of ozone levels on the course of a viral infection is a dynamic result of many factors such as dose, type of virus, length of exposure, and many others.

Results of a more recent research conducted by Yongjian et al. showed that a 10μg/m^3 increase in ozone levels led to 4.76% increase in the number of confirmed daily cases of Coronavirus patients. Thus, the authors concluded that there is a significant positive correlation between exposure to O_3 and the daily counts of confirmed COVID-19 cases [14]. A similar study performed by Zoran et al. in Milan, Italy, where authors investigated the effect of ground levels of O_3 and NO_2 on COVID-19. Their initial findings showed a negative correlation between the produced amount of NO_2 and that of O_3, indicating that as NO_2 decreased during the lockdown period in Milan, its titration of ozone gas was reduced as well [71]. As the increase in ozone levels during the periods of lockdown in Milan is consistent with the findings of Sethi and Mittal, the authors of this study decided to further explore the effect of toxic levels of O_3 on the epidemic growth of COVID-19 [71, 72]. Their results showed that the increase in the ozone concentration that people were exposed to, had a positive correlation with the number of daily new confirmed COVID-19 cases, deaths, and total cases [71].

In a different study, Sethi & Mittal investigated the impact of air pollution on Coronavirus fatalities in Delhi, India [72]. The results of this study showed that ozone is the third most important gas positively affecting the fatality in COVID-19 cases. Moreover, it is important to note that, unlike all other air pollutants, they found that concentration of O_3 has increased during the lockdown period following the pandemic. Therefore, they concluded that O_3 is an important air pollutant that should be more closely controlled as it positively correlates with the Coronavirus mortality rate [72]. In a comparable research, conducted

in China, Wu, Zhan and Zhao, investigated the effect of different air pollutants on the morbidity of COVID-19. In the method of this study, the annual means for different ambient concentrations of air pollutants in China were used to estimate the exposure of their population, with a use of COVID-19 incidence rate based statistical analysis. The results of this research showed that an increase of 1μg/m^3 in the concentration of O_3 can cause a decrease of 2.05% in the morbidity of COVID-19 [73].

Association between Sulfur Dioxide and respiratory viral infections

Exposure to sulfur dioxide causes respiratory symptoms and changes in airway physiology as it increases airway resistance. Experimental studies on animals have shown that prolonged exposure to SO_2 can produce goblet cells, epithelial hyperplasia and hypertrophy of the submucosal glands. These damages to the epithelium of airways are similar to chronic bronchitis in humans. Moreover, the sensitivity of different people to SO_2 effects is variable because it depends on different factors. SO_2 can cause bronchospasm, but exposure to the same concentration may not have a significant effect on some people. For instance, studies have shown that asthmatic people are more vulnerable [74, 75]. As SO_2 is highly soluble, it can be easily absorbed from mucus membrane of the nose and upper respiratory tract which is the reason why the maximum dose of SO_2 is introduced to the human body by inhalation [74, 76].

Su et al. explored the correlation between short-term exposure to 6 major air pollutants and ILI counts from 2016 to 2017 in different age groups. They reported that a 10 μg/ m^3 increase in concentration of SO_2 was positively correlated with 1.0008 relative risk of ILI [10]. As it is shown in this research, all age groups had noticeable susceptibility to SO_2. Previous studies were conducted to investigate the effects of exposure to SO_2 and influenza infection. For example, Ukai, studied the impact of constant exposure to low levels of SO_2 on pathogenesis of influenza virus infection in mice. These researchers transferred influenza A virus in unanesthetized mice by intranasal inoculation and mixed Sulfur dioxide (with a concentration of 0.03-0.1 ppm) with filtered air and together; they were introduced to the exposure chamber for 4 weeks. Mice exposed to SO_2 plus virus, compared to mice receiving the virus alone, had shown a more rapid and severe inflammatory response in their nasal tissues. Also, hemagglutination inhibition titers in the exposed group rapidly reached higher levels as antibodies appeared earlier. These results suggested that continued exposure to low levels of SO_2 can increase the severity of influenza infection and the destructive dangers of the virus [77]. In addition, researchers performed another experimentation on the effects of SO_2 on influenza A2 virus-induced pneumonia. These researchers divided mice into 3 groups: influenza A2 virus and sulfur dioxide exposure, each alone and in combination. It was observed that the highest number of pneumonia cases was for combination exposures [78]. Furthermore, researchers have noted that SO_2 is one of the major air pollutants associated with influenza virus transmission [79]. Meng et al. conducted another investigation about short-term effect of ambient air pollution on the incidence of influenza in Wuhan, China. They used a generalized additive model to estimate the connection between air pollutants (NO_2, SO_2, O_3, PM) and the risk of influenza during 2015–2017. They obtained daily data on the influenza incidence and daily concentration of air pollutants from Hubei Provincial Disease Control and Prevention and ten national air-sampling stations in Wuhan, respectively. The results of this study have shown that a 10 μg/m^3 addition in concentration of SO_2 led to a 1.099 increase in the relative risk of influenza, which was the higher relative risk than that of NO_2 and O_3 [80].

According to a time-series analysis that was done in Beijing, China, to show the connection between ambient air pollution and daily mortality of SARS, an increase of each 10 μg/m^3 over a moving average of SO_2 was correlated to 0.74 relative risk of daily SARS mortality [11]. Also, another study has

explored the short-term impacts of air pollutants on respiratory tract infections by causative pathogens in children of different age groups in Suzhou City, China. The results of single-pollutant models used in this study reported that the SO_2, $PM_{2.5}$, PM_{10}, NO_2 and CO had a positive relationship with respiratory tract infections in children under 3 years old [81]. Another study regarding the influence of atmospheric conditions, outdoor air virus presence, and immune system-related genetic polymorphisms on RV infection has mentioned that atmospheric SO_2 levels are connected to nostril's RV detection [82]. In addition, according to meta-analysis conducted by Nhung et al. there is a positive correlation between short-term exposure to ambient levels of SO_2 and hospitalization of children due to pneumonia. Findings of this study demonstrated that 1000 ppb increment of SO_2 levels led to 2.9% excess risk, which was the highest excess risk among that of other air pollutants [7]. Also, the findings of another study on the relationship between ALRI admissions of children and short-term exposure to air pollution have shown general positive links between ambient levels of SO_2 and hospital admissions for ALRI in dry season [49].

According to recent studies, connections between SO_2 exposure and different aspects of COVID-19 are not cleared yet. According to findings of a recent study performed by Yongjian et al., a 10μg/m^3 increase in concentration of SO_2 was related to a 7.79% reduction in COVID-19 confirmed cases [14]. In addition, another research project in China investigated the risk of COVID-19 infection in people who are continuously exposed to ambient air pollution. Results of this study demonstrated a nonsignificant association between SO_2 and COVID-19 morbidity [73]. Considering the achievement of contradictory results by different scientists, more studies are required to prove these correlations.

Association between heavy metals and respiratory viral infections

According to the World Health Organization, heavy metals including mercury, cadmium, and lead are a part of earth's natural crust, and as major products of industrialization they are considered as air pollutants [83]. Moreover, the difference between these pollutants and the organic ones is that heavy metals are not degraded with time, and are continuously deposited in soil; later found in the food chain–mainly in fishes [83]. Moreover, exposure to heavy metals is found to cause a variety of adverse health effects including bone and kidney damage, cancer, and neurological developmental deficiencies in infants. More specifically, Thun et al. and Stayner et al. found the association between the occurrence of lung cancer and exposure to cadmium to be positive by analyzing the mortality of workers from a cadmium recovery plant in the United States [84, 85].

Checconi et al. conducted another study to investigate the effect of Cadmium on the replication of Influenza virus in Madin-Darby Canine Kidney (MDCK) cells [86]. Moreover, these researchers explored the impact of $CdCl_2$ exposure on alterations in many steps of viral pathogenesis such as the amount of viral protein synthesis, virus release from the infected cell, and redox state of the cell [86]. In their first experiment, the researchers exposed confluent monolayers of MDCK cells to different concentrations of $CdCl_2$ ranging from 25 to 500 μm. The researchers observed that no changes occurred in cells treated with 25 and 50 μm; whereas, cytotoxic effects (such as detachment of cells/loss of intercellular contact and rounded shape) were seen in ones exposed to high doses of $CdCl_2$ [86]. In the second part of this experiment, Checconi et al. used Bradford assay to measure the concentration of protein that was obtained from lysis of $CdCl_2$-exposed cells. The results of this part showed that low levels of this compound (1-50 μm) did not affect the protein synthesis of cells; whereas, in MDCK cells exposed to high concentration of $CdCl_2$ (75, 100, and 500 μm), a reduction of cellular protein synthesis was observed. In the next part of this project, the impact of $CdCl_2$ on metabolic activity of the MDCK cells was examined. The findings of this part showed that in cells exposed to low concentrations of $CdCl_2$ (1-50 μm), no changes were

observed in the viability of the cell; whereas, with exposure to higher levels of this compound (75-500 μm), cellular proliferation was reduced significantly [86]. Moreover, the authors investigated the effect of $CdCl_2$ on the GSH/GSSG ratio by measuring the levels of free thiols, GSH (Glutathione), and GSSG (Glutathione disulfide) after exposure to $CdCl_2$. Their findings showed that cells exposed to high doses of this compound face an imbalance of their redox state by changes in their GSH/GSSG ratio. This observation led the researchers to finally examine the vulnerability of $CdCl_2$-exposed cells to Influenza A infection. Their observations from this experiment were consistent with their previous findings as the cells were more vulnerable to this infection due to an increased viral protein production. Thus, Checconi et al. concluded that exposure to high levels of $CdCl_2$ results in more vulnerability to viral infections due to the following consequences: cytotoxic effects (such as cell detachment), reduction of cellular protein synthesis and proliferation, and increase in viral protein synthesis and replication [86]. Another study done by Bouley et al. contradicts the conclusion that Checconi et al. reached by the experiments mentioned earlier in this paragraph. These researchers investigated the effect of inhaled cadmium on both viral and bacterial infection [87]. In this study, 48 hours before being infected with Pasteurella multocida (bacterial) and Orthomyxovirus influenza A (viral), 489 mice (including both test and control group) were exposed to 10mg/m^3 of CdO for 15 minutes. The results of this study showed that the death-rate in the test group that was exposed to cadmium microparticles increased in bacterial infection and decreased in viral infections [87].

Associations between carbon monoxide and respiratory viral infections

There are not many studies regarding CO gas and its effect on the respiratory system [88, 89]. In one of the studies done on this topic, Nhung et al. showed a negative connection between CO and bronchitis and asthma. However, they observed a positive correlation between $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3 levels and respiratory syndrome among children aged 0-17 in Hanoi, Vietnam [8]. However, in a study conducted by Li YR et al., an increased amount of some pollutants including CO increased hospitalized patients (aged 0 -14) with URTIs [6]. In another study done in Jinan, China, the association between air pollutants and ILI was observed in 3 hospitals from 2016 to 2017. From their results, it was illustrated that exposure to pollutants including $PM_{2.5}$, PM_{10} and CO has a strong connection with ILI in patients aged 0-4 and 4-14 [10].

Conclusion

To begin with, several studies have demonstrated a positive correlation between exposure to air pollution and the incidence of viral respiratory diseases [4-10, 14, 26, 49]. Further in this paragraph, details on similar studies that have established such relationships will be provided. Findings from two studies on COVID-19 have shown that there is a significant positive association between the number of viral respiratory disease case admissions and exposure to ambient O_3 levels [64, 71]. Similar findings for NO_2 were found in several studies which concluded that NO_2 is one of the major air pollutants affecting the number of daily hospital admissions due to viral respiratory infections [6, 8, 42, 46-48, 51, 52, 56]. In a study conducted by Zhang et al. using a single-pollutant model, a positive correlation between respiratory tract infections (caused by all agents, including viruses) and exposure to SO_2, $PM_{2.5}$, PM_{10}, NO_2, and CO was found [81]. These results are consistent with those of two other research groups which observed a positive association between SO_2 and influenza infection [78, 80]. Moreover, in several studies, a positive relationship between exposure to PM and the number of case admissions due to viral respiratory disease was established [28-31, 36, 39]. Contradictory to the findings of previously mentioned studies, multiple projects have found a negative association between the incidence of viral respiratory disease and exposure to ambient levels of SO_2, O_3, and NO_2 [5, 13, 14, 71].

According to the results of a research conducted by Woodward et al., it has been suggested that exposure to air pollution induces an increase in the inflammatory reaction of cells [90]. In contrast, multiple studies reported a unilateral result of reduction in the virus-induced inflammatory response in the presence of air pollutants [27, 33, 34, 38, 50]. Several studies have demonstrated the positive effect of exposure to O_3 and NO_2 on the enhancement of the inflammatory response by increasing the secretion of proinflammatory cytokines [15, 42-45, 53, 54, 59-61, 64, 68, 69]. Contradictory to these results, Jakab and Helminski found that exposure to O_3 suppresses the inflammatory response [66]. In another study, Henderson et al. reported that exposure to O_3 had no impact on the development of RV-induced respiratory infections [70]. Consistent with the previous findings on other air pollutants, in a study conducted by Ukai, a more rapid and severe virus-induced inflammatory response in SO_2-exposed nasal tissues was observed [77].

Although air pollution is not the only factor affecting respiratory viral infections, in many studies, a connection between air pollutants and different aspects of respiratory illness, including its transmission, was demonstrated [6, 36]. For instance, the results of two studies were common to establish that PM increases the transmission of viral infections by acting as a carrier and being able to survive in media for a long time [20, 21]. According to another study conducted by Kesic et al., exposure of NECs to O_3 results in no interference with the antiviral activity of cells and leads to an increase in viral titers and viral replication in cells [64]. Findings of another study about the effects of heavy metals, showed that exposure to $CdCl_2$ increases the vulnerability of cells to viral infection via following mechanism: cell detachment, a decrease in proliferation and synthesis of cellular proteins, and an increase in replication and protein synthesis of viruses [86].

According to the literature, it is established that air pollution leads to lung injury, but the severity of such outcome has been a matter of dispute [74, 75]. It was found that exposure to NO_2 and other air pollutants leads to an increase in the severity of viral infection through oxidative stress [2]. Consistent with these results, in three other projects an increase in the severity of respiratory viral infections was seen with exposure to SO_2 and PM [27, 38, 77]. Contradictory to these findings on exposure to the mentioned air pollutants, a few studies have shown that exposure to O_3 reduces the severity and the lung injury caused by a viral respiratory disease [66, 67, 73]. Moreover, in a study conducted by Wu et al., a nonsignificant correlation between COVID-19 morbidity and exposure to SO_2 was found [73].

Results from multiple studies showed a positive association between ambient air pollutants and daily mortality due to viral respiratory infections [9, 11, 12]. For instance, in several studies, researchers found a positive association between the ambient O_3 level and mortality due to viral respiratory infections [62, 63, 71, 72]. In similar studies, an increase in COVID-19 fatalities was found in correlation with long-term exposure to NO_2 and PM [13, 40, 41, 55]. In contrast, in another study conducted by Bouley et al., following an exposure to heavy metals, a decrease in death-rate as a result of viral infection was noted [87]. Furthermore, in a study conducted by Marques et al., another negative and non-significant correlation was reported between ambient levels of O_3 and mortality due to COVID-19 infection [13].

Financial supports

This study did not receive any supporting funds from any financial resource.

Competing interests

The Authors declare that there is no conflict of interest.

Acknowledgements

No acknowledgement to declare.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or fal-

sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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