

Effects of air pollutants on the transmission and severity of respiratory viral infections

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ABSTRACT

Particulate matter, sulfur dioxide, nitrogen oxides, ozone, carbon monoxide, volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs) are among the outdoor air pollutants that are major factors in human's diseases, causing especially adverse respiratory effects in humans. On the other hand, the role of respiratory viruses in the pathogenesis of severe respiratory infections is an issue of great importance. The present literature review was aimed at assessing the potential effects of air pollutants on the transmission and severity of respiratory viral infections. We have reviewed the scientific literature regarding the association of outdoor air pollution and respiratory viruses on respiratory diseases. Evidence supports a clear association between air concentrations of some pollutants and human respiratory viruses on the adverse effects on the respiratory system. Given the rabid news of the subject, we have also paid special attention to the association between air pollutants and the transmission and severity of the effects caused by the coronavirus named SARS-CoV-2, which is the responsible of the COVID-19. Although to date, and by obvious reasons, the number of studies on this issue are still scarce, most results indicate that chronic exposure to air pollutants impairs recovery of patients of COVID-19 and leads to more severe and lethal forms of this disease. This deserves immediate and in-depth experimental investigations.

Keywords: air pollutants; respiratory viral infections; human respiratory problems; COVID-19

1. Introduction

In recent decades, air pollution has been/is being a major environmental health hazard for the general population. Increases in outdoor air exposure affect people's health outcomes, directly and indirectly (Burns et al., 2019, 2020; Sun and Zhu, 2019a,b; Manisalidis et al., 2020). However, the scientific literature regarding the extent, range, and nature of the influence of outdoor air pollution with respect to human health outcomes is not especially abundant. Recently, Sun and Zhu (2019a) reviewed the effects of exposure to air pollution on human health. Among the eight categorized health outcomes, asthma and mortality were the most common. Moreover, adverse health outcomes involving respiratory diseases among children accounted for the largest group. Among the total studies included in the review, 95.2% reported at least one statistically positive result, while only 0.4% showed ambiguous results. In turn, Pothirat et al. (2019) investigated the association between daily average seasonal air pollutants and daily mortality of hospitalized patients and community individuals, as well as emergency and hospitalization visits for serious respiratory, cardiovascular, and cerebrovascular diseases. It was found that air pollutants were associated with higher mortality of the hospitalized patients and community dwellers, with varying effects on severe acute respiratory, cardiovascular, and cerebrovascular diseases. In relation to the age of the individuals who are affected by outdoor air pollution -with particular attention to the respiratory system- the elderly is one of the most sensitive groups (Lee et al., 2007; Bentayeb et al., 2012; Simoni et al., 2015; Kotaki et al., 2019). The outdoor air pollutants that are major factors in human's diseases, causing especially adverse respiratory effects, are particulate matter, sulfur dioxide, nitrogen oxides, volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs), while ozone can also affect the respiratory and cardiovascular systems (Manisalidis et al., 2020). In addition, climate change resulting from environmental pollution can also affect the geographical distribution of many infectious diseases (Akkina et al., 2019; Bezirtoglou et al., 2011; Linares et al., 2020).

On the other hand, the role of respiratory viruses in the pathogenesis of severe respiratory infections is an issue of great importance. Moreover, while until recently human coronaviruses were considered to be relatively harmless respiratory pathogens, after the outbreak of the severe acute respiratory syndrome (SARS), the emergence of the Middle East respiratory syndrome (MERS), and very especially the recent appearance of

the SARS-CoV-2, with the tremendous health and socioeconomic impact that has generated, coronaviruses are receiving worldwide attention as very serious pathogens, especially in respiratory tract infections (Singh, 2016; Walter and Wunderink, 2017; Yin and Wunderink, 2018; Contini et al., 2020; Xu et al., 2020; Zimmermann and Curtis, 2020). Taking the above into account, we have prepared the present literature review whose main purpose has been to help to understand the effects of air pollution on the transmission and severity of respiratory viral infections. The available scientific literature on that hypothetical association was reviewed on PubMed (www.ncbi.nlm.nih.gov/pubmed) and Scopus (www.scopus.com) databases by using “air pollutants and human respiratory viral infections”, “air pollution and viruses”, “air pollutants and respiratory viruses”, and “air pollution and COVID-19” as keywords. The final search date for both databases was April 30, 2020.

2. Respiratory viral infections

Nowadays, each year the well-known seasonal influenza viruses continue to cause epidemics around the world. Infected individuals can be affected by severe respiratory and cardiovascular morbidity and mortality. Although flu may be caused by four types of influenza viruses (A, B, C and D), influenza A virus (IAV), the most common type, is continuously threaten public health. Infection by influenza A virus leads to respiratory failure, which is characterized by acute lung injury associated to alveolar edema, necrotizing bronchiolitis, as well as excessive bleeding (Sanders et al., 2011; Herold et al., 2015). An exuberant host response, with excessive inflammation and damage to the epithelial cells, which mediate respiratory gas exchange, are often attributed to severe reactions to infection that lead to hospitalizations and possible death (Tamura and Kurata, 2004; Herold et al., 2015). On the other hand, influenza-like illness (ILI) is clinically characterized by a series of common symptoms, which can be caused by influenza virus or other pathogens, being also a great contributor to morbidity and mortality worldwide (Liu et al., 2019).

3. Association of outdoor air pollution and respiratory viruses on respiratory diseases

In recent years, a number of studies have shown that air pollution can be an important risk factor for adverse respiratory and cardiovascular health outcomes. In addition, increasing evidence supports the association between air pollution and respiratory infections. It has been demonstrated that exposure to air pollutants can induce oxidative stress, resulting in the production of free radicals, which in turn, may damage the respiratory system, reducing the resistance to viral and bacterial infections (Ciencewicki and Jaspers, 2007). Regarding this, Huang et al. (2016) investigated the effects of some air pollutants (PM_{2.5}, PM₁₀, NO₂) on respiratory infections in the Nanjing area (China). The acute effects of air pollutants on ILI were also assessed. Air pollution effects tended to be null -or negative- for patients aged over 25 years, a result that could be due to the small number of influenza-like cases in that age group. With respect to the age, epidemiological investigations on the health effects of air pollution have found that children and the elderly are the two groups that are more probably affected, which would be probably due to their relatively weak immune systems (Wang and Chau, 2013). Recently, Su et al. (2019) quantified the short-term effects of six air pollutants on ILI in Jinan (China). The average concentrations of PM_{2.5}, PM₁₀, O₃, CO, SO₂ and NO₂ were determined in that area. It was noted that subjects aged 25-59, 5-14 and 0-4 years were significantly susceptible to PM_{2.5}, PM₁₀ and CO, while all age groups were significantly sensitive to SO₂. In turn, people aged ≥ 60 , 5-14 and 0-4 years showed a significant negative sensitivity associated with the levels of O₃. The authors concluded that air pollutants, focused in that study on PM_{2.5}, PM₁₀, CO and SO₂, might increase the risk of ILI. In turn, Chen and co-workers (2017) also in China, observed that ambient PM_{2.5} might increase the risk of exposure to influenza, especially in the cooler days. It was found that 10.7% of incident influenza cases might result from exposure to ambient PM_{2.5}. Based on these findings, the authors suggested that all measures addressed to decrease PM_{2.5} concentrations, would be potentially beneficial to reduce the risk of exposure and subsequent transmission of influenza. Similar conclusions were also drawn by Feng et al. (2016), who investigated the association between daily PM_{2.5} and ILI risk in Beijing (China). Ambient PM_{2.5} concentrations were significantly related with ILI risk at the flu season. However, the effect of PM_{2.5} differed across age groups, being more pronounced in adults (25-59 years), followed by young adults (aged 15-24), school children (aged 5-14) and the elderly (> 60 years). The effect of PM_{2.5} was much less pronounced for

children under 5 years of age. In contrast, the levels of PM₁₀ and a warmer climate zone, were found to be other risk factors for common cold among pre-school children. Recently, Chen et al. (2018) investigated in 11 cities and counties of Taiwan the causal relationship between human influenza cases and air pollution, quantified by PM_{2.5}. According to the age-groups, the elderly group resulted clearly affected in all study sites. It was concluded that minimizing exposure to air pollutants –and specifically to PM_{2.5}- would be of great importance for the elderly, as well as for susceptible individuals with respiratory diseases.

Sooryanarain and Elankumaran (2015) reviewed the environmental drivers of influenza outbreak. In addition to meteorological factors, air pollutants such as ozone, sulfur dioxide, nitrogen dioxide, nitric oxide and particulate matter –among other frequent environmental pollutants- could affect influenza transmission. Even haze has been suggested to have a potential epidemiologic association with respiratory viruses (Pan et al., 2014, 2016; Ye et al., 2016). Anyhow, environmental pollutants would be potential drivers in influenza A virus survival, stability, and transmissibility (Sooryanarain and Elankumaran, 2015). In relation to this, a study conducted in Brisbane (Australia) examined the interaction effects between the concentrations of some air pollutants (particulate matter, O₃ and NO₂) with temperature, during pediatric influenza. Significant interactions between PM and mean temperature were observed, while the ozone level–influenza incidence relationship resulted to be independent of the temperature (Xu et al., 2013). In turn, Sloan et al. (2011) reported that the correlation between air pollution and infectious diseases varied depending on the city, region, and the specific pollutant(s) under investigation. Other study evaluated short-term effect of 3 risk factors: low temperatures, the influenza epidemic, and air pollution in Milan region in winter of 2016-2017 (Murtas and Russo, 2019). The authors found statistically significant interactions between PM₁₀ and influenza for cardiovascular-related mortality, as well as between influenza and cold temperatures for natural causes mortality.

In addition to influenza, a number of studies have shown that regulated proteolysis is required for the spread/propagation of many human viruses, including human immunodeficiency virus (HIV), Nipah, Ebola, severe acute respiratory syndrome coronavirus (SARS-CoV), and metapneumoviruses (Kesic et al., 2012a,b). Among the air pollutants that are associated with increased respiratory morbidities and susceptibility to infections, ozone is a commonly found oxidant. However, its effects on influenza

infections in humans are not well known yet. In Hong Kong, Ali et al. (2018) examined the relationship of influenza transmissibility with common air pollutants –with special attention to ozone- as well as other environmental factors such as UV radiation and absolute humidity, which were also included. Interestingly, an association of ozone with a reduction in influenza transmissibility was observed. Anyway, these authors also stated that as a highly reactive oxidant air pollutant, ozone might decrease host defenses against bacterial and fungal infections in the airways, aggravating pre-existing diseases such as asthma.

The investigation about the effects on respiratory -and also cardiovascular- diseases derived of the association between air pollutants and respiratory virus infections is not a new topic. However, the tremendous impact on health -and on other important socioeconomic aspects of our daily life- derived of the pandemic generated by the SARS-CoV-2 has generated an extraordinary interest in everything related with this serious infection. In recent years, it has been reported that exposure to environmental factors - including air pollutants- could influence the immune system and affect its ability to limit the spread of infectious agents like the Respiratory Syncytial Virus (RSV) (Vandini et al., 2013; Nenna et al., 2017). In relation to the immune system, Zhao et al. (2016) suggested that short-term exposure to PM_{2.5} could act on the balance of inflammatory M1 and anti-inflammatory M2 macrophage polarizations, a fact that might be involved in air pollution-induced immune disorders and diseases. In turn, Yan et al. (2016) reported that exposure to particulate matter or ozone might activate cellular signaling networks including membrane receptors, intracellular kinases and phosphatases, as well as transcription factors that regulate inflammatory responses. PM-induced cell signaling would be associated with resultant ROS, while ozone-induced cell signaling would implicate phosphates. Recently, Glencross et al. (2020) reviewed the effects of air pollution on individual cell types, as well as subsequent effects on multicellular immune responses. The intracellular signaling pathways that air pollution can trigger to start the cascade of immune dysfunction, which in turn leads to pollution-induced pathology, were also reviewed. Since inhaled air pollutants deposit primarily on the respiratory mucosa, the authors focused their review on the mechanisms of respiratory diseases. It was concluded that the clinical effects of air pollution, in particular the known association between elevated ambient pollution and exacerbations of asthma and chronic obstructive

pulmonary disease (COPD), were consistent with the identified immunological mechanisms

In the past decade, Ciencewicky and Jaspers (2007) published an interesting review on the potential interactions between various air pollutants and respiratory viral infections. The outdoor pollutants examined were NO₂, ozone and particulate matter. The studies reviewed by Ciencewicky and Jaspers (2007) showed how exposure to these common air pollutants might alter host immunity to respiratory viral infections, meaning important public health implications for people worldwide. It was noted that air pollution-induced enhanced susceptibility to respiratory viral infections, could mean even more serious implications for subjects who were already affected by preexisting pulmonary diseases (asthma or COPD, for example). These patients could have a significant increased risk of morbidity/mortality after suffering infections with respiratory viruses. In Hong Kong, Wong et al. (2010) conducted the first Asian study aimed at examining the interactions between air pollution, influenza, and social deprivation from an epidemiological perspective. The concentrations of NO₂, SO₂, PM₁₀ and ozone were daily measured, while the activity of influenza and RSV was also determined. The excess risk estimates for the short-term effects of air pollution on mortality and hospitalization were higher in individuals older than 65 years, compared with all-ages group. Interaction effects between influenza activity and air pollution were found in the estimated risks for hospitalization due to respiratory diseases. A complex issue regarding the association between air pollution with infectious diseases lies in the fact that some investigations of pollution revealed conflicting results according to different cities, regions, and air pollutants (Sloan et al., 2011). Therefore, an important question to be assessed is whether air pollution showing seasonal variation is dependent on different pollutants and regions.

The impact of air pollutants on RSV has been also investigated. The possible link between climate factors, air pollution and increased childhood morbidity/mortality from respiratory diseases is an issue of great interest. Nenna et al. (2017) studied the association between acute viral bronchiolitis, weather conditions, and air pollution in children of Rome (Italy). Epidemiological data for 14 respiratory viruses detected in nasal washing samples, along with air pollutant concentrations and mean weekly data for weather conditions, were assessed. A strong correlation between peak RSV activity (but not for the remaining 13 viruses) and cold temperatures, higher relative humidity, and air

pollutants (especially benzene) was found. Experimental models have shown the pathogenetic mechanisms underlying benzene-induced toxic damage to the respiratory airways, which cause apoptotic changes in the parenchymal components of the lungs. Carugno et al. (2018) investigated whether PM₁₀ exposure was associated with hospitalization due to RSV bronchiolitis among infants of Lombardy (Italy). The results showed a clear association between short- and medium-term exposure to PM₁₀ and an increased risk of hospitalization due to RSV bronchiolitis. On the other hand, with data obtained in 1990-2016 in 195 countries, Troeger et al. (2018) reported that the interventions conducted to improve ambient particulate matter pollution –among others such as wasting, household air pollution and expanded antibiotic use- could avert one under-5 deaths due to lower respiratory infection for every 4000 children treated in the countries with the highest lower respiratory infection burden.

Since respiratory viral infections (RVIs) are the most common causes of the infection in the respiratory system, Silva et al. (2014) examined in the city of Porto Alegre (Brazil) the number of emergency visits for ILI and severe acute respiratory infection (SARI). The association between ILI/SARI, RVI prevalence, and meteorological factors and air pollution was also examined. Surprisingly, it was found that SARI cases were associated with a decrease in mean concentration of air pollutants, which suggested that it could be related with a higher rainfall in the same period of data collection. In that study, special relevance was given to indoor air pollution. Nhung et al. (2017) conducted a systematic review and meta-analysis (including 17 studies) on the acute effects of ambient air pollution on pneumonia in children. It is important to note that pneumonia is the leading cause of childhood death, being caused by viral pneumonia influenza and RSV. Pollutant-specific excess risk percentage and confidence intervals were estimated using random effect models for PM₁₀, PM_{2.5}, sulfur dioxide, ozone, nitrogen dioxide and carbon monoxide. The results of the meta-analysis confirmed that short-term increases in ambient air pollution, measured by the concentrations of PM₁₀, PM_{2.5}, SO₂, O₃ and NO₂, were associated with increases in hospital admissions due to pneumonia. It has been demonstrated that long-term exposure to PM_{2.5} reduces the resistance to influenza virus via down-regulating pulmonary macrophage Kdm6a and mediates histones modification in IL-6 and IFN- β promoter regions (Ma et al., 2017). On the other hand, Tang et al. (2018) conducted an integrated data analysis to quantify the association among air quality index (AQI), meteorological variables, and respiratory infection risk in Shaanxi (China),

whose main goal was to measure the impact of air pollution on that risk. A statistically significantly positive correlation between AQI and the number of ILI cases was observed. This finding was in agreement with the results of previous studies on the association between PM_{2.5} and ILI cases in Beijing (Feng et al., 2016), and data on hospital admissions in Guangzhou related with air pollution (Zhang et al., 2014). Zhang et al. (2019) assessed the short-term effects of air pollutant concentrations in Suzhou City (China) on respiratory infections in children of different age groups. The results of single-pollutant models showed that PM_{2.5}, PM₁₀, NO₂, SO₂ and CO had significant associations with respiratory tract infections in children < 3 years. In turn, the multi-pollutant model found that PM_{2.5} concentrations were significantly associated with viral respiratory in children under 7 months, while PM₁₀ levels were associated with viral infections in preschool children.

Croft and co-workers (2017) investigated nearly 500,000 adults from the state of New York with a diagnosis of influenza, bacterial pneumonia, or culture-negative pneumonia, between 2005 and 2016, with the objective of associating the rate of these infections to the increases of PM_{2.5}. The authors concluded that *“increased rates of culture-negative pneumonia and influenza were associated with increased PM_{2.5} concentrations during the previous week”*. However, they also pointed that these associations could be due to an altered toxicity of PM_{2.5} or a higher pathogen virulence, and therefore, further studies are required. In the same line, Horne et al. (2018) studied the relationship between PM_{2.5} levels and acute lower respiratory infection (ALRI). Similarly, these authors concluded that short-term exposure to high levels of PM_{2.5} was associated with greater healthcare use for ALRI in young children, older children, and adults.

Recently, Nhung et al. (2019) investigated the effects of various air pollutants (PM₁₀, PM_{2.5}, PM₁, SO₂, NO, NO₂, NO_x, CO and O₃) on the length of hospital stay (LOS) among children (0–5 years) of Hanoi (Vietnam) suffering acute lower-respiratory infections (ALRI). Among children aged 2–5 years, positive associations were found between increased concentrations of O₃ and extended LOS. Similar results were also observed for PM₁₀. It is well known that ozone generates oxidative stress. Therefore, exposure to high ozone concentrations might reduce the lung lining fluid antioxidant level. In contrast, increases in SO₂, NO₂, NO_x and CO concentrations were associated

with shorter LOS in single-pollutant models. Notwithstanding, these inverse results were less stable and more inconsistent across subgroups, as well as in two-pollutant models. In turn, Pfeffer et al. (2019) found that higher levels of ambient NO_x were associated with prolonged exacerbations of likely viral etiology, supporting toxicological effects of air pollution. It would increase susceptibility to infection and its severity. It was noted that the recovery for viral-type exacerbations, after higher ambient levels of NO_x, was significantly prolonged. On the other hand, rhinovirus (RHV), which is among the smallest RNA viruses, it is well known that infects the upper and sometimes lower respiratory apparatus, being responsible of half of the cases of common human cold. In individuals suffering chronic respiratory diseases, or in the elderly, RHV can be also responsible of life-threatening diseases. Regarding this, recently Rodrigues et al. (2019) reported that RHV circulation was determined by environmental conditions, including air pollution.

4. Air pollution, H1N1 and SARS

Epidemiological and experimental evidences have suggested a link between air pollution exposure and the symptoms associated with respiratory viral infections. H1N1 flu is a subtype of influenza A. In the spring of 2009, it was detected first in the USA and spread rapidly across that country and the world. The new H1N1 virus contained a unique combination of influenza genes, which had not been previously identified in animals or people. It was designated as influenza A (H1N1)pdm09 virus, being very different from the H1N1 viruses that were circulating at the time of the pandemic (CDC, 2019). "Swine flu" was the popular name for that virus, which was responsible for a global flu pandemic in 2009-2010.

Despite the wide number of investigations assessing the different factors influencing susceptibility to viral infections, the mechanisms by which inhaled oxidants can modify viral pathogenesis are very complex, and at the time of that pandemic were not well established. It has been shown that oxidative stress increases severity of viral infections. Ozone, an elemental form of oxygen, is one of the most abundant air pollutants in urban areas. It is a potent inducer of oxidative stress that may cause airway inflammation and increased respiratory morbidities. Kesic et al. (2012a,b) demonstrated

that secreted proteases from primary human respiratory nasal epithelium proteolytically, activated influenza virions, while exposure to an air oxidant pollutant such as ozone increased these effects. On the other hand, associations between PM pollution exposure and adverse health outcomes are well documented. They include respiratory diseases such as COPD and asthma. In turn, associations between PM exposure and increased susceptibility to infectious respiratory diseases have been also reported. Environmentally persistent free radicals (EPFRs) were detected in PM samples collected from various cities in USA (Dellinger et al., 2001). In relation to this, Lee et al., (2014) demonstrated that EPFRs associated with combustion derived PM were important in enhancing severity and mortality following respiratory tract viral infections. Moreover, Hirota et al. (2015) showed that urban PM increased human airway epithelial cell IL-1 β secretion, following scratch wounding and H1N1 influenza A exposure *in vitro*. A number of investigations have been aimed at capturing the global mortality impact of influenza A (H1N1)pdm09 and identifying factors to explain mortality variations seen across populations. Some studies have been focused on risk factors such as pollution exposure. For example, Xu et al. (2013) found a significant interaction effect between PM₁₀ and mean temperature on pediatric influenza in Brisbane (Australia). Searching for possible explanations for why some countries were harder hit by the pandemic H1N1 virus in 2009, Morales et al. (2017) highlighted the need to look at environmental exposure such as air pollution, which is a burden on the respiratory system immune-compromising chronic infections.

Regarding SARS, in an ecologic study conducted in China on air pollution - evaluated by air pollution index (API)- and case fatality of SARS, Cui et al. (2003) found that SARS patients from regions with moderate APIs had an 84% increased risk of dying in comparison to patients residing in regions with low APIs. In turn, SARS patients from regions with high APIs were twice as likely to die from SARS, in relation to patients living in regions with low APIs. The results showed a positive association between air pollution and SARS case fatality in Chinese population. Similar results were also reported by Kan et al. (2005), who in the population of Beijing (China) studied the association between air pollution and daily SARS mortality. It was found that an increase of each 10 $\mu\text{g}/\text{m}^3$ over a 5-day moving average of PM₁₀, SO₂ and NO₂ corresponded to 1.06, 0.74 and 1.22 relative risks of daily SARS mortality, respectively. Cai et al. (2007) carried out an ecological study in mainland China in order to assess the potential relationship between the outbreak of SARS with meteorological factors and air pollution. In contrast to the

results of Cui et al. (2003), these authors (Cai et al., 2007) did not find a correlation between air pollution and the SARS outbreak. Although theoretically, air pollution should not affect survival of SARS-CoV *in vitro*, it could exert its effect by influencing local resistance of the host. The authors recommended conducting further investigations on this topic.

5. Air pollution and COVID-19

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although in December 2019, a novel coronavirus disease epidemic was already reported in Wuhan (China), the outbreak was officially confirmed as a pandemic on February 11, 2020 (WHO, 2020). In recent weeks/months, a considerable number of papers on SARS-CoV-2 and COVID-19 are being published. However, there are a very important number of research questions that need prompt responses (Yuen et al., 2020). One of this concerns the potential association between the transmission of the coronavirus 2 and the levels of air pollutants, a question that we next discuss based on data from very recent papers.

The link between severe viral respiratory diseases, which cause infection in 10-20% of the population and air pollution, is well established (Iuliano et al., 2018). A number of the studies already above discussed corroborate this statement. As commented, air pollutants such as PM_{2.5} and PM₁₀, sulfur dioxide, nitrogen dioxide, carbon monoxide and ozone, can affect airways through inhalation, exacerbating the susceptibility to respiratory virus infections, as well as the severity of these infections (Cienciewicki and Jaspers, 2007). In relation to this, Frontera et al. (2020) recently hypothesized that an atmosphere with a high content of air pollutants, together with certain climatic conditions, might promote a longer permanence of the viral particles in the air. It would favor an indirect diffusion of SARS-CoV-2, in addition to the direct diffusion individual to individual. Martelletti and Martelletti (2020) have noticed how the Italian Northern Regions, which are the most affected by COVID-19, match those areas showing also the highest concentrations of PM₁₀ and PM_{2.5}. These authors have suggested that the SARS-CoV-2 could find suitable transporters in air pollutant particles. In addition, in a linear relationship, the viruses would survive longer and could become more aggressive in an

immune system already aggravated by the air pollutants themselves. Individuals residing in zones with high concentrations of air pollutants are more prone to develop respiratory diseases (Marquès et al., 2020) and suitable to viral infections (Xie et al., 2019). Pollution impairs the first line of defense of upper airways, mainly cilia (Cao et al., 2020). Based on this, Conticini et al. (2020) have investigated whether communities living in polluted area such as Lombardy and Emilia Romagna were more predisposed to die of COVID-19, due to their worse previous health status caused by air pollution. It has been concluded that the usual high concentrations of air pollutants in Northern Italy should be considered an additional co-factor of the high level of lethality recorded in that area. In China, Zhu et al. (2020) have investigated the relationship between the concentrations of six air pollutants ($PM_{2.5}$, PM_{10} , CO, NO_2 and O_3) and daily confirmed COVID-19 cases in 120 cities of that country. Significant positive associations of these pollutants with COVID-19 confirmed cases, were found. However, SO_2 levels were negatively associated with the number of daily confirmed cases. Anyhow, the results of that study also support that air pollution can be an important factor in COVID-19 infection. In the same line, Ogen (2020) has assessed the contribution of a long-term exposure to NO_2 on coronavirus fatality. For that purpose, 3 databases were combined: the tropospheric concentrations of NO_2 , the atmospheric condition (expressed by the vertical airflow), and the number of fatality cases. Data from the Sentinel-5P showed two main NO_2 hotspots over Europe: Northern Italy and Madrid metropolitan area, regions in which the mortality caused by COVID-19 has been particularly high. In contrast to these results, Bomptemti (2020), for the first time, analyzed the PM_{10} situation in Lombardy (Italy) from February 10 to March 27, 2020, several days before the sanitary emergency explosion. The available data about PM_{10} concentrations and infections cases in Lombardy and Piedmont were analyzed and showed that direct correlations between the presence of high quantities of PM_{10} and the diffusion of the COVID-19 virus were not evident. The assumption that the virus diffusion in Lombardy was favored by PM_{10} transport effects would be an invalid assessment of health risk. On the other hand, Ribeiro and Barros (2020) have recently tested the hypothesis that air pollution increases susceptibility to COVID-19. For this, the authors used publicly available data on the cumulative number of COVID-19 confirmed cases by municipality in Continental Portugal until the 2nd of May 2020 and the average annual levels of PM_{10} , $PM_{2.5}$ and NO_2 in the same municipalities. Adjusted models revealed a positive and significant association between COVID-19 notification rates and PM_{10} and $PM_{2.5}$, while association with NO_2 disappeared after adjustment for

confounders. These results as those also shown in Italy (Conticini et al., 2020) and in the USA (Wu et al., 2020), indicate that chronic exposure to air pollutants impairs recovery and leads to more severe and lethal forms of disease. In this same line, Coccia (2020) has recently examined the mechanisms of transmission dynamics of COVID-19 in the environment for a possible strategy to cope with future epidemics similar to coronavirus diseases. The study was focused on case study of Italy, one of the countries with the highest level of deaths worldwide. The results revealed that accelerated transmission dynamics of COVID-19 in specific environments was due to two mechanisms given by: air pollution-to-human transmission, and human-to-human transmission in a context of high density of population. The two main findings were: 1) the acceleration of transmission dynamics of COVID-19 in North Italy has a high association with air pollution of cities, and 2) cities having more than 100 days of air pollution (exceeding the limits set for PM₁₀), show a very high average number of infected individual (about 3,340 infected individuals), while cities having less than 100 days of air pollution show a lower average number of infected (about 1450 infected individuals) on April 27, 2020. Regarding this same topic, Sanità di Toppi et al. (2020) have hypothesized that the SARS-CoV-19 might be using a species of “highways”, which would be made up of atmospheric particulates, increasing its indirect transmission. For these authors, this is an issue that deserves further, immediate, and in-depth experimental investigations. Based on the results from various recent papers, here discussed, we fully agree with this recommendation.

Finally and rather as a scientific curiosity, it is interesting to note that considering the huge decrease in air pollution following the quarantine, the COVID-19 pandemic might paradoxically have decreased the total number of deaths during this period, by drastically decreasing the number of deaths due to the own air pollution (Dutheil et al., 2020).

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