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The Interplay Between Air Pollution and Coronavirus Disease (COVID-19)

To the Editor:

Coronavirus disease (COVID-19) is a respiratory disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has an enormous impact worldwide in terms of healthcare, economy, and the environment. Many factors have been connected to the contagiousness and virulence of COVID-19, including patient characteristics like genetics and co-morbidities, as well as social, economic, and environmental factors. Epidemiological data and the underlying pathophysiologic mechanisms suggest that air pollution may contribute to the spread and severity of COVID-19. The present letter explores the interaction between air pollution and COVID-19.

CORONAVIRUS DISEASE (COVID-19)

COVID-19 constitutes to a very serious respiratory virus, like the H1N1 influenza pandemic of 1918.[1] The outbreak of COVID-19 has caused 44,816,606 confirmed cases and 1179,992 deaths worldwide (as of October 29th, 2020) and has struck in approximately 60 countries worldwide.[2] COVID-19 has a fatality rate of 5%[3] and the estimated mean reproduction number (R0) for COVID-19 is around 3.28.[4] The large majority of confirmed SARS-CoV-2 cases are mild (81%), however 14% of the patients have severe pneumonia and 5% develop acute respiratory distress syndrome.[5]

AIR POLLUTION

Air pollution is reflected by substances like nitrogen oxide (NO_x), ozone (O_3), sulphur dioxide (SO_2), ammonia, and volatile organic compounds or contaminating particles as sulphates, nitrates, elemental carbons, organic carbons, and crustal materials.[6] Particulate matter (PM) is dispersed in the air and, because of its small size, can be inhaled, transported, and distributed in the human body. It can be roughly subdivided between coarse particles PM10 ($<10\,\mu m$), fine particles PM2.5 ($<2.5\,\mu m$), and ultrafine particles ($<0.1\,\mu m$).[7]

PM may have effects on the lungs and systemic effects on other organs and the unborn child.[8] Ambient air pollution causes significant excess mortality and loss of life expectancy and is considered a global health risk. Achakulwisut et al showed that NO_2 is responsible for 20% of new childhood asthma cases in 125 major cities.[9] Increased ambient O_3 and NO_x concentrations can be linked to emphysema, as assessed by CT imaging and lung function.[10] In 10% of people with lung cancer, a relationship with air pollution is demonstrated.[11] Besides respiratory mortality, Liu et al have demonstrated that there is an association between exposure to PM2.5 and PM10 and cardiovascular mortality in more than 600 cities across the globe.[12] Lelieveld et al estimated that air pollution reduces the mean life expectancy in Europe by about 2.2 years and even suggested that the negative effect of air pollution outweighs smoking.[11]

AIR POLLUTION: A DETERMINANT OF CORONAVIRUS DISEASE (COVID-19)

Epidemiology

Early in the COVID-19 pandemic, it was already suggested that air pollution had a negative effect on outcomes of SARS-CoV-2 infection. Areas such as Wuhan region in China, the United States and Northern Italy combine a poor air quality with a high incidence and detrimental outcome of COVID-19.[13,14] A statistically significant relationship between short-term exposure to concentrations PM, CO, NO_2, ozone and COVID-19 was demonstrated in 120 cities in China.[15] Fattorini and Regoli demonstrated using air-quality data of 71 Italian provinces that air pollution correlates with COVID-19 cases.[16] Riccardo Pansini investigated this worldwide and demonstrated that infection spreading was correlated with several annual satellite and ground indexes of air quality in China, the United States, Italy, Iran, France, Spain, Germany, and the United Kingdom. They found a higher incidence of SARS-CoV-2 in areas with high PM and NO_2 concentrations (Fig. 1.).[17]

The study by Pozzer et al demonstrated that particulate air pollution contributed 15% to COVID-19 mortality worldwide, 27% in East Asia, 19% in Europe, and 17% in North America and that globally, 50% to 60% of the attributable, anthropogenic fraction is related to fossil fuel use, up to 70% to 80% in Europe, West Asia, and North America.[18]

It was also shown that of the 4443 COVID-19 fatalities that had occurred worldwide as of March 19th, 2020, 3487 (78%) occurred in five regions of northern Italy and central Spain (Lombardia, Emilia-Romanga, Piemonte and Veneto and the Community of Madrid), regions with the highest NO_2 concentrations.[19] These results indicate that (long-term) exposure to air pollutants may be an important contributor to the mortality rate of COVID-19. Poor air quality and high NO_2 and ozone concentrations were found to be associated with COVID-19 morbidity in different regions of England.[20] Using data from 355 municipalities in the Netherlands, the relationship between air pollution and COVID-19 cases, hospital admissions and deaths was also established. That data show that 1 mug/m^3 more PM concentrations cause 9.4 more COVID-19 cases, 3.0 more hospital admissions, and 2.3 more deaths.[21]

Recently, researchers at Harvard University found that a minimal increase in the concentration of fine particles in air lead to 15% more deaths from COVID-19, corrected for various confounders such as the number of hospital beds, socio-economic status, smoking status, and obesity.[22] All these epidemiological studies suggest a correlation between air pollution and COVID-19 that might imply causality.

Biological Plausibility

Carrier for SARS-CoV-2

Airborne virus in aerosols might be an important route for virus transmission. It is established that SARS-CoV-2 remains

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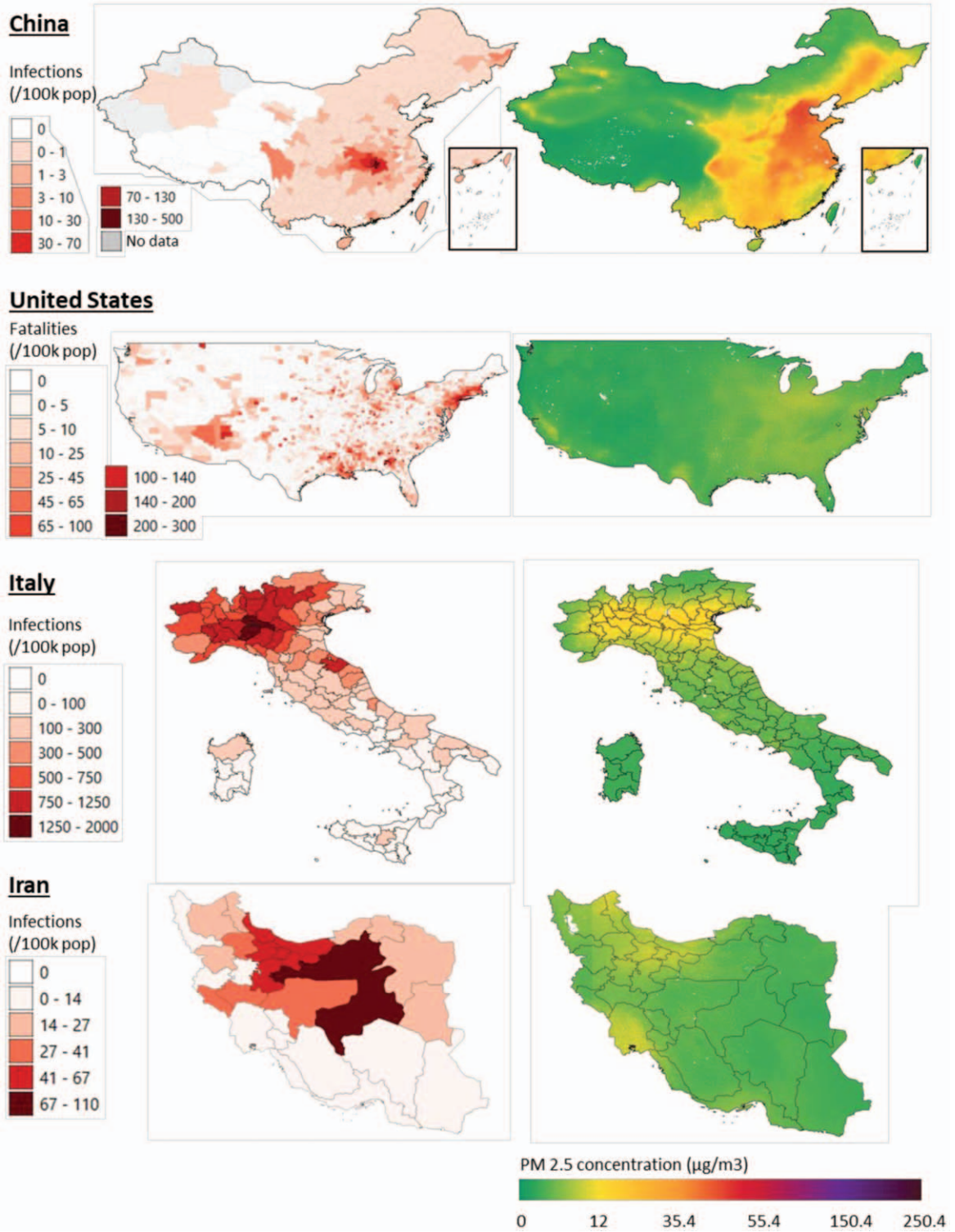

FIGURE 1. Maps comparisons of satellite-derived PM 2.5 distributions and COVID-19 infections, fatalities (per 100,000 inhabitants), or mortality rates (deaths/infections)[17]. Riccardo Pansini, June 23, 2020.

viable in the aerosol for hours and this facilitates rapid distribution of the virus over great distances.[23] Contaminated aerosols can be inhaled deep into the lung, which causes infection in the alveolar tissues of the lower respiratory tract. PMs could act as a carrier through the aerosol, conveying viruses and further increasing the spread and survival of the associated virus. By this mechanism, PM could play an important role in the spread of SARS-CoV-2. Setti et al revealed that SARS-CoV-2 was present in PM samples obtained in the Bergamo area, the epicentre of the Italian COVID-19 epidemic.[24]

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Barrier Function

Air pollution impairs the activities of the respiratory mucosa, including production of airway surface lining fluid with host defence peptides, mucus production, and the tight junctions between epithelial cells. Air pollution can cause ciliary dysfunction with altered surfactant composition and increased airway epithelial permeability.[7,25] The impairment of the mucosal barrier impedes the lungs' defences against inhaled pathogens like SARS-CoV-2.[26]

Entry Points

Angiotensin-converting enzyme 2 (ACE2) receptors on the human epithelial cells in the upper airway epithelia are the entry points for SARS-CoV-2.[27] SARS-CoV-2 binds with S-proteins to the host cell and causes fusion of the viral membrane with the epithelial cell membrane.[28] The viral RNA is released into the host cell cytoplasm and viral replication takes place. Air pollution causes an increase in airway expression of ACE2 and this upregulation of the ACE2 receptor may increase susceptibility to SARS-CoV-2. This upregulation may be associated with increased severity of COVID-19. Cardiac co-morbidity, adiposity, and smoking show an increase in ACE-receptor expression and COVID-19 may have added to this.[29] ACE2 receptors are mainly present in airways, in the mucus-producing goblet cells and cilia cells, but also in the heart, digestive tract, liver, kidney, brain, and other organs and upregulation of these receptors may be important in the systemic effects of SARS-CoV-2.[30]

Inflammatory Pattern

Accumulation of PMs in the lungs, translocation through the air-blood barrier to extra pulmonary locations results in low grade systemic inflammation.[31] Previous studies have shown that patients with systemic diseases have an increased risk of severe COVID-19 infection. In addition, the low-grade inflammation induced by air pollution may amplify COVID-19 inflammation: the pattern is characterized by oxidative stress, IL-6 increase and activation of the bradykinin system.[32]

Defence Mechanisms

Exposure to air pollution inhibits phagocytic function of macrophages and a decrease in the T-cell response.[7] There is mounting evidence that PM exposure weakens protective antimycobacterial host-immunity; air pollution increases the risk of new infections with Mycobacterium tuberculosis.[33] In this perspective, there are suggestions that BCG vaccines have a protective effect on COVID-19. The BCG vaccination reduces the viremia from viral respiratory tract infections by boosting non-specific Th1 an Th17 response.[34]

Hypercoagulability

Short term exposure to PM, analogous to cigarette smoking, induces endothelial damage and microthrombi. We hypothesize that this effect potentiates the observed coagulopathy in COVID-19 patients and compounds cerebral damage, pulmonary embolism, and cardiac dysfunction.[35]

CORONAVIRUS DISEASE (COVID-19): A DETERMINANT FOR AIR POLLUTION

To limit transmission of the virus, many countries implemented strict measures as the lockdown. This lockdown has had a positive effect in terms of the reduction of (air) traffic and industrial activities, which have a major environmental impact. The air quality of India improved significantly during the COVID-19 lockdown. Mumbai and Delhi have observed a substantial decrease in NO_2 (40–50%) compared to the same period last year.[36] Levels of air pollution in New York decreased by almost 50% during lockdown.[37] In China and Europe, a modelling study estimated that 24,200 premature deaths due to air pollution were avoided in China and 2,190 in Europe during the lockdown period.[38]

CORONAVIRUS DISEASE (COVID-19) AND AIR POLLUTION: A COMMON PATHWAY

Many observations suggest a correlation between the severity of the COVID-19 pandemic and exposure to air pollution. This might suggest causality; however, many confounders are present, and there may be no causal relation per se, rather a mutual common pathway deriving from the devastating effects on health the environment of today's lifestyles (Fig. 2).

Close contact between humans and animals is probably the cause of SARS-

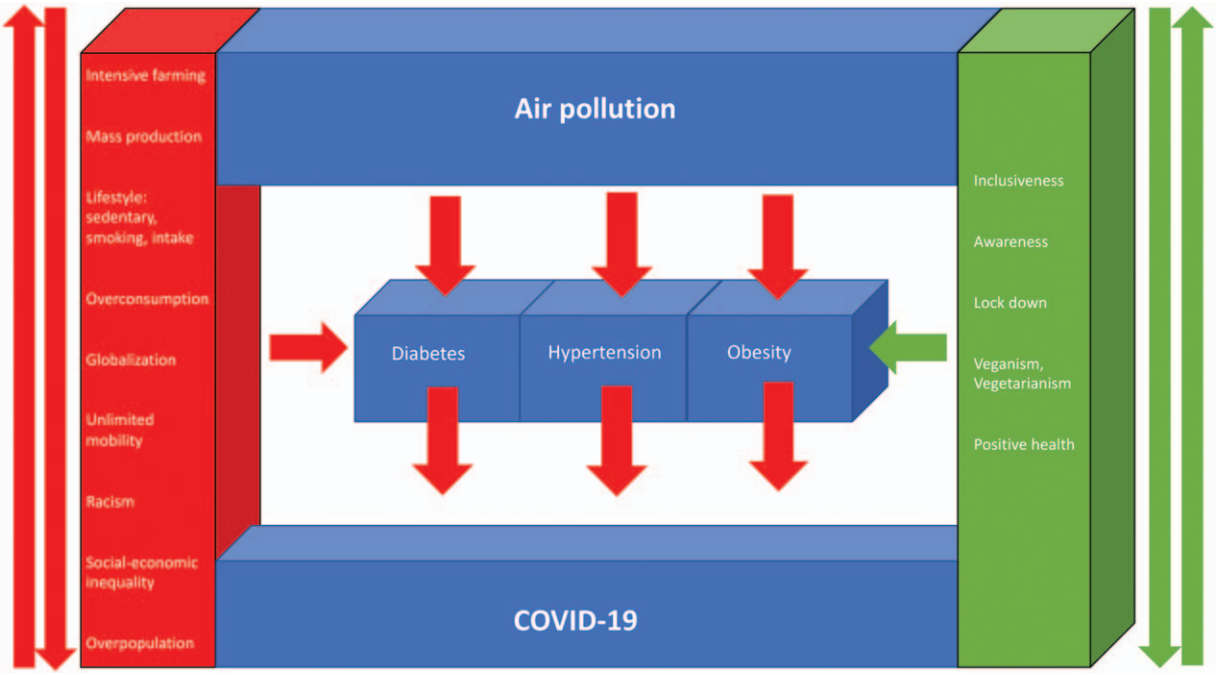

FIGURE 2. The interplay between the viral pandemic, air pollution, lifestyle and lifestyle diseases and environment.

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CoV-2 transmission. The overcrowded food market in Wuhan with close contact between people and animals and the absence of animal welfare created a breeding ground for the development of SARS-CoV-2. The virus spread quickly worldwide due to overpopulation and unrestricted globalization with international travel. The virus especially affected patients with comorbid conditions like obesity, diabetes, and hypertension.[39] All these factors are lifestyle-related and result from sedentary behaviour, addiction to cigarettes, and poor diet. Conversely, these factors also contribute to air pollution and poor air quality. For example; approximately 16% of methane emissions are caused by livestock farming (for meat industry) and methane is responsible for a large share of greenhouse gases. Methane is released during the digestion of ruminants, such as cows. Cattle manure also affects the climate, as the manure used to improve crop cultivation accounts for approximately 80% of NO emissions. Plant-based diets could lead to a reduction in CO_2 emissions and contribute to the prevention of global warming.[40]

Moreover, with globalization and ever-increasing access to products from around the world, shipping contributes substantially to air pollution. Socio-economic inequality also plays a role in COVID-19 and exposure to air pollution. This inequality ensures that vulnerable groups are additionally affected by both air pollution and COVID-19. Vulnerable groups are more exposed to pollution and have less knowledge of the risks thereof, and thus are less able to protect themselves, while this group generally contributes less to air pollution per capita. The same applies to COVID-19: vulnerable groups have higher rates of obesity, live closer together, have less access to protective material and poorer knowledge about contagiousness of COVID-19. Unhealthy lifestyles with insufficient exercise are also related to air pollution as well as COVID-19. Encouragingly, a new global Ipos survey on the World Economic Forum of 21,000 adults from 27 countries indicated that 86% of respondents would prefer to see the world change following the COVID pandemic and that they would prefer a more sustainable and equitable world.[35]

In conclusion, there are strong indications that air pollution plays a role in the contagiousness and virulence of COVID-19 based on epidemiological data substantiated with pathophysiologic mechanisms. There may be no causal relation per se, rather a mutual common pathway deriving from the devastating effects on health the environment of today's lifestyles. Either way, improvements in terms of air pollution, lifestyle, and environment will help to prevent future viral pandemics. There are hopeful indicators in this respect: a large part of the population would prefer to see permanent change in response to the COVID pandemic to achieve a more sustainable and equitable world.

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