Pros and cons for the role of air pollution on COVID-19 development

Isabella Annesi-Maesano[1], Cara Nichole Maesano[1], Maria D'Amato[2], Gennaro D'Amato[3]

[1]INSERM and Sorbonne University, Epidemiology of Allergic and Respiratory Diseases Department, IPLESP, Paris, France

[2]First Division of Pneumology, High Speciality Hospital V. Monaldi and University Federico II Medical School Naples, Napoli, Italy.

[3]Division of Respiratory and Allergic Diseases, Department of Chest Diseases, High Specialty A. Cardarelli Hospital, Napoli, Italy and Medical School of Specialization in Respiratory Diseases, University on Naples Federico II

Correspondence: Prof. Isabella Annesi-Maesano, Epidemiology of Allergic and Respiratory Diseases Department, IPLESP, INSERM and Sorbonne University, Medical School Saint-Antoine, 27 rue Chaligny 75012 Paris, France

As SARS-CoV-2 has spread across the globe, it has been difficult to ignore patterns suggesting that regions with poor air quality are witnessing disproportionate impacts in terms of the frequency and severity of COVID-19 infection. Consequently, researchers have rightly recognized the importance of considering the role of air pollution in the COVID-19 pandemic. Here, we discuss the pros and cons of air pollution as a contributing factor to COVID-19, according to existing research questions (Table 1).

What data exist on the relation of air pollution to SARS-CoV-2 or COVID-19?

At the general population level, infection rates for SARS-CoV-2 have skyrocketed in countries, regions and towns characterized by high levels of air pollution (e.g., Lombardy, Iran, China, South Korea, New York, Madrid) where COVID-19 hospitalizations and deaths have occurred in excess. Early in the pandemic, an Italian study positively related the proportion of daily exceedances of concentrations of particulate matter (PM) with 10 µm of diameter or less (PM_{10}) with the number of COVID-19 admissions reported within the following 14 days[1]. Since then, various studies have confirmed the existence of a significant association between air pollution exposure and SARS-CoV-2 infection or COVID-19 mortality[2]. A recent study that calculated the extent to which air pollution could be blamed for COVID-19 deaths worldwide clearly showed that when both long-term exposure to air pollution and infection with the COVID-19 virus come together there is a significant adverse effect on health[3]. In East Asia, which has some of the highest levels of harmful pollution on the planet, it found that 27% of COVID-19 deaths could be attributed to the health effects of poor air quality. The proportion was 19% in Europe, and 17% in North America. Not surprisingly, previous research has already shown the significant impact of air pollution on other respiratory viruses, such as SARS, influenza, syncytial virus and measles, also transmissible via the respiratory route[2].

How can this be explained?

Two patterns seem possible[2] (Figure 1). Air pollution may contribute to the damage caused by the COVID-19 pandemic by rendering people more susceptible to infection by SARS-CoV-2. It is well established that gases such as nitrogen dioxide (NO_2) or ozone (O_3) and respirable PM may modify the permeability of airways mucosa. In particular, exposure to either fine PM or ultrafine particles including black carbon may significantly damage lung epithelial cilia, the first line of defence against SARS-CoV-2, decrease the ability of macrophages to phagocytize the virus as well as mount an effective immune response against the infection. Additionally, air pollution enhances respiratory virus-induced inflammation through oxidative stress also involved in air pollution-related short- and long-term health effects. Long-term endemic exposure to air pollution is responsible for chronic systemic inflammation at the origin of the comorbidities that put COVID-19 patients at higher risk of severe events and death. Air pollution makes known COVID-19 risk factors, such as lung and heart problems, more likely. Specifically, PM has been shown to increase the activity of the Angiotensin-converting enzyme 2 (ACE-2) receptor on lung cell surfaces, which is known to be involved in the way COVID-19 infects patients[2]. This has been described as a double hit: air pollution damages the lungs and increases the activity of ACE-2, which in turn leads to enhanced uptake of the virus.

Additionally, there is now growing evidence that SARS-CoV-2 is exhaled as a result of regular breathing, becoming airborne and hence inhalable by others[4]. Once in the air, the virus can either be carried by fine particles or mix with secondary ultrafine aerosols[2]. Experimentally, it has also been observed that SARS-CoV-2 remains viable in aerosols for up to 3 hours, with a reduction in infectious titer comparable to that found for SARS-CoV-1, confirming a possible route of infection transmission other than respiratory droplets and contact via contaminated surfaces[5].

The viability and long range transport of respiratory viruses in open air, and thus their potential to infect individuals, have also been observed under real life conditions[2], and for SARS-Cov-2 both indoors[4] and outdoors[2]. A recent study observed that the overburdening of

the health services and hospitals, as well as the high over-mortality due to COVID-19 observed in various regions of Europe in the Spring of 2020 may be linked to peaks of $PM_{2.5}$ and likely particular weather situations that have favored the spread and enhanced the virulence of the virus[6]. Ergo, air pollution may be an important factor in viral disease transmission and further investigations into the interaction of SARS-Cov-2 and air pollution are warranted.

In which matters should we be cautious?

The role of airborne SARS-CoV-2 transmission due to small respiratory droplets of diameter < 5 µm emitted by symptomatic as well as asymptomatic, but infected, individuals at the origin of droplet nuclei remaining suspended in the air is, however, still challenged by a lack of studies. A major drawback in this respect is that the minimum infectious dose, as expressed in viral RNA copies necessary to promote the infection, is not yet defined. In addition, very few studies so far have assessed RNA copies in outdoor air and they are not conclusive. In a Chinese study, the observed RNA concentrations were above the detection limits only in crowded areas[7]. In Italy, a study also observed detectable SARS-Cov-2 RNA in congested zones, but not in less polluted zones (below 10 $\mu g/m^3$ in mean)[8]. A previous Italian study had similarly found traces of SARS-Cov-2 RNA in 23% of the sampled PM_{10} in a polluted zone but without assessing RNA copies[9]. However, sampling the virulence of the sampled virus has proved challenging so far.

Other major criticisms to the population-based data are methodological. Studies of air pollution and SARS-Cov-2 or COVID-19 have relied mainly on ecological measures of exposures and outcomes, and are susceptible to important sources of bias: selection bias, underreporting of health data, exposure misclassification, no taking into account of the infection dynamics, and poor adjustment for confounders[10]. Only in the UK biobank dataset individual data and adjustment were possible[2]. Longitudinal studies with individual-level data are needed to adequately address this topic. In addition, careful peer review is necessary.

Though more studies are imperative, collectively the data existing so far suggest that air pollution – regardless of origin – should be considered as a contributing factor to the dynamics of COVID-19 epidemics in terms of both viral transmission as well as pre-existing susceptibility to viral infection, and advocate the need to diminish air pollution emissions in the interest of public health.

References

1. Setti L, Passarini F, De Gennaro G, Barbieri P, Licen S, Perrone MG, Piazzalunga A, Borelli M, Palmisani J, Di Gilio A, Rizzo E, Colao A, Piscitelli P, Miani A. Potential role of particulate matter in the spreading of COVID-19 in Northern Italy: first observational study based on initial epidemic diffusion. BMJ Open. 2020 Sep 24;10(9):e039338. doi: 10.1136/bmjopen-2020-039338. PMID: 32973066; PMCID: PMC7517216.
2. Bourdrel T, Annesi-Maesano I, Alahmad B, Maesano C, Bind MA. The impact of outdoor air pollution on COVID-19: a review of evidence from *in vitro,* animal, and human studies. Eur Respir Rev (in press)
3. Pozzer A, Dominici F, Haines A, Witt C, Münzel T, Lelieveld J. Regional and global contributions of air pollution to risk of death from COVID-19. Cardiovasc Res. 2020 Dec 1;116(14):2247-2253. doi: 10.1093/cvr/cvaa288. PMID: 33236040.
4. Morawska L, Milton DK. It Is Time to Address Airborne Transmission of Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2020 Dec 3;71(9):2311-2313. doi: 10.1093/cid/ciaa939. PMID: 32628269; PMCID: PMC7454469.
5. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med 2020;
6. Rohrer, M., Flahault, A. & Stoffel, M. Peaks of Fine Particulate Matter May Modulate the Spreading and Virulence of COVID-19. *Earth Syst Environ* (2020). https://doi.org/

10.1007/s41748-020-00184-4
7. Liu Y., Ning Z., Chen Y., Guo M., Liu Y., Gali N.K. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature. 2020;582:557–560. doi: 10.1038/s41586-020-2271-3. - DOI - PubMed
8. Chirizzi D, Conte M, Feltracco M, Dinoi A, Gregoris E, Barbaro E, La Bella G, Ciccarese G, La Salandra G, Gambaro A, Contini D. SARS-CoV-2 concentrations and virus-laden aerosol size distributions in outdoor air in north and south of Italy. Environ Int. 2020 Nov 12;146:106255. doi: 10.1016/j.envint.2020.106255. Epub ahead of print. PMID: 33221596; PMCID: PMC7659514.
9. Setti L, Passarini F, De Gennaro G, Barbieri P, Perrone MG, Borelli M, Palmisani J, Di Gilio A, Torboli V, Fontana F, Clemente L, Pallavicini A, Ruscio M, Piscitelli P, Miani A. SARS-Cov-2RNA found on particulate matter of Bergamo in Northern Italy: First evidence. Environ Res. 2020 Sep;188:109754. doi: 10.1016/j.envres.2020.109754. Epub 2020 May 30. PMID: 32526492; PMCID: PMC7260575.
10. Villeneuve PJ, Goldberg MS. Methodological Considerations for Epidemiological Studies of Air Pollution and the SARS and COVID-19 Coronavirus Outbreaks. Environ Health Perspect. 2020 Sep;128(9):95001. doi: 10.1289/EHP7411. Epub 2020 Sep 9. PMID: 32902328; PMCID: PMC7480171.

Table 1: Research questions on air pollution as a contributing factor to COVID 19 infection

Research question	**Certainty vs. Uncertainty**
Is SARS-Cov-2 exhaled?	Yes
Is SARS-Cov-2 airborne?	Yes
Is SARS-Cov-2 found in PM aerosols?	Potentially, as it can be carried by or mixed with secondary aerosols
Is SARS-Cov-2 viable once in suspension?	Yes, but needs to be confirmed
Is air pollution a co-factor of SARS-Cov-2 infection?	Yes, based on several mechanisms. A link has already been observed in the cases of SARS, influenza, syncytial virus and measles.
Is COVID-19 significantly related to air pollution?	Yes, but lacking sufficient data. In addition, the mechanisms are not understood.