Examining the Intersection of Air Pollution Exposure and COVID-19: Opportunities and Challenges for Research

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A look at the ongoing research into the links between air pollution and human health during the COVID-19 pandemic, as well as an illustration of some of the opportunities and challenges often encountered in this type of research, and a preview of the Health Effects Institute's newly funded COVID-19 studies.

The ongoing COVID-19 pandemic is affecting human health and global economies on a scale that has not been seen in the last 100 years. Air pollution is one of many factors that has received some attention in recent months as a factor that may facilitate the spread, severity, and prognosis of the disease.[1] The lockdown measures to control the spread of COVID-19 have led to unprecedented improvements in air quality in many parts of the world. Air quality data have shown substantial reductions in concentrations of pollutants such as nitrogen dioxide (NO_2) and, in some cases, modest reductions for other pollutants such as fine particulate matter ($PM_{2.5}$).[2-4] Simultaneously, levels of ozone (O_3) appear to have increased, in part due to the reductions in NO_2 and changes in meteorological factors including temperature. As evidence from some countries has already shown, these changes were only temporary. As restrictions have lifted, emissions have risen—rapidly erasing any improvements in air quality.

While there is an enormous cost to this pandemic, both human and economic, it has created unprecedented conditions that lend themselves to timely and novel air pollution research aimed at exploring policy-relevant topics, including key factors that contributed to changing patterns of air pollution over space and time, potential benefits to human health associated with such changes in exposures, and relationships between past and/or current exposures to air pollution and susceptibility to the effects of COVID-19 infections.

Researchers have quickly commenced investigations into the links between air pollution and health in this uncommon situation. The U.S.-based Health Effects Institute (HEI) recently issued a request to fund research on novel and important aspects of the intersection of exposure to air pollution and COVID-19. Several other major funders—including the National Institute of Environmental Health Sciences and National Aeronautics and Space Administration in the United States; the Department for Environment, Food, and Rural Affairs in the United Kingdom; and the European Space Agency in the European Union—have also made special provisions for supporting work in this area.

The Intersection of Air Pollution Exposure and COVID-19

Given the extent of the pandemic and the documented associations between air pollution and cardiovascular and respiratory disease, including respiratory infections,[5,6] the question whether the occurrence and prognosis of COVID-19 disease can in part be influenced by ambient air pollution is timely, relevant, and plausible. Despite some early claims that air pollution may increase the severity of COVID-19—which attracted considerable media attention—current evidence should be reviewed with caution.

First, there are methodological aspects to consider as elegantly discussed by recent critical papers and reports.[1,7,8] For example, almost all epidemiologic studies published thus far employed an "ecologic design". This refers to a study design that uses aggregate data (e.g., municipalities, counties) rather than individual data. Population characteristics included in these aggregated units typically vary widely within and between units. A limitation of this design is that associations at the aggregate level may not reflect the true relationship between exposure and disease at the individual level. Results of such studies should be cautiously interpreted, particularly if they lack adjustment for the dynamics of the disease, social contacts, and population mobility, which are important drivers of the COVID-19 pandemic.

The fact that some of the research was published ahead of rigorous peer-review is also of concern. At best, these studies should be viewed as "hypothesis generating". For example, a nationwide U.S. study raised headlines globally in May 2020 by estimating that a small increase of 1 $\mu g/m^3$ in long-term average county-level concentrations of $PM_{2.5}$ was associated with a sizeable 15% increase in the county-level COVID-19 death rate.[9] Notably, this estimate was soon corrected to 8% by taking into account the disease dynamics in terms of the time of virus introduction in each county, demonstrating the necessity of correcting for those factors. Another U.S. study using the same data, but with more complete control for confounding and spatial autocorrelation, found no associations between COVID-19 mortality and $PM_{2.5}$. The latter study does report an association between COVID-19 mortality and NO_2.[10] Individual-level studies are now starting to emerge. For example, a nationwide cohort of U.S. veterans with a COVID-19 positive test documented an association between COVID-19 hospitalization and $PM_{2.5}$, and account for relevant individual-level characteristics, though generalizability may be an issue.[11]

As a further complication, COVID-19 outcomes are incredibly difficult to study. To date, COVID-19 incidence data—and to a lesser extent mortality data—have been underestimated in all countries, thus affecting all analyses.[12] Moreover, the spread of the disease is highly dynamic in both time and space. The virus is transmitted from person to person, with infected persons differing vastly from each other in how much virus they shed, and clusters of cases often occur. There is also considerable transmission heterogeneity. Most transmission is caused by a limited number of superspreading events[1] influenced by human behavior, socio-economic and demographic factors (e.g., household size, multi-generation households), and compliance with control measures.[13,14] Moreover, emerging SARS-CoV-2 variants demonstrate higher transmission rates.[15]

Consequently, with the current lack of rigorous individual-level studies, attempts to quantify the fraction of global COVID-19 deaths attributed to ambient air pollution is premature.[16,17] The early studies motivated calls for individual level (cohort) data with careful control for relevant

confounders and underlined the importance of rigorous research on air pollution and COVID-19. Hence, HEI and other institutes are launching new studies that address some of the concerns from earlier published research.

New HEI Research Underway

HEI expects to make a valuable contribution to this rapidly expanding new field of research with the launch of five new studies funded after rigorous competition under Request for Applications 20-1B, "Air Pollution, Covid-19, and Human Health." These one- and two-year studies are now underway (see Table 1). These studies in the United States, Europe, and East Asia will focus on two key areas, namely, effects of air pollution exposure on COVID-19 disease course, while taking into account race, ethnicity, and socioeconomic status (susceptibility), and evaluation of air quality improvements due to lockdowns (accountability).

Susceptibility

Zorana Andersen of the University of Copenhagen and colleagues will investigate whether long- and short-term exposure to several common air pollutants increases the risk of COVID-19 (i.e., incidence, hospitalization, and mortality). They also plan to identify the most susceptible groups by socioeconomic status, ethnicity, and comorbidities. They will leverage a large and detailed nationwide dataset of more than three million adults in Denmark.

Michael Kleeman of the University of California, Davis and colleagues will study the chronic and acute effects of air pollution exposure on COVID-19 incidence, mortality, and long-term complications, including onset of disease formation. They will use a large medical records database in Southern California from Kaiser Permanente, with assessments at both the neighborhood and individual levels.

Jeanette Stingone of Columbia University and colleagues will conduct a retrospective evaluation of the interactions between long-term exposure to air pollution and neighborhood vulnerability to adverse COVID-19 outcomes. They will investigate both single and multipollutant air pollution exposures in relation to COVID-19 hospitalization, inpatient length of stay, ICU admission, ventilator use, and death among a racially diverse population in New York City.

Cathryn Tonne of ISGlobal and colleagues will test whether long- or short-term exposure to air pollution increases the risk of COVID-19 hospital admissions or mortality and identify vulnerable subgroups among 6 million residents of Catalonia, Spain. They will link air pollution exposures to residents' individual addresses, with inpatient and outpatient electronic medical records.

Accountability

Kai Chen of Yale University and colleagues will conduct a

Table 1. New HEI-funded epidemiologic studies examining the intersection of air pollution exposure and COVID-19.[a]

Principal investigator and institution	Location	Study design and population	Strengths
Andersen, Zorana; University of Copenhagen	Denmark	Cohort study. Population-based nation-wide cohort of all Danes age 40 years or older (N > 3 million).	Large national population-wide cohort with rich individual-level data, incidence data and fine-resolution exposure data.
Chen, Kai; Yale University	China, Germany, Italy, and the United States.	Time series study. Populations in 4 countries: China (Jiangsu Province), Italy, Germany, and the U.S (California).	Use of difference-in-differences analysis and inclusion of countries from different world regions.
Kleeman, Michael; University of California—Davis	California, United States	Cohort study. Population-based cohort using a medical records database in Southern California from Kaiser Permanente.	Detailed array of exposure estimates and a multi-pollutant focus, use of individual level data, and focus on both short- and long-term health effects.
Stingone, Jeannette; Columbia University	New York City, United States	Cohort study. Population-based cohort using harmonized electronic health records in NYC.	Detailed datasets for a very diverse population and an innovative approach to studying disparities and chronic air pollution exposures as risk factors in COVID-19 morbidity and mortality.
Tonne, Cathryn; ISGlobal	Catalunya, Spain	Cohort study. Population based region-wide cohort of 6 million residents of Catalonia, Spain.	Population-based cohort with rich individual-level data and fine-resolution exposure data.

[a]more detailed information is available at www.healtheffects.org/research/ongoing-research.

multi-country study (in China, Germany, Italy, and the United States) to evaluate whether changes in mortality are associated with changes in ambient NO_2 and $PM_{2.5}$ levels before, during, and after pandemic lockdowns, and propose to disentangle the short-term effects of NO_2 versus $PM_{2.5}$ on mortality.

Conclusions

The extraordinary changes taking place during the COVID-19 pandemic offer substantial opportunities for innovative air pollution and health studies that could significantly advance understanding on this important public health topic. In pursuing those opportunities, we caution that there should be no compromise to rigorous research and statistical design, data quality assurances, or independent peer review. Moreover, policy actions are best not based on results from one or even a handful of studies, but rather must be informed by a body of evidence that demonstrates some consistency of findings. Meanwhile, the global burden of disease from air pollution is very large and there is now broad expert consensus that exposure to air pollution causes a range of adverse health effects, providing ample evidence for governments to act to reduce air pollution. If effects of air pollution on COVID-19 have been established more clearly, there will be a further public-health-driven stimulus to pursue air quality policies. **em**

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References

1. Brunekreef, B.; Downward, G.S.; Forastiere, F; Gehring, U; Heederik, D.J.J.; Hoek, G., Koopmans, M.P.; Smit, L.A.M.; Vermeulen, R.C.H. Air pollution and COVID-19. Including elements of air pollution in rural areas, indoor air pollution and vulnerability and resilience aspects of our society against respiratory disease, social inequality stemming from air pollution. Study for the committee on Environment, Public Health and Food Safety, Policy Department for Economic, Scientific and Quality of Life Policies, European Parliament, Luxembourg, 2021. https://www.europarl.europa.eu/RegData/etudes/STUD/2021/658216/IPOL_STU(2021)658216_EN.pdf (accessed 2021-04-12).
2. European Environment Agency (EEA). Air quality in Europe, 2020 report (EEA Rep. 2020).
3. Liu, F.; Wang, M.; Zheng, M. Effects of COVID-19 lockdown on global air quality and health; *Sci. Total Environ.* 2021, *755*(Pt 1), 142533; DOI: 10.1016/j.scitotenv.2020.142533.
4. Venter, Z.S.; Aunan, K.; Chowdhury, S.; Lelieveld, J. COVID-19 lockdowns cause global air pollution declines. *Proc. Natl. Acad. Sci U.S.A.* 2020, *117* (32), 18984-18990; DOI: 10.1073/pnas.2006853117.
5. U.S. EPA. Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (Final Report, Jan 2016); U.S. Environmental Protection Agency, Washington, DC; EPA/600/R-15/068, 2016; https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879 (accessed 2021-04-12).
6. U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019); U.S. Environmental Protection Agency, Washington, DC; EPA/600/R-19/188, 2019; https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534 (accessed 2021-04-12).
7. Heederik, D.J.J.; Smit, L.A.M.; Vermeulen, R.C.H. Go slow to go fast: A plea for sustained scientific rigor in air pollution research during the COVID-19 pandemic; *Eur. Respir. J.* 2020, *56*, 2001361; DOI: 10.1183/13993003.01361-2020.
8. Villeneuve, P.J., Goldberg, M.S. Methodological Considerations for Epidemiological Studies of Air Pollution and the SARS and COVID-19 Coronavirus Outbreaks; *Environ. Health Perspect.* 2020, *128* (9), 95001; DOI: 10.1289/EHP7411.
9. Wu, X.; Nethery, R.C.; Sabath, M.B.; Braun, D.; Dominici, F. Exposure to air pollution and COVID-19 mortality in the United States: A nationwide cross-sectional study; *Sci. Adv.* 2020, *6*, eabd4049; DOI: 10.1126/sciadv.abd4049.
10. Liang, D.; Shi, L.; Zhao, J.; Liu, P.; Sarnat, J.A.; Gao, S.; Schwartz, J.; Liu, Y.; Ebelt, S.T.; Scovronick, N.; Chang, H.H. Urban Air Pollution May Enhance COVID-19 Case-Fatality and Mortality Rates in the United States. *Innovation*, 2020, 100047; DOI: 10.1101/2020.05.04.20090746.
11. Bowe, B.; Xie,Y.; Gibson, A.K.; Cai, M.; van Donkelaar, A.; Martin, R.V.; Burnett, R.; Al-Aly, Z. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: Cohort study; *Environ. Int.* 2021, *154*, 106564; DOI: 10.1016/j.envint.2021.106564.
12. Copat, C.; Cristaldi, A.; Fiore, M.; Grasso, A.; Zuccarello, P.; Signorelli, S.S.; Conti, G.O.; Ferrante, M. The role of air pollution (PM and NO2) in COVID-19 spread and lethality: A systematic review; *Environ. Res.* 2020, *191*, 110129; DOI: 10.1016/j.envres.2020.110129.
13. Chang, S.; Pierson, E.; Koh, P.W.; Gerardin, J.; Redbird, B.; Grusky, D.; Leskovec, J. Mobility network models of COVID-19 explain inequities and inform reopening; *Nature* 2021, *589*, 82-87; DOI: 10.1038/s41586-020-2923-3.
14. Samet, J.M.; Prather, K.; Benjamin, G.; Lakdawala, S.; Lowe, J.; Reingold, A.; Volckens, J.; Marr, L.C. Airborne Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): What We Know; *Clin. Infect. Dis.* 2021, ciab039; DOI: 10.1093/cid/ciab039.
15. van Oosterhout, C.; Hall, N.; Ly, H.; Tyler, K.M. COVID-19 evolution during the pandemic – Implications of new SARS-CoV-2 variants on disease control and public health policies; *Virulence* 2021, *12* (1), 507-508; DOI: 10.1080/21505594.2021.1877066.
16. 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, *116* (14), 2247-2253; DOI: 10.1093/cvr/cvaa288.
17. Venter, Z.S.; Aunan, K.; Chowdhury, S.; Lelieveld, J. Air pollution declines during COVID-19 lockdowns mitigate the global health burden; *Environ. Res.* 2021, *192*, 110403; DOI: 10.1016/j.envres.2020.110403.