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COMMENTARY BY THE
HEI REVIEW COMMITTEE

# Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)

Tonne et al.

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# Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)

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with a Commentary by the HEI Review Committee

Research Report 220

Health Effects Institute

Boston, Massachusetts

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# CONTENTS


About HEI iii

Contributors iv

**COMMENTARY** *by the Review Committee* 1

INTRODUCTION 1

SCIENTIFIC BACKGROUND 1

SUMMARY OF APPROACH AND METHODS 2
- Study Objectives 2
- Methods and Study Design 2
  - Study Population 2
  - Exposure Assignment 3
  - Main Epidemiological Analyses 3

SUMMARY OF KEY FINDINGS 3
- Cohort and Exposure Characteristics 3
- Epidemiological Results 5
  - Effects of Long-Term Exposure to Air Pollution on COVID-19 Outcomes 5
  - Effects of Short-Term Exposure to Air Pollution on COVID-19 Outcomes 5
  - Modification of the Effects of Long-Term Exposure to Air Pollution on COVID-19 Outcomes 5
  - Comparing COVID-19 to Influenza and Pneumonia 5

HEI REVIEW COMMITTEE'S EVALUATION 6
- Evaluation of Study Design, Datasets, and Epidemiological Approaches 6
- Discussion of the Findings and Interpret10ation 7
- Conclusions 8

ACKNOWLEDGMENTS 8

REFERENCES 8

Abbreviations and Other Terms 10

HEI Board, Committees, and Staff 11

# ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- identifies the highest-priority areas for health effects research
- competitively funds and oversees research projects
- provides an intensive independent review of HEI-supported studies and related research
- integrates HEI's research results with those of other institutions into broader evaluations
- communicates the results of HEI's research and analyses to public and private decision-makers.

HEI typically receives balanced funding from the US Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 380 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 2,500 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters, annual conferences, and presentations to legislative bodies and public agencies.

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# Research Report 220, *Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)*, C. Tonne et al.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19*) pandemic created unprecedented conditions that lent themselves to timely and novel air pollution research exploring key policy-relevant questions. As described in the Preface to this report, HEI issued Request for Applications 20-1B: "Air Pollution, COVID-19, and Human Health" to solicit applications for research on novel and important aspects of the intersection of exposure to air pollution and COVID-19 health outcomes. In particular, HEI was interested in studies that considered whether populations who had been exposed to higher levels of air pollution were at greater risk of mortality from COVID-19 compared with others, and whether the potential associations between air pollution and COVID-19 outcomes differed by race, ethnicity, or measures of socioeconomic status (SES).

In response to the Request for Applications, Dr. Cathryn Tonne of the Barcelona Institute for Global Health (ISGlobal) submitted an application to HEI titled "Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)." Dr. Tonne and colleagues proposed to investigate whether long- or short-term exposure to certain forms of air pollution — fine particulate matter <2.5 μg/m$^3$ in aerodynamic diameter ($PM_{2.5}$), coarse particulate matter <10 μg/m$^3$ in aerodynamic diameter ($PM_{10}$), nitrogen dioxide ($NO_2$), and ozone ($O_3$) — increased the risk of COVID-19–related hospitalization and mortality among the adult population of Catalonia, Spain. HEI's Research Committee recommended funding Dr. Tonne's study because it thought that the proposal was strong, with little risk of outcome measurement bias, excellent exposure data, and good information to capture the SES characteristics of cohort participants.

This Commentary provides the HEI Review Committee's independent evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

## SCIENTIFIC BACKGROUND

Research from toxicological, clinical, and population health studies have linked air pollution exposure with the risk of acute lower respiratory infections (i.e., bronchitis, bronchiolitis, and pneumonia), influenza, and respiratory syncytial virus (Monoson et al. 2023; Thurston et al. 2017). Research on such respiratory infections is complicated, however, and has shown mixed results regarding the role of air pollution (HEI 2022; Loaiza-Ceballos et al. 2022).

Some early epidemiological studies suggested potential associations between air pollution and COVID-19 (Bashir et al. 2020; Travaglio et al. 2021; Wu et al. 2020), but the potential for biased results was high, partly because early in the pandemic it was difficult to have reliable data that identified people who were infected or seriously ill with COVID-19, and because accuracy and availability of testing varied over space and time. Varying degrees of severity and duration of (and inability to control for potential compliance with) lockdown policies also had important implications for estimating potential exposures to ambient air pollution. Specifically, lockdown policies were associated generally with atypical emission patterns (i.e., decreased levels) from cars and other sources, and atypical daily mobility patterns for most people.

Results from early studies were difficult to compare and generalize because of differences in study designs, approaches to exposure estimation (i.e., short-term vs. long-term exposures), and outcome definitions (e.g., disease incidence, prevalence, severity, or case fatality rates). Moreover, nearly all of the first studies published on this topic were based on cross-sectional analyses or ecological study designs (Bashir et al. 2020; Coker et al. 2020; Cole et al. 2020; Konstantinoudis et al. 2021; Liang et al. 2020; Travaglio et al. 2021; Wu et al. 2020), which evaluated the association of area-based estimates of pollution (i.e., averaged across counties rather than estimated for each individual) with area-based rates of disease incidence or mortality, for which individual-level risks could not be derived.

Three early reviews (Copat et al. 2020; Katoto et al. 2021; Villeneuve and Goldberg 2020) all concluded that although the early body of evidence indicated that both short- and

Dr. Cathryn Tonne's 2-year study, "Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain," began in May 2021. Total expenditures were $500,000. The draft Investigators' Report from Tonne and colleagues was received for review in June 2023. A revised report, received in December 2023, was accepted for publication in January 2024. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and clarify issues in both the Investigators' Report and the Review Committee's Commentary.



* A list of abbreviations and other terms appears at the end of this volume.

long-term exposure to air pollution could affect COVID-19 outcomes, all studies to date had moderate to high overall risks of bias that precluded them from providing any firm conclusions about potential causal associations.

When Dr. Tonne's study began, the available literature included little high-quality evidence. Given the many design limitations of the previous studies on this topic, it was important to conduct this study, which aimed to address many of them.

## SUMMARY OF APPROACH AND METHODS

### STUDY OBJECTIVES

The overarching purpose of Dr. Tonne's study was to quantify associations between long- or short-term exposure to air pollution and the risk of COVID-19–related hospital admissions or mortality in Catalonia, Spain, and to identify any populations who had greater associations with exposures than others. Specifically, the investigators aimed to evaluate whether:

1. long-term exposure to air pollution was associated with COVID-19–related hospital admission or mortality in the general population
2. short-term exposure to air pollution was associated with COVID-19–related hospital admission in the general population and whether the association differed by individual- and area-level factors
3. the influence of long-term exposure to air pollution on COVID-19 outcomes differed according to individual- and area-level factors
4. the influence of long-term air pollution exposure on COVID-19 hospital admissions differed from that for respiratory infections not due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

Briefly, the investigators created a cohort that covered nearly the full adult population of Catalonia in 2015 (a total of 4.6 million people) by linking records from medical and population registries, with follow-up to December 31, 2020. Exposures at residential addresses were estimated using newly developed spatiotemporal models of several pollutants at a spatial resolution of 250 meters. In their main analyses, Tonne and colleagues estimated associations between the air pollution exposure and several health outcomes, including COVID-19–related hospital admissions, indicators of disease severity, and deaths. The datasets and statistical approaches used in these analyses are described in greater detail in the following sections.

### METHODS AND STUDY DESIGN

#### Study Population

The main study cohort included all individuals 18 years and older who were registered in the Catalan public health system in 2015 and were still alive and residing in Catalonia on March 1, 2020. Participants were followed until the end of December 2020, which is before the start of public vaccinations in Spain. The cohort was compiled by linking the Catalan Central Registry of Insured Persons (which included information on age, sex, individual-level income group, and individual-level health risk group) with administrative databases of primary care, urgent care, and acute hospital discharges (which included information on comorbidities, hospitalizations, tobacco smoking status, and body mass index). An income group variable (low, medium, and high) was based on the copayment system for drug dispensations, which depends largely on income. A health risk group variable (which has four categories) is a validated index that captures patient comorbidities (Monterde et al. 2020).

Tonne and colleagues also linked many contextual covariates at several different spatial scales to cohort participants' residential addresses. For example, they created an urbanicity index that indicated whether the participant lived in a city, a town or suburb, or a rural area. They also created a deprivation index, calculated the percentage of non-Spanish residents, and then computed the Gini index (a marker of income inequality across a population) at the census tract level ($N$ = 5,038, median area 0.13 km$^2$). They assigned a small area socioeconomic index at the scale of primary care service areas ($N$ = 374, median area 14 km$^2$). They calculated the average weekly proportion of positive polymerase chain reaction (PCR) and rapid antigen tests to diagnose COVID-19 infection aggregated to healthcare management areas ($N$ = 43, median area 389 km$^2$). These proportions of positive tests were meant to estimate both the number of infected people in the local area and the potential availability and accessibility of testing. As a final contextual covariate, they calculated the distance from each participant's address to the nearest primary healthcare unit (in meters) as a surrogate for access to the public healthcare system.

The cohort was also linked to the Acute Respiratory Infections Sentinel Surveillance System in Catalonia, which includes information on PCR and rapid antigen test results, and nursing home residence status. COVID-19 diagnoses were defined as a positive PCR or rapid antigen test, or a clinical diagnosis of COVID-19. The investigators defined COVID-19–related hospitalization as an admission for any cause occurring within 30 days of a person's first ever COVID-19 diagnosis. As indicators of disease severity for each COVID-19–related hospital admission, they counted the length of hospital stay (in days) and identified patients who were admitted to an intensive care unit (ICU). Similarly, they defined COVID-19–related deaths as death from any cause occurring within 30 days of a first COVID-19 diagnosis. They also identified hospital admissions for influenza or pneumonia specifically, as well as for all lower respiratory tract infections (including influenza and pneumonia). Analyses for Aim 2 were restricted to individuals diagnosed with COVID-19. Main analyses for Aims 1, 2, and 3 excluded individuals who were living in nursing homes.

### Exposure Assignment

Tonne and colleagues developed exposure models of daily and annual average $NO_2$, $PM_{2.5}$, $PM_{10}$, air temperature, and maximum 8-hour average $O_3$ at a spatial resolution of 250 m for the period 2018–2020 covering the territory of Catalonia (Milà et al. 2023). Briefly, the models were developed with numerous data inputs, including observations from ground-based monitoring networks, satellite-derived aerosol optical depth (a measure of aerosols in the atmosphere), normalized difference vegetation index (a measure of green vegetation on the ground), and light at night, surface temperature estimates, atmospheric composition (produced by the Copernicus Atmosphere Monitoring Service), and variables that describe road density, locations of point sources of pollution, and land use. The investigators assigned these exposure estimates to the participants' residential addresses at the beginning of 2021 (the most representative address available for the study period) or the last address available.

As outlined in the **Commentary Table**, the investigators used exposure data from 2019 for the main analyses for Aims 1 and 3 (i.e., analyses on long-term exposures) because those exposures preceded the COVID-19 outcomes. In the sensitivity analyses for those aims, they also used data from 2018 and 2019. For Aim 2, they used daily estimates from 2020 because the focus was on associations with short-term exposures (i.e., days preceding the COVID-19 outcomes). For Aim 4, they used exposure data from 2018, the year before the lower respiratory infection hospital admissions occurred (before the start of the pandemic).

### Main Epidemiological Analyses

The Commentary Table summarizes the various outcomes examined and exposures considered for the study's four aims.

To address Aim 1, Tonne and colleagues used Cox proportional hazard models to examine associations between annual mean air pollution exposures and COVID-19–related hospital admission, ICU admission, and death among all cohort participants. They used negative binomial regression models to estimate the associations between annual mean exposures and length of hospital stay among hospitalized individuals. Their main model adjusted for age, sex, tobacco smoking status, individual income, health risk group, and many contextual covariates described earlier (i.e., rural/urban indicator, area deprivation index, Gini index, small area socioeconomic index, average weekly proportion of positive PCR and rapid antigen tests in the local healthcare management area, and distance to the nearest primary healthcare unit). They used single- and two-pollutant models to assess these outcomes.

To address Aim 2, the investigators used Cox proportional hazard models to examine associations between daily air pollution exposures and hospital admission among cohort participants diagnosed with COVID-19. Given that hospital admission might be related to air pollution exposure on that day (i.e., lag0) or on previous days (lag>0), they also used distributed lag nonlinear models that accounted for exposures up to 7 days preceding each hospital admission. The main epidemiological models here included the same covariates as above, with the addition of temperature and annual average air pollution in 2019. Models were stratified by epidemic wave. The investigators identified two waves, with June 21, 2020, as the cut point between them. They also conducted stratified analyses to assess possible effect modification by clinical and sociodemographic characteristics.

To address Aim 3, the investigators evaluated whether the combined effects of experiencing long-term exposures to relatively high concentrations of air pollution and having one of several potential indicators of vulnerability (e.g., lower SES or pre-existing health conditions) were associated with elevated risk of COVID-19–related hospital admission as compared to other groups of the population. Here, they considered models that explored interaction on the additive scale (i.e., whether the combined effect of exposure and vulnerability was larger than the *sum* of these individually) and on the multiplicative scale (i.e., whether the combined effect was larger than the *product* of these individually).

To address Aim 4, the investigators used Cox proportional hazard models to examine associations between annual mean air pollution exposures and (1) hospital admission for influenza or pneumonia and (2) hospital admission for all acute lower respiratory infections (including influenza and pneumonia).

Overall, the investigators explored many additional models to evaluate the sensitivity of their results by adjusting for additional covariates. Details of these analyses can be found in the Investigators' Report.

## SUMMARY OF KEY FINDINGS

### COHORT AND EXPOSURE CHARACTERISTICS

Although the study cohort included about 4.6 million adults, the number varied based on different inclusion and exclusion criteria for the analyses to address each aim (see Commentary Table and Investigators' Report Table 3). The models for $NO_2$ and $O_3$ had very good model performance (i.e., mean overall $R^2$ for 2018–2020 of 0.78 and 0.87, respectively), whereas the models for $PM_{2.5}$ and $PM_{10}$ performed somewhat

**Commentary Table**. Summary of Health Outcomes and Exposures According to Study Aims

| Study Aim | Health Outcomes | Exposure | Study Population |
|---|---|---|---|
| **Aim 1**: Evaluate whether long-term exposure to air pollution is associated with COVID-19–related hospital admission or mortality in the general population | Hospital admission for any cause occurring within 30 days of the first COVID-19 diagnosis<br>Hospital admission for any cause occurring during the 10 days before the first COVID-19 diagnosis<br>Death by any cause occurring within 30 days of first COVID-19 diagnosis<br>ICU admission (for each COVID-19–related hospital admission, was patient admitted to the ICU or not)<br>Length of hospital stay for each COVID-19–related hospital admission, in days | Annual average (2019) estimates for $NO_2$, $PM_{2.5}$, $PM_{10}$, and 8-hr $O_3$ warm season | All individuals 18 years and older registered in the public health system in 2015 and who were alive and residing in Catalonia on March 1, 2020<br>Excluded individuals living in nursing homes<br>After exclusions, *N* = 4,639,184 |
| **Aim 2**: Evaluate whether short-term exposure to air pollution is associated with COVID-19–related hospital admission following COVID-19 diagnosis and whether there were vulnerable subgroups | Hospital admission for any cause occurring within 30 days of the first COVID-19 diagnosis | Daily average (2020) estimates for $NO_2$, $PM_{2.5}$, $PM_{10}$, and 8-hr $O_3$ warm season | Subset of individuals from Aim 1 diagnosed with COVID-19 between March 1 and December 31, 2020<br>Restricted to people not living in nursing homes or diagnosed in primary care<br>After exclusions, *N* = 240,902 |
| **Aim 3**: Evaluate whether the influence of long-term exposure to air pollution on COVID-19–related hospital admission differed according to individual-level socioeconomic and demographic factors, comorbidities, and area-level socioeconomic factors | Hospital admission for any cause occurring within 30 days of the first COVID-19 diagnosis<br>Hospital admission for any cause occurring during the 10 days before the first COVID-19 diagnosis | Annual average (2019) estimates for $NO_2$, $PM_{2.5}$, and $PM_{10}$<br>Note: $O_3$ not included in these analyses due to a null association with hospital admissions in Aim 1 | Same as Aim 1<br>After exclusions, *N* = 4,639,184 |
| **Aim 4**: Compare the influence of long-term air pollution exposure on hospital admissions for COVID-19 with those from respiratory infections not due to SARS-CoV-2 infection | Hospital admission for any cause occurring within 30 days of the first COVID-19 diagnosis<br>Hospital admission for pneumonia and influenza<br>Hospital admission for lower respiratory infection | Annual average (2018) estimates for $NO_2$, $PM_{2.5}$, $PM_{10}$, and 8-hr $O_3$ warm season | All individuals 18 years and older registered in the public health system in 2015 and who were alive and residing in Catalonia on March 1, 2019<br>After exclusions, *N* for influenza and pneumonia as main outcome = 4,708,849; *N* for lower respiratory infections as main outcome = 4,681,207 |

less well (i.e., mean overall $R^2$ for 2018–2020 = 0.59 and 0.63, respectively; Investigators' Report Appendix Table A3, available on the *HEI Website*). Mean estimates of annual exposures (and standard deviations) to $NO_2$, $PM_{2.5}$, $PM_{10}$, and $O_3$ in 2019 for the full cohort were 26.2 (10.3), 13.9 (2.2), 22.4 (3.0), and 91.6 (8.2) μg/m$^3$, respectively (Investigators' Report Table 5). Correlations between short- and long-term exposures were low to modest (ranging from 0.10 to 0.55).

## EPIDEMIOLOGICAL RESULTS

### Effects of Long-Term Exposure to Air Pollution on COVID-19 Outcomes

In analyses for Aim 1, Tonne and colleagues reported elevated risks of COVID-19–related outcomes associated with long-term (annual mean) exposures to all pollutants except $O_3$. Such associations were observed in both single- and multipollutant models (see **Commentary Figure** and Investigators' Report Table 6). In single-pollutant models per interquartile range (IQR) increase in exposure to $NO_2$ (16.1 μg/m$^3$), they found higher risks for hospitalization (hazard ratio [HR] 1.25), ICU admission (HR 1.42), death (HR 1.18), and length of hospital stay (incidence rate ratio [IRR] 1.06). In equivalent models per IQR increase in exposure to $PM_{2.5}$ (3.2 μg/m$^3$), they found elevated risks for hospitalization (HR 1.19), ICU admission (HR 1.16), death (HR 1.13), and length of hospital stay (IRR 1.06). Per IQR increase in exposure to $PM_{10}$ (4.2 μg/m$^3$), they found elevated risks for hospitalization (HR 1.21), ICU admission (HR 1.23), death (HR 1.14), and length of hospital stay (IRR 1.06). They found that higher exposures to $O_3$ were associated with lower risks for all four outcomes. In two-pollutant models, associations between exposure and the various outcomes generally remained positive; in some cases, the associations were weaker, and in others, the risk estimates were increased. In particular, they found increased risks of COVID-19–related ICU admission associated with $O_3$ exposures when adjusting for $NO_2$ (i.e., HR 1.10).

### Effects of Short-Term Exposure to Air Pollution on COVID-19 Outcomes

In analyses for Aim 2, Tonne and colleagues reported that higher short-term exposures to $NO_2$, $PM_{2.5}$, and $PM_{10}$ were associated with elevated risks for COVID-19–related hospital admissions during the second wave. Specifically, cumulative exposures to an IQR increase in $NO_2$ up to 7 days preceding the event were associated with increased risks of hospital admissions ranging from HR 1.08–1.15 (Investigators' Report Appendix Table A11). For $PM_{2.5}$ and $PM_{10}$, the risks for hospitalizations associated with exposures up to 7 days preceding the event ranged from HR 1.06–1.09 and 1.04–1.09, respectively. For $O_3$, Tonne and colleagues reported inverse associations ranging from HR 0.83–0.91.

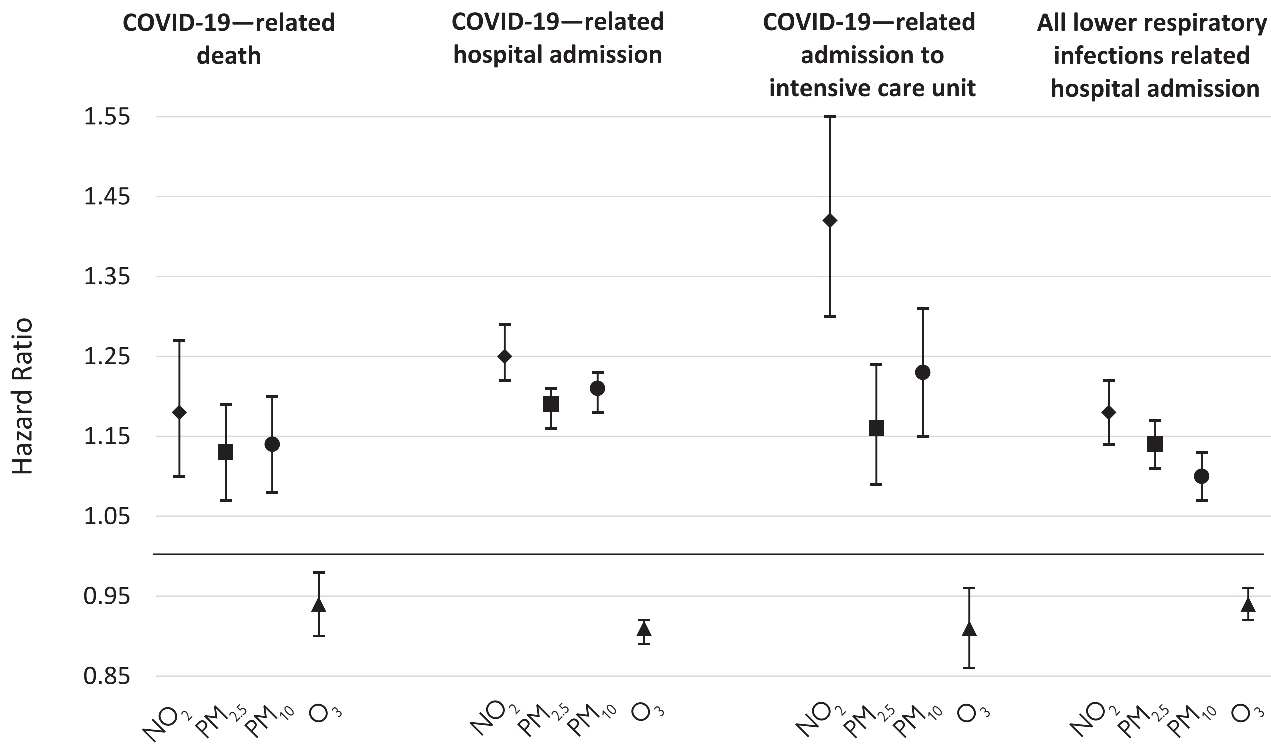
The investigators found only some evidence of associations between short-term exposures to any of the pollutants and risk of hospital admissions during the first wave (e.g., same-day exposure to $NO_2$ and the cumulative exposure to $NO_2$ up over the previous 2 days were associated with hospitalization). Additionally, they found no evidence of effect modification by sociodemographic characteristics or comorbidities in the associations between short-term exposure to air pollution and COVID-19–related hospital admission (Figure 5).

### Modification of the Effects of Long-Term Exposure to Air Pollution on COVID-19 Outcomes

In analyses for Aim 3, Tonne and colleagues examined whether the combined effects of exposures to air pollution and selected characteristics of the population (e.g., age, sex, SES, pre-existing health conditions) were associated with increased risk of COVID-19–related hospital admission. Here they reported that interactions on the multiplicative scale were difficult to interpret and that those on the additive scale provided more consistent, biologically plausible results. The most consistent findings for both scales were related to SES, for which the combination of high exposure to air pollution (i.e., $NO_2$, $PM_{2.5}$, or $PM_{10}$) and lower SES (measured at both the individual and contextual level) was associated with a higher risk of COVID-19–related hospital admission (Investigators' Report Table 7 and Table 8). They also reported that the combined effects of having a chronic comorbidity (i.e., diabetes, hypertension, and COPD) and being exposed to relatively high concentrations of air pollution was not associated with greater risk of severe COVID-19 as compared to other groups (Investigators' Report Tables 7 and 8, and Appendix Table A14).

### Comparing COVID-19 to Influenza and Pneumonia

In analyses for Aim 4, Tonne and colleagues investigated whether associations between long-term exposure to air pollution and COVID-19–related hospital admissions differed from those for non-COVID-19 respiratory infections (not during the pandemic). Here, they reported that, in single-pollutant models, exposures to $NO_2$, $PM_{2.5}$, and $PM_{10}$ were associated with increased risks of hospital admissions for influenza or pneumonia and for lower respiratory infections in general. Specifically, admissions for all lower respiratory infections (including influenza and pneumonia) were associated with exposure to $NO_2$ (HR per IQR [16.4 μg/m$^3$]: 1.18), $PM_{2.5}$ (HR per IQR [2.6 μg/m$^3$]: 1.14), and $PM_{10}$ (HR per IQR [3.9 μg/m$^3$]: 1.10) (Commentary Figure and Investigators' Report Table 9). Admissions for all lower respiratory infections were associated negatively with exposure to $O_3$ in single-pollutant models (HR per IQR [10.3 μg/m$^3$]: 0.94), but positively in two-pollutant models adjusted for $NO_2$ (HR 1.04). Overall, the estimates of risk for hospitalization for respiratory infections were slightly lower than those reported for hospitalization for COVID-19, as reported earlier.




**Commentary Figure. Associations between estimated annual average air pollution concentrations and COVID-19–related outcomes among cohort participants.** Data shown are HRs and 95% confidence intervals estimated per IQR increases in 1-year mean exposure, 16.1 μg/m³ for $NO_2$, 3.2 μg/m³ for $PM_{2.5}$, 4.2 μg/m³ for $PM_{10}$, and 10.8 μg/m³ for $O_3$. Results are from the analyses using all available individual- and contextual-level variables (Model 4). (Source: Investigators' Report Tables 5, 6, and 9).

## HEI REVIEW COMMITTEE'S EVALUATION

### EVALUATION OF STUDY DESIGN, DATASETS, AND EPIDEMIOLOGICAL APPROACHES

This study made important contributions to understanding potential associations between exposure to ambient air pollution and severe COVID-19–related health outcomes. In its independent evaluation of the Investigators' Report, the HEI Review Committee identified several strengths of the study design, including the use of large administrative datasets to create the study cohort of 4.6 million participants, the high-quality exposure models developed by the investigators, and the exploration of many sensitivity analyses. Tonne and colleagues explored associations between several COVID-19–related outcomes and exposures to multiple pollutants (i.e., $PM_{2.5}$, $PM_{10}$, $NO_2$, and $O_3$) and found elevated risks for COVID-19 outcomes with all pollutants except $O_3$. Associations were observed with both long-term exposures (i.e., with mortality, hospital admissions, and ICU admissions) and short-term exposures (i.e., with hospital admissions). The investigators also identified groups potentially most vulnerable to air pollution–related COVID-19 outcomes, with SES emerging as the most consistent factor.

The strength of the cohort was related to the linkage of several national-level registers that allowed for inclusion of the full population of Catalonia. Additionally, the datasets included many different indicators of SES, both for individuals and aggregated to several scales of geography ranging from local to regional. The Committee was impressed with the exposure models, which covered the whole study area and had high spatiotemporal resolution. As noted earlier, the models for $NO_2$ and $O_3$ had relatively good model performance. Although the models for $PM_{2.5}$ and $PM_{10}$ did not perform as well as those for $NO_2$ and $O_3$, the Committee still found them acceptable and did not feel that their performance reduced confidence in the results. The Committee noted that the investigators appropriately excluded air pollution data from 2020 in their analyses with longer-term, annual exposures when pandemic-related restrictions on mobility led to decreased emissions from traffic and other sources.

The Committee was also impressed by the thoroughness of the investigation of this topic, with many sensitivity analyses (as evidenced by over 30 pages of additional tables and figures presented in the Appendix). For example, Tonne and colleagues considered the sensitivity of the epidemiological results to exposure estimates averaged over different periods, to adjustment to potential confounders not included in their main models (e.g., comorbidities, other indicators of SES, and tobacco smoking status), and to alternative definitions for the outcomes of interest. It was reassuring to see that the key messages and findings from the main analyses were supported and corroborated by the many additional analyses. The Committee also commends the investigators for considering analyses that explored interactions on both the additive and multiplicative scales.

The Committee noted a few limitations in the study design. For example, the choice of defining deaths as only those occurring within 30 days of a COVID-19 diagnosis might have been too restrictive, especially considering much of the study's focus on the risk of developing a severe case of COVID-19, which might take longer than 30 days. However, the investigators estimated that this definition of COVID-19–related deaths likely captured 85% of the deaths that would have been identified within 90 days, suggesting that the 30-day window is a reasonable compromise between specificity (i.e., including only events truly related to COVID-19) and capturing every potential COVID-19–related death.

Relatedly, all health outcomes examined in the study were restricted to cohort participants' first event as opposed to all possible events experienced by cohort participants. Although this approach is common and acceptable, the Committee wondered if other insights might have been gained if the investigators had explored an approach that included multiple hospital admissions by the same person in some of the analyses. Overall, however, the Committee was very impressed with the datasets and approaches used in these thorough analyses.

## DISCUSSION OF THE FINDINGS AND INTERPRETATION

The Committee noted that the presentation of multipollutant epidemiological models and the exploration of associations between COVID-19 outcomes and both short- and long-term estimates of exposure were key contributions of the study. Most other studies typically have had access to data on only short- or long-term exposure, not both, and many do not have access to such high-quality exposure models for so many pollutants.

The Committee wondered about the comparability of the findings reported here to those reported in other locations. On the one hand, the methods of exposure assessment (i.e., assigning estimates of exposure at a spatial resolution of 250 m to addresses of residence) and the choices of outcome definition were generally similar to those used in other studies of COVID-19 and air pollution. On the other hand, strictness of lockdown policies to prevent spreading of the disease, availability of testing, and hospital capacity (all of which varied throughout the study period) might have been different from conditions in other locations. As such, it is somewhat difficult to compare, for example, rates and risks of COVID-19–related hospitalizations found here with those reported elsewhere. These issues, along with varying availability and accuracy of case ascertainment data between places also pose challenges to comparing results relating to any COVID-19 outcomes between studies conducted in different counties.

Generally, the Committee found the presentation and discussion of results to be thorough, thoughtful, and fair. Although not presented in detail in this Commentary, the many sensitivity analyses generally demonstrated findings consistent with the main analyses and thus supported the robustness of the results. Several of the results, however, were difficult to interpret and understand.

For example, the associations reported between exposures to $O_3$ and the risk of severe COVID-19 outcomes were unexpected and difficult to explain (e.g., exposure to $O_3$ was associated with reduced risks of some outcomes in single pollutant models and with increased risks in two-pollutant models). Some of the challenges to interpreting those results are because the annual average exposures to $O_3$ were highly negatively correlated with those to $NO_2$ (i.e., –0.82) and because of the relatively small fraction of spatial variation captured by the $O_3$ model. Additionally, the Committee agreed with the investigators that there were also challenges to interpreting and explaining some of the differences in results observed between the two waves of the pandemic. Between waves, there were differences in the strictness and duration of lockdown policies (which would have affected daily mobility patterns and potential exposures to air pollution), varying levels of availability and accessibility of testing (which would have affected the likelihood of one testing positive for COVID-19), and different spatiotemporal patterns in health system capacity, all of which might have contributed to the differing findings between waves. Ultimately, the Committee agreed with the investigators that the results from the second wave were likely more generalizable to other locations.

Relatedly, it is somewhat challenging to understand the differences in implications between findings linking air pollution with having a COVID-19 diagnosis (reported elsewhere, e.g., Hernandez Carballo et al. 2022; Marquès and Domingo

2022) versus those presented here linking air pollution with severe COVID-19 outcomes (because one needs to have the former to also have the latter).

Despite some of the findings being difficult to explain or interpret, the results of the main analyses were generally reported clearly, and the findings were robust to the many sensitivity analyses.

## CONCLUSIONS

In summary, this study represents an important contribution to our knowledge about potential associations between exposures to ambient air pollution and the risk of severe cases of COVID-19. The study design used very high-quality datasets, including a population-based cohort with many individual and contextual characteristics, and exposure models for several pollutants with very good spatiotemporal resolution. The study demonstrated elevated risks for severe COVID-19 outcomes associated with daily and annual exposures to $NO_2$, $PM_{2.5}$, and $PM_{10}$ in this population-based cohort of 4.6 million adults, with opposing results for $O_3$. The results also suggested that individuals with lower individual- and area-level SES had the strongest associations with long-term exposures to $NO_2$, $PM_{2.5}$, and COVID-19–related hospitalization.

The associations reported here between long-term exposures to $PM_{2.5}$ and COVID-19–related hospital admissions were generally consistent with those reported in cohort studies based in Ontario, Canada (Chen C et al. 2022), and in California, USA (Chen Z et al. 2022). Associations between long-term exposures to air pollution and COVID-19–related deaths have been more inconsistent in the literature and therefore more difficult to compare, and there is little other evidence on associations between short-term exposures and COVID-19–related outcomes.

Ultimately, this study has provided important evidence that exposures to ambient air pollution were associated with severe COVID-19 outcomes, as well as with hospital admissions for influenza, pneumonia, and for lower respiratory infections generally. These findings therefore have relevance not just for the COVID-19 pandemic, but for potential future epidemics of pathogens that cause respiratory infections.

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## REFERENCES

Bashir MF, Ma BJ, Bilal, Komal B, Bashir MA, Farooq TH, et al. 2020. Correlation between environmental pollution indicators and COVID-19 pandemic: A brief study in Californian context. Environ Res 187:109652; doi:10.1016/j.envres.2020.109652.

Chen C, Wang J, Kwong J, Kim J, van Donkelaar A, Martin RV, et al. 2022. Association between long-term exposure to ambient air pollution and COVID-19 severity: A prospective cohort study. CMAJ 194:E693–E700; doi:10.1503/cmaj.220068.

Chen Z, Sidell MA, Huang BZ, Chow T, Eckel SP, Martinez MP, et al. 2022. Ambient air pollutant exposures and COVID-19 severity and mortality in a cohort of patients with COVID-19 in Southern California. Am J Respir Crit Care Med 206:440–448; doi:10.1164/rccm.202108-1909OC.

Coker ES, Cavalli L, Fabrizi E, Guastella G, Lippo E, Parisi ML, et al. 2020. The effects of air pollution on COVID-19-related mortality in Northern Italy. Environ Resour Econ (Dordr) 76:611–634; doi:10.1007/s10640-020-00486-1.

Cole MA, Ozgen C, Strobl E. 2020. Air pollution exposure and COVID-19 in Dutch municipalities. Environ Resour Econ (Dordr) 76:581–610; doi:10.1007/s10640-020-00491-4.

Copat C, Cristaldi A, Fiore M, Grasso A, Zuccarello P, Signorelli SS, et al. 2020. The role of air pollution (PM and $NO_2$) in COVID-19 spread and lethality: A systematic review. Environ Res 191:110129; doi:10.1016/j.envres.2020.110129.

HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution. 2022. Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution. Special Report 23. Boston, MA: Health Effects Institute.

Hernandez Carballo I, Bakola M, Stuckler D. 2022. The impact of air pollution on COVID-19 incidence, severity, and mortality: A systematic review of studies in Europe and North America. Environ Res 215:114155; doi:10.1016/j.envres.2022.114155.

Katoto PDMC, Brand AS, Bakan B, Obadia PM, Kuhangana C, Kayembe-Kitenge T, et al. 2021. Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity, and mortality of COVID-19: A rapid systematic review. Environ Health 20:41; doi:10.1186/s12940-021-00714-1.

Konstantinoudis G, Padellini T, Bennett J, Davies B, Ezzati M, Blangiardo M. 2021. Long-term exposure to air pollution and COVID-19 mortality in England: A hierarchical spatial analysis. Environ Int 146:106316; *https://doi.org/10.1016/j.envint.2020.106316*.

Liang D, Shi L, Zhao J, Liu P, Sarnat JA, Gao S, et al. 2020. Urban air pollution may enhance COVID-19 case fatality and mortality rates in the United States. Innovation (Camb) 1:100047; doi:10.1016/j.xinn.2020.100047.

Loaiza-Ceballos MC, Marin-Palma D, Zapata W, Hernandez JC. 2022. Viral respiratory infections and air pollutants. Air Qual Atmos Health 15:105–114; doi:10.1007/s11869-021-01088-6.

Marquès M, Domingo JL. 2022. Positive association between outdoor air pollution and the incidence and severity of COVID-19. A review of the recent scientific evidences. Environ Res 203:111930; *https://doi.org/10.1016/j.envres.2021.111930*.

Milà C, Ballester J, Basagaña X, Nieuwenhuijsen MJ, Tonne C. 2023. Estimating daily air temperature and pollution in Catalonia: A comprehensive spatiotemporal modelling of multiple exposures. Environ Poll 337:122501; *https://doi.org/10.1016/j.envpol.2023.122501*.

Monoson A, Schott E, Ard K, Kilburg-Basnyat B, Tighe RM, Pannu S, et al. 2023. Air pollution and respiratory infections: The past, present, and future. Toxicol Sci 192:3–14; doi:10.1093/toxsci/kfad003.

Monterde D, Vela E, Clèries M, Garcia-Eroles L, Roca J, Pérez-Sust P. 2020. Multimorbidity as a predictor of health service utilization in primary care: A registry-based study of the Catalan population. BMC Fam Pract 21:39; doi:10.1186/s12875-020-01104-1.

Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. 2017. A joint ERS/ATS policy statement: What constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 49; doi:10.1183/13993003.00419-2016.

Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. 2021. Links between air pollution and COVID-19 in England. Environ Pollut 268:115859; doi:10.1016/j.envpol.2020.115859.

Villeneuve PJ, Goldberg MS. 2020. Methodological considerations for epidemiological studies of air pollution and the SARS and COVID-19 coronavirus outbreaks. Environ Health Perspect 128:095001; doi:10.1289/EHP7411.

Wu X, Braun D, Schwartz J, Kioumourtzoglou MA, Dominici F. 2020. Evaluating the impact of long-term exposure to fine particulate matter on mortality among the elderly. Sci Adv 6:eaba5692; doi:10.1126/sciadv.aba5692.

# ABBREVIATIONS AND OTHER ITEMS

| | |
|---|---|
| AOD | aerosol optical depth |
| CI | confidence interval |
| COPD | chronic obstructive pulmonary disorder |
| COVAIR-CAT | COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain |
| COVID-19 | coronavirus disease 2019 |
| DF | degrees of freedom |
| DLNM | distributed lag nonlinear model |
| HR | hazard ratio |
| ICD | International Classification of Diseases |
| ICU | intensive care unit |
| IQR | interquartile range |
| IRR | incidence rate ratio |
| ISGlobal | Barcelona Institute for Global Health |
| LOS | length of stay |
| LRI | lower respiratory infection |
| LST | land surface temperature |
| $NO_2$ | nitrogen dioxide |
| $O_3$ | ozone |
| OR | odds ratio |
| PCR | polymerase chain reaction |
| $PM_{2.5}$ | particulate matter with aerodynamic diameter ≤2.5 µm |
| $PM_{10}$ | particulate matter with aerodynamic diameter ≤10 µm |
| QA | quality assurance |
| RERI | relative excess risk due to interaction |
| RR | relative risk |
| RT-qPCR | reverse transcription-quantitative polymerase chain reaction |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SD | standard deviation |
| SES | socioeconomic status |
| tpp | test positive proportion |

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