HEI
Health Effects Institute

NUMBER 220
SEPTEMBER 2024

RESEARCH REPORT

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

Cathryn Tonne, Otavio Ranzani, Anna Alari, Joan Ballester, Xavier Basagaña, Carlos Chaccour, Payam Dadvand, Talita Duarte, Maria Foraster, Carles Milà, Mark J. Nieuwenhuijsen, Sergio Olmos, Alex Rico, Jordi Sunyer, Antònia Valentín, and Rosa Vivanco

INCLUDES A COMMENTARY BY THE INSTITUTE'S REVIEW COMMITTEE

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with a Commentary by the HEI Review Committee

Research Report 220
Health Effects Institute
Boston, Massachusetts

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Publishing history: This document was posted at *www.healtheffects.org* in September, 2024.

Citation for report:

Tonne C, Ranzani O, Alari A, Ballester J, Basagaña X, Chaccour C, et al. 2024. Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT). Research Report 220. Boston, MA: Health Effects Institute.

 Compositor: David Wade, Virginia Beach, VA. Library of Congress Catalog Number for the HEI Report Series: WA 754 R432.

ISSN 2688-6855 (online)

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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.

ABOUT THIS REPORT

Research Report 220, *Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)*, presents a research project funded by the Health Effects Institute and conducted by Dr. Cathryn Tonne, ISGlobal, Barcelona, Spain, and her colleagues. The report contains three main sections:

The **HEI Statement**, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The **Investigators' Report**, prepared by Tonne and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The **Commentary**, prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses the remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. Outside technical reviewers and a biostatistician first examine the draft report. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who are not involved in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

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PREFACE

HEI's Program on Air Pollution, COVID-19, and Human Health

INTRODUCTION

On January 20, 2020, the US Centers for Disease Control and Prevention (CDC) confirmed the first case of COVID-19 in the United States. On March 20, after more than 118,000 cases in 114 countries and 4,291 deaths, the World Health Organization (WHO) declared a global COVID-19 pandemic, and countries around the world began instituting preventive measures (e.g., lockdowns) to slow the spread of disease. The closing of nonessential businesses in many locations around the world led to reduced emissions of air pollutants from the energy sector and other industries and significantly reduced traffic volumes due to stay-at-home policies.

Although there has been an enormous cost to this pandemic, both human and economic, it created unprecedented conditions that lent 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 or current exposures to air pollution and susceptibility to the effects of COVID-19 infections (Boogaard et al. 2021).

Because of known associations between air pollution and respiratory hospitalizations and mortality, researchers quickly initiated investigations into potential links between air pollution exposure and COVID-19 (Liang et al. 2020; Wu et al. 2020). There were many unique challenges to this task because the context within which we study associations between air pollution and health was altered due to widespread changes to daily life related to the pandemic (e.g., changes in emission sources, behaviors that affect exposures, and healthcare access and use). Furthermore, COVID-19 outcomes are difficult to study due to various factors, including initial lack of testing, inconsistency in diagnoses, and healthcare systems being overloaded. COVID-19 incidence data — and to a lesser extent mortality data — have also been underestimated in all countries, thus affecting all analyses (Copat et al. 2020). Moreover, the spread of the disease has been shown to be highly dynamic both in time and space. Most transmission has been caused by a few superspreading events influenced by human behavior, socioeconomic and demographic factors (e.g., household size and multigeneration households), and compliance with control measures (Chang et al. 2021, Samet et al. 2021).

In May 2020, only 2 months after the WHO declared the COVID-19 outbreak a global pandemic, HEI issued RFA 20-1B that sought to fund studies to investigate potential associations between air pollution, COVID-19, and human health. HEI formulated specific research objectives where it expected to make a valuable contribution to this rapidly expanding new field of research. HEI was interested in applications for studies designed specifically to address the following questions on this topic:

1. **Accountability Research:** What are the effects of the unprecedented interventions implemented to control the COVID-19 pandemic on emissions, air pollution exposures, and human health? Emerging evidence suggested that changes in economic activity and human mobility following government restrictions led to noticeable reductions in pollutant emissions and pollutant concentrations in ambient air — in particular, nitrogen dioxide (NO_2) — in many cities around the world (Ogen 2020; Schiermeier 2020; Zhang et al. 2020).

The observed changes in air quality presented a unique opportunity for accountability research on this "natural experiment." HEI acknowledged that it could be difficult for investigators to find control populations not affected by the interventions; in addition, interventions in various locations occurred during different periods. Moreover, there would be challenges related to the major reorientating of healthcare systems to deal with COVID-19 and accompanying challenges in estimating comparable hospitalization rates and other health outcomes at a time when utilization of healthcare was changed and diagnostic criteria for COVID-19 and respiratory outcomes were also variable across time and space. Studies investigating health effects are needed to account for those kinds of changes.

2. **Susceptibility Factors:** Are individuals or populations who have been chronically or acutely exposed to higher levels of air pollution at greater risk of mortality from COVID-19 compared to those exposed to lower levels of air pollution? Do the potential effects differ by race or ethnicity or by measures of socioeconomic status?

   Limited evidence from the 2002–2004 SARS outbreak indicated a possible association between higher air pollution concentrations and higher-than-expected death rates (Cui et al. 2003; Kan et al. 2005). Early evidence suggested that individuals with existing comorbidities (e.g., diabetes, high blood pressure, or heart and lung diseases) might be more susceptible to the effects of a COVID-19 infection and at higher risk of mortality from COVID-19 (Wang et al. 2020; Yang et al. 2020). There was also evidence that racial and socioeconomic disparities might lead to higher observed risks (Brandt et al. 2020).

   Because exposure to air pollution is also known to contribute to the development of such underlying diseases (Cohen et al. 2017; HEI 2019), air pollution might also increase susceptibility to morbidity and mortality from COVID-19, possibly in ways that we do not fully understand (Conticini et al. 2020).

STUDY SELECTION

HEI established an independent Panel of outside experts to review all applications submitted in response to the RFA. The HEI Research Committee reviewed the Panel's suggestions and recommended five studies for funding to HEI's Board of Directors, which approved funding in December 2020. Members of the Research Committee with any conflict of interest were recused from all discussions and from the decision-making process. This Preface summarizes the five studies, HEI's oversight process, and the review process for the final reports.

OVERVIEW OF THE AIR POLLUTION, COVID-19, AND HUMAN HEALTH STUDIES

HEI expected to make a valuable contribution to this rapidly expanding new field of research with the five studies funded under RFA 20-1B (**Preface Table**).

Zorana Andersen of the University of Copenhagen and colleagues proposed to use a population-based nationwide cohort of 3.7 million Danish adults to investigate whether long-term exposure to air pollution is associated with increased risk of COVID-19-related morbidity and mortality and to identify the most susceptible groups by age, sex, socioeconomic status, ethnicity, and comorbidities.

Kai Chen of Yale University and colleagues proposed to assess the impact of ambient air pollution reduction on mortality during COVID-19 lockdowns in four countries (Germany, Italy, China, and the United States). First, they proposed to evaluate whether changes in mortality are associated with changes in concentrations of NO_2 and $PM_{2.5}$ before, during, and after the lockdown (study period 2015–2020). Next, they proposed to disentangle the short-term effects of NO_2 versus $PM_{2.5}$ on mortality.

Michael Kleeman of the University of California Davis and colleagues proposed to evaluate the chronic and acute effects of air pollution exposure on COVID-19 incidence, mortality, and long-term complications among the approximately 10 million residents of 432 health neighborhoods in Los Angeles, California. First, they planned to use chemical transport and land use regression models to develop chronic and acute daily $PM_{2.5}$, NO_2, and O_3 exposure estimates at multiple spatial resolutions. They then proposed to assess the association between exposure and COVID-19 incidence and mortality between March 16 and September 4, 2020, and with new and exacerbated long-term COVID-19 complications up to 18 months following initial infection.

Jeanette Stingone of Columbia University and colleagues proposed to evaluate the interactions between chronic air pollution exposure and neighborhood vulnerability in relation to adverse COVID-19 outcomes in New York City. They first

Preface Table. HEI's Research Program on Air Pollution, COVID-19, and Human Health

Investigator (institution)	Study Title	Location	Study Design and Population	Theme	Final Report Published
Zorana Andersen (University of Copenhagen)	Long-Term Exposure to Air Pollution and COVID-19 Mortality and Morbidity in Denmark: Who Is Most Susceptible?	Denmark	Cohort Study: Population-based nationwide cohort of all Danes aged 40 years or older (N > 3 million)	Susceptibility	HEI Report 214, 2023
Kai Chen (Yale University)	Effect of Air Pollution Reductions on Mortality During the COVID-19 Lockdown: A Natural Experience Study	China, Germany, Italy, and the United States	Time Series Study: Populations in 4 countries: China (Jiangsu Province), Italy, Germany, and the US (California)	Accountability	Expected Fall 2024
Michael Kleeman (University of California Davis)	Ambient Air Pollution and COVID-19 in California	California, United States	Cohort Study: Population-based cohort using a medical records database in Southern California from Kaiser Permanente	Susceptibility	Expected Spring 2025
Jeanette Stingone (Columbia University)	Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization Outcomes (REACH OUT Study)	New York City, United States	Cohort Study: Population-based cohort using harmonized electronic health records in NYC	Susceptibility	Expected Spring 2025
Cathryn Tonne (ISGlobal)	Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain	Catalonia, Spain	Cohort Study: Population-based regionwide cohort of 6 million residents of Catalonia, Spain	Susceptibility	HEI Report 220, 2024

would use electronic health record data with more than 37,000 COVID-19 patients from five large hospital systems to evaluate single and multipollutant air pollution exposures in relation to COVID-19 hospitalization, inpatient length of stay, ICU admission, ventilator use, and death. Then they would complete a validation study, sampling all patients from four of the hospital systems to ensure the quality of harmonized data.

Cathryn Tonne of ISGlobal and colleagues proposed to assess whether long-term exposure to air pollution increases the risk of COVID-19 hospitalization and mortality in the general population of 5 million people in Catalonia, Spain, and whether short-term exposure to air pollution increases the risk of COVID-19 hospitalization and mortality among the 300,000 people who tested positive for SARS-COV-2 during the study period.

STUDY OVERSIGHT AND REVIEW OF FINAL REPORTS

Members of HEI's Research Committee provided advice and feedback on the study designs, analytical plans, and study progress throughout the duration of the research program. Each study team submitted biannual progress reports. The studies were subject to HEI's special quality assurance procedures that included an audit by an independent audit team (see *www.healtheffects.org/research/quality-assurance*). The five studies commenced in Spring 2021 and final reports are expected to be published in 2023 and 2024. HEI is planning to publish an overall summary and interpretation of the COVID-19 research program once all studies have been reviewed.

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HEI STATEMENT

Synopsis of Research Report 220

Exposure to Air Pollution and Severe COVID-19 Outcomes in Catalonia, Spain

BACKGROUND

Research from toxicological, clinical, and population health studies has linked air pollution exposure with a risk of respiratory infections, influenza, and respiratory syncytial virus. Some early epidemiological studies reported that rates of COVID-19 deaths were higher in areas with higher levels of air pollution, raising the possibility of a link between air pollution and risk of COVID-19 infection or poor outcomes. These early studies had pronounced methodological limitations (e.g., lacking detailed information on individual- and community-level socioeconomic status or challenges to identifying COVID-19 diagnoses accurately) such that the potential for biased results was high. In May 2020, only two months after the World Health Organization declared the COVID-19 outbreak *a global pandemic*, HEI issued Request for Applications 20-1B, soliciting proposals for studies to investigate the potential links between air pollution, COVID-19, and human health. Five studies in various countries were selected, and this Statement highlights a study by Dr. Cathryn Tonne and colleagues at the Barcelona Institute for Global Health (ISGlobal).

What This Study Adds

- This study evaluated associations between exposure to outdoor air pollution and risk of hospital admissions, disease severity, and death related to coronavirus disease 2019 (COVID-19) among 4.6 million adults in Catalonia, Spain.
- Tonne and colleagues reported higher risk of these COVID-19–related outcomes associated with higher short- and long-term exposures to nitrogen dioxide and to fine and coarse atmospheric particles.
- They reported that people who experienced long-term exposures to relatively high concentrations of outdoor air pollution and are characterized as having a lower socioeconomic status had a higher risk of COVID-19–related hospitalization than did others.
- Important strengths of the study include the high quality of the datasets, namely a population-based cohort that included many individual and area characteristics, and exposure models for several pollutants with high spatiotemporal resolution.
- This study provides evidence that both short- and long-term exposures to outdoor air pollution could increase the risk of severe COVID-19 outcomes.

APPROACH

Tonne and colleagues aimed to evaluate whether long- and short-term exposure to outdoor air pollution was associated with COVID-19–related hospital admissions or mortality in Catalonia, Spain, and to identify subgroups of the population at greater risk to the effects of exposure. Briefly, the investigators linked records from medical and population registries to create a population-based cohort that included nearly the full adult population of Catalonia (a total of 4.6 million people), with follow-up from January 1, 2015, to December 31, 2020. Levels of various air pollutants at residential addresses were estimated using newly developed spatiotemporal models for nitrogen dioxide, fine particles (particulate matter <2.5 $\mu g/m^3$ in aerodynamic diameter), coarse particles (particulate matter <10 $\mu g/m^3$ in aerodynamic diameter), and ozone at a spatial resolution of 250 meters. They considered several health outcomes, including COVID-19–related hospital admissions, deaths, and other outcomes indicating disease severity.

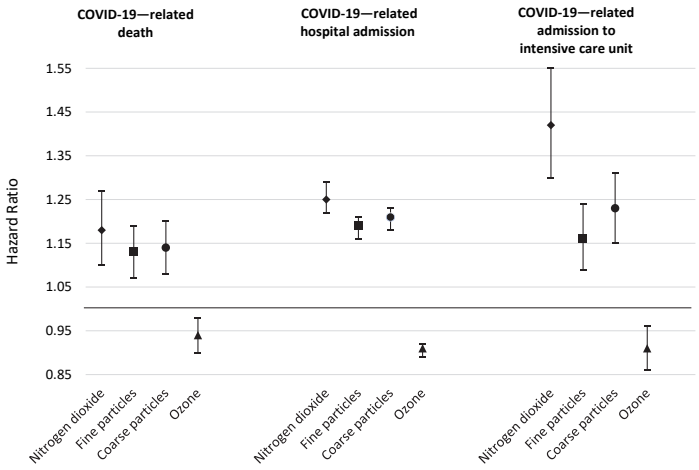
In their main analyses, Tonne and colleagues used Cox proportional hazards models to estimate associations between the air pollution exposure estimates and the selected health outcomes. Their main statistical models adjusted for age, sex, tobacco smoking status, individual income, health risk group, and many area-level variables; some models were also adjusted for daily temperature and wave of the pandemic. They evaluated whether the association between long-term exposures to air pollution and COVID-19–related hospital admissions varied among subgroups defined by age, sex, hypertension, diabetes mellitus, chronic obstructive lung disease, individual income, and neighborhood socioeconomic status. They also explored many additional models to evaluate the sensitivity of their results by adjusting for additional covariates (e.g., comorbidities, other indicators of socioeconomic status, and tobacco smoking status).

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Cathryn Tonne at ISGlobal, Barcelona, Spain, and colleagues. Research Report 220 contains the detailed Investigators' Report and a Commentary on the study prepared by the HEI Review Committee.

KEY RESULTS

The exposure models for nitrogen dioxide and ozone developed for this study were able to describe the patterns of these pollutants across the study area and for all years relatively well. Those for coarse and fine particles, however, were somewhat less accurate in describing pollutant patterns.

The investigators reported elevated risks of COVID-19–related outcomes associated with exposures to higher annual mean levels of all pollutants except ozone, with which they reported lower risks (**Statement Figure**). Estimates of risk from models with annual mean exposures to nitrogen dioxide were greater than those from models with annual mean exposures to the other pollutants considered. Results from two-pollutant models were generally similar to those from single-pollutant models.



Statement Figure. Associations between estimated annual average air pollution concentrations and COVID-19–related outcomes among cohort participants. Data shown are hazard ratios and 95% confidence intervals estimated per interquartile range increases in 1-year mean exposure. (Source: Investigators' Report Table 6.)

The investigators also reported that higher short-term exposures (i.e., over the previous few days) to nitrogen dioxide and both fine and coarse particles were associated with an elevated risk of COVID-19–related hospital admissions during the second wave of the pandemic. Specifically, they reported that risk of hospital admissions was associated with cumulative exposures measured up to seven days preceding an event. Short-term variations in ozone concentrations, however, were associated with lower risk of hospital admission.

The investigators also examined whether the combined effects of exposures to air pollution and selected characteristics of the population (e.g., age, sex, socioeconomic status, pre-existing health conditions) were associated with increased risk of COVID-19–related hospital admission. Here, they reported evidence that those characterised by lower socioeconomic status (according to several indicators at the individual and area levels) and who had long-term exposures to relatively high concentrations of nitrogen dioxide or fine particles were at increased risk of hospital admission for COVID-19 as compared to others. They also reported that the risk of hospitalization did not vary appreciably among subgroups defined by the presence of chronic comorbid conditions (i.e., diabetes, hypertension, and chronic obstructive lung disease).

INTERPRETATION AND CONCLUSIONS

In its independent evaluation of the Investigators' Report, the HEI Review Committee concluded that this study represents an important contribution to the scientific knowledge about potential associations between exposures to outdoor air pollution and the risk of severe cases of COVD-19.

The Committee was impressed that the investigators were careful to exclude air pollution data from 2020 from their analyses of longer-term, annual exposures when pandemic-related restrictions on mobility led to decreased emissions from traffic and other sources. The study demonstrated elevated risks for severe COVID-19 outcomes associated with daily and annual exposures to nitrogen dioxide and fine and coarse particles (and opposite results with ozone) in this population-based cohort of 4.6 million adults. Most other studies typically have had access to data on only short- or long-term exposures, not both, and many do not have access to such high-quality exposure models for multiple pollutants. The study also provides evidence suggesting that individuals with lower individual- and area-level socioeconomic status might have been more susceptible than others to the effects of long-term exposures to nitrogen dioxide and fine particles on COVID-19–related hospitalization. This susceptibility among those of lower socioeconomic status could be due to many factors, including more frequent or more intense exposures to pollutants, higher levels of psychosocial stress, or higher incidence of pre-existing health conditions or genetic traits that increase susceptibility to effects of exposure.

The many sensitivity analyses generally demonstrated findings consistent with the main analyses and thus supported the robustness of the results. Some results, however, were difficult to interpret and understand. For example, the associations reported between ozone and the risk of severe COVID-19 outcomes were unexpected and difficult to explain. Some of the challenges to interpreting those results are because the long-term exposures to ozone were negatively correlated with those to nitrogen dioxide and because the range of spatial variation captured by the ozone model was relatively small.

Ultimately, this study has provided important additional evidence that short- and long-term exposures to outdoor air pollution do appear to be associated with severe COVID-19 outcomes.

INVESTIGATORS' REPORT

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

Cathryn Tonne[1], Otavio Ranzani[1], Anna Alari[1], Joan Ballester[1], Xavier Basagaña[1], Carlos Chaccour[1], Payam Dadvand[1], Talita Duarte[2], Maria Foraster[1], Carles Milà[1], Mark J. Nieuwenhuijsen[1], Sergio Olmos[1], Alex Rico[1], Jordi Sunyer[1], Antònia Valentín[1], and Rosa Vivanco[3]

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ABSTRACT

Introduction Evidence from epidemiological studies based on individual-level data indicates that air pollution may be associated with coronavirus disease 2019 (COVID-19) severity. We aimed to test whether (1) long-term exposure to air pollution is associated with COVID-19–related hospital admission or mortality in the general population; (2) short-term exposure to air pollution is associated with COVID-19–related hospital admission following COVID-19 diagnosis; (3) there are vulnerable population subgroups; and (4) the influence of long-term air pollution exposure on COVID-19–related hospital admissions differed from that for other respiratory infections.

Methods We constructed a cohort covering nearly the full population of Catalonia through registry linkage, with follow-up from January 1, 2015, to December 31, 2020. Exposures at residential addresses were estimated using newly developed spatiotemporal models of nitrogen dioxide (NO_2*), particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$), particulate matter ≤10 μm in aerodynamic diameter (PM_{10}), and maximum 8-hr-average ozone (O_3) at a spatial resolution of 250 m for the period 2018–2020.

Results The general population cohort included 4,660,502 individuals; in 2020 there were 340,608 COVID-19 diagnoses, 47,174 COVID-19–related hospital admissions, and 10,001 COVID-19 deaths. Mean (standard deviation) annual exposures were 26.2 (10.3) μg/m^3 for NO_2, 13.8 (2.2) μg/m^3 for $PM_{2.5}$, and 91.6 (8.2) μg/m^3 for O_3. In Aim 1, an increase of 16.1 μg/m^3 NO_2 was associated with a 25% (95% confidence interval [CI]: 22%–29%) increase in hospitalizations and an 18% (10%–27%) increase in deaths. In Aim 2, cumulative air pollution exposure over the previous 7 days was positively associated with COVID-19–related hospital admission in the second pandemic wave (June 20 to December 31, 2020). Associations of exposure were driven by exposure on the day of the hospital admission (lag0). Associations between short-term exposure to air pollution and COVID-19–related hospital admission were similar in all population subgroups. In Aim 3, individuals with lower individual- and area-level socioeconomic status (SES) were identified as particularly vulnerable to the effects of long-term exposure to NO_2 and $PM_{2.5}$ on COVID-19–related hospital admission. In Aim 4, long-term exposure to air pollution was associated with hospital admission for influenza and pneumonia: (6%; 95% CI: 2–11 per 16.4-μg/m^3 NO_2 and 5%; 1–8 per 2.6-μg/m^3 $PM_{2.5}$) as well as for all lower respiratory infections (LRIs) (18%; 14–22 per 16.4-μg/m^3 NO_2 and 14%; 11–17 per 2.6-μg/m^3 $PM_{2.5}$) before the COVID-19 pandemic. Associations for COVID-19–related hospital admission were larger than those for influenza or pneumonia for NO_2, $PM_{2.5}$, and O_3 when adjusted for NO_2.

Conclusions Linkage across several registries allowed the construction of a large population-based cohort, tracking COVID-19 cases from primary care and testing data to hospital admissions, and death. Long- and short-term exposure to ambient air pollution were positively associated with severe COVID-19 events. The effects of long-term air pollution exposure on COVID-19 severity were greater among those with lower individual- and area-level SES.

INTRODUCTION

As a major risk factor for respiratory and other diseases (Cohen et al. 2017), both long- and short-term exposure to air pollution has been investigated in relation to COVID-19 incidence and to COVID-19–related hospitalization or mortality. Several pathways have been proposed to explain the role of air pollution in the increased risk of COVID-19 incidence and severity (Weaver et al. 2022). First, short- and long-term exposure to air pollution may modify host susceptibility to infection and disease severity by exacerbating inflammatory

This Investigators' Report is one part of Health Effects Institute Research Report 220, which also includes a Commentary by the Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Cathryn Tonne, ISGlobal, Doctor Aiguader 88 Barcelona 08003, Spain; email: *cathryn.tonne@isglobal.org*. No potential conflict of interest was reported by the authors.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83998101 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

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

response and oxidative stress. Second, short-term air pollution may contribute to immune system dysfunction, increasing viral replication. Third, long-term exposure to air pollution may exacerbate comorbidities (e.g., diabetes and high blood pressure), which are predisposing factors for severe COVID-19 and death. A growing body of evidence reports positive and robust associations between long-term exposure to air pollution and COVID-19 infection or poor COVID-19 outcomes (Bowe et al. 2021; Kogevinas et al. 2021b; Wu et al. 2020; Zang et al. 2022, Zhang et al. 2023). However, several uncertainties remain, and several methodological challenges in investigating the relationship between air pollution and COVID-19 outcomes, particularly incidence, have been highlighted (Villeneuve and Goldberg 2020). These challenges include outcome definition (diagnosis, COVID-19–related hospital admission, and death) in the early phases of the pandemic before definitions were standardized; selection bias related to greater availability of testing in urban areas with high air pollution levels; and adjustment for spatiotemporal patterns in COVID-19 cases as the pandemic evolved.

Several individual-level studies reported positive associations between long-term exposure to air pollution and hospital admission or death, particularly for $PM_{2.5}$, but less consistently for NO_2. These studies followed cohorts of positive COVID-19 cases (Chen C et al. 2022a; Chen Z et al. 2022b; English et al. 2022) or selected populations (Sheridan et al. 2022). One analyzed the general population (Nobile et al. 2022). Several knowledge gaps remained due to the heterogeneity in observed estimates for COVID-19 severity and death (Marquès et al. 2022; Sheridan et al. 2022), limited sample size in previous studies, and lack of multipollutant models.

Inconsistent findings have been reported for short-term exposure (López-Feldman et al. 2021; Marian et al. 2022; Zang et al. 2022). Evidence of the effects of short-term air pollution exposure on COVID-19 outcomes is mainly from ecological study designs, primarily time-series studies with aggregated data (Adhikari and Yin 2020; Azuma et al. 2020; Dales et al. 2021; Fernández et al. 2021; Filippini et al. 2020; Khorsandi et al. 2021; Lorenzo et al. 2021; Marian et al. 2022; Sanchez-Piedra et al. 2021; Stufano et al. 2021; To et al. 2021; Wang et al. 2020a; Xu et al. 2022; Zhou et al. 2021; Zhu et al. 2020), which are affected by methodological issues (Benmarhnia 2020; Heederik et al. 2020; Villeneuve and Goldberg 2020, 2022). Compared with aggregated data, individual-level data allow for exposure linkage at residential addresses and a more detailed exploration of effect modification by individual sociodemographic characteristics or comorbidities (Burn et al. 2021; Williamson et al. 2020). Time-to-event analyses based on individual-level data allow the independent effects of short- and long-term exposures to be better disentangled.

Several risk factors have been identified as contributing to the progression of severe COVID-19; these include older age, male sex, chronic comorbidities, and lower SES (Burn et al. 2021; Du et al. 2021). Although these are now well-documented attributes that increase vulnerability to severe COVID-19, it is not clear whether the effect of air pollution on COVID-19 severity would be higher among individuals with these risk factors. Few previous studies evaluated modification of the air pollution effect on COVID-19 outcomes, and results regarding vulnerable groups have been largely inconsistent (Kogevinas et al. 2021a; Mendy et al. 2021; Sheridan et al. 2022). Overall, no clear patterns of modification of the effect of air pollution on COVID-19 severity by age, sex, and chronic comorbidities have emerged in the literature. However, results are more consistent regarding SES, indicating stronger associations between air pollution and COVID-19 severity among those with lower SES (Bowe et al. 2021; Bozack et al. 2022; Chen Z et al. 2022b). Most studies were not specifically designed to identify vulnerable groups, had limited sample size to evaluate interactions, and did not evaluate interaction on both additive and multiplicative scales, leading to potentially misleading conclusions regarding who is most vulnerable to the effects of air pollution on COVID-19 outcomes (Knol and VanderWeele 2012; VanderWeele and Knol 2014).

Previous studies have reported associations of greater magnitude between long-term exposure to air pollution and COVID-19–related compared with all-cause mortality (Nobile et al. 2022; Zhang et al. 2023). However, it remains unclear whether the role of air pollution was more pronounced for hospital admission due to infection with the novel, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than for respiratory infections caused by established bacterial and viral agents.

The present study, COVAIR-CAT, aims to address these evidence gaps using a large population-based cohort covering nearly the entire adult population of Catalonia, an autonomous community in northeastern Spain (32,113 km^2). Barcelona, the capital city, has a population of 1.7 million inhabitants while its metropolitan area includes 4.9 million, 63% of the total population of Catalonia (7.7 million) (Barcelona 2020). The Catalan population is largely urban; 95% reside in municipal districts that have more than 2,000 inhabitants (Catalunya 2022). Catalonia is an ideal setting to conduct well-powered studies investigating the role of air pollution in the COVID-19 health burden due to its (1) wide spatial variation in air pollution levels; (2) good spatial distribution of COVID-19 cases; and (3) powerful electronic health registries in a universal health system covering nearly the entire population. Given the important role of policy and health system response to the pandemic, and given differences in the distribution of factors (e.g., deprivation) that confer vulnerability to severe COVID-19 outcomes, evidence from other settings (e.g., the United States) is likely to have limited generalizability to Europe.

SPECIFIC AIMS

The overarching objective of COVAIR-CAT was to test whether long- or short-term exposure to air pollution increased the risk of COVID-19–related hospital admissions or mortality

and to identify vulnerable subgroups. Specifically, we aimed to test 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 following COVID-19 diagnosis and whether the effect 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–related hospital admissions differed from that for respiratory infections not due to SARS-CoV-2 infection.

During the study, a few modifications were made to the specific aims compared with the proposal: (1) analyses in Aim 2 focused on hospital admissions; mortality was not evaluated due to limited statistical power; (2) we evaluated effect modification of short-term exposure simultaneously with the main analysis rather than as part of Aim 3; (3) Aim 3 focused on hospital admissions and interaction on both the additive and multiplicative scale on a selected subset of potential modifiers mentioned in the proposal; and (4) mortality was not evaluated as part of Aim 4 due to the lack of cause-specific mortality at the time of record linkage to generate the cohort.

STUDY DESIGN AND METHODS

We linked registry data obtained through the Program for Data Analysis for Health Research and Innovation within the Catalan Agency for Health Quality and Evaluation to construct a large, population-based cohort covering nearly all the adult population of Catalonia. We included all individuals aged 18 years and older registered in the public health system in 2015 and followed them prospectively through the end of 2020.

The overall study design was a longitudinal cohort study.

STUDY POPULATION

The COVAIR-CAT cohort included all individuals aged 18 years and older registered in the public health system in 2015 (5,127,059) who were alive and residing in Catalonia on March 1, 2020 (4,669,011). Participants were followed prospectively through the end of 2020 (December 31). The cohort was constructed by linking registry data from multiple databases (Appendix Tables A1 and A2; the Appendix is available on the HEI website). Participants were identified from the Catalan Central Registry of Insured Persons through a unique identifier, which allowed linkage of comorbidities and hospitalizations (based on the International Classification of Diseases (ICD) codes from administrative databases of primary care, urgent care, and acute hospital discharges. Information on SARS-CoV-2 reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and rapid antigen tests among cohort participants was obtained from the surveillance system in Catalonia.

Research Roadmap

Aims and Research Conducted	Methods Description
Aim 1: Test whether long-term exposure to air pollution was associated with COVID-19–related hospital admission or mortality in the general population	Cox proportional hazard models estimated an association between the 2019 annual average of NO_2, $PM_{2.5}$, PM_{10}, and O_3 at each participant's residential address and severe COVID-19 in the general population.
Aim 2: Test whether short-term exposure to air pollution was associated with COVID-19–related hospital admission following COVID-19 diagnosis and whether there were vulnerable subgroups	Cox proportional hazard model with daily NO_2, $PM_{2.5}$, PM_{10}, and O_3 estimated at each participant's residential address and distributed lag nonlinear models accounting for exposures up to 7 days in the population diagnosed with COVID-19.
Aim 3: Test 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	Cox proportional hazard models estimated an association between the 2019 annual average of NO_2, $PM_{2.5}$, and PM_{10} at each participant's residential address and COVID-19–related hospital admission, evaluating effect modification on the multiplicative and additive scales.
Aim 4: Compare the influence of long-term air pollution exposure on hospital admission for COVID-19 with respiratory infections not due to SARS-CoV-2	Cox proportional hazard models estimated an association between the 2018 annual average of NO_2, $PM_{2.5}$, PM_{10}, and O_3 at each participant's residential address and respiratory infections in the general population.

AIMS

Aim 1 From 4,669,011 adult individuals alive and residing in Catalonia on March 1, 2020, we excluded 409 (<0.1%) because of loss to follow-up, 589 (<0.1%) due to inconsistent dates, 1,512 (<0.1%) missing residential address, and 5,999 (0.1%) missing air pollution exposure values. The Aim 1 cohort included 4,660,502 individuals (**Figure 1**), although the main analysis was based on individuals not residing in nursing homes (N = 4,639,184). The population is described in detail in the publication of Aim 1 results (Ranzani et al. 2023).

Aim 2 Analyses were based on the subset of individuals diagnosed with SARS-CoV-2 infection from March 1 until December 31 (340,608 individuals). To reduce possible bias in the date of diagnosis and to focus on a more homogeneous and representative population, the main analysis was restricted to people not living in nursing homes and diagnosed in primary care (240,902 individuals) (**Figure 2**) and is described in detail in the publication of Aim 2 results (Alari et al. 2024).

Aim 3 Analysis was based on the same population as for Aim 1, with the additional exclusion of 21,318 individuals diagnosed with COVID-19 in nursing homes, resulting in 4,639,184 individuals included in the analysis. The population is described in detail in the publication of Aim 3 results (Ranzani et al. 2024).

Aim 4 Analysis for Aim 4 included all individuals aged 18 years and older registered in the public health system in 2015 (5,127,059) who were alive and residing in Catalonia on March 1, 2019 (4,762,953). We excluded 409 individuals (<0.1%) because of loss to follow-up, 6 (<0.1%) due to inconsistent dates, 2,884 (<0.1%) missing residential addresses, and 6,160 (0.1%) missing air pollution exposure values. Because only the first hospital admission was considered, we further excluded 44,645 (1%) individuals with previous hospital admission for influenza or pneumonia and 72,287 (2%) with previous admission for all LRIs during the 2015–2018 period, resulting in 4,708,849 individuals included in the analysis focused on influenza or pneumonia and 4,681,207 in the analysis of LRIs. Participants were followed prospectively from January 1 to December 31, 2019.

HEALTH OUTCOME DEFINITION

The project considered several different health outcomes summarized in **Table 1**. COVID-19 severity outcomes were defined relative to COVID-19 diagnosis, which was defined as positive RT-qPCR or rapid antigen test (laboratory-confirmed COVID-19 diagnosis) or clinical diagnosis of COVID-19. Clinical diagnosis of COVID-19 was defined by the respective ICD-10 codes, as notified in the administrative healthcare databases. The first COVID-19 diagnosis could be at the primary care, urgent care units, or hospitals. We used hospital admission by any cause within 30 days of COVID-19 diagnosis in our main analyses to address the lack of standardized coding for COVID-19 early in the pandemic. All health outcomes were restricted to the first event.

EXPOSURE ASSESSMENT

Exposure models developed as part of the COVAIR-CAT project were used throughout the project. We developed exposure models of daily 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, as described in detail in Milà and colleagues (2023). In brief, we used meteorological and air pollution data from the Catalan and Spanish monitoring networks and a list of predictors that included: meteorological models (ERA5 and ERA5-land reanalysis products); atmospheric models (CAMS European reanalysis for 2018, and analysis for 2019–2020); remote sensing products (MODIS Aerosol Optical Depth [AOD] and Land Surface Temperature [LST]; OMI and TROPOMI tropospheric NO_2 and total O_3 columns, VIIRS nighttime lights, and Sentinel 2 NDVI); a set of spatial variables (road density, point sources, land use indicators, terrain variables, coordinates, and distance from sea); and leave-one-out inverse distance weighting estimates from the nearest stations to capture residual spatial autocorrelation. The modeling strategy was divided into two steps: first, we imputed missing cells of daily remote sensing products (MODIS AOD and LST, OMI and TROPOMI gas columns) using random forest models with nonmissing cells as the outcome, while prediction features included temporally collocated climate (ERA5-land reanalysis) and atmospheric (CAMS global reanalysis) products at the satellite overpass time, in addition to other ancillary data. The second step used the full set of predictors to model the station data using quantile random forest models, which allowed for uncertainty quantification of the predictions. Maps with examples of exposure model predictions for two selected days are shown in Appendix Figure A1. Spatial variable selection was performed to reduce spatial overfitting, and models were validated using a nested cross-validation strategy at the station level (Appendix Table A3, available on the *HEI Website*). We used individual residential addresses at the beginning of 2021 (the most representative address available for the study period), or the last available, to assign daily air pollution and temperature exposure during follow-up. A summary of exposure metrics (e.g., model, averaging time) used in each analysis is included in **Table 2**. We selected annual average exposures from 2019 as our primary exposure metric for Aims 1 and 3 based on the high correlations between the 2018 and 2019 annual average exposures (ranging from 0.95 for O_3 to 0.98 for NO_2 and $PM_{2.5}$). We tested sensitivity by using different averaging times for Aim 1.

COVID-19 lockdowns in Catalonia during 2020 involved severe mobility restrictions that led to decreased air pollution emissions from traffic and other sources, and lower $PM_{2.5}$, NO_2, and O_3 concentrations measured during the lockdown (Querol et al. 2021). This was taken into account in the exposure assessment in several ways. First, it was captured by the respective atmospheric composition remote sensing products (e.g., see [Bauwens et al. 2020] for Sentinel 5-P tropospheric NO_2). Second, we used CAMS atmospheric analysis products with real-time observations, including the impact of lockdowns. Lastly, our modeling approach consisted of random forests where Julian day was one of the predictors.

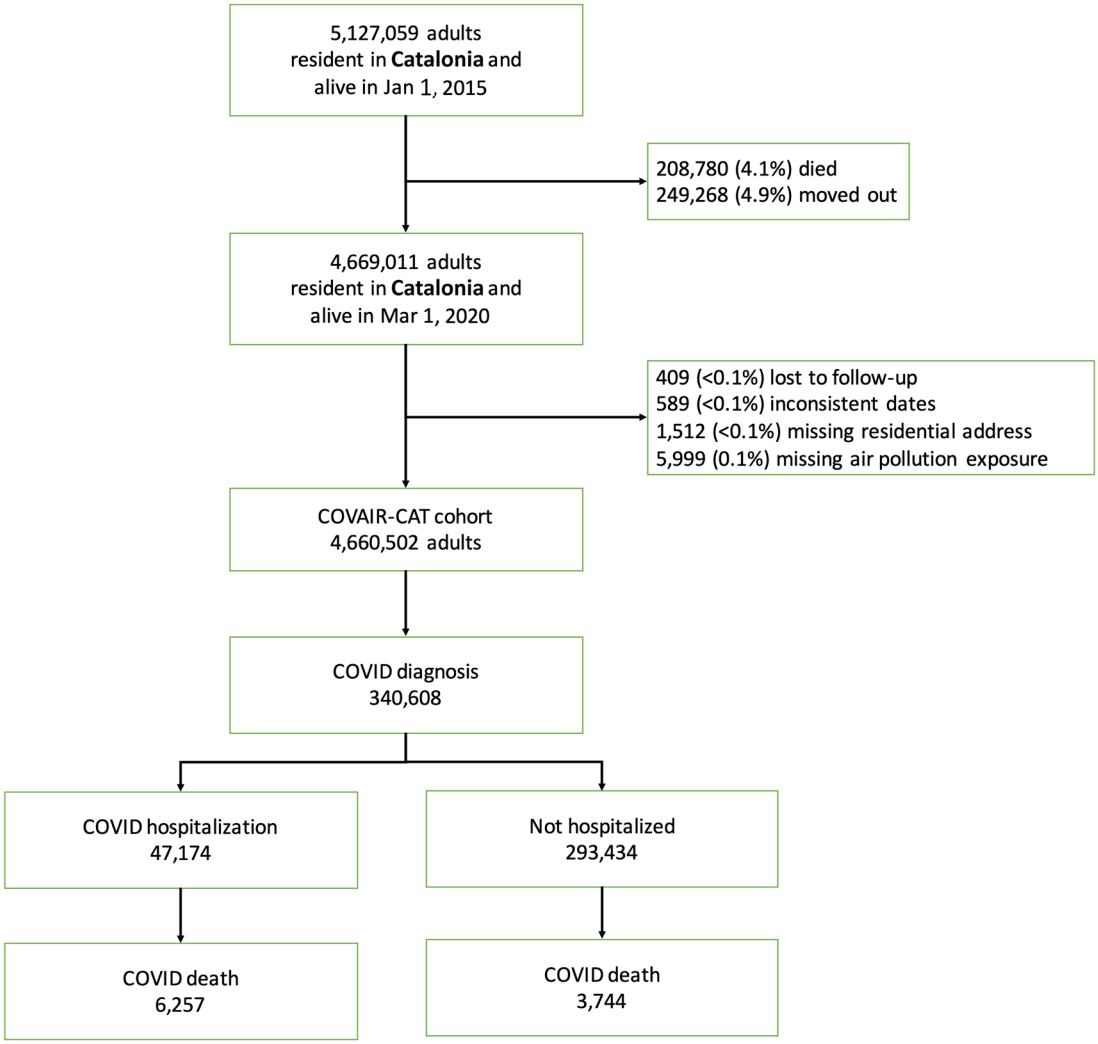

Figure 1. Flow diagram of study population for Aim 1 analysis.

This approach captured time-varying baseline concentration levels, but also as a tree-based ensemble, it accounted for interactions of time with other predictors (e.g., land use or road density), accommodating their time-varying impact on predicted concentrations (Elith et al. 2008). Appendix Figure A2 describes model performance over each month in 2020.

COVARIATE DATA

We obtained data for age, sex, individual-level income, and health risk group in 2015 from the Central Registry of Insured Persons. Individual income group was based on the copayment system for drug dispensations, which largely depends on income (Avellaneda-Gómez et al. 2022). Individual health risk group is a validated ordinal index that encompasses multimorbidity and levels of patient complexity, accounting for acute, chronic, or oncological morbidities (single or multimorbidity); medications; and demand on the health system (Appendix Table A2) (Monterde et al. 2020; Vivanco-Hidalgo et al. 2021).

Tobacco smoking status (e.g., nonsmoker, former smoker, or active smoker), previous chronic comorbidities, and body mass index were obtained from the primary care database. Selected chronic comorbidities were also obtained from the hospital admissions database (e.g., chronic obstructive pulmonary disease [COPD]) (Avellaneda-Gómez et al. 2022). Nursing home status for those with COVID-19 diagnosis was obtained from the COVID-19 surveillance system.

Health regions in Catalonia administer the public health system, accounting for geographical, socioeconomic, demographic, and health facility availability differences, with the aim of guaranteeing equitable healthcare access. Healthcare management areas (N = 43, median area 389 km^2) are territorial boundaries based on the aggregation of nested primary care service areas (N = 374, median area 14 km^2).

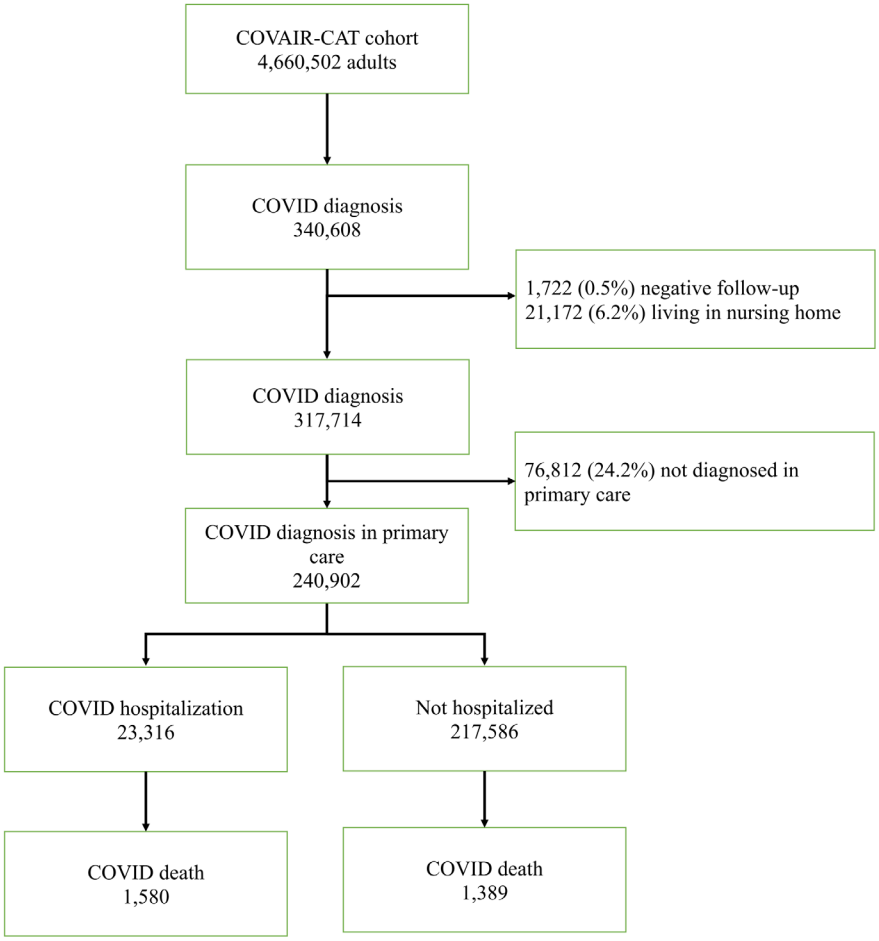

Figure 2. Flow diagram for study population of Aim 2 analysis.

We used area-level indicators to identify spatially varying contextual factors potentially linked to air pollution levels and the risk of severe COVID-19. Area-level indicators were linked to individuals' residential addresses. The urbanicity index divided municipalities into towns, urban areas, and rural areas. The Small Area Socioeconomic Index was ascertained at the primary care service area level (Avellaneda-Gómez et al. 2022), while the deprivation and Gini indexes and the proportion of non-Spanish residents were ascertained at the census-tract level. The study population resided in 5,038 census tracts with a median area of 0.13 km^2. We derived the distance from the residence to the closest primary care center as a surrogate for public health system accessibility. Finally, we obtained the weekly test-positive proportion of RT-qPCR and rapid antigen tests at the healthcare management area level to reflect the spatiotemporal evolution of the pandemic (Hitchings et al. 2021).

There were missing values for tobacco smoking and body mass index covariates. For the main analysis, we considered a missing value for tobacco smoking as nonsmoker because the value is most often omitted for nonsmokers in the primary care service, while body mass index was used only for sensitivity analysis after multiple imputation.

DATA ANALYSIS

We used directed acyclic graphs to inform covariate adjustment for each aim, and the graphs for Aims 1 and 2 are shown in Appendix Figure A3 (available on the *HEI Website*).

Aim 1 We fit Cox proportional hazards models to estimate the association between the 2019 annual average air pollution and COVID-19–related hospital admission, intensive care unit (ICU) admission, and death, with separate models for each pollutant and outcome. We evaluated single- and two-pollutant models. We accounted for the competing event of death when evaluating COVID-19–related hospital and ICU admission by censoring at death using the cause-specific hazard ratios (HRs) framework (Lau et al. 2009; Wolkewitz et al. 2014). Follow-up started on March 1, 2020. For the primary outcome (COVID-19–related hospital admission), right-censoring occurred at the first instance of one of the following:

Table 1. Summary of Health Outcomes According to Relevant Study Aim

Outcome	Definition	Aim
COVID-19–related hospital admission	Hospital admission by any cause occurring within 30 days of first COVID-19 diagnosis from March 1, 2020, to December 31, 2020 Aim 1 and Aim 3 also included hospital admissions that occurred in the previous 10 days of the first COVID-19 diagnosis to account for individuals who were hospitalized before diagnosis (particularly during the first pandemic wave)	Aim 1, Aim 2, Aim 3, Aim 4
COVID-19–related death	Death by any cause occurring within 30 days of first COVID-19 diagnosis from March 1, 2020, to December 31, 2020	Aim 1
Intensive care unit (ICU) admission	For each COVID-19–related hospital admission, patient was admitted to ICU	Aim 1
Hospital length-of-stay (LOS)	For each COVID-19–related hospital admission, length of stay in days	Aim 1
Hospital admission for pneumonia + influenza	ICD-10 codes J09[a]–J18[a] for influenza and pneumonia	Aim 4
Hospital admission for lower respiratory infection	ICD-10 codes J09[a]–J18[a], J20[a]–J22[a]	Aim 4

ICD = International Classification of Diseases.

[a] Indicates all subcategories within the included code.

Table 2. Summary of Exposure Metrics According to Study Aim

Aim	Primary Exposure	Exposure in Sensitivity Analysis
Aim 1	Annual average (2019) COVAIR-CAT estimates for NO_2, $PM_{2.5}$, PM_{10}, 8-hr O_3 warm season	Annual (2018) and 2-year (2018–2019) average COVAIR-CAT estimates for $PM_{2.5}$, PM_{10}, NO_2, 8-hr O_3 warm season
Aim 2	Daily average (2020) COVAIR-CAT estimates for NO_2, $PM_{2.5}$, PM_{10}, 8-hr O_3	–
Aim 3	Annual average (2019) COVAIR-CAT estimates for NO_2, $PM_{2.5}$, PM_{10}	–
Aim 4	Annual average (2018) COVAIR-CAT estimates for NO_2, $PM_{2.5}$, PM_{10}, 8-hr O_3 warm season	–

30 days after the first COVID-19 diagnosis, emigration outside the study area, the end of the study period, or death. We used days since March 1, 2020, as the time scale. We fitted negative binomial regression models to estimate the association between the 2019 annual average air pollution and hospital length of stay (LOS) among hospitalized individuals. Associations for air pollutants were reported as HR or incidence rate ratios (IRRs) per interquartile range (IQR) increase, with their 95% confidence intervals.

We performed the following sequential adjustment for all exposures and outcomes, defined a priori:

1. **Model 1:** Adjusted for age (penalized spline, DF = 6) and sex (strata, two levels)
2. **Model 2:** Model 1 plus tobacco smoking status (factor, three categories), individual income (factor, three categories), and health risk group (factor, four categories)
3. **Model 3:** Model 2 plus area-level covariates: Small Area Socioeconomic Index (continuous term), proportion of non-Spanish nationals (continuous term), distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) and average weekly of test-positive proportion (continuous term)
4. **Model 4 (main model):** Model 3 plus health region (strata, 7 categories)

We performed six sensitivity analyses defined a priori:

1. **Model 5** included comorbidities.
2. **Model 6** included other socioeconomic indexes (inequity index, Gini index, and deprivation index) to Model 4.
3. **Model 7** included multiple imputation of tobacco smoking status and body mass index, running Model 5 and replacing obesity by body mass index in 10 imputed datasets.

4. **Model 8** included Model 4 with the outcomes restricted to laboratory-confirmed COVID-19.
5. **Model 9** was Model 4 but included COVID-19 diagnoses at nursing homes.
6. **Model 10** included Model 4 in the subpopulation who did not change primary care service area between 2015 and 2020.

We also explored the sensitivity of our main model to (1) alternative outcome definitions based on cause-specific hospital admissions; (2) alternative exposure averaging times; and (3) stratification by smoking status. **Table 3** describes the population included in each analysis and the corresponding model.

To account for pandemic dynamics, as well as the population and health system response during 2020, we stratified analysis by pandemic wave. Two pandemic waves were identified (March 1 to June 20, 2020, and June 21 to December 31, 2020) using the week with the lowest number of COVID-19 cases to define the cut point between waves (June 21, 2020). We evaluated the proportional hazards assumption of our models by visual inspection of score residuals plotted against event time to ensure that the Cox model with daily time steps and temporal covariate adjustment adequately handled the temporal patterns in the outcome.

Further details of the statistical analysis are described in Ranzani and colleagues (2023).

Aim 2 We fit a Cox proportional hazard model with time-dependent covariates. The time scale was based on days since COVID-19 diagnosis. Individuals were followed until a COVID-19–related hospital admission or until one of the right-censoring events: end of follow-up (30 days after diagnosis), end of the study period (December 31, 2020), or death. Hospital admission on a given day may be related to air pollution exposure on the same day (i.e., lag0), but also to exposures experienced on previous days (lag>0). We fitted distributed lag nonlinear models (DLNMs) accounting for exposures up to 7 days preceding each day of follow-up (Gasparrini et al. 2010; Gasparrini 2014). We used a linear function to model the relationship between daily air pollution and hospital admission (Lavigne et al. 2022). Based on Akaike information criterion values of different models (Appendix Table A4), we chose a flexible B-spline function with 5 degrees of freedom (DF, three for the degree of the polynomial, one for the intercept, and one for one internal knot) to model the lag–response function (Yu et al. 2022).

The fully adjusted model was the same as Model 4 above, except that it did not include the health risk group and did include: (1) temperature as a cross-basis function to adjust for both the temperature-response (natural spline with three internal knots at the 10th, 75th, and 95th percentile) and lag–response (eight lags, natural spline with two internal knots); and (2) annual average air pollution in 2019. To account for pandemic dynamics, as well as the population and health system response during 2020, we stratified analysis by pandemic wave (Lavigne et al. 2022; Lipsitt et al. 2021; Marian et al. 2022). We adjusted for temporal trends and seasonality using a smooth function of time with an internal knot corresponding to each pandemic peak based on the number of COVID-19 cases and a binary factor for weekend days. Single-pollutant models were fitted for NO_2, $PM_{2.5}$, and PM_{10}. Because O_3 is a secondary pollutant of which NO_2 is a precursor, models relating short-term exposure to O_3 with hospitalization were also adjusted for NO_2. As for Aim 1, we checked model residuals from the main model to ensure the proportional hazards assumption was met.

We performed seven sensitivity analyses. First, we replicated the main analysis on a larger population by including individuals who tested positive for COVID-19 infection or were diagnosed in hospital or emergency care (N = 317,714 individuals included in the analysis). Second, we defined the outcome as admission with COVID-19 as the main diagnostic code. Third, we evaluated exposure measurement error due to residential mobility by restricting the analysis to individuals who did not change addresses between 2015 and 2021 (i.e., residential addresses recorded at the beginning of 2015 were no more than 300 meters from the addresses in 2021). Fourth, we ran models considering death as a competing risk for hospitalization (Lau et al. 2009). Fifth, we accounted for spatial autocorrelation by considering clustered model errors at primary care service area levels (378 clusters). Sixth, we tested the robustness of the model results to a different definition of pandemic waves by setting the end of the first pandemic wave as the last day of the first lockdown in Catalonia (May 25, 2020). Finally, we explored nonlinearity of the relationship between air pollution and hospitalization using a B-spline with 4 DF for the exposure–response (Appendix Table A4).

We conducted a stratified analysis to assess possible effect modification by clinical and sociodemographic characteristics. We fit separate models for each level of the potential modifier, and we visually compared predicted HRs at lag0.

Further details of the statistical analysis are described in (Alari et al. 2024).

Aim 3 We evaluated potential effect modification of the association between long-term exposure to NO_2, $PM_{2.5}$, and PM_{10} and COVID-19–related hospital admission in the equivalent of the main model from Aim 1 on the additive and multiplicative scale (O_3 not included due to null association with hospital admissions in Aim 1). It has long been understood that evaluating whether an effect is larger in particular population subgroups is scale-dependent, but this is widely ignored in practice. Although statistical interaction on the multiplicative scale has been examined in previous studies of air pollution and COVID-19 outcomes, few (Bowe et al. 2021) have considered additive interaction, which is more informative regarding the public health significance. Positive additive interaction for a vulnerability factor indicates that a larger number of hospital admissions could be prevented among

Table 3. Overview of Populations Included in Analyses According to Study Aim[a]

Aim	Main Analysis	Sensitivity Analysis (where different from Main Analysis)
Aim 1	*N* = 4,639,184 individuals in general population excluding individuals residing in nursing homes 42,174 all-cause hospital admissions	*N* = 4,639,184 33,521 hospital admissions based on laboratory-confirmed diagnosis (Model 8) *N* = 4,660,502 47,174 hospital admissions including diagnosis at nursing homes (Model 9) *N* = 3,739,528 34,664 hospital admissions in population that did not move between 2015–2020 (Model 10) 4,639,184 individuals in general population 36,505 admissions with COVID-19 or respiratory as ICD-10 first position 4,639,184 individuals in general population 33,981 admissions with COVID-19 as ICD-10 first position
Aim 2	*N* = 240,902 individuals diagnosed with COVID-19 in primary care 23,316 hospital admissions	*N* = 317,714 individuals diagnosed with COVID-19 in primary care or tested positive 41,165 hospital admission**s**
Aim 3	*N* = 4,639,184 individuals in general population 42,741 hospital admissions	
Aim 4	Influenza and pneumonia as main outcome: *N* = 4,708,849 individuals in general population 17,608 hospital admissions for influenza and pneumonia LRIs as main outcome: *N* = 4,681,207 individuals in general population 28,121 hospital admissions for all LRIs	

ICD = International Classification of Diseases; LRI = lower respiratory infection.

[a] All analyses were conducted in R (R Core Team, 2020) software (version 4.1.2).

those with the vulnerability factor if air pollution exposure were reduced (VanderWeele and Knol 2014). We adopted the terminology from VanderWeele (2019) to assess where on the interaction continuum our results are located (e.g., 11 states ranked according to strength of positive interaction). Where two exposures have positive associations with the outcome, the probability of the outcome in the doubly exposed group will determine the location on the continuum (VanderWeele 2019).

We used two approaches to evaluate effect modification on the additive scale. First, we created a 10-level category for each exposure and vulnerable group of interest by combining quintiles of exposure and a binary indicator of vulnerability. Second, we created a 4-level category using binary exposure above or below the median and a binary indicator of vulnerability to estimate the relative excess risk due to interaction (RERI), a measure of departure from additivity. RERI tests whether the combined effect of exposure and vulnerability is greater than the sum of their effects. HRs were fit with the reference group set to those with the lowest level of exposure (either first quintile or below the median) and without the vulnerability indicator. Confidence intervals for RERI were estimated using the delta method (Assmann et al. 1996). Models to evaluate interaction on the additive scale were adjusted by age (factor, two categories) + sex (factor, two categories) + smoking (factor, three categories) + health risk group (factor, four categories) + Small Area Socioeconomic Index (factor, two categories) + distance to the closest primary care unit (continuous term) + urbanicity (factor, two categories) + average weekly test-positive proportion (continuous term) + health region (strata, seven categories).

We investigated interaction on the multiplicative scale using two approaches. First, we evaluated multiplicative interaction estimated from the model used to calculate the RERI. Second, we added an interaction term between the long-term air pollutant (continuous term) and the binary vulnerability indicator in Model 4 from Aim 1.

Further details of the statistical analysis are described in (Ranzani et al. 2024).

Aim 4 We fit a Cox proportional hazard model with calendar time as timescale to assess the association between long-term exposure and two outcomes: (1) hospital admission for influenza or pneumonia, and (2) hospital admission for all LRIs (including influenza and pneumonia). Individuals were followed up until occurrence of the outcome of interest or until one of the right-censoring events: emigration outside the study area, the end of the study period (December 31, 2019), or death. As we considered only the first event since the beginning of the cohort (2015), individuals who already experienced the outcome of interest before the beginning of the follow-up (January 1, 2019) were excluded from the main analysis.

Models 1–4 with identical sequential adjustment as for Aim 1 were fit, and both single- and two-pollutant models were considered. HRs were reported per IQR increase in the 2018 exposure distribution or in the 2019 exposure distribution when compared with estimates for COVID-19–related hospitalization from Aim 1.

We gauged the potential interaction of the air pollution effect on hospital admission for all LRIs in Model 4 by several binary vulnerability indicators including age (<65 vs. ≥65 years), male sex, selected comorbidities (including hypertension, diabetes, and COPD), low individual-level income, and low area-level SES. Multiplicative interactions were evaluated by including interaction terms between each air pollutant and vulnerability indicators in the main model with continuous air pollution exposures (Model 4) and the model used to calculate the RERI. Additive interactions were assessed by estimating the RERI in a model with a four-level category factor (binary exposure above or below the median combined with a binary indicator of vulnerability) and visually by creating a 10-category factor for each combination of exposure quintile and vulnerability indicator.

RESULTS

The description of the COVAIR-CAT cohort and COVID-19–related events is shown in **Table 4**; the distribution of COVID-19 diagnosis during 2020 is presented in Appendix Figure A4 (available on the *HEI Website*). Exposure distributions for the full cohort (Aims 1 and 3) are presented in **Table 5** and for those diagnosed with COVID-19 in primary care (Aim 2) according to pandemic wave in Appendix Figure A5 and Table A5. Correlations between annual average exposures for 2019 (Aim 1) and daily exposures for 2020 (Aim 2) are presented in Appendix Table A6.

Aim 1 Our analysis to address Aim 1 resulted in several key findings (Ranzani et al. 2023). We observed a positive association between long-term exposure to NO_2 and $PM_{2.5}$ with severe COVID-19. In sensitivity analyses, associations were stable in two-pollutant models when accounting for different adjustments and using different outcome definitions. O_3 was positively associated with severe outcomes when adjusted by NO_2.

In single-pollutant models (Model 4), a higher annual average exposure to NO_2, $PM_{2.5}$, and PM_{10} was associated with a greater hazard of COVID-19–related events (**Table 6, Figure 3,** and Appendix Figures A6–A8). For NO_2, there were positive associations for hospitalization (HR 1.25; 95% CI: 1.22–1.29), ICU admission (HR 1.42; 1.30–1.55), and death (HR 1.18; 1.10–1.27) per IQR increase. For $PM_{2.5}$, there were positive associations for hospitalization (HR 1.19; 1.16–1.21), ICU admission (HR 1.16; 1.09–1.24), and death (HR 1.13; 1.07–1.19) per IQR increase. For PM_{10}, there were positive associations for hospitalization (HR 1.21; 1.18–1.23), ICU admission (HR 1.23; 1.15–1.31), and death (HR 1.14; 1.08–1.20) per IQR increase.

For all three pollutants, positive associations were observed for hospital LOS. In two-pollutant models, NO_2 remained positively associated with hospital and ICU admission after adjustment for $PM_{2.5}$. Similarly, positive associations for $PM_{2.5}$ remained for hospital admission and hospital LOS after adjustment for NO_2. Positive associations for PM_{10} remained for all outcomes after adjustment for either NO_2 or O_3.

For O_3, the association was negative for COVID-19–related events in single-pollutant models and null or positive when co-adjusted for NO_2: HR 1.10 (95% CI: 1.02–1.18) for ICU admission and 1.01 (0.95–1.07) for death per IQR in O_3. Regarding hospital LOS, O_3 was positively associated with hospital LOS in two-pollutant models (Table 6).

All associations were comparable with Model 4 in sensitivity analyses, except when including cases diagnosed at nursing homes and evaluating COVID-19 deaths (Appendix Figure A7). When evaluating associations by pandemic wave, the estimated measures of effect for the first wave were larger than for the second wave for hospitalization (Appendix Table A7). Most (80.4%) of the hospital admissions had COVID-19 mentioned as a cause of hospital admission (results not shown). Associations were slightly larger for COVID-19–related hospital admission when defined by COVID-19 or respiratory causes, or by COVID-19 only, as the main cause of admission compared with all-cause admissions (Appendix Table A8). Using alternative averaging times (e.g., 2018–2019 average) had minimal impact on effect estimates (Appendix Table A9), and results were consistent between the main analysis and sensitivity analysis stratified by smoking status (Appendix Table A10).

Aim 2 Our analysis among adults with COVID-19 infection in Catalonia resulted in several key findings. First, cumulative exposure to short-term air pollution was positively associated with COVID-19–related hospital admissions during the second pandemic wave. For NO_2, cumulative exposure of up to seven days was associated with hospital admission, while for $PM_{2.5}$ and PM_{10}, cumulative exposure was associated with hospital admission over a shorter period of two to three days. Second, associations of cumulative exposure during the second wave were driven by associations with lag0 exposure. Third, results from the first wave were less consistent than for the second wave. Fourth, there was no evidence of effect modification by sociodemographic characteristics or comorbidities.

Table 4. Characteristics of the COVAIR-CAT Cohort Overall and According to COVID-19 Outcomes

	Overall[a]	Diagnosed with COVID-19 in Primary Care[b]	COVID-19 Hospital Admission[a]	COVID-19 ICU Admission[a]	COVID-19 Death[a]
n	4,660,502	240,902	47,174	4,699	10,001
Age, years, mean (SD)	53.6 (17)	50.71 (16)	65.7 (17)	63.3 (12)	81.7 (10)
Female, *n* (%)	2,446,855 (52.5)	133,523 (55.4)	22,288 (47.2)	1,508 (32.1)	5,149 (51.5)
Tobacco Smoking, *n* (%)					
Nonsmoker	3,033,731 (65.1)	160,756 (66.7)	31,911 (67.6)	2,878 (61.2)	6,943 (69.4)
Former smoker	680,895 (14.6)	37,313 (15.5)	10,057 (21.3)	1,242 (26.4)	2,254 (22.5)
Active smoker	945,876 (20.3)	42,833 (17.8)	5,206 (11.0)	579 (12.3)	804 (8.0)
Individual Income Group, *n* (%)					
Low	3,240,314 (69.5)	167,770 (69.6)	34,119 (72.3)	3,229 (68.7)	7,909 (79.1)
Middle	1,393,153 (29.9)	71,974 (29.9)	12,826 (27.2)	1,441 (30.7)	2,055 (20.5)
High	27,035 (0.6)	1,158 (0.5)	229 (0.5)	29 (0.6)	37 (0.4)
Health Risk Group, *n* (%)					
Healthy	2,334,035 (50.1)	118,504 (49.2)	11,681 (24.8)	1,250 (26.6)	567 (5.7)
Low	1,394,963 (29.9)	72,053 (29.9)	13,601 (28.8)	1,563 (33.3)	1,903 (19.0)
Moderate	698,598 (15.0)	37,336 (15.5)	13,133 (27.8)	1,252 (26.6)	3,838 (38.4)
High	232,906 (5.0)	13,009 (5.4)	8,759 (18.6)	634 (13.5)	3,693 (36.9)
Chronic Comorbidities, *n* (%)					
Diabetes mellitus	471,419 (10.1)	20,756 (8.6)	11,959 (25.4)	1,350 (28.7)	3,731 (37.3)
Obesity	1,160,099 (24.9)	64,805 (26.9)	19,701 (41.8)	2,341 (49.8)	3,927 (39.3)
COPD	223,500 (4.8)		6,128 (13.0)	557 (11.9)	2,116 (21.2)
Hypertension	1,181,252 (25.3)	51,168 (21.2)	22,578 (47.9)	2,229 (47.4)	6,839 (68.4)
Other cardiovascular disorders	364,787 (7.8)	58,266 (24.2)	9,538 (20.2)	785 (16.7)	3,662 (36.6)
Dyslipidemia	1,305,896 (28.0)	60,056 (24.9)	20,539 (43.5)	2,209 (47.0)	5,119 (51.2)
Area of Residence Indicators					
Urbanicity, *n* (%)					
City	2,893,786 (62.1)	159,927 (66.4)	33,434 (70.9)	3,287 (70.0)	6,630 (66.3)
Town and Suburb	1,360,492 (29.2)	63,819 (26.5)	11,021 (23.4)	1,122 (23.9)	2,740 (27.4)
Rural	406,224 (8.7)	17,156 (7.1)	2,719 (5.8)	290 (6.2)	631 (6.3)

continued next page

Table 4. (*continued*)

	Overall[a]	Diagnosed with COVID-19 in Primary Care[b]	COVID-19 Hospital Admission[a]	COVID-19 ICU Admission[a]	COVID-19 Death[a]
Socioeconomic Indexes					
Small area socio-economic index, median [IQR]	41.05 [32.20, 49.45]	41.63 [32.69, 50.78]	41.71 [32.69, 50.90]	42.32 [33.72, 51.26]	40.78 [32.16, 49.50]
Deprivation index, z-score, median[c] [IQR]	–0.54 [–1.04, –0.04]	–0.52 [–1.02, 0.009]	–0.52 [–1.03, 0.02]	–0.45 [–0.98, 0.09]	–0.60 [–1.09, –0.06]
Percentage of non-Spanish residents, %, median [IQR]	11.8 [7.0, 18.2]	12.3 [7.2, 19.4]	12.5 [7.6, 19.3]	13.2 [8.0, 20.4]	12.0 [7.3, 18.2]
Gini index, median [IQR]	29.5 [27.2, 32.3]	29.5 [27.2, 32.1]	29.6 [27.2, 32.2]	29.6 [27.3, 32.2]	29.7 [27.3, 32.4]
Health Access					
Distance to closest primary care unit, metres, median [IQR]	422 [262, 644]	409.9 [256.5, 617.4]	409 [258, 600]	397 [252, 587]	422 [264, 632]
Average weekly TPP, %, median [IQR]	9.16 [7.95, 10.01]	8.89 [4.85, 15.28]	9.19 [8.09, 10.01]	9.19 [8.09, 10.14]	9.16 [8.09, 10.14]

SD = standard deviation; TPP = test-positive proportion.

[a] Including individuals residing in nursing homes.

[b] Excluding individuals residing in nursing homes because they were excluded from Aim 2 analysis.

[c] Higher values of the deprivation index reflect increasing deprivation; z-score standardized to the Spanish average.

Table 5. Annual Average (2019) Air Pollution Exposure from COVAIR-CAT Models

Pollutant	Mean (SD) μ/m^3	Min–Max μ/m^3	Median (percentiles 25–75) μ/m^3	IQR μ/m^3
NO_2	26.19 (10.3)	1.31–62.04	28.26 (17.98–34.06)	16.1
$PM_{2.5}$	13.85 (2.2)	5.18–21.06	13.9 (12.11–15.35)	3.2
PM_{10}	22.41 (3)	8.63–30.68	22.77 (20.21–24.46)	4.2
O_3 (warm season)	91.64 (8.2)	61.35–113.97	92.47 (87.38–98.22)	10.8

SD = standard deviation.

Table 6. Fully Adjusted Associations Between Long-Term Air Pollution and COVID-19 Outcomes in Single- and Two-Pollutant Models[a]

		COVID-19 Hospital Admission	COVID-19 ICU Admission	COVID-19 Death	Hospital Length of Stay
	Exposure	HR (95% CI)	HR (95% CI)	HR (95% CI)	IRR (95% CI)
NO_2 (IQR: 16.1)	Single-pollutant	**1.25 (1.22–1.29)**	**1.42 (1.30–1.55)**	**1.18 (1.10–1.27)**	**1.06 (1.03–1.09)**
$PM_{2.5}$ (IQR: 3.2)	Single-pollutant	**1.19 (1.16–1.21)**	**1.16 (1.09–1.24)**	**1.13 (1.07–1.19)**	**1.06 (1.04–1.08)**
PM_{10} (IQR: 4.2)	Single-pollutant	**1.21 (1.18–1.23)**	**1.23 (1.15–1.31)**	**1.14 (1.08–1.20)**	**1.06 (1.04–1.08)**
O_3 (warm season) (IQR: 10.8)	Single-pollutant	**0.91 (0.89–0.92)**	**0.91 (0.86–0.96)**	**0.94 (0.90–0.98)**	**0.99 (0.97–1.00)**
NO_2 (IQR: 16.1)	Adjusted for $PM_{2.5}$	**1.12 (1.08–1.17)**	**1.51 (1.33–1.72)**	**1.10 (0.99–1.22)**	0.99 (0.95–1.03)
NO_2 (IQR: 16.1)	Adjusted for O_3	**1.24 (1.19–1.29)**	**1.58 (1.39–1.79)**	**1.19 (1.08–1.31)**	**1.07 (1.03–1.12)**
$PM_{2.5}$ (IQR: 3.2)	Adjusted for NO_2	**1.12 (1.08–1.15)**	0.93 (0.85–1.03)	**1.08 (1.00–1.16)**	**1.07 (1.04–1.10)**
$PM_{2.5}$ (IQR: 3.2)	Adjusted for O_3	**1.16 (1.13–1.19)**	**1.13 (1.04–1.22)**	**1.12 (1.05–1.19)**	**1.07 (1.05–1.10)**
PM_{10} (IQR: 4.2)	Adjusted for NO_2	**1.16 (1.13–1.19)**	**1.09 (1.00–1.18)**	**1.10 (1.03–1.17)**	**1.06 (1.03–1.09)**
PM_{10} (IQR: 4.2)	Adjusted for O_3	**1.19 (1.16–1.22)**	**1.21 (1.13–1.31)**	**1.13 (1.07–1.19)**	**1.07 (1.04–1.09)**
O_3 (warm season) (IQR: 10.8)	Adjusted for $PM_{2.5}$	**0.97 (0.95–0.99)**	0.96 (0.90–1.02)	0.98 (0.93–1.03)	**1.01 (1.00–1.03)**
O_3 (warm season) (IQR: 10.8)	Adjusted for NO_2	0.99 (0.97–1.01)	**1.10 (1.02–1.18)**	1.01 (0.95–1.07)	1.02 (0.99–1.04)

[a] **Bolding** indicates significant values. The analyses of COVID-19–related hospital admission, ICU admission, and death were conducted in the whole population, while hospital length-of-stay was conducted among those with COVID-19–related hospital admission. Model 4 included age (continuous term, penalized spline with 6 DF) + sex (strata, 2 categories) + smoking status (factor, 3 categories) + individual income (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (continuous term) + percentage of non-Spanish nationals (continuous term) + distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories).

Patterns of association between air pollution and hospital admission differed by pandemic wave (**Figure 4**). During the first wave, immediate same-day exposure to NO_2 (lag0) and the cumulative exposure to NO_2 up to the lag2 showed a positive association with hospitalization (HRs: 1.08; 95% CI: 1.02–1.14 and 1.07; 1.01–1.15, respectively) (Appendix Table A11). Air pollution exposure at longer lags was negatively associated with hospital admission during the first wave, resulting in negative cumulative HRs over the lag7 for NO_2 and $PM_{2.5}$: 0.84 (95% CI: 0.76–0.93) for NO_2, and 0.92 (0.87–0.98) for $PM_{2.5}$ per IQR increase.

In contrast, air pollution exposure was positively associated with hospital admission during the second pandemic wave (Figure 4). An IQR increase in daily air pollution at lag0 was associated with a 15% increase (95% CI: 11%–20%) in hospital admission for NO_2, 9% (5%–14%) for $PM_{2.5}$, and 7% (4%–10%) for PM_{10} (Appendix Table A11). The cumulative HRs for an IQR increase in air pollution over the 7 lags were 12% (4%–20%) for NO_2, 8% (1%–16%) for $PM_{2.5}$, and 9% (3%–15%) for PM_{10}. Appendix Table A12 presents estimates for long-term exposure, co-adjusted for short-term exposure. Long-term exposure to $PM_{2.5}$ and PM_{10} was positively associated with hospital admissions in both waves, whereas NO_2 was positively associated with hospital admissions only in the first pandemic wave.

For both waves, cumulative HRs associated with O_3 showed an opposite pattern compared with the other pollutants. Positive associations were observed at longer lags during the first wave and negative associations for the same-day exposure (lag0) during the second wave (Appendix Table A11 and Figure A9).

No significant effect measure modification was observed in stratified analyses (**Figure 5**).

Pandemic wave 2 results for lag0 and lag7 were largely consistent with estimates from the main analysis in sensitivity analyses (Appendix Table A13). Including individuals who tested positive for COVID-19 infection attenuated results for all pollutants. Results from DLNMs (when accounting for possible nonlinearity of exposure) were consistent with those from main models but were generally more imprecise.

Aim 3 Our analysis of whether the influence of long-term exposure to air pollution on COVID-19–related hospital admission differed according to individual- and area-level factors resulted in several key findings. First, patterns of interaction differed considerably when evaluated on the additive versus multiplicative scale. Second, the strongest form of interaction (positive multiplicative, positive additive) was observed for individuals with low income or living in the most deprived neighborhoods. The next strongest form of

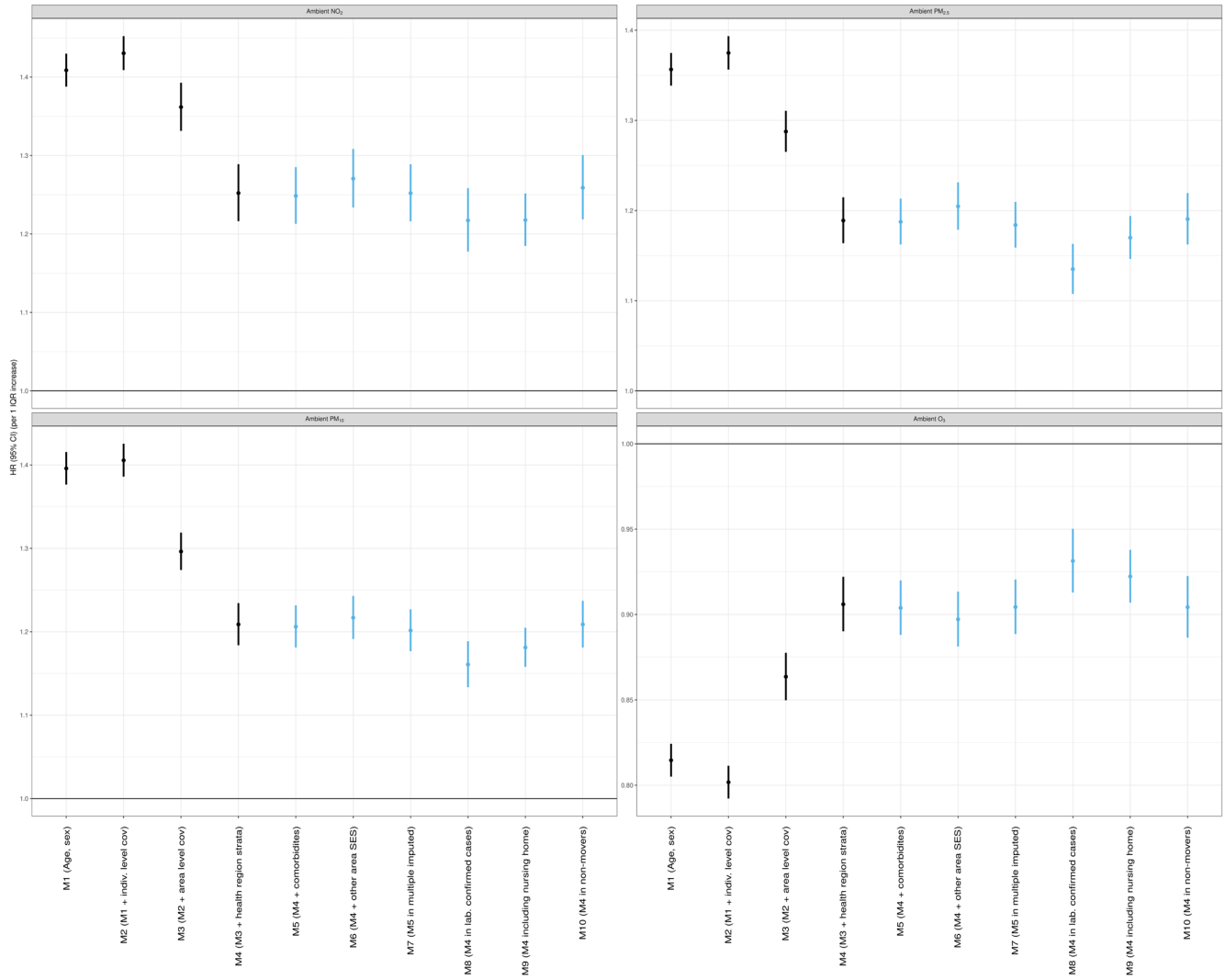

Figure 3. Sequential adjustment and sensitivity analyses for associations between long-term air pollution exposure and COVID-19 related hospitalization (single pollutant models). Main analysis (black); a priori sensitivity analysis (blue).

interaction (no multiplicative, positive additive) was observed for males. For indicators of vulnerability with strong associations with COVID-19–related hospital admissions, evaluating interaction on the additive compared with multiplicative scale provided more interpretable results, and was more consistent with theory and evidence regarding vulnerability to environmental hazards.

The additive effects of exposure and indicators of vulnerability are shown in **Figure 6** for NO_2, $PM_{2.5}$, and PM_{10}. Relative to the least exposed quintile without vulnerability, the risk of COVID-19–related hospital admission was highest in the most exposed quintile for each vulnerability indicator. For age, sex, and most comorbidities, the increase in risk of COVID-19–related hospital admission was close to monotonic across the ten categories. However, a distinct, nonmonotonic pattern was observed for individual and area-level SES indicators, for which the effect of the vulnerability indicator on the risk of COVID-19–related hospital admission alone (e.g., comparison of with and without vulnerability in the first quintile of exposure) was modest.

A similar pattern was observed with dichotomous vulnerability indicators (**Table 7**). Based on the RERI, there was evidence for a joint effect larger than the sum of effects (positive additive) of air pollution exposure and the vulnerability indicator for sex and SES indicators. The RERI for the joint effect of NO_2 and vulnerability indicators was positive and statistically significant for male sex (0.21; 95% CI: 0.15–0.27), low individual income (0.13; 0.09–0.18) and higher area-level deprivation (0.17; 0.12–0.22). There was no evidence of additive synergistic effects for chronic comorbidities. For hypertension, the RERI was negative (negative additive), indicating that their combined effect was less than the sum of their individual effects. Broadly similar patterns were observed for $PM_{2.5}$ and PM_{10} as for NO_2 (Table 7, **Table 8,** and Appendix Table A14).

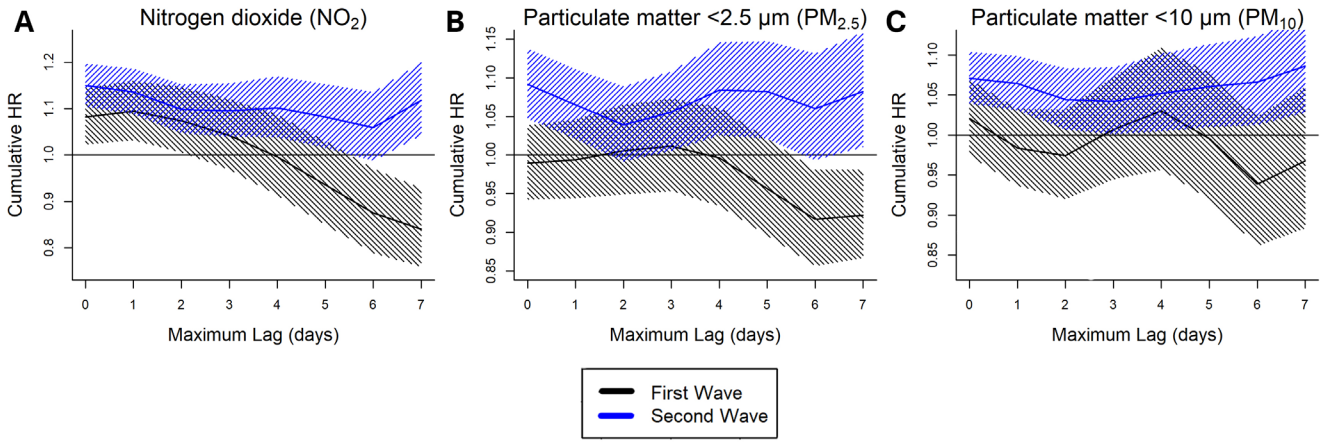

Figure 4. Cumulative hazard ratios (HRs) for hospital admission per IQR increase in air pollution among individuals diagnosed with COVID-19 in primary care (*N* = 240,902) by pandemic wave. Shading represents 95% confidence intervals. Predictions were adjusted for age, sex (stratification variable), tobacco smoking status, individual income, Small Area Socioeconomic Index, health region (AGA), proportion of non-Spanish nationals, distance to the closest primary care unit, urbanicity (stratification variable), the weekly average of test-positive proportion (TPP) at AGA level, long-term exposure to air pollution, temperature, and time and day (weekend or not). Wave 1 = March 1 to June 20, 2020; Wave 2 = June 21 to December 31, 2020.

When evaluating multiplicative interaction between binary air pollution categories and vulnerability indicators, we observed a negative interaction for age and chronic comorbidities, a null interaction for sex, and a positive interaction for low individual income for all pollutants (Table 7, Table 8, and Appendix Table A14). A similar pattern was observed when evaluating the multiplicative interaction between continuous air pollution and vulnerability indicators (**Figure 7**). For example, the HR for one IQR increase in NO_2 among those without diabetes was 1.35 (95% CI: 1.31–1.39), while among those with diabetes, it was 1.25 (1.20–1.30), $P_{interaction}$<0.001. For strong predictors of COVID-19–related hospital admission such as age and comorbidities, the effect of air pollution was smaller among the more vulnerable group.

To further illustrate the multiplicative interaction, we plotted the probability of COVID-19–related hospital admission for the average individual with and without diabetes mellitus and with and without low individual income. The probability of hospital admission increased with increasing NO_2 in both those with and without diabetes. Those with diabetes consistently had a higher risk of hospital admission (**Figure 8**), with the gap between the two groups slightly smaller at the highest levels of NO_2, consistent with an effect estimate of multiplicative interaction less than one (negative multiplicative). In other words, the relative increase in risk of hospital admission in high versus low NO_2 exposure was greater among individuals without diabetes. In contrast, the risk of hospital admission was similar among those with and without low income at low levels of NO_2; however, the difference in risk between those with and without low income increased with increasing NO_2, with low-income individuals having a higher risk of hospital admission consistent with an effect estimate of multiplicative interaction greater than one (positive multiplicative). In other words, the relative increase in risk of hospital admission in high versus low NO_2 exposure was greater among individuals with low income.

Aim 4 Our analysis of whether the association between long-term exposure to air pollution and hospital admission differed between COVID-19 and other respiratory infections resulted in two key findings. First, long-term exposure to NO_2, $PM_{2.5}$, and PM_{10} was positively associated with hospital admission for LRI not due to SARS-CoV-2 infection; and positive associations for O_3 and LRI were observed after adjustment for NO_2. Second, associations for NO_2, $PM_{2.5}$, and PM_{10} with hospital admission for influenza and pneumonia were smaller compared with equivalent estimates for COVID-19. Associations for the broader group of LRI were more similar to those for COVID-19.

Compared with the population with COVID-19–related hospital admission (Table 4), those admitted to the hospital for influenza and pneumonia (Appendix Table A15) were older (mean age 72 vs. 66 years), more likely to be active smokers (20% vs. 11%); have a higher health risk profile (33% vs. 19% in highest risk category); were less likely to be obese (37% vs. 42%); but were more likely to have other comorbidities (31% vs. 25% for diabetes, and 57% vs. 48% for hypertension).

In single-pollutant models (Model 4), an IQR increase in long-term exposure to NO_2, $PM_{2.5}$, and PM_{10} was associated with a 6% (95% CI: 2%–11%), 5% (1%–8%) and 4% (0%–7%) increase in hospital admission for influenza or pneumonia (**Table 9**). An IQR increase in O_3 was positively associated with hospital admission for influenza or pneumonia only in two-pollutant models: 1.02 (0.99–1.05) adjusted for $PM_{2.5}$ and 1.05 (1.01–1.09) adjusted for NO_2. Mutually adjusted associations for $PM_{2.5}$ and NO_2 remained positive, but their 95% CIs included the null: HR for NO_2 was 1.04 (95% CI: 0.98–1.11) and $PM_{2.5}$ was 1.02 (0.97–1.08). Adjustment for O_3 resulted in

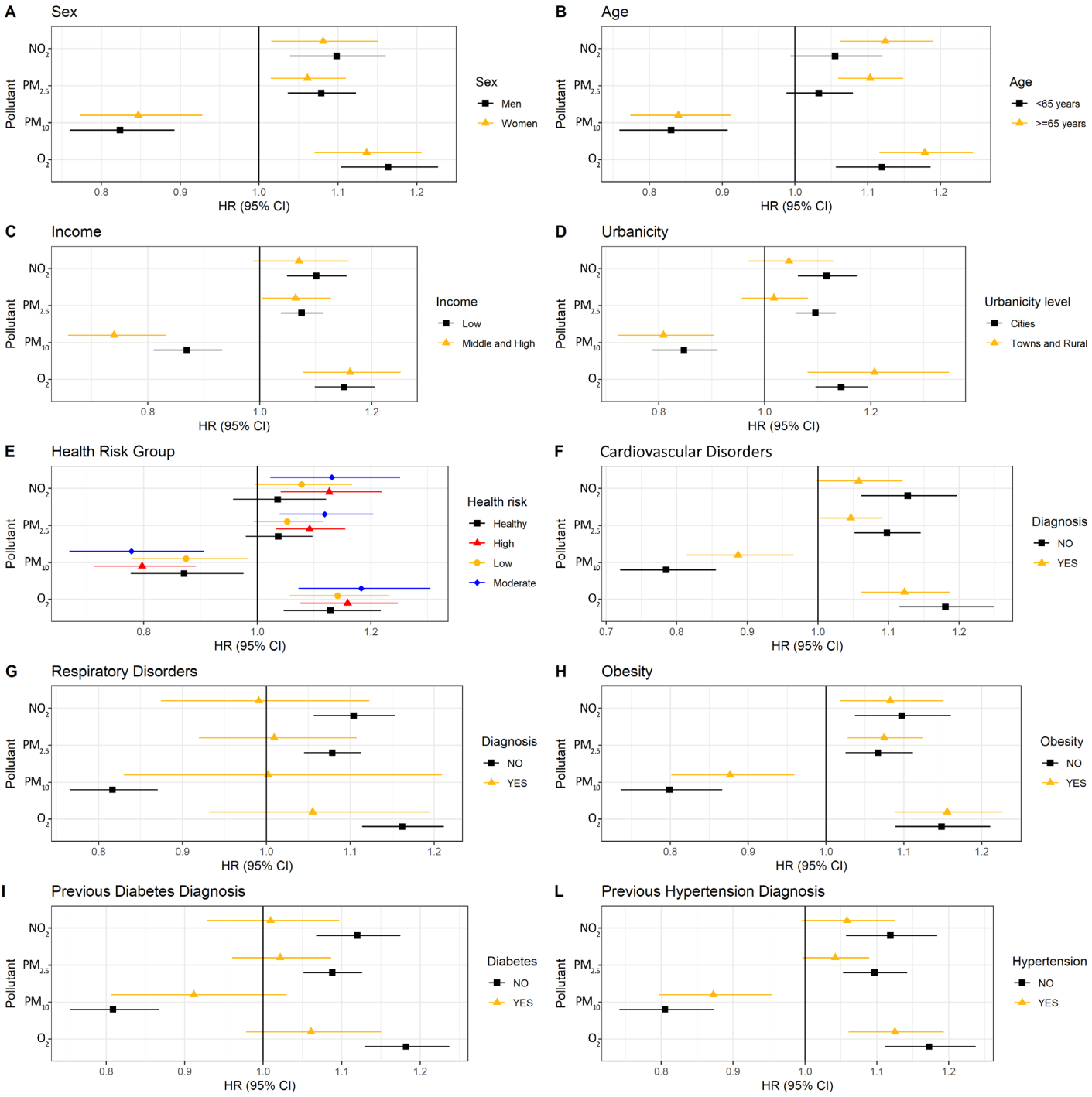

Figure 5. Hazard ratios (95% CI) for hospital admission per IQR increase in air pollution for lag0 among individuals diagnosed with COVID-19 in primary care according to sociodemographic and clinical factors during the second wave (June 21 to December 31, 2020).

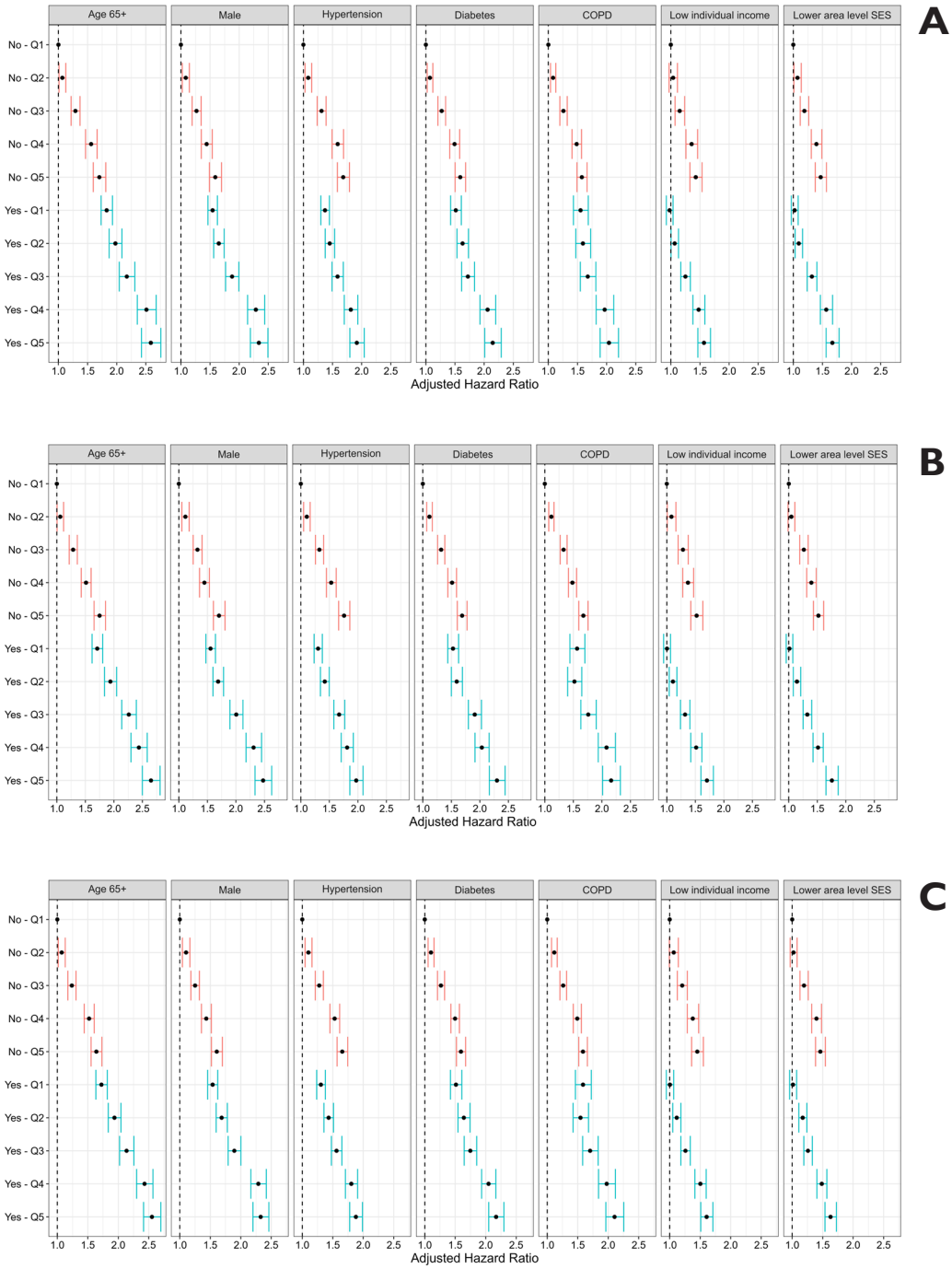

Figure 6. Combined effects of long-term ambient (A) NO_2 (B) $PM_{2.5}$ (C) PM_{10} and vulnerability indicators on COVID-19–related hospital admission. The 10 category levels were created by combining the vulnerability indicator and quintiles of the long-term exposure. The hazard ratio was estimated with a Cox Proportional Hazards model, adjusted by age (factor, 2 categories) + sex (factor, 2 categories) + smoking (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (factor, 2 categories) + distance to the closest primary care unit (continuous term) + urbanicity (factor, 2 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories). The reference group was always absence of the vulnerability indicator and the first quintile of exposure.

Table 7. Association Between Ambient NO_2 and COVID-19 Hospital Admission by Vulnerability Indicators and Their Interaction on Additive and Multiplicative Scales[a]

	NO_2 [b]		Interaction in Multiplicative Scale	Interaction in Additive Scale	Type of Interaction
	Low	High	HR (95% CI)	RERI (95% CI)	(VanderWeele 2019)
Age, Years					
23–64	1.00 (Reference)	**1.49 (1.44 to 1.55)**	**0.87 (0.84 to 0.91)**	0.06 (–0.01 to 0.12)	Negative multiplicative zero additive
65+	1.81 (1.75 to 1.87)	2.36 (2.26 to 2.45)			
Male					
No	1.00 (Reference)	**1.39 (1.34 to 1.45)**	1.00 (0.96 to 1.04)	**0.21 (0.15 to 0.27)**	No multiplicative positive additive
Yes	1.52 (1.47 to 1.57)	2.12 (2.03 to 2.20)			
Hypertension					
No	1.00 (Reference)	**1.49 (1.43 to 1.54)**	**0.87 (0.84 to 0.90)**	**–0.10 (–0.16 to –0.05)**	Negative multiplicate negative additive
Yes	1.32 (1.28 to 1.37)	1.71 (1.64 to 1.78)			
Diabetes					
No	1.00 (Reference)	**1.43 (1.38 to 1.48)**	**0.91 (0.87 to 0.95)**	0.01 (–0.06 to 0.09)	Negative multiplicative zero additive
Yes	1.49 (1.44 to 1.55)	1.94 (1.86 to 2.02)			
Chronic Obstructive Pulmonary Disease					
No	1.00 (Reference)	**1.41 (1.36 to 1.46)**	**0.91 (0.85 to 0.97)**	0.00 (–0.10 to 0.10)	Negative multiplicative zero additive
Yes	1.45 (1.38 to 1.53)	1.86 (1.77 to 1.95)			
Low Individual Income					
No	1.00 (Reference)	**1.30 (1.25 to 1.36)**	**1.10 (1.05 to 1.15)**	**0.13 (0.09 to 0.18)**	Positive multiplicative positive additive
Yes	1.00 (0.97 to 1.04)	1.44 (1.38 to 1.50)			
Lower Area-Level SES					
No	1.00 (Reference)	**1.34 (1.29 to 1.39)**	**1.10 (1.06 to 1.15)**	**0.17 (0.12 to 0.22)**	Positive multiplicative positive additive
Yes	1.07 (1.04 to 1.11)	1.59 (1.53 to 1.65)			

[a] **Bolding** indicates significant values.

[b] NO_2 categories defined by the median value (28.3); the low category has a mean of 17.4 (standard deviation = 6), while the high category has a mean of 35.0 (standard deviation = 5).

Table 8. Association Between Ambient $PM_{2.5}$ and COVID-19 Hospital Admission by Vulnerability Indicators and their Interaction on Additive and Multiplicative Scales[a]

	$PM_{2.5}$[b]		Interaction in Multiplicative Scale HR (95% CI)	Interaction in Additive Scale RERI (95% CI)	Type of Interaction (VanderWeele 2019)
	Low	High			
Age, Years					
23–64	1.00 (Reference)	**1.40 (1.35 to 1.45)**	**0.89 (0.86 to 0.93)**	0.04 (–0.02 to 0.11)	Negative multiplicative zero additive
65+	1.78 (1.72 to 1.84)	2.22 (2.14 to 2.30)			
Male					
No	1.00 (Reference)	**1.32 (1.27 to 1.36)**	1.00 (0.96 to 1.04)	**0.16 (0.11 to 0.22)**	No multiplicative positive additive
Yes	1.52 (1.47 to 1.57)	2.00 (1.94 to 2.07)			
Hypertension					
No	1.00 (Reference)	**1.37 (1.33 to 1.42)**	**0.91 (0.87 to 0.95)**	–0.05 (–0.11 to 0.00)	Negative multiplicative zero additive
Yes	1.29 (1.24 to 1.33)	1.61 (1.55 to 1.67)			
Diabetes					
No	1.00 (Reference)	**1.34 (1.30 to 1.38)**	**0.93 (0.89 to 0.97)**	0.02 (–0.05 to 0.09)	Negative multiplicative zero additive
Yes	1.47 (1.42 to 1.53)	1.83 (1.77 to 1.90)			
Chronic Obstructive Pulmonary Disease					
No	1.00 (Reference)	**1.33 (1.29 to 1.36)**	**0.93 (0.87 to 0.99)**	0.01 (–0.09 to 0.10)	Negative multiplicative zero additive
Yes	1.43 (1.36 to 1.51)	1.77 (1.69 to 1.85)			
Low Individual Income					
No	1.00 (Reference)	**1.26 (1.21 to 1.31)**	**1.07 (1.03 to 1.12)**	**0.10 (0.05 to 0.14)**	Positive multiplicative positive additive
Yes	1.02 (0.99 to 1.06)	1.37 (1.32 to 1.43)			
Lower area-level SES					
No	1.00 (Reference)	**1.29 (1.25 to 1.33)**	**1.04 (1.00 to 1.09)**	**0.09 (0.05 to 0.14)**	Positive multiplicative positive additive
Yes	1.11 (1.07 to 1.14)	1.49 (1.44 to 1.54)			

[a] **Bolding** indicates significant values.

[b] $PM_{2.5}$ categories defined by the median value (13.9); the low category has a mean of 12.1 (standard deviation = 1), while the high category has a mean of 15.6 (standard deviation = 1).

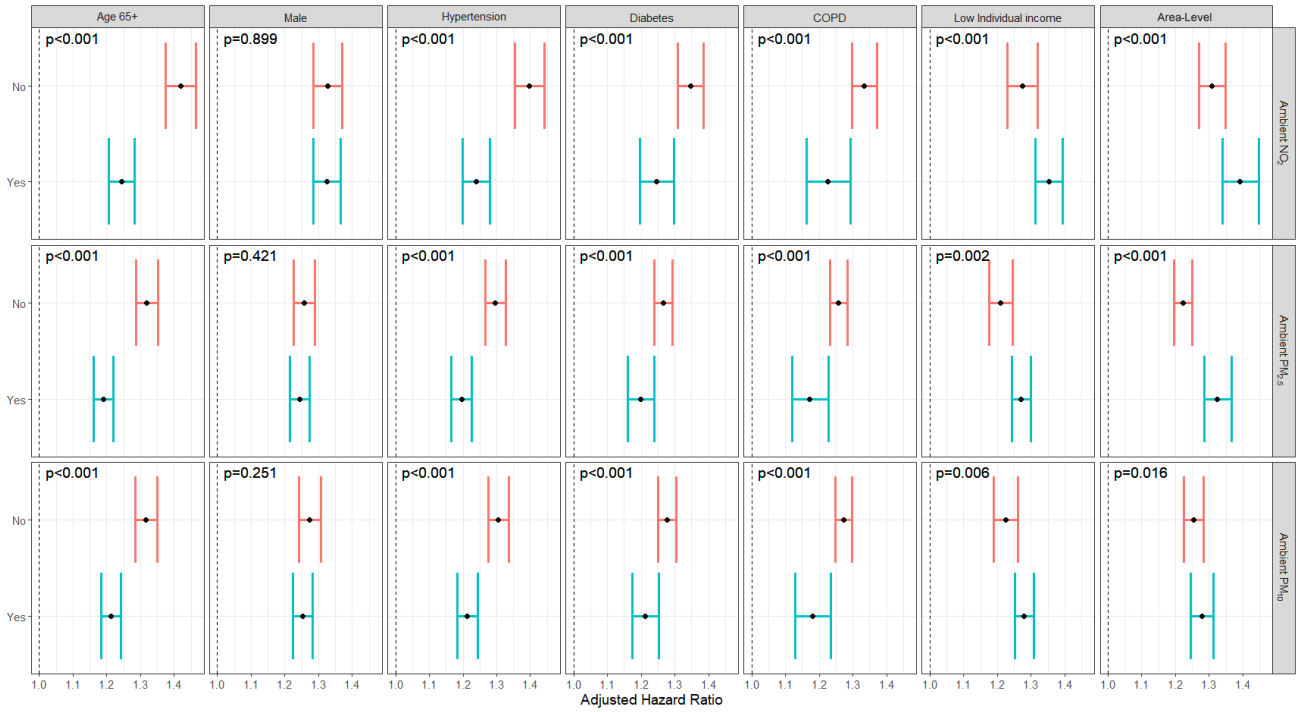

Figure 7. Adjusted association between ambient NO_2, $PM_{2.5}$, and PM_{10} and COVID-19–related hospital admission per IQR increase by vulnerability indicators. *P* values for significance of multiplicative interaction. Output of main model with air pollutants as continuous term and interaction term between pollutant and vulnerability indicator. IQRs were 16.1 µg/m³ for NO_2, 3.2 µg/m³ for $PM_{2.5}$, and 4.2 µg/m³ for PM_{10}.

a larger HR for NO_2 compared with single-pollutant models: 1.12 (1.05–1.20).

Compared with estimates for influenza and pneumonia, associations for LRIs were stronger for all pollutants except for O_3 (Table 9). In single-pollutant models, an IQR increase of NO_2, $PM_{2.5}$, and PM_{10} was associated with 18% (95% CI: 14%–22%), 14% (11%–17%), and 10% (7%–13%) increases in LRI hospital admission. Mutually adjusted estimates were attenuated for both NO_2 and $PM_{2.5}$: 1.10 (1.05–1.16) and 1.07 (1.03–1.12), respectively. Larger positive associations were observed in mutually adjusted estimates for NO_2 and O_3 compared with respective single-pollutant estimates (Table 9).

Figure 9 presents the comparison of estimates of long-term exposure to air pollution and hospital admission for non-SARS-CoV-2 respiratory infections in 2019 with estimates of hospital admission for COVID-19 during 2020. HRs for COVID-19–related hospital admission were higher than those for influenza or pneumonia for NO_2, $PM_{2.5}$, and PM_{10}. Associations for hospital admission for all non-COVID LRIs were similar to estimates for COVID-19 for $PM_{2.5}$, whereas for NO_2 and PM_{10}, the estimates for COVID-19 were greater than for LRIs.

Multiplicative interactions were observed between air pollution and age for all pollutants (*P* value interaction <0.05) (Appendix Figure A10). An IQR increase in NO_2, $PM_{2.5}$, and PM_{10} was associated with a 19%, 15%, and 11% increase in hospital admission risk among people older than 65, whereas the same unit change increased hospital admissions by 13%, 11%, and 7% among people younger than 65. The opposite pattern was observed for O_3.

The additive effect of increasing exposure according to vulnerability indicators is shown in **Figure 10** and Appendix Figure A11**.** Relative to the least exposure quintile without vulnerability, the risk of hospital admission for LRI was highest in the most exposed quintile among each vulnerable group — except for individuals with hypertension or in the lowest area level deprivation group, for which the risk was similar for the most exposed individuals regardless of their vulnerability status.

We observed synergistic (greater than additive) interactions for age ≥65 years (significant, positive RERIs for NO_2, $PM_{2.5}$, PM_{10}), males (for PM_{10} and $PM_{2.5}$), and individuals with low income (for NO_2 and $PM_{2.5}$) (Appendix Tables A16 to A18). The overall pattern of the combined effect of long-term exposure and vulnerability for hospital admission for LRI was similar to that for COVID-19 (Figure 6) for male sex and diabetes. The effect of increasing exposure among those with hypertension or living in areas with low SES was less clear for hospital admission for LRI compared with COVID-19.

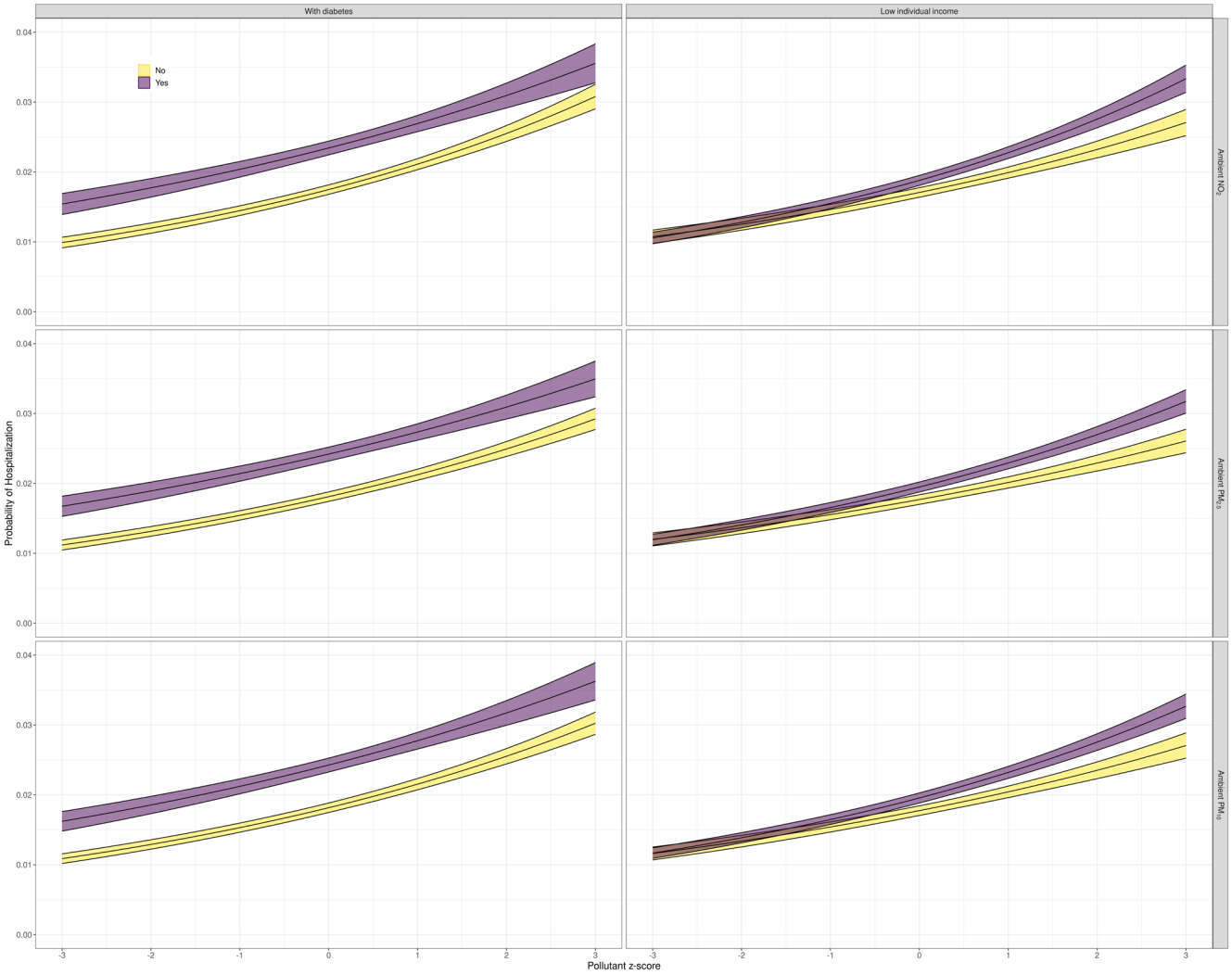

Figure 8. Cumulative probability of COVID-19–related hospital admission by diabetes mellitus and individual-level income status. Illustrative cumulative probability of COVID-19–related hospital admission at 305 days of follow-up (maximum follow-up time in the cohort) representing individuals with average age, male, nonsmoker, low individual income status (for the diabetes plot), moderate health risk group, average small area socioeconomic index, average distance to the nearest primary healthcare unit, residence in urban municipality, average test-positive proportion, and health region of Barcelona. These cumulative probabilities are from the main model of analysis which included an interaction term between the pollutant and diabetes mellitus (left plots) and between the pollutant and individual income status (right plots).

DISCUSSION AND CONCLUSIONS

In brief, below are the main findings of the COVAIR-CAT project:

- We observed positive associations between long-term exposure to NO_2, $PM_{2.5}$, and PM_{10} with severe COVID-19 in this large population-based cohort of adults (Aim 1).
- Results from the second pandemic wave during 2020 indicated a positive association between exposure to NO_2, $PM_{2.5}$, and PM_{10} over the previous 7 days and hospital admission for COVID-19, largely driven by the same-day exposure (Aim 2). Results from the first wave were more difficult to interpret.
- The strongest evidence for increased vulnerability to the effects of long-term ambient NO_2, $PM_{2.5}$, and hospital admission for COVID-19 was for individuals with lower individual- and area-level SES (Aim 3).
- We observed positive associations between long-term exposure to NO_2, $PM_{2.5}$, PM_{10}, and O_3 (adjusted for NO_2) with hospital admission for pneumonia and influenza, as well as for all LRI the year before the start of the COVID-19 pandemic. Effect estimates scaled to the same unit change were stronger for hospital admission for COVID-19 compared with LRI for PM_{10} and NO_2, and were roughly equivalent for $PM_{2.5}$.

Table 9. Hazard Ratios (95% CI) Between Long-Term Air-Pollution Exposure and Hospital Admissions for Influenza or Pneumonia (N = 17,608) and for Lower Respiratory Infections[a] (N = 28,121) from Single- and Two-Pollutant Models (Model 4[b])

			Influenza and Pneumonia	All LRIs
Pollutant	**IQR Value**	**Model**	**HR (95% CI)**	**HR (95% CI)**
NO_2	16.4	Single pollutant	**1.06 (1.02–1.11)**	**1.18 (1.14–1.22)**
		Adjusted for $PM_{2.5}$	1.04 (0.98–1.11)	**1.10 (1.05–1.16)**
		Adjusted for O_3	**1.12 (1.05–1.20)**	**1.23 (1.17–1.30)**
$PM_{2.5}$	2.55	Single pollutant	**1.05 (1.01–1.08)**	**1.14 (1.11–1.17)**
		Adjusted for NO_2	1.02 (0.97–1.08)	**1.07 (1.03–1.12)**
		Adjusted for O_3	**1.06 (1.02–1.11)**	**1.14 (1.10–1.17)**
PM_{10}	3.91	Single pollutant	**1.04 (1.00–1.07)**	**1.10 (1.07–1.13)**
		Adjusted for NO_2	1.01 (0.97–1.06)	1.03 (0.99–1.06)
		Adjusted for O_3	**1.04 (1.00–1.08)**	**1.08 (1.05–1.12)**
O_3	10.3	Single pollutant	0.99 (0.97–1.02)	0.94 (0.92–0.96)
		Adjusted for $PM_{2.5}$	1.02 (0.99–1.05)	1.00 (0.97–1.02)
		Adjusted for NO_2	**1.05 (1.01–1.09)**	**1.04 (1.01–1.08)**

[a] Including influenza and pneumonia.

[b] **Bolding** indicates significant values. Models were adjusted for age, sex (stratification variable), tobacco smoking status, individual income, health risk group, small area socioeconomic index, proportion of non-Spanish nationals, distance to the closest primary care unit, and urbanicity (stratification variable).

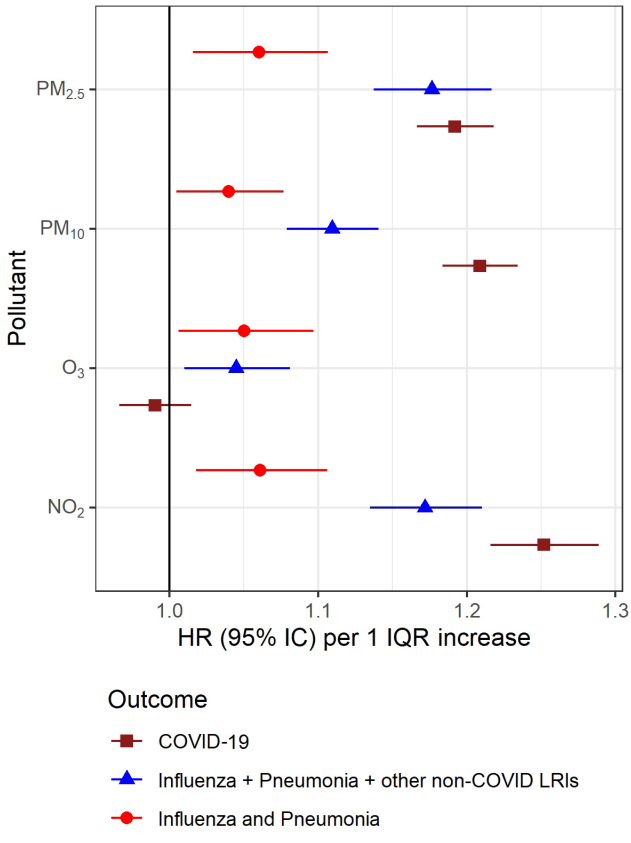

Figure 9. Associations between long-term air pollution exposure and hospital admission for influenza or pneumonia (red), lower respiratory infections including influenza and pneumonia and excluding COVID-19 (blue), and for COVID-19 (brown). Estimates from single-pollutant models for NO_2, $PM_{2.5}$, and PM_{10}, and for O_3 adjusted for NO_2. IQR values are for 2019 as in Ranzani and colleagues (2023). NO_2: 16.1; $PM_{2.5}$: 3.2; PM_{10}: 4.2; O_3: 10.8. LRI = lower respiratory infection.

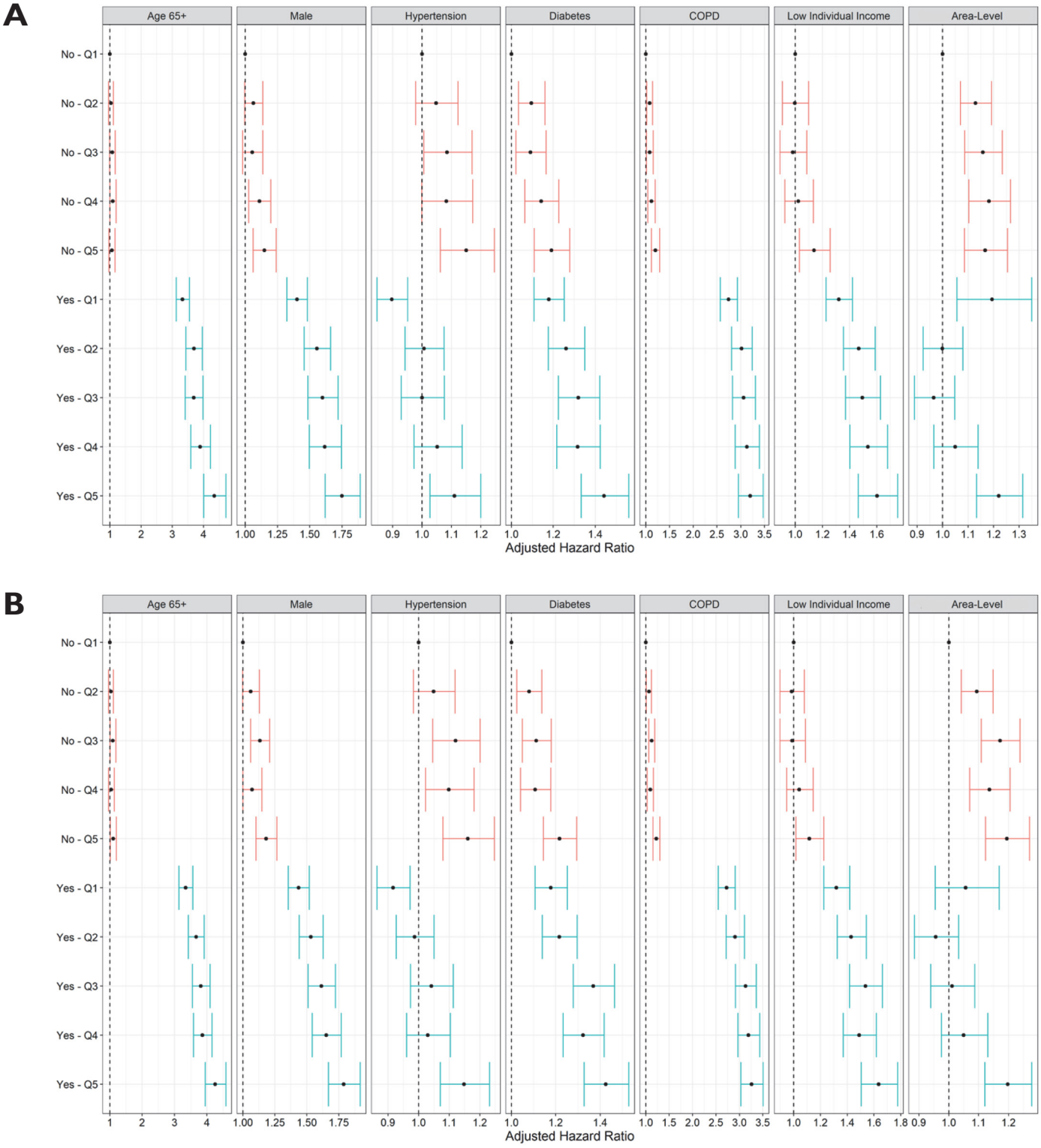

Figure 10. Combined effects of long-term ambient (A) NO_2 and (B) $PM_{2.5}$ and vulnerability indicators on the risk of hospital admission for lower respiratory infections.

INTERPRETATION OF RESULTS AND COMPARISON WITH LITERATURE ACCORDING TO AIM

Our Aim 1 estimates for long-term $PM_{2.5}$ and COVID-19–related hospital admission are broadly consistent with other cohorts of COVID-19 cases (Chen C et al. 2022a; Chen Z et al. 2022b). The association for hospital admission ranged from an odds ratio (OR) of 1.06 (95% CI: 1.01–1.12, per 1.7-μg/m^3 [IQR] increase) to HR of 1.24 (1.16–1.32, per 1.5-μg/m^3 [standard deviation] increase) in analyses conducted in 150,000 COVID-19 cases in Ontario, Canada (Chen C et al. 2022a) and 75,000 cases in California, USA (Chen Z et al. 2022b). In contrast with our findings, analyses in these two cohorts and other individual-level studies observed no evidence of an association between long-term NO_2 and hospital admission (Kogevinas et al. 2021a; Marquès et al. 2022; Sheridan et al. 2022). The smaller sample sizes and selected populations compared with ours could explain differences in our findings.

We observed greater estimates during the first pandemic wave, which may reflect higher levels of susceptibility to severe COVID-19 compared with the second wave or unmeasured contextual confounding factors, such as spatiotemporal patterns in health system capacity (which were less influential in the second wave).

Overall, our estimates are slightly greater in magnitude than those reported in previous literature for COVID-19–related hospital admission (Appendix Table A20), although a direct comparison is not straightforward due to differences in exposure assessment, confounder adjustment, and outcome definition. One possible explanation for the observed differences is that we analyzed a population-based cohort, thus our estimates encompassed the risk of infection and the associated risk of severe COVID-19 following infection. In contrast, cohorts including only COVID-19–diagnosed individuals estimated the risk of severe COVID-19 following infection (Westreich et al. 2022). We took this approach for several reasons. First, we wanted to avoid an expected and likely important selection bias when restricted to COVID-19–diagnosed individuals. Particularly for the first pandemic wave, and even in the second wave, underdiagnosis of COVID-19 was high. Access to testing was likely associated with air pollution levels, and unmeasured factors associated with both testing positive and air pollution could result in a well-described selection/collider bias (Griffith et al. 2020; Millard et al. 2023). When evaluating cohorts of COVID-19–diagnosed individuals in sensitivity analyses for Aim 1, we observed smaller estimates compared with the main analysis, indicating that estimates based only on individuals who were tested were likely affected by selection bias (Griffith et al. 2020; Millard et al. 2023). Second, our goal was to derive estimates for the target population (i.e., the adult population of Catalonia). Third, all individuals in the cohort were at risk of the outcome; those who had not been diagnosed were still at risk of becoming infected and subsequently having a severe event within 30 days.

Estimates for the association of long-term air pollution exposure with COVID-19 death are more inconsistent in the literature compared with those for hospital admission (Chen C et al. 2022a; English et al. 2022; Marquès et al. 2022; Nobile et al. 2022; Sheridan et al. 2022). A population-based cohort study from the general adult population in Rome (N = 1,594,308) observed an HR of 1.08 (95% CI: 1.03–1.13, per IQR 0.92-μg/m^3 increase) for long-term $PM_{2.5}$ and 1.09 (1.02–1.16, per IQR 9.22-μg/m^3 increase) for long-term NO_2 for COVID-19–related deaths (Nobile et al. 2022). Smaller estimates were observed in a population-based cohort of COVID-19 cases (N = 3,139,804) in California, USA, where the estimated long-term $PM_{2.5}$ association with death was a relative risk (RR) of 1.04 (1.03, 1.05) (English et al. 2022), which was similar to the COVAIR-CAT estimate for an equivalent 1 μg/m^3 increase in $PM_{2.5}$ (HR of 1.04; 1.02–1.06). However, a cohort with 150,000 COVID-19 cases in Canada reported null associations for death, while positive associations were reported for hospital and ICU admission (Chen C et al. 2022a); a cohort of a selected population from the UK (UK–Biobank cohort, N = 424,721) observed null results for death for $PM_{2.5}$ (HR 1.00; 0.89–1.11, per IQR 1.2-μg/m^3 increase) and NO_2 (HR 1.03; 0.90–1.16, per IQR 9.93-μg/m^3 increase) (Sheridan et al. 2022).

Our results investigating Aim 2 differed considerably by the pandemic wave. We observed more consistent positive associations for same-day (lag0) exposure and COVID-19–related hospital admission in wave 2. Estimates for the second wave are likely to have better internal and external validity compared with the first pandemic wave for several reasons. Negative associations estimated during the first wave for lagged exposures likely reflect confounding by strict COVID-19 restriction policies, which led to sharp reductions in air pollution at times when case numbers were high. COVID-19 restriction policies were stricter and lasted longer during the first compared with the second wave (González-Pardo et al. 2022; Hernandez Carballo et al. 2022; Schneider et al. 2022). Moreover, underdiagnosis at the population level was particularly high during the first pandemic wave (Krantz and Rao 2020; Lau et al. 2021), and selection bias might have played a role by identifying only more severe COVID-19 cases, which were more likely to be diagnosed or receive testing when the testing capacity was limited. Results from the second wave, when mobility and gathering restrictions were relaxed and access to testing was widespread, are more likely to be generalizable to the broader, ongoing pandemic. Negative associations at lag2 between NO_2, PM_{10}, and hospital admission during the second wave may be explained by harvesting, in which the most vulnerable people were hospitalized on the same day as the increase in air pollution, leaving a more resilient population less affected by this increase in the following two days.

Our Aim 2 analysis indicated that both short- and long-term exposure to air pollution were associated with COVID-19–related hospital admission. By adjusting for long-term exposure in the model, the Cox approach allows for separate estimation of both effects. Although we cannot completely rule out residual confounding from long-term exposure, the

correlation between short- and long-term exposures was modest, particularly for pollutants other than NO_2 (0.55 for NO_2, 0.10–0.27 for other pollutants; results not shown), indicating that the extent of possible residual confounding by long-term exposure is fairly limited.

We have not identified other individual-level studies of short-term air pollution exposure and COVID-19–related hospital admission. Our Aim 2 results are therefore not directly comparable to other studies evaluating COVID-19–related hospital admission but are broadly comparable to the handful of individual-level studies evaluating other COVID-19 outcomes. An individual-level case-crossover study by Lavigne and colleagues (2022) provided evidence of an association between short-term exposure to NO_2 and $PM_{2.5}$ and increased risk of COVID-19–related emergency department visits in Canada. Positive associations were reported for NO_2 and $PM_{2.5}$, but not O_3. Yu and colleagues (2022) focused on the risk of COVID-19 infection in a population-based cohort of young adults in Sweden. The authors observed an association between daily $PM_{2.5}$, PM_{10}, and black carbon exposure and a positive PCR test result, but no association was observed with nitrogen oxides. No effect modification was observed for sex or other clinical characteristics. López-Feldman and colleagues (2021) found weak evidence to support an association between short-term exposure to $PM_{2.5}$ and COVID-19–related deaths in Mexico City, while Kim, Samet, and Bell reported positive associations of both particulate matter and O_3 concentrations with COVID-19 mortality, which differed by demographic characteristics and some comorbid conditions (Kim et al. 2022).

In the analysis of Aim 3, we found that for strong predictors of COVID-19–related hospital admission (e.g., age and comorbidities), multiplicative interactions based on Cox proportional hazards models could be difficult to interpret and that the additive scale provided more consistent, biologically plausible results. Although age has been consistently identified as a main predictor of COVID-19 severity, our results based on the multiplicative scale indicated that the effect of air pollution was lower for those above compared with those under 65 (Tables 7 and 8), whereas the effect of air pollution exposure combined with older age was clearly associated with a higher risk of hospital admission compared with younger age on an additive scale (Figure 6). The literature overall regarding vulnerability according to age has been inconsistent, likely because most studies have evaluated interaction on a multiplicative scale. Some have reported a U-shaped pattern, with a higher risk of severe COVID-19 among young and older adults (Chen Z et al. 2022b), while others observed a higher risk among older adults (Hyman et al. 2023) or found no evidence for interaction on the multiplicative scale but a positive association in the additive scale (Bowe et al. 2021).

A pattern similar to that for age was observed for comorbidities, in which air pollution had a smaller effect on COVID-19–related hospital admission among those with comorbidities on a multiplicative scale. A few previous studies have reported evidence of effect modification on the multiplicative scale, including one cohort based on selected COVID-19 patients (N =1,128), which reported an association between $PM_{2.5}$ and hospital admission only among individuals with chronic respiratory diseases (Mendy et al. 2021). Another cohort of COVID-19–diagnosed individuals (N = 313,657) in Manchester, UK, showed stronger associations between long-term exposure to air pollution and COVID-19–related hospital admission among individuals who were older, overweight, or had chronic comorbidities (Hyman et al. 2023).

We observed a positive additive interaction between air pollution and male sex but no interaction on the multiplicative scale. Other studies found no evidence of effect modification on either scale or when subsetting the analysis by sex (Bowe et al. 2021; Chen Z et al. 2022b; Hyman et al. 2023; Kogevinas et al. 2021a; Stafoggia et al. 2023). Results from many previous studies are challenging to interpret regarding vulnerability by sex because they were not population-based and were often based on a cohort of COVID-19 cases with notably different sex distributions from what would be expected in the general population (Bowe et al. 2021).

The most consistent findings across scales were related to lower SES, for which the combination of high air pollution exposure and lower SES at the individual and area level was associated with a higher risk of COVID-19–related hospital admission on both additive and multiplicative scales for NO_2, $PM_{2.5}$, and PM_{10}. Positive interaction on both scales provides the strongest evidence that the effects of air pollution on COVID-19–related hospital admission are greater in a population subgroup (VanderWeele 2019). These results are consistent with findings from a cohort of COVID-19 cases (N = 169,102) from the US Department of Veterans Affairs healthcare databases, in which the risk of hospital admission was higher for those living in high-deprived areas compared with those in low-deprived areas on the multiplicative (RR 1.15; 95% CI: 1.12–1.18, for high deprivation vs. RR 1.08; 1.05–1.11 for low deprivation, per 1.9-μg/m^3 increase of $PM_{2.5}$, $P_{\text{interaction}} \leq 0.001$) and additive scales (RERI 0.04; 0.02–0.06) (Bowe et al. 2021). The same pattern was observed for race, with higher risk of hospital admission for Black compared with White individuals on the multiplicative (RR 1.17; 1.13–1.21, for Black versus RR 1.12; 1.10–1.16 for White, per 1.9-μg/m^3 increase of $PM_{2.5}$, $P_{\text{interaction}}$ = 0.045) and additive scales (RERI 0.06; 0.04–0.07). However, the broader literature is not consistent regarding vulnerability according to race/ethnicity or education level in relation to air pollution on the multiplicative scale (Bozack et al. 2022; Chen Z et al. 2022b).

In our Aim 4 analysis, air pollution effect estimates differed considerably for hospital admission for influenza and pneumonia compared with all LRIs, which had larger estimates more similar to those for COVID-19. This pattern may reflect the influence of vaccines available against the pathogens responsible for influenza (influenza virus) and for most pneumonia cases (*Streptococcus pneumoniae*). On the other hand, vaccines are not readily available against the

mostly viral pathogens responsible for other LRIs (e.g., respiratory syncytial virus). Pneumococcal conjugate vaccines have been shown to have a direct protective effect on young children and an indirect protective effect on unvaccinated adults (Rodgers et al. 2021; Shiri et al. 2016) and may have conferred some protection against the adverse effects of air pollution exposure. Influenza vaccination may also moderate the detrimental effects of ambient air pollution on respiratory outcomes, a mechanism previously described among children (Liu et al. 2020).

Our results for the association between long-term exposure and hospital admission for influenza and pneumonia, and LRIs more broadly, are consistent with the few studies that were conducted among adults. Neupane and colleagues (2010) found that long-term exposure to NO_2 and $PM_{2.5}$ was positively associated with hospital admission for pneumonia among older adults (>65 years old). Although sensitive to the choice of exposure assessment approaches, their estimate was considerably higher than ours: ORs from 1.70 to 2.30 (depending on exposure metric) for a 5th to 95th percentile range increment in NO_2 and ORs from 1.70 to 2.26 for the same increment in $PM_{2.5}$. A large retrospective cohort study using administrative data from primary care reports for adults ≥40 years residing in London found nonsignificant positive associations between both exposure to NO_2 and $PM_{2.5}$ and pneumonia (Carey et al. 2016): 1.08 (95% CI: 0.98–1.20) and 1.04 (0.95–1.15) per 1-μg/m^3 of NO_2 and $PM_{2.5}$, respectively. Long-term exposures to $PM_{2.5}$ and O_3 (but not NO_2) were also positively associated with hospital admission for pneumonia among individuals 65 years or older in the United States (Danesh Yazdi et al. 2021). Wang and colleagues conducted a large prospective cohort of individuals 40 to 69 years in the UK and reported associations per IQR increase in NO_2, $PM_{2.5}$, and PM_{10} with hospital admission for pneumonia of 12%, 6%, 10% (Wang et al. 2023). However, no associations between NO_2, $PM_{2.5}$, and hospital admission for pneumonia were identified by Salimi and colleagues (2018) among individuals aged >45 years residing in Sidney. A 2022 systematic review and meta-analysis published by HEI provided a summary estimate for the association between NO_2 and LRIs of 1.07 (0.71–1.61) per 10-μg/m^3 increase (Boogaard et al. 2022; HEI 2022). To our knowledge, no other studies have directly compared estimates of the effect of long-term air pollution on hospital admission for COVID-19 with LRI from non-SARS-CoV-2 pathogens.

THE ROLE OF O_3

In Aim 1 analyses, single-pollutant models estimated negative effects for O_3 and COVID-19 severity. However, associations adjusted for NO_2 were either null or positive for COVID-19 ICU admission. In Aim 2 analyses for pandemic wave 2, the cumulative HR for O_3 with hospital admission for COVID-19 adjusted for NO_2 was null; however, the lag0 estimate was significant and negative. Because the O_3 effect on COVID-19–related hospital admission was null after adjusting for NO_2 in Aim 1, we did not include O_3 in the Aim 3 analysis. In the Aim 4 analysis, O_3 was positively associated with hospital admission for influenza and pneumonia as well as for the broader set of LRI after adjustment for NO_2.

Overall, the role of O_3 on COVID-19 severity was difficult to interpret because of the high negative correlation with NO_2 for annual average exposure (–0.82) and moderate for daily exposure (–0.46) (Appendix Table A6). The exposure distribution to O_3 was also markedly different according to the pandemic wave, with a considerably higher mean exposure during wave 1 (Appendix Figure A5). Although the COVAIR exposure model performance was good overall for O_3 (Appendix Table A3), it better captured temporal (R^2 temporal 0.88) rather than spatial (R^2 spatial 0.40) variation. The model may not have captured finer-spatial scale variation in O_3 due to the relative sparseness of O_3 measurements, and the coarse spatial resolution of the CAMS model, which was the main predictor reflecting the complex chemistry of O_3. These limitations likely resulted in exposure measurement error for O_3 greater than for the other pollutants. Some authors have speculated that the antiviral properties of O_3 may explain negative associations observed with COVID-19 outcomes (Bayarri et al. 2021). However, these properties should apply to many viruses broadly, including those that cause LRI, not just SARS-CoV-2. This seems an unlikely explanation for the negative effects we observed for O_3 in single-pollutant models or for lag0 (adjusted for NO_2) in Aim 2.

BIOLOGICAL PLAUSIBILITY

There are several biological mechanisms through which long-term air pollution could increase the risk of severe COVID-19. An initial hypothesis was that long-term air pollution increases the baseline risk of the population exposed to higher levels, resulting in a greater prevalence of chronic comorbidities associated with severe COVID-19 such as hypertension. In this case, chronic comorbidities associated with long-term exposure would mediate the association between long-term air pollution exposure and severe COVID-19. Although we did not perform a formal causal mediation analysis in our Aim 1 analysis (Lapointe-Shaw et al. 2018), adjustment for chronic comorbidities associated with air pollution in the sensitivity analysis (Aim 1, model 5) resulted in minimal change in the estimates. These results, which are similar to findings in other cohort studies, suggest other direct pathways are more relevant (English et al. 2022; Nobile et al. 2022). Aim 3 analyses indicated no positive additive interaction between long-term exposure and chronic comorbidities. In summary, our results indicate that chronic comorbidities did not play an important role in the pathway linking long-term exposure to air pollution and severe COVID-19.

Another hypothesis is that air pollution exposure could facilitate SARS-CoV-2 binding based on evidence that exposure to particulate matter upregulates the expression of SARS-CoV-2 receptors in the lung (e.g., angiotensin-converting enzyme 2) (Kogevinas et al. 2021a; Sagawa et al. 2021).

Exposure to air pollution may also be related to changes in immune defense that are key to mitigating SARS-CoV-2, such as a decrease in type II interferon response to SARS-CoV-2 and antibody response (Allouche et al. 2022; Kogevinas et al. 2021a). All hypothesized mechanisms would result in a population susceptible to severe COVID-19. Our Aim 4 results for all LRI — for which the population would have already had some level of immunity — yielded effect estimates nearly as large as those from COVID-19, suggesting that relevant mechanisms apply to novel as well as established pathogens that cause LRI. However, further studies are needed to provide stronger evidence regarding the main biological pathways involved in the effects of COVID-19 in particular and LRI more broadly.

Our findings related to short-term exposure in Aim 2 indicate that air pollution on the same day was associated with hospital admission for COVID-19. These results indicate that an acute response is most relevant such as exacerbated symptoms due to an effect of air pollution on acute pulmonary response. Other hypothesized pathways such as immune system dysfunction leading to viral replication are not consistent with our results as they would occur on a longer time scale.

The biological and social mechanisms underpinning the patterns of effect modification for COVID-19–related hospital admission (Aim 3) and LRI (Aim 4) are not well understood. Those over 65 years were identified as being vulnerable to the effect of long-term air pollution exposure on hospital admission for LRI, which may reflect a reduced capacity to manage oxidative stress and inflammation due to air pollution or lower immune response. These pathways would however also be expected to play a role in COVID-19–related hospital admission. Males were identified as being vulnerable to the effect of air pollution for hospital admission for COVID-19 as well as LRI, which may reflect differences in innate and adaptive immunity (Chaturvedi et al. 2022; Takahashi et al. 2020). Individuals with low income were identified as being vulnerable to air pollution for hospital admission for COVID-19 and LRI, and those living in areas with low SES were vulnerable to hospital admission for COVID-19. Our results suggest these patterns do not operate through comorbidities and instead may be related to occupational exposure to high viral loads or differences in healthcare access or utilization (Mena et al. 2021).

Strengths Strengths of COVAIR-CAT include the combination of population representativeness spanning large urban and rural areas, with detailed individual-level data for exposures and confounding adjustment in a country heavily affected by the pandemic during 2020. This yielded good statistical power and external validity, and it allowed us to evaluate two-pollutant models, a range of complementary outcomes including health system burden, several sensitivity analyses, and to explore the shape of the exposure–response function over a relatively wide exposure range in the European context. The granularity of the administrative data allowed us to restrict the Aim 2 analysis to a fairly homogeneous population subset (e.g., individuals diagnosed in primary care) and to explore the sensitivity of our results to this selection criteria. For example, including individuals who tested positive but were not diagnosed in primary care attenuated the estimates of short-term exposure to COVID-19 and hospital admission, so it is a strength that we were able to exclude them in some analyses. We assessed the risk of COVID-19–related hospital admission in the specific population of people who had been infected with COVID-19 rather than the general population, allowing us to estimate the risk of adverse COVID-19 prognosis associated with air pollution, independent of the risk of infection. Follow-up ended on December 31, 2020, reflecting a period before the arrival of SARS-CoV-2 Variants of Concern in Catalonia (Hodcroft et al. 2021); we therefore did not have to take into account the timing of different Variants of Concern in our analysis.

We used a state-of-the-art exposure assessment model developed for COVAIR-CAT for the study period, providing updated estimates of ambient air pollution in the region at fine spatiotemporal resolution. Exposure linkage was based on residential address, reducing exposure measurement error.

We conducted an in-depth evaluation of effect modification according to a range of individual attributes as well as area-level SES on both the multiplicative and additive scales. Our results indicated important differences by scale, and that results on the multiplicative scale from Cox models can be misleading for several predictors that are strong predictors of COVID-19 severity.

Limitations We evaluated the first year of the pandemic, a period without COVID-19 vaccines and Variants of Concern, thus our estimates may not be representative of the effect of air pollution on COVID-19 in later phases of the pandemic. However, another study that evaluated associations between ambient $PM_{2.5}$ and NO_2 and severe COVID-19 over a longer follow-up period including the Delta Variant of Concern period and the introduction of vaccines showed an association between ambient pollution and severe COVID-19 outcomes in both vaccinated and unvaccinated individuals (Chen Z et al. 2022c).

We a priori defined COVID-19–related hospital admission and death based on 30 days from clinically or laboratory-confirmed COVID-19 diagnosis for several reasons: (1) it is the most frequently used time window to define mortality due to community-acquired pneumonia; (2) at the time the study protocol was developed, it was the most frequently used time window to define COVID-19 deaths in clinical trials and health policy response; (3) we did not have data on cause-of-death from death certificates and therefore aimed to select a time window close to diagnosis to increase the sensitivity of the outcome definition (i.e., longer time window increases the likelihood of including events not related to COVID-19). This approach allowed us to deal with the lack of access to testing during the first wave and avoid selection bias (Pollán et al. 2020), although some misclassification in COVID-19 diagnosis

may have been present for cases that were not laboratory-confirmed. This pragmatic time-defined definition, used in previous studies and policy decisions for COVID-19 (Chen C et al. 2022a; Nobile et al. 2022), captured acute complications of COVID-19 occurring within 30 days of infection, but could also include some hospital admissions unrelated to COVID-19. However, results from our sensitivity analyses addressing these limitations in Aim 1, such as analyzing only laboratory-confirmed cases and cause-specific hospital admissions, yielded similar estimates. In post hoc analyses, we estimated that a definition of COVID-19–related death based on 30 days since diagnosis captures 85% of deaths that would be identified using a 90-day window, indicating that a 30-day window is a reasonable balance between sensitivity and completeness of outcome detection. However, not all individuals would have been diagnosed at the same stage of the infection; therefore, our analysis based on days since diagnoses may not fully reflect the biological process of progressing from infection to hospital admission, potentially leading to bias. We selected a semiparametric Cox modeling approach for the project overall as it allowed for the tightest control for confounding by time by including time in the baseline hazard. In analyses for Aims 1 and 3, follow-up time was based on days since March 1, 2020, adjusting for the temporal evolution of the pandemic. Other approaches for modeling event occurrence (e.g., logistic regression) rather than time-to-event could have been used but would require careful evaluation of the functional form to adequately adjust for confounding by time.

The spatial resolution of our exposure estimates was 250 m, which was a compromise between the spatial resolution of 1 km typically used in daily spatiotemporal studies (Schneider et al. 2020), and the 100-m spatial resolution or finer used in annual spatial studies (de Hoogh et al. 2018). While a 250-m resolution likely captures the spatial variation of air pollutants with longer autocorrelation such as $PM_{2.5}$ (Wang et al. 2020b) and PM_{10}, it may lead to overly smooth NO_2 not fully reflecting local variations (Apte et al. 2017). This smoothing effect has been identified as a source of Berkson-like exposure measurement error, which should not bias epidemiological estimates but would likely lead to less precise estimates (Szpiro et al. 2011).

We lacked data on some individual-level potential confounders, such as race and ethnicity, migration status, physical activity, and occupation. Although adjustment for individual-level income could partially adjust for some of these variables, residual confounding cannot be ruled out.

IMPLICATIONS OF FINDINGS

The key implications of the findings of the COVAIR-CAT project for public health:

- While it is well documented that ambient air pollution is associated with a broad range of adverse health outcomes, COVAIR-CAT shows that air pollution also contributed to COVID-19 severity in 2020.
- Beyond broad public health benefits, reducing air pollution should also be part of pandemic and epidemic preparedness and would likely reduce the risk of disease severity in future epidemics and for endemic pathogens such as those that cause LRI.
- Not all adults are affected by long-term exposure to air pollution equally. There are vulnerable groups (e.g., individuals with low individual- and area-level SES) who would have benefited most in terms of reduced COVID-19 severity from air pollution reduction measures.
- Associations for COVID-19–related hospital admission were higher than those for influenza or pneumonia for NO_2, $PM_{2.5}$, and PM_{10}, and for LRIs for NO_2 and PM_{10}. Whether stronger associations for COVID-19 compared with LRIs more broadly would persist after 2020 when there was widespread immunity from vaccines requires further investigation.
- While uncertainties remain regarding the role of O_3 in COVID-19 severity and the mechanisms by which air pollution affects COVID-19 severity and vulnerability, these uncertainties should not detract from the public health priority to reduce air pollution.

ACKNOWLEDGMENTS

OTR was supported by a Sara Borrell fellowship from the Instituto de Salud Carlos III (CD19/00110). TDS acknowledges receiving financial support from the Instituto de Salud Carlos III (ISCIII; Miguel Servet 2021: CP21/00023) which is cofunded by the European Union. We acknowledge support from the Spanish Ministry of Science and Innovation and State Research Agency through the "Centro de Excelencia Severo Ochoa 2019–2023" Program (CEX2018-000806-S) and from the Generalitat de Catalunya through the CERCA Program.

We are grateful to the COVAIR-CAT external scientific advisors, Professors Beate Ritz and Francesco Forastiere, for their constructive feedback on the project.

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HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to independent audits by RTI International staff members Dr. Linda Brown, Dr. David Wilson, and Mr. Ryan Chartier. These staff members are experienced in quality assurance (QA) oversight for air quality monitoring, modeling and exposure assessment, epidemiological methods, and statistical modeling.

The QA oversight program consisted of a remote audit of the final report (2 versions) and the data processing steps. Key details of the dates of the audit and the reviews performed are listed below.

Audit 1: Final Remote Audit

Date: April 2024 – May 2024

Remarks: The final remote audit consisted of two parts: (1) review of the final project report, and (2) audit of data processing steps. The review of the final report focused on ensuring that the methods are well documented, and the report is easy to understand. The review also examined if the

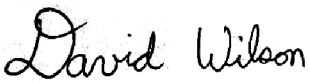
report highlighted key study findings and limitations. The data audit included a review of the datasets and codes for data reduction, processing and analysis, and model development. This portion of the audit was restricted to the key components of the study and associated findings. Selected codes for exposure modelling and epidemiological model development were sent to RTI. No raw health data were sent to RTI due to data confidentiality restrictions.

The codes were reviewed at RTI to verify, to the extent feasible, linkages between the various scripts; confirmation of the models reported; and verification of key tables, figures, and data outputs. The codes appear to be largely consistent with the models described in the report and followed the overall model development procedure described. The values themselves were verified by RTI using the data and scripts provided by the investigators.

Except for a few minor discrepancies, no major quality-related issues were identified from the review of the codes and the report. Recommendations were made to address noted discrepancies and typographical errors and included general edits for improved clarity. Those recommendations were addressed in the final report.

A written report was provided to HEI. The QA oversight audit demonstrated that the study was conducted according to the study protocol. The final report appears to be representative of the study conducted.

Linda Morris Brown, MPH, DrPH, Epidemiologist, Quality Assurance auditor



David Wilson, PhD, Statistician, Quality Assurance auditor

Ryan Chartier, MS, Air Quality and Exposure Scientist, Quality Assurance auditor

Date: May 29, 2024

SUPPLEMENTARY APPENDIX ON THE HEI WEBSITE

Appendix A contains 11 figures and 20 tables not included in the main report. It is available on the HEI website at *www.healtheffects.org/publications*.

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

ABOUT THE AUTHORS

Cathryn Tonne, a research professor at the Barcelona Institute for Global Health with an ScD in environmental health and epidemiology from Harvard University, is an environmental epidemiologist focusing on the health effects of air pollution from traffic and household sources. Her research has investigated exposure patterns and health effects of air pollution in high- as well as low- and middle-income countries and the health cobenefits of climate change mitigation via air pollution. She is codirector of the Lancet Countdown for Health and Climate Change in Europe and leads the working group focused on health cobenefits of mitigation. She is the coordinator of CATALYSE, a five-year Horizon Europe project focused on climate change and health. She was awarded the Tony McMichael Mid-Term Career Award from the International Society for Environmental Epidemiology in 2022 for her contributions to environmental epidemiology. Cathryn was the principal investigator of COVAIR-CAT and supervised the data management and analyses.

Otavio Ranzani, MD, MSc (Epi), PhD, believes in science as a social construct to improve and promote global health. He completed his medical training in Brazil (Internal Medicine and Critical Care specialist), his MSc in epidemiology at the London School of Hygiene & Tropical Medicine, and his PhD at the University of São Paulo. Otavio has a strong methodological focus and research experience in low- and middle-income countries and Europe. His current work focuses on the study of emerging viral and bacterial diseases, with a particular emphasis on respiratory infections and their relationship with environmental exposures. His research interests include understanding the short- and long-term impacts of these infections on both community and critically ill patients. Otavio supervised the data management and led the Aims 1 and 3 analyses in COVAIR-CAT.

Anna Alari, PhD in epidemiology in the Biostatistics, Biomathematics, Pharmacoepidemiology, and Infectious Diseases research unit of the Pasteur Institute in Paris, focused on temporal and geographic variations of pneumococcal meningitis and the effects of conjugate vaccines in France (2018). In 2019, she conducted a post doctoral fellowship in Environmental Epidemiology and Policy Evaluation at INSERM (France) and the University of California, San Diego. She investigated the effect of exposure to air pollution and heat waves on human mortality; in specific, she worked on an evaluation of the effectiveness of the measures undertaken in the region of Paris to fight against pollution peaks (using quasi-experimental methods), and she studied the role of ozone as a causal intermediate in the relationship between heat and mortality. Her research interests include the impact of climate change and air pollution on human health, and

she is particularly interested in exploring the environmental determinants of infectious diseases to better understand disease transmission and seasonality. Anna led the Aims 2 and 4 analyses in COVAIR-CAT.

Joan Ballester, PhD in climate and health from the University of Barcelona, is an associate research professor at ISGlobal. His primary research focus is the link between climate variability and health impacts. He aims to describe the major sources of vulnerability as well as which and to what extent societies have already started to adapt to climate change. He is also analyzing weather and climate predictability at a range of timescales (from days to seasons) so it can be used for the generation of skillful, early warning systems of disease risk. Joan's ultimate goal is to improve the well-being of societies by increasing human resilience and adaptation to climate variability and change.

Xavier Basagaña, PhD in biostatistics from Harvard University, is a research professor at ISGlobal. The focus of his research has three main areas: air pollution and health, temperature and health, and development and improvement of statistical methods for epidemiological research. He has led and participated in several national and European projects including *CitieS-Health*, a citizen science project on urban environment and health. Xavier currently leads *ATENC!Ó*, a project investigating whether air pollution can affect attention in high-school students.

Carlos Chaccour, MD, has an MSc in tropical medicine and hygiene from the London School of Hygiene and Tropical Medicine and a PhD from the University of Navarra, Spain. He is a global health researcher focused on infectious disease control.

Payam Dadvand, MD, has a PhD in environmental epidemiology. For the last decade, he has conducted pioneering studies on the impacts of both environmental stressors (e.g., air pollution) and environmental mitigation measures (e.g., green spaces) on maternal and child health applying his expertise in using remote sensing data, GIS-based spatial analytical methods, and spatiotemporal modeling approaches. He has been involved in several national and European projects on the health effects of air pollution. Payam is now coordinating the HEI-funded project FRONTIER (Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status).

Talita Duarte, MPH, PhD, is a senior epidemiologist leading real-world evidence at IDIAPJGol, a primary care research institute located in Barcelona, Spain, and an assistant professor at Erasmus Medical Centre, Netherlands. Since 2015, she has been involved as project lead in different research projects using electronic health records databases, mainly the SIDIAP (*www.sidiap.org*) in Spain. She has also collaborated on many European research projects with other databases, such as the United Kingdom's CPRD, Denmark's Danish Health Registries, Spain's BIFAP, Italy's HSD, and the Netherlands' IPCI. She was a postdoctoral fellow for 3 years at the International Agency for Research on Cancer (IARC-WHO), where she was involved in the EPIC study focusing on the role of diet, body adiposity, and metabolomics on cancer development and discovery of early cancer biomarkers. Talita's scientific research interests focus on the relationships between environment and lifestyle factors and cancer development, as well as the use of data from electronic healthcare records in observational research.

Maria Foraster, MPH, MPharm, PhD (2013), is an assistant research professor at ISGlobal (2018–2022) and associate professor of public health at Universitat Ramon Llull (Barcelona). Her research interests focus on how the environment affects health over the life course, with emphasis on the assessment of traffic-related noise and air pollution and their underlying biological mechanisms. Maria has participated in 17 projects funded through different Swiss, Spanish, French, European, and USA competitive calls on the association of air pollution and noise with chronic diseases in adults, including cardiovascular morbidity and mortality and respiratory diseases, and early life development.

Carles Milà, PhD, is an ISGlobal researcher with a background in statistics, data science, and geoinformatics. He also holds an MSc in statistics (Polytechnic University of Catalonia) and in geoinformatics (New University of Lisbon). His research interests lie in the intersection between spatial data science and planetary health. His research experience includes analysis of complex environmental data, such as ambient and personal air pollution and temperature exposures, land use change, and image and GPS data, as well as methodological research on statistical and machine learning-based predictive mapping. Carles developed the COVAIR-CAT exposure models.

Mark J. Nieuwenhuijsen, PhD, is a research professor at ISGlobal and a world-leading expert in environmental exposure assessment, epidemiology, and health risk and impact assessment with a strong interest in healthy urban living. In 2018, Mark was awarded the ISEE John Goldsmith Award for Outstanding Contributions to Environmental Epidemiology.

Sergio Olmos, MSc in statistics, is a statistician and data scientist. He led the construction of the cohort and contributed to statistical analyses in COVAIR-CAT.

Alex Rico, MSc in data science from the Autonomous University of Barcelona, led the construction of the cohort in collaboration with PADRIS in COVAIR-CAT.

Jordi Sunyer, PhD, is a research professor at ISGlobal and environmental epidemiologist with a long history of high-ranked journal publications, international collaborations, and experience supervising early career researchers (over 35 PhD dissertations supervised). In 2014, he received the John Goldsmith Award, which recognizes environmental epidemiologists who serve as models of excellence and integrity in research and unwavering promotion of environmental health. Also in 2014, Jordi received the award for excellence in medical research from the Catalan College of Medicine and the award for excellence in environmental research from the Catalan College of Environmental Scientists.

Antònia Valentín, MSc, is an expert in geographic information systems and led the management of geographic data in COVAIR-CAT.

Rosa Vivanco, MD, PhD (Autonomous University of Barcelona) and MPH (Pompeu Fabra University, Barcelona) in biostatistics, is a neurologist and research consultant at the Research Institute of Medicine at Parc de Salut Mar, Barcelona, where she led projects related to environmental factors and stroke. She is the current director of the Health Technology Assessment Unit at the Agency of Health Assessment and Quality of Catalonia. She has conducted research as part of commissioned projects for the Catalan Health Ministries as well as national and international research projects related to stroke. Rosa has specific expertise in quality assurance of electronic health records data in Catalonia.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Exposure model:

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 Pollut 337:122501; doi:10.1016/j.envpol.2023.122501.

Aim 1 analysis:

Ranzani O, Alari A, Olmos S, Milà C, Rico A, Ballester J, et al. 2023. Long-term exposure to air pollution and severe COVID-19 in Catalonia: A population-based cohort study. Nat Commun 14:2916; doi:10.1038/s41467-023-38469-7

Aim 2 analysis:

Alari A, Ranzani OT, Olmos S, Milá C, Rico A, Ballester J, et al. 2023. Short-term exposure to air pollution and progression to hospital admission among individuals diagnosed with COVID-19 in primary care in Catalonia: A population-based cohort study (COVAIR-CAT). Int J Epidemiol 53:dyae041; doi:10.1093/ije/dyae041.

Aim 3 analysis:

Ranzani O, Alari A, Olmos S, Milá C, Rico A, Basagaña X, et al. 2023. Identifying vulnerable subgroups in the association between long-term air pollution and COVID-19 hospitalization: A population-based cohort. Environ Int 185:108530; doi:*https://doi.org/10.1016/j.envint.2024.108530*.

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 Hospital admission for any cause occurring during the 10 days before the first COVID-19 diagnosis Death by any cause occurring within 30 days of first COVID-19 diagnosis ICU admission (for each COVID-19–related hospital admission, was patient admitted to the ICU or not) 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 Excluded individuals living in nursing homes 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 Restricted to people not living in nursing homes or diagnosed in primary care 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 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} Note: O_3 not included in these analyses due to a null association with hospital admissions in Aim 1	Same as Aim 1 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 Hospital admission for pneumonia and influenza 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 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/m³, 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/m³), 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/m³), 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/m³), 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.

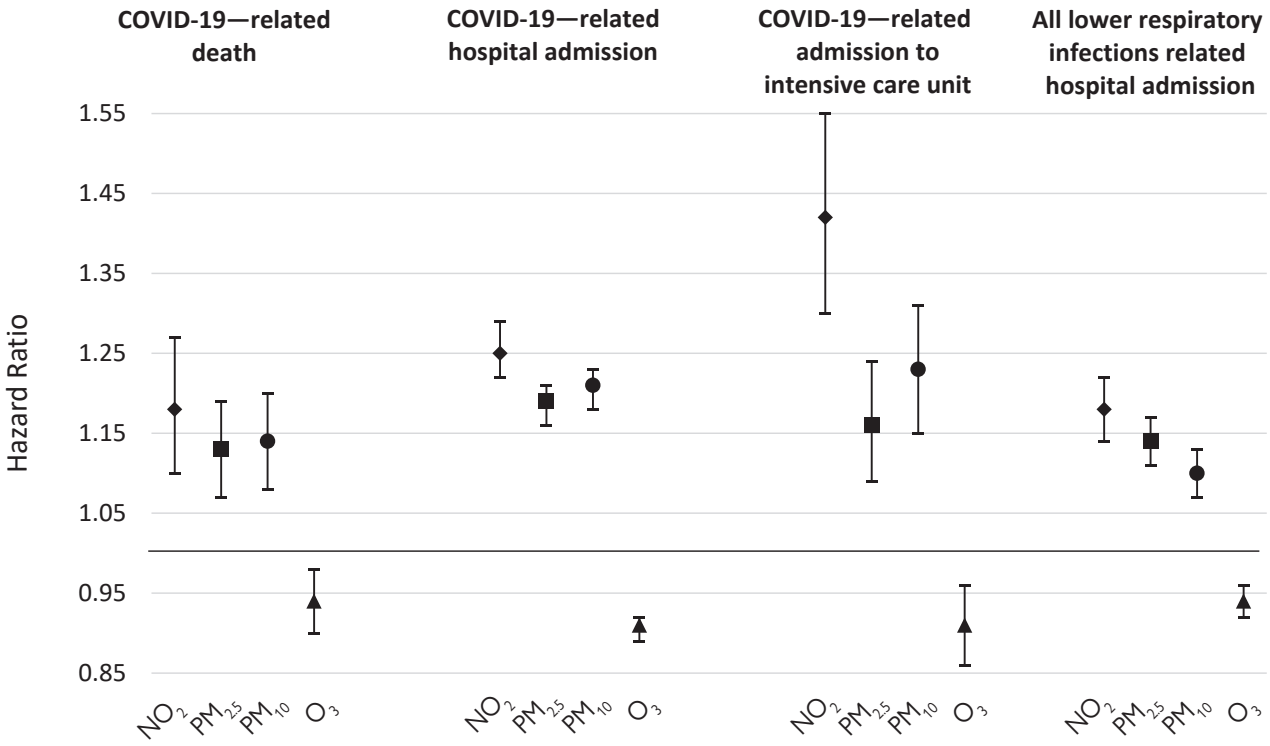
The investigators found only some evidence of associations between short-term exposures to any of the pollutants and risk of hospital admissions during the first wave (e.g., same-day exposure to NO_2 and the cumulative exposure to NO_2 up over the previous 2 days were associated with hospitalization). 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/m³]: 1.18), $PM_{2.5}$ (HR per IQR [2.6 μg/m³]: 1.14), and PM_{10} (HR per IQR [3.9 μg/m³]: 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/m³]: 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/m^3 for NO_2, 3.2 μg/m^3 for $PM_{2.5}$, 4.2 μg/m^3 for PM_{10}, and 10.8 μg/m^3 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.

ACKNOWLEDGMENTS

The HEI Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Eva Tanner for her oversight of the study, to Dan Crouse for assistance with the review of the report and in preparing its Commentary, to Carol Moyer for editing this Report and its Commentary, and to Kristin Eckles and Hope Green for their roles in preparing this Research Report for publication.

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ABBREVIATIONS AND OTHER TERMS

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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RESEARCH REPORT

NUMBER 220
SEPTEMBER 2024

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