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RESEARCH REPORT

REACH-OUT: Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes

Jeanette A. Stingone, Stephanie Lovinsky-Desir, Sneha Kannoth, Mehr Shafiq, Cong Zhang, Sandra Albrecht, Alexander Azan, Earle C. Chambers, Min Qian, Perry Sheffield, Azure B. Thompson, and Jennifer Woo Baidal

INCLUDES A COMMENTARY BY THE INSTITUTE'S REVIEW COMMITTEE

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with a Commentary by the HEI Review Committee

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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 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 390 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 275 comprehensive reports published by HEI, as well as in more than 2,500 articles in 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 or Panel, 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 or Panel 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 230, *REACH-OUT: Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes*, presents a research project funded by the Health Effects Institute and conducted by Jeanette A. Stingone at Columbia University Mailman School of Public Health 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 Stingone and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Commentary, prepared by members of the Review Commitee 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 first examine this 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.

Although this report 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; thus, no official endorsement by it should be inferred. The contents of this report also have not been reviewed by private party institutions, including those that support the Health Effects Institute, and may not reflect the views or policies of these parties; thus, no endorsement by them should be inferred.

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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 Request for Applications (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 used 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 comorbidity (Andersen et al. 2023).

Kai Chen of Yale University and colleagues assessed the effects of the first COVID-19 lockdowns on air quality and associated mortality in regions of four countries (Germany, Italy, China, and the United States). First, they evaluated changes in NO_2 and $PM_{2.5}$ concentrations, before and after accounting for meteorology and temporal trends in air quality. Then they found prepandemic associations of mortality with NO_2 and $PM_{2.5}$ concentrations and applied those to the changes in air quality during the lockdowns to estimate the effects of lockdowns on mortality related to air pollution (Chen et al. 2025).

Michael Kleeman of the University of California Davis and colleagues are evaluating the chronic and short-term effects of air pollution exposure on COVID-19 progression, mortality, and long-term complications among hospitalized patients across southern California using electronic health records from the Kaiser Permanente healthcare database. First, they will use chemical transport and land use regression models to develop chronic and short-term daily $PM_{2.5}$, NO_2, and O_3 exposure estimates at multiple spatial resolutions. They then will assess the association between exposure and COVID-19 outcomes between June 2020 and January 2021, and with new and exacerbated long-term COVID-19 complications up to 12 months following discharge from the hospital.

Jeanette Stingone of Columbia University and colleagues evaluated the interactions between chronic air pollution exposure and neighborhood vulnerability in relation to adverse COVID-19 outcomes in New York City. They used electronic health record data with more than 37,000 COVID-19 patients from five large hospital systems to evaluate long-term air pollution exposures in relation to COVID-19 hospitalization after visiting the emergency department, inpatient length of stay, acute respiratory distress syndrome, pneumonia, ventilator use, need for dialysis, and death. They also conducted an additional analysis evaluating excess all-cause mortality using public administrative data.

Cathryn Tonne of ISGlobal and colleagues are assessing whether long-term exposure to air pollution increased 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 increased the risk of COVID-19 hospitalization after visiting the emergency department and mortality among the 300,000 people who tested positive for SARS-COV-2 during the study period (Tonne et al. 2024).

PROTOCOLS AND FUTURE DIRECTIONS

Throughout its portfolio, HEI emphasizes the importance of data access and transparency because they underpin high-quality research that is used in policy settings (see *Policy on the Provision of Access to Data Underlying HEI-Funded Studies*). During the studies, members of HEI's Research Committee provided advice and feedback on the study designs, analytical plans, and study progress. The studies were subject to HEI's special *quality assurance procedures* that included quality assurance audits by an independent audit team prior to publication of the final reports. HEI plans to publish an overall summary and interpretation of the COVID-19 research program once all studies have been reviewed.

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

Investigator (institution)	Study or Report 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 40 years or older (N > 3 million)	Susceptibility	HEI Research Report 214, 2023
Kai Chen (Yale University)	Effect of Air Pollution Reductions on Mortality During the COVID-19 Lockdowns in Early 2020	China, Germany, Italy, and the United States	Time Series Study: Populations in 4 countries: China (Jiangsu Province), Italy, Germany, and the US (California)	Accountability	HEI Research Report 224, 2025
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 late 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	October 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 Research Report 220, 2024

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HEI STATEMENT

Synopsis of Research Report 230

Neighborhood Vulnerability, Air Pollution, and Severe COVID-19 Health Outcomes

BACKGROUND

Exposure to air pollution has been linked with increased 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 greater levels of air pollution, suggesting a possible association between air pollution and risk of COVID-19 infection or poor COVID-19–related health outcomes. However, these early studies had pronounced methodological limitations (e.g., lack of detailed information on individual- and community-level socioeconomic status), leading to a high potential for biased results. To investigate the potential associations between air pollution, COVID-19, and human health, HEI funded five studies in several countries in the fall of 2020. This Statement highlights a study by Dr. Jeanette Stingone and colleagues at Columbia University and other NYC-based institutions.

APPROACH

Stingone and colleagues aimed to evaluate whether long-term outdoor air pollution exposures were associated with severe COVID-19 health outcomes and whether these associations varied by neighborhood-level environmental vulnerability (as defined by social and structural characteristics such as income and housing quality) in New York City. In brief, the investigators used electronic health records from emergency department visits and hospital admissions within the INSIGHT clinical healthcare network. They assembled a cohort of more than 20,000 patients who had been diagnosed with COVID-19 between March 1, 2020, and February 28, 2021.

The investigators used data from the New York City Community Air Survey to estimate long-term exposures (based on 11-year averages for 2009–2019) to black carbon, fine particulate matter (<2.5 μg/m^3 in aerodynamic diameter), nitrogen dioxide, and ozone by patient zip code of residence. Using a statistical profiling and clustering approach, the investigators constructed a novel index of environmental vulnerability by zip code that was based on neighborhood social and structural characteristics. They considered several severe COVID-19 health outcomes, including admission to the hospital after entering the emergency department, patient length of stay in the hospital, acute respiratory distress syndrome,

What This Study Adds

- The study evaluated whether associations between long-term air pollution exposures and severe COVID-19 health outcomes varied by New York City neighborhoods that differed in environmental vulnerability, as defined by social and structural charac teristics.
- This study was based on a cohort of patients who were diagnosed with COVID-19 and received care within private hospi tals.
- Long-term exposures to black carbon, fine particulate matter, and nitrogen dioxide, but not ozone, were associated with risk of being admitted to the hospital with a COVID-19 diagnosis among those who went to the emergency department.
- By contrast, results for risk of pneumonia, need for mechanical ventilation, and death among hospitalized patients with a COVID-19 diagnosis were mixed across pollutants and outcomes.
- Neighborhood vulnerability consistently elevated the risk of being admitted to the hospital with a COVID-19 diagnosis after visiting the emergency department, but this modifying effect was not consistent for other health outcomes.
- Overall, this study demonstrates the complexity of the relationship among air pollution, COVID-19, and neighborhood vulnerability. It highlights the need for additional research to better understand this relationship in the context of future respiratory infectious disease outbreaks.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Jeanette A. Stingone at Columbia University Mailman School of Public Health and colleagues. Research Report 230 contains the detailed Investigators' Report and a Commentary on the study prepared by the HEI Review Committee.

pneumonia, need for mechanical ventilation, need for dialysis, and death.

In their main analyses, Stingone and colleagues used Cox proportional hazards or Poisson regression models to evaluate associations between estimated long-term air pollution exposures and severe COVID-19 health outcomes. The models adjusted for demographic (age and sex) and health (chronic disease, smoking, and body mass index) characteristics and a neighborhood environmental vulnerability index score. Models were also stratified by phase of the COVID-19 pandemic. To assess the potential modifying effects of neighborhood vulnerability on these associations, the investigators also stratified models by tertile of the neighborhood environmental vulnerability index score within New York City.

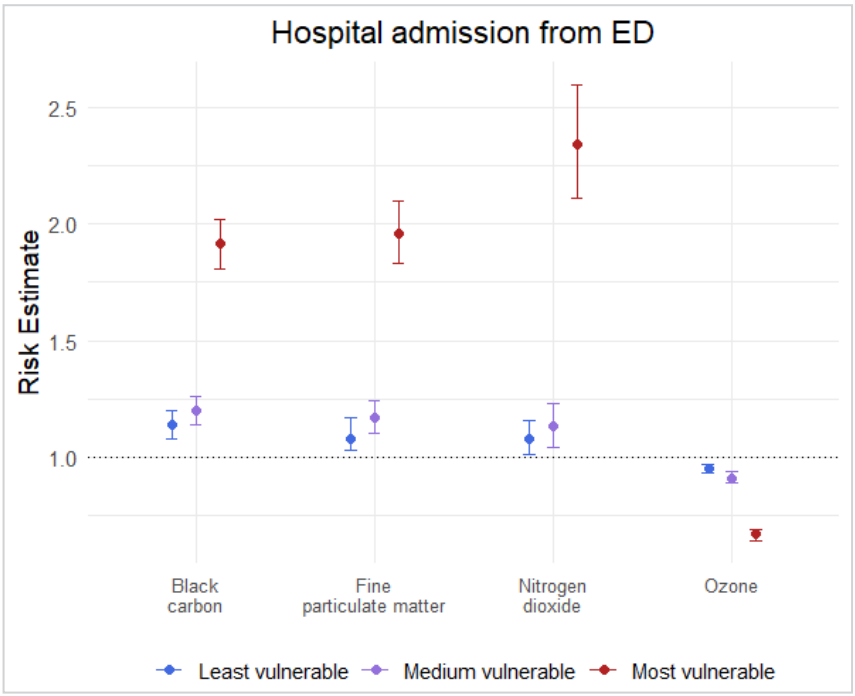
The investigators conducted multiple additional analyses to address potential biases in the study. Because some patients might have sought treatment at hospitals located further from where they lived, one analysis evaluated a subset of the study population that was restricted to zip codes where 40% or more of the total hospitalizations related to COVID-19 were patients who lived in those neighborhoods.

KEY RESULTS

Of the cohort of 20,318 hospitalized patients with a COVID-19 diagnosis, 52% of patients who were hospitalized experienced severe COVID-19 health outcomes, and 17% of hospitalized patients ultimately died. Of the 19,898 emergency department patients with a COVID-19 diagnosis, 22.3% were admitted to the hospital. Median long-term air pollution exposures were estimated at 1.1 absorbance units for black carbon, 9.0 $\mu g/m^3$ for fine particulate matter, 21.0 parts per billion (ppb) for nitrogen dioxide, and 30.4 ppb for ozone. The majority of New York City zip codes had neighborhood environmental vulnerability index scores between 0.25 and 0.45, with scores ranging from 0 (the lowest level of vulnerability) to 1 (the highest level of vulnerability).

Stingone and colleagues reported that increased estimated long-term exposures to black carbon, fine particulate matter, and nitrogen dioxide were associated with elevated risks of being admitted to the hospital with a COVID-19 diagnosis after visiting the emergency department. Conversely, across all phases of the pandemic, increased exposures to those three air pollutants were associated with a decreased risk of death during COVID-19 hospitalization, and patterns of association with ozone exposure were opposite from those observed for the other pollutants. For other severe COVID-19 outcomes, associations generally varied in magnitude and direction, depending on the air pollutant, health outcome, and phase of the pandemic.

The investigators reported that the association between exposure to outdoor air pollutants and being admitted to the hospital with a COVID-19 diagnosis after entering the emergency department was notably stronger in areas of higher neighborhood vulnerability, as compared to areas with lower neighborhood vulnerability. However, the modifying effect of neighborhood environmental vulnerability on the association between outdoor air pollution and other severe COVID-19 health outcomes was inconsistent across different air pollutants and health outcomes (Statement Figure), as well as across phases of the pandemic. For example, the investigators did not generally observe strong modifying effects of neighborhood environmental



Statement Figure. Neighborhood environmental vulnerability modifies the association between long-term exposures to outdoor air pollutants and risk of hospital admission with COVID-19 diagnosis after entering the emergency department in New York City. ED = emergency department. (Adapted from Investigators' Report Figure 12.)

vulnerability on the risk of acute respiratory distress syndrome, length of stay in the hospital, or need for dialysis.

Within the restricted study population (that is, neighborhoods in which more than 40% of hospitalized patients are residents of the surrounding neighborhood), results from additional analyses of associations between air pollution exposures and severe COVID-19 outcomes were similar to the results of analyses conducted in the full study population for some outcomes (such as death and need for mechanical ventilation) but not all outcomes (such as acute respiratory distress syndrome and need for dialysis). The associations observed in the restricted population were generally stronger in magnitude compared to the associations in the full population. In the restricted population, the modifying effect of neighborhood environmental vulnerability remained inconsistent among health outcomes; both positive and inverse associations were generally stronger in magnitude compared to the associations observed in the full study population, but some associations differed in direction compared to those in the full study population.

INTERPRETATION AND CONCLUSIONS

In its independent evaluation of the Investigators' Report, the HEI Review Committee concluded that this study provided some evidence of potential associations between exposures to outdoor air pollution and the risk of severe COVID-19 health outcomes, but that the role of neighborhood environmental vulnerability remains unclear. Stingone and colleagues reported that higher estimated long-term exposures to outdoor air pollution were associated with elevated risks of some severe COVID-19 health outcomes; however, these associations generally differed among pollutants, outcomes, and phase of the pandemic, and the effect of neighborhood vulnerability on these associations demonstrated similarly mixed results.

The Committee noted that key strengths of the study included using a large and diverse study population with individual-level patient information, conducting the study in a location (New York City) that experienced a high number of COVID-19 cases early in the pandemic, and constructing a novel environmental vulnerability index that included many neighborhood-level social and structural characteristics. The Committee appreciated that the investigators conducted multiple analyses to address potential biases in their study, but also noted that possible selection bias remained an important limitation of the study. In particular, the findings might be limited in their generalizability because the cohort largely comprised hospitalized patients and because the INSIGHT data do not include data from public hospitals.

The Committee found several of the reported results difficult to explain. For example, the seemingly protective effects of outdoor air pollution exposures were observed in association with some of the outcomes, such as the risk of death. Those results largely conflict with results observed in other studies of outdoor air pollution and COVID-19 health outcomes. The Committee agreed with the investigators that the findings might be partly driven by factors such as a lack of standard treatment protocols early in the pandemic, which could have particularly affected results in New York City, where a large peak in cases occurred during the first phase of the pandemic and overwhelmed hospitals. The Committee also suggested that the zip code–level scale of the exposure estimates was possibly too large to capture the true variations in exposure and that there could have been model-induced correlations among the outdoor air pollutants that affected the exposure estimates.

Assessing the intersection between air pollution, COVID-19 outcomes, and social and structural factors is challenging. The Committee commended the investigators for their efforts in addressing this complicated research question. The study showed that neighborhood environmental vulnerability might affect the association between long-term exposure to air pollution and some severe health outcomes. Overall, this study demonstrates the complexity of this relationship and highlights the need for additional research on such multifaceted interactions to better understand this relationship in the context of future respiratory infectious disease outbreaks.

INVESTIGATORS' REPORT

REACH-OUT: Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes

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ABSTRACT

Introduction Determining whether chronic exposure to air pollution contributes to observed disparities in COVID-19 outcomes requires integrating multiple determinants of patient vulnerability to COVID-19, given the complex interactions that contribute to health disparities. Exposure to adverse social and structural factors heightens vulnerability to environmental exposures, potentially resulting in increased risk of unfavorable COVID-19 outcomes. Additionally, as populations are often exposed to various co-occurring adverse factors in the setting of disinvested neighborhoods and communities, examining such factors individually may not be sufficient to fully understand how they may modify the effects of air pollutant exposures. In an effort to explain COVID-19–related disparities observed in New York City (NYC*), this study aimed to estimate the effect of chronic air pollutant exposures on the risk of COVID-19 morbidity and mortality and to determine whether these effects vary by neighborhood-level vulnerability as defined by social and structural factors.

Methods We used harmonized electronic health record (EHR) data from five healthcare systems in NYC to derive a study population of hospitalized or emergency department (ED) patients diagnosed with COVID-19 from March 1, 2020, through February 28, 2021, who had a NYC zip code of residence. To reduce potential selection bias, we also constructed a subset of the study population restricted to patients with residential zip codes in the typical catchment area of the hospitals affiliated with the EHR data repository. We estimated air pollutant concentrations for fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3) by using zip code–level 11-year averages based on data from the 2009–2019 New York City Community Air Survey. For each pollutant, we constructed Cox proportional hazards models to estimate the hazards of fatality (i.e., dying from COVID among individuals with COVID) and hospital length of stay. Additionally, for each pollutant, we constructed Poisson regression models to estimate RRs (RRs) for acute respiratory distress syndrome (ARDS), pneumonia, mechanical ventilation, and dialysis during hospitalization and risk of hospitalization among ED patients. Models were adjusted for age, sex, body mass index, smoking status, history of chronic disease, and a neighborhood environmental vulnerability index (NEVI). Interaction terms were used to evaluate effect modification between pollutant exposures and the NEVI metric. Additionally, we conducted supplementary analyses to determine the joint effects of air pollution and pre-existing chronic diseases and whether those relationships varied by NEVI tertile. To supplement the fatality analysis, we conducted an excess mortality analysis among the full urban population using all-cause mortality data from public health records for 2015–2020. Sensitivity analyses were performed to evaluate the effect of selection bias.

Results Exposures to NO_2, $PM_{2.5}$, and BC were positively associated with risks of ARDS, pneumonia, and dialysis, whereas O_3 exposure was inversely associated with these morbidity outcomes, likely because of the strong inverse correlation between O_3 and NO_2. Conversely, we observed an unexpected inverse association between exposures to NO_2, $PM_{2.5}$, and BC and risks of fatality and mechanical ventilation. We observed statistically significant effect modification by NEVI for some of the associations between NO_2, $PM_{2.5}$, O_3, and BC exposures and risks of ARDS, pneumonia, and dialysis. In areas with greater environmental vulnerability (i.e., higher NEVI metrics), there were generally stronger positive associations between air pollutant exposures and the risk of hospitalization among ED patients and risks of ARDS, pneumonia, and dialysis among hospitalized patients. Exposures to NO_2, $PM_{2.5}$, and BC were generally negatively associated with the

This Investigators' Report is one part of Health Effects Institute Research Report 230, 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. Jeanette A. Stingone, Columbia University Mailman School of Public Health, 722 West 168th Street, New York, NY 10032; email: *js5406@cumc.columbia.edu*. No potential conflict of interest was reported by the authors.

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

risk of fatality, even in areas with higher NEVI metrics. Most positive associations between air pollution and COVID-19 outcomes were limited to the initial phase of the pandemic, except for the risk of hospitalization, which was positively associated with NO_2, $PM_{2.5}$, and BC exposures throughout the study period. Even after accounting for the NEVI metric and pre-existing chronic disease, racial disparities persisted in the effect of air pollution on risks of pneumonia and hospitalization, with the largest RRs among Black and Hispanic populations. Results of the all-cause mortality analysis also showed no evidence of greater excess mortality in areas with higher levels of air pollution. The greatest excess mortality was observed in areas with high NEVI metrics, regardless of air pollutant exposures.

Conclusions When limiting to individuals in the hospital's typical catchment areas, the observed positive associations between air pollutant exposures and COVID-19–related morbidities such as ARDS, pneumonia, and use of dialysis were strongest in areas with higher neighborhood-level environmental vulnerability. Inverse associations between air pollutant exposures and severe outcomes like death and use of mechanical ventilation were unexpected findings that highlighted challenges in examining such associations at the population level in NYC.

INTRODUCTION

The COVID-19 pandemic illuminated pre-existing population-level health disparities in the United States and globally,[1–5] highlighting the need for deeper investigation into how population-level exposures, including exposure to chronic air pollution, may influence outcomes of COVID-19. In exploring the relationship between chronic exposure to air pollution and unfavorable COVID-19 outcomes, it is important to note that urban neighborhoods with greater proportions of Black and Hispanic individuals experienced a greater burden of adverse health events during the pandemic, including intensive care unit (ICU) admissions and mortality.[4–10] Furthermore, Black and Hispanic communities often experience greater exposure to air pollution as a result of both historical and contemporary environmental injustice and racism. Thus, it is crucial to understand the mechanisms underlying the intersection of chronic air pollution exposure, race, and ethnicity as risk factors for severe COVID-19 health outcomes; however, these issues represent a gap in current knowledge that needs to be addressed. This need is especially pertinent as public health officials deliberate on how to strategically allocate resources to mitigate the adverse impacts of future pandemics. Determining whether chronic exposure to air pollution contributes to disparities in COVID-19 outcomes requires a holistic approach that integrates multiple determinants of COVID-19 vulnerability to ascertain how these factors may interact with air pollution exposure to influence health-related endpoints.

Chronic air pollution exposure is defined as continuous or intermittent exposure to air pollutants over the long term (i.e., >1 year) in outdoor environments.[11,12] The US Environmental Protection Agency has designated six common disease-causing pollutants as "criteria pollutants," which are regulated by ambient air quality standards; these pollutants are carbon monoxide, lead, nitrogen oxides, ozone (O_3), particulate matter, and sulfur dioxide.[13]

Ecological studies have demonstrated that the burden of COVID-19 outcomes was greater in geographic areas with higher concentrations of ambient air pollutants, including particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$),[14–19] nitrogen dioxide (NO_2),[16,18–22] O_3,[16,19,22] and black carbon (BC), which is a form of particulate matter.[23] Therefore, it can be inferred that chronic exposure to ambient air pollution is positively associated with group-level COVID-19 outcomes measured at the county or city level.[14–27] In addition, the literature includes reports from multiple studies that have examined the effects of chronic exposure to criteria pollutants on adverse COVID-19 outcomes at the individual level.[22,26,28–52] These studies have investigated a variety of outcomes, including fatality, risk of hospitalization, and ICU use, with the majority of results demonstrating positive associations between air pollution exposure and risk of unfavorable health consequences of COVID-19.

Several challenges and limitations of previous studies of the relationship between air pollution and COVID-19 have been discussed in the literature and prior commentaries.[53] Challenges in identifying associations between air pollution and COVID-19 outcomes include difficulties in operationalizing comprehensive estimates of air pollution exposure, with inconsistent levels of spatial and temporal granularity across studies. Most studies have lacked access to closed populations for which COVID-19 testing and diagnostic data were collected and recorded, relying instead on populations of individuals seeking medical care, including hospitalized patients and those using the emergency department (ED). Additionally, the quality of data on reported COVID-19 fatalities among hospitalized populations can vary as a result of a lack of testing, deaths that occur outside of hospitals, and other factors that disproportionately affect Black and Hispanic communities. Fatality and mortality studies based on hospitalization records may be affected by selection bias due to the exclusion of individuals who die before hospitalization.[54] Importantly, studies that defined mortality based on COVID-19 diagnoses early in the pandemic were likely to underestimate COVID-19 mortality.[55] In the United States, deaths attributed to COVID-19 accounted for only two-thirds of estimated excess mortality during the first year of the COVID-19 pandemic. This finding is thought to reflect observed erroneous over-reporting of mortality due to other nonrespiratory illnesses (e.g., diabetes or heart disease), disparities in access to COVID-19 testing, and out-of-hospital COVID-19 deaths.[56–58] Accordingly,

numerous studies have concluded that excess all-cause mortality may be the best predictor of COVID-19 mortality in the first year of the pandemic, as this measure accounts for the multifaceted effects of the disease on overall mortality.[59,60]

Moreover, it is important to note that climatic conditions and air pollution are among the numerous contributing factors that affect the transmission and prevalence of COVID-19. Social factors, such as isolation protocols, social distancing measures, population density, personal hygiene practices, and neighborhood characteristics, may not only directly affect COVID-19 outcomes but also potentially influence the relationship between air quality and COVID-19–related health effects and even exacerbate observed racial disparities.[61] Thus, in investigating the relationship between chronic exposure to ambient air pollution and COVID-19 outcomes, it is essential to consider how social and structural factors that often co-occur with air pollution exposures may affect the level of vulnerability within specific populations.

Differential vulnerability among populations is often rooted in systemic racism that limits opportunities to improve health among minoritized and marginalized populations.[62–64] For example, residential redlining — a practice whereby the US federal government discouraged insuring mortgages for homes in predominantly Black neighborhoods — was rooted in systemic racism.[65–69] This policy was one of many that contributed to disinvestment in predominantly Black communities,[70–72] contributing to a range of factors (e.g., overcrowding in residential units,[76] increased population density,[77,78] and concentrated poverty) that continue to adversely affect these neighborhoods.[65–69,73–75,79,80] Exposure to adverse social and structural factors heightens vulnerability to environmental exposures,[81] potentially leading to an increased risk of unfavorable COVID-19 outcomes.

Studies have examined the contribution of social and structural factors in explaining the relationship between air pollution and COVID-19–related morbidities. The authors of most of these studies have hypothesized that neighborhood-level social and structural factors confound the relationship between air pollution and COVID-19 outcomes; thus, the models in such studies are often adjusted for these factors.[30,33,82] However, it is plausible that such factors could modify the effect of air pollution on COVID-19–related morbidities. Existing studies have typically examined the potential for effect modification due to individual social factors.[83] Given that populations in disinvested neighborhoods and communities are often simultaneously exposed to a range of co-occurring adverse factors, it is reasonable to look at the combination of social and structural factors that collectively determine neighborhood-level vulnerability to environmentally related health outcomes.[84,85]

To examine the intersection of chronic air pollution exposure, social and structural vulnerabilities, and COVID-19 outcomes, we conducted a retrospective cohort study of COVID-19–related hospitalizations and ED visits between March 2020 and February 2021 by using a harmonized repository of electronic health record (EHR) data from multiple healthcare institutions in New York City (NYC). Given the large number of COVID-19 cases, the variability in exposures, and the combinations of exposures resulting from the racial, ethnic, and socioeconomic diversity of the neighborhoods, NYC is an ideal setting for investigating the effects of pollution, race, and ethnicity in the context of COVID-19. We hypothesized that higher levels of chronic air pollution exposure interact with existing COVID-19–related vulnerabilities at the neighborhood level, contributing to the observed disparities in adverse COVID-19 outcomes recorded at or during hospital admissions in NYC.

Given the inherent potential for bias in hospital-based studies of fatality, we also conducted a supplementary mortality analysis aimed at calculating estimates of excess deaths due to COVID-19 by using current and historical all-cause mortality data from public health records. We sought to determine whether neighborhoods with higher levels of chronic air pollution had more excess deaths among patients hospitalized for COVID-19. Comparing overall mortality rates to historical trends can strengthen the ability to conclude how chronic air pollution contributes to observed disparities in COVID-19 morbidity and mortality. We postulated that demonstrating consistent results across varied investigational approaches, each subject to different types of biases, would enhance our capacity to make inferences about the relationship between chronic air pollution exposure and COVID-19 mortality, particularly among racially diverse populations.

SPECIFIC AIMS

This study aimed to determine whether the effect of chronic air pollution exposure on the risk of COVID-19 morbidity and mortality varies by neighborhood-level social and structural factors in individuals who are hospitalized or visit the ED. Our goal was to determine whether chronic air pollution exposure and neighborhood-level vulnerability to environmental exposures can account for observed racial and ethnic disparities in COVID-19 outcomes among hospitalized or ED patients. Given the constraints in reporting data on COVID-19 outcomes and the potential for selection bias when using hospitalized populations, our secondary objective was to further investigate the relationship between air pollution exposure and COVID-19 mortality. We sought to achieve this objective by calculating excess all-cause mortality in 2020 across neighborhoods with different levels of chronic air pollution exposure and varying degrees of neighborhood-level environmental vulnerability.

STUDY DESIGN AND METHODS

This study was reviewed and approved by the Institutional Review Board at Columbia University.

STUDY POPULATION

The study population was derived from harmonized EHR data from five healthcare systems in NYC. The dataset was compiled by the INSIGHT Clinical Research Network (INSIGHT-CRN), the largest clinical data network in the United States, which receives data from the following large health systems: Albert Einstein College of Medicine/Montefiore Medical Center, Columbia University and Weill Cornell Medicine/New York-Presbyterian Hospital, Icahn School of Medicine/Mount Sinai Health System, and NYU Grossman School of Medicine/Langone Medical Center.[86] Institutions affiliated with INSIGHT-CRN agree to harmonize their clinical records (e.g., hospital inpatient and ED records) to a standardized vocabulary/coding system and upload their data into a centralized repository that can be accessed by the scientific community for research purposes, enabling the linkage of data on individuals across time and institutions in NYC. Currently, this repository maintains data on more than 12 million unique patients. The INSIGHT-CRN repository was selected as the source of data for this study because it enabled us to expand the analyses beyond the geographic catchment area of a single institution without needing to obtain individual permissions or harmonize the data ourselves. Additionally, using data from multiple large hospitals can improve the generalizability of the findings and avoid the concern of limited variability in individual exposures, as may occur in data restricted to a single hospital. The INSIGHT-CRN data repository does not include records from public hospitals but does represent patients with a variety of insurance types, including Medicare and Medicaid.[87] The INSIGHT-CRN created a COVID-19-specific data extraction composed of records for all individuals with a positive COVID-19 test or diagnosis and made available to the scientific community for research purposes. The extracted data included any INSIGHT-CRN records maintained on the selected patients since the start of data collection in the repository in 2011.

Our study population was primarily restricted to hospitalized patients with a COVID-19 diagnostic code assigned from March 1, 2020, through February 28, 2021, who reported a NYC zip code of residence. In addition, to analyze the risk of hospitalization among ED patients, we created a second dataset consisting of all ED and hospital inpatient records for individuals with a COVID-19 diagnostic code. Although the INSIGHT-CRN data repository includes a partial subset of records for ambulatory care patients, we did not include these patients in the study population.

We used dates of hospital admission to stratify the study population by three phases of the pandemic: Phase 1, representing the initial peak (March 2020 through June 2020); Phase 2, representing a period of reduced case numbers (July 2020 through October 2020); and Phase 3, representing a portion of the second peak in cases that occurred before the widespread introduction of COVID-19 vaccines (November 2020 through February 2021).

Lastly, to supplement the analysis of the INSIGHT-CRN data and to calculate excess mortality during the pandemic, we used data obtained from the Office of Vital Statistics in the NYC Department of Health and Mental Hygiene to compile a dataset consisting of monthly all-cause mortality data from January 1, 2015, through December 31, 2020, for each zip code in NYC.

OUTCOMES OF INTEREST AND HOSPITAL-BASED DATA

We examined hospital-based outcomes and procedures that generally correspond to more severe morbidity during hospitalization for COVID-19.[88–90] These outcomes included fatality during the index hospitalization, length of stay, and diagnostic codes for morbidity outcomes experienced during the index hospitalization. Other COVID-19–related outcomes of interest included diagnoses of pneumonia or acute respiratory distress syndrome (ARDS), a severe sequela of COVID-19 that is characterized by fluid build-up in the lungs and contributes to difficulty in breathing.[91] Among individuals requiring supplemental ventilation support, only invasive mechanical ventilation was considered in this study. We also assessed the risk of inpatient admission among the larger group of individuals who presented to the ED.

International Classification of Diseases, Tenth Revision (ICD-10) and Current Procedural Terminology (CPT) codes were used to identify patients who experienced the COVID-19 outcomes of interest, including ARDS (ICD-10 codes J80, B97), viral pneumonia (ICD-0 codes J12.8, J12.81, J12.82, J12.9),[94,95] mechanical ventilation (CPT codes 94002–94005), and dialysis (CPT code 90935). Individual-level patient length of stay was calculated as the interval between the admission date and either the discharge date or date of death during the hospitalization, as recorded in the discharge disposition.[96] Adjacent admissions (as indicated by the discharge date of a first hospitalization being the same date as the admission date of a second hospitalization) were merged into a single encounter. In accordance with clinical guidance from various authors, repeat inpatient admissions with 1 or more full days between the initial discharge and subsequent admission were retained as discrete admissions, indicating clinically significant distinctions between episodes of care that were separated by intervening time out of hospital.

Data on individual patient characteristics, including age, sex, race, ethnicity, body mass index (BMI), and smoking status, were obtained from the admission record at the time of COVID-19–related hospital admission. In instances in which data on BMI and smoking status were missing from the COVID-19 admission record, these data were imputed using previous hospital-based records within the INSIGHT-CRN data repository, if available. Similarly, for individuals with chronic diseases documented in INSIGHT-CRN data before the COVID-19–related admission, the dataset for our study was updated to identify the individuals as having those documented conditions. Chronic disease variables were created for diabetes, asthma, and hypertension by using data on ICD-10 codes. Individuals with a record of undergoing dialysis before their COVID-19–related admission were excluded from analyses regarding dialysis.

HISTORICAL AIR POLLUTANT EXPOSURES BY RESIDENTIAL ZIP CODE

This study builds on rich data and innovative modeling techniques associated with the NYC Community Air Survey (NYCCAS), which was developed by the NYC Department of Health and Mental Hygiene and Queens College of the City University of New York.[97] Since December 2008, NYCCAS has been measuring multiple pollutants, temperature, and humidity by using data loggers at systematically distributed sites throughout NYC. Monitors are mounted at 10–12 feet on public utility poles. The large number and variety of sampling sites enable the generation of exposure estimates with finer spatial resolution than estimates derived from current regulatory networks. Furthermore, given their placement, the NYCCAS monitors tend to better capture data on street-level environmental exposures.[98] Monitoring data from NYCCAS differ from data obtained from other emerging nonregulatory data sources, as the NYCCAS data are gathered by trained professionals using calibrated instrumentation and following a strict quality control system.[99] Prior research has demonstrated a high correlation between data from NYCCAS monitors and data from collocated regulatory monitors.[99] The NYCCAS monitoring network stands out as the most extensive and continuous urban air monitoring program among similar programs in US cities,[100] and NYCCAS data have been widely used in epidemiological and environmental justice studies in NYC.[101–104]

Sampling data from NYCCAS are combined with land use variables in a land use regression model to construct annual averages of pollutants represented geospatially at a 300-m resolution. Given drastic seasonal fluctuations, O_3 estimates are modeled as a summer average rather than an annual average.[97] For this study, we aggregated data on each pollutant from 2009 to 2019 at the zip-code level, as residential zip code was the smallest geographic indicator available for the clinical data. Aggregations were performed by extracting air pollution concentration values from the NYCCAS raster file for each zip code boundary and computing the mean zip code-specific concentrations for each year with available NYCCAS data from 2009 to 2019.

We hypothesized that air pollution exposure before the pandemic could increase vulnerability to COVID-19. For this study, we defined these historical prepandemic air pollution exposures as chronic, or long-term, as the study was focused on annual averages that reflect general exposures experienced by a person living in an area, rather than isolated or acute exposures that occurred shortly before infection with the SARS-CoV-2 virus that causes COVID-19. Pollutant concentrations have declined across NYC over the past decade, likely as a result of local legislation aimed at improving air quality.[75] However, these declines have not occurred equally across all communities. Thus, to capture the potential impact of recent higher pollutant concentrations, we used 11-year averages in our analysis. Specifically, for each zip code, we calculated 11-year pollutant concentration averages for each of four pollutants: $PM_{2.5}$, BC, NO_2, and O_3. Aggregating pollution to the zip-code level and averaging concentrations over 11 years can reduce variability. Thus, the pollutant variables used in this study were centered and scaled so that a one-unit change would correspond to an increment equal to the interquartile range to maximize the contrast supported by our data rather than examine single-unit changes in pollutant concentrations. Additionally, to evaluate linearity, we constructed categorical variables for pollutant concentrations based on quartiles. Each individual was assigned an exposure level based on the residential zip code documented in their hospital admission record. We also calculated 5-year (2015–2019) pollution concentration averages as well as 1-year averages for 2019, for each zip code.

NEIGHBORHOOD VULNERABILITY METRIC

The primary aim of this study was to determine whether neighborhood-level environmental vulnerability, as defined by social and structural factors, modifies the relationship between chronic air pollution exposure and COVID-19 outcomes. We constructed a holistic neighborhood environmental vulnerability index (NEVI) for each residential zip code in NYC by using a profiling and clustering approach based on the Toxicological Priority Index (ToxPi).[105] Using the ToxPi and data from both the 2015–2019 American Community Survey conducted by the US Census Bureau and the 2020 PLACES project of the US Centers for Disease Control and Prevention, we quantified neighborhood vulnerability overall, in four primary domains (demographic, economic, residential, and health status) and 24 subdomains, and across 54 distinct area-level features for NYC (Appendix Table A1; available on the HEI website).

To select the domains, subdomains, and area-level features, we conducted a literature search on social and structural drivers of vulnerability to environmental pollution. We also reviewed published vulnerability indices, including the HGBEnviroScreen tool and the National Institute of Environmental Health Sciences COVID-19 Pandemic Vulnerability Index,[106,107] to compile and adapt characteristics of the domains used in those applications of ToxPi for our study. Additionally, we relied on the subject matter knowledge of our research team to determine the final set of variables to be included in the domains for this study. Overall and domain-specific indices were calculated by summing the values of standardized features within the subdomains and then aggregating and weighting scores based on the number of features within each subdomain, with equally weighted primary domains. Scores were originally calculated at the census tract level and then aggregated to the zip code level by using population-based weights. Each individual was assigned both an overall NEVI score and domain-specific NEVI scores based on the residential zip code in their hospital admission record. Each overall and domain-specific NEVI score has a potential range of 0 to 1, with higher values indicating greater neighborhood vulnerability. In previously published work, we have demonstrated that the NEVI is correlated with other area-level vulnerability measures, such as the Neighborhood Deprivation Index and the Social Vulnerability Index.[108] Additionally, the NEVI is associated with area-level measures of environmentally related diseases, such as childhood asthma, across multiple cities in the United States.[109]

DATA ANALYSIS

Analysis of Harmonized EHR Data

Cox proportional hazards models were constructed to examine associations between air pollutant exposures and both COVID-19 fatality and hospital length of stay, as represented in the INSIGHT-CRN data. Modified Poisson models with robust standard errors were used to estimate RRs corresponding to the associations between air pollutant exposures and COVID-19 morbidity, including diagnoses of ARDS or pneumonia as well as the use of mechanical ventilation or dialysis. For fatality analyses, follow-up time was calculated as the time from admission to death, censored by discharge; for length-of-stay analyses, follow-up time was calculated as the time from admission to discharge, censored by death. Note, we use the term fatality as we are estimating the risk of death among individuals who have been diagnosed with the condition of interest, COVID-19. We also constructed modified Poisson models to estimate the risk of hospital admission among the broader group of individuals who presented to the ED. Because both environmental and social factors at the zip code level were included as fixed effects, we did not include a random effect for zip code. Given the smaller sample sizes in the later periods of the COVID-19 pandemic, we combined pandemic Phases 2 and 3 for data analysis.

For all presented results, pollutant concentrations were modeled as single linear terms. Pollutant contrasts were constructed so that a 1-unit change corresponds to an increment equal to the interquartile range. Concentrations of O_3 and $PM_{2.5}$ were modeled as 1-unit differences in parts per billion and micrograms per cubic meter ($\mu g/m^3$), respectively. BC was scaled as a 0.2-unit difference in absorbance units, and NO_2 was scaled to represent a change of 5 parts per billion. Categorical analysis was performed to evaluate for the presence of nonlinearity. Additionally, all analyses that produced the presented results used the overall NEVI score. Models were also constructed with each NEVI domain individually.

Confounding and Effect Modification

Relevant confounders were identified via analysis of directed acyclic graphs.[110] Using Dagitty,[111] we obtained a minimally sufficient adjustment set that included age, neighborhood vulnerability, chronic disease, sex, smoking status, and BMI to obtain an estimate of the association between air pollutant concentrations and COVID-19 morbidity and fatality (Appendix Figure A1). Because historical air pollution was the exposure of interest, short-term factors associated with acute air pollution exposure (e.g., temperature, humidity, and other seasonal effects) at the time of the COVID-19 pandemic were not conceptualized as confounders of these associations. Effect modification due to single air pollutants and NEVI score was formally assessed on a multiplicative scale (i.e., with interaction terms), using an α level of 0.05 as the threshold for statistical significance. We then stratified by tertile of the NEVI distribution within NYC and reported stratum-specific estimates of the effect of air pollutant exposures; we used this approach (rather than reporting coefficients for the interaction between two continuous variables) to increase the interpretability of the results. NEVI tertiles were constructed using the full NEVI distribution across NYC rather than only in the study population. When a statistically significant interaction was observed, we marked plots with a red asterisk and interpreted the stratum-specific estimates. When the interaction was not statistically significant, we interpreted the coefficients from the adjusted model, where NEVI was included as a confounder. To evaluate potential competing effects of multiple pollutants, we constructed a series of two-pollutant models to determine whether the effects changed with the inclusion of a second pollutant.

We further sought to examine the role of pre-existing chronic disease in the associations between estimated chronic exposures to ambient air pollutants and COVID-19 morbidity and fatality. Effect modification by pre-existing chronic disease was formally assessed on an additive scale by calculating the relative excess risk due to effect mod-

ification.[112] Relative excess risk due to interaction (RERI) analyses were conducted only if both the air pollutant and the chronic disease were associated with an increased risk of a particular COVID-19 outcome. If evidence of departure from additivity was observed, we stratified the RERI analysis by NEVI tertile and estimated the RERI within each tertile. We also evaluated the persistence of racial and ethnic disparities by stratifying data by race and Hispanic ethnicity and then rerunning models that included variables representing air pollutant concentrations, NEVI scores, chronic disease diagnoses, and individual-level confounders. This approach enabled us to simultaneously model interactions between air pollution and NEVI score and examine racial differences. This study lacked sufficient power to examine three-way interactions between air pollutant concentrations, NEVI scores, and race and ethnicity. However, if the hypothesized effect modification by neighborhood-level social and structural factors fully explains racial disparities in associations between air pollution exposures and COVID-19 outcomes, we would expect these analyses to reveal no stratum-specific differences by race. In this report, we have reported results only for those analyses that demonstrated considerable differences across racial and ethnic subpopulations.

Excess Mortality Analysis

The excess mortality analysis using all-cause mortality data from public health records did not exclude deaths that occurred outside of a hospital or potentially misclassify COVID-19–related deaths due to an incorrect assignment of cause of death. Thus, this analysis lacks some of the potential for selection bias that may have affected the results of our analyses of EHR data. Note, we use the term mortality as our population consists of all deaths, and not just individuals with a specific condition. For consistency with the baseline period for the all-cause mortality data, zip codes in NYC were stratified into chronic exposure tertiles based on the zip code–specific 5-year (2015–2019) average ambient $PM_{2.5}$ concentrations. Chronic $PM_{2.5}$ exposure and NEVI score tertiles were combined to create nine exposure categories: (1) low $PM_{2.5}$ exposure and low NEVI tertile, (2) low $PM_{2.5}$ exposure and medium NEVI tertile, (3) low $PM_{2.5}$ exposure and high NEVI tertile, (4) medium $PM_{2.5}$ exposure and low NEVI tertile, (5) medium $PM_{2.5}$ exposure and medium NEVI tertile, (6) medium $PM_{2.5}$ exposure and high NEVI tertile, (7) high $PM_{2.5}$ exposure and low NEVI tertile, (8) high $PM_{2.5}$ exposure and medium NEVI tertile, and (9) high $PM_{2.5}$ exposure and high NEVI tertile. Monthly counts of excess all-cause mortality for each exposure category were then calculated using a time-series periodic regression model that has previously been employed to detect epidemics of influenza or other infectious diseases.[113–116]

Given the availability of exposure and outcome data for the study period, we were able to conduct analyses for 166 zip codes, representing 94% of residential zip codes in NYC. The aggregation of data into these nine groupings ensured adequate sample sizes for stable estimation of the baseline mortality estimates. All-cause mortality counts for 2015–2019 were used to develop an initial training dataset. Calculating excess mortality requires a stable estimate of baseline mortality in a given spatial area. Thus, in this study, the first step involved removing the effects of mortality due to any prior epidemics (e.g., influenza) that could artificially inflate the calculated baseline mortality. This is especially important for the time of the COVID-19 pandemic, as the incidence of other illnesses that contribute to local epidemics, like influenza, may have been suppressed as a result of COVID-19 lockdown policies. Consistent with previous studies, prior epidemics were identified in this training dataset by first purging the data to exclude the highest values of mortality, which could indicate a prior epidemic.[113] We selected 5% as the threshold for the highest values and then confirmed the presence of epidemic activity (primarily influenza) by reviewing prior public health data for NYC.

A second training dataset was created using all-cause mortality counts for 2015–2019. These training data were purged of monthly all-cause mortality counts that exceeded the epidemic threshold previously identified in the 2015–2019 training dataset. A variety of models (linear, Poisson, etc.) and variable constructions, including polynomials, were compared to identify the best-fitting regression equation to estimate baseline mortality. The best-fitting model was selected using an iterative comparison process, beginning with the simplest models and gradually increasing the model complexity. We used analysis of variance comparisons to select between nested models and the Akaike information criterion to select between non-nested models. Once additional model complexity no longer improved the model fit, a final baseline model was selected.

Excess all-cause mortality counts were calculated by quantifying deviations of observed monthly all-cause mortality counts from those predicted by the baseline periodic regression model, which accounted for seasonal fluctuations within the mortality data. Monthly excess all-cause mortality rates for populations in each exposure category were calculated as excess all-cause mortality counts divided by population totals obtained from the NYC Department of Health and Mental Hygiene.

Sensitivity Analyses

We performed several sensitivity analyses to assess the role of selection biases in the study results. To evaluate the completeness of the available harmonized EHR data across multiple institutions within the INSIGHT-CRN, we compared the proportion of missing data in the harmonized EHR data from the INSIGHT-CRN to that among data extracted from medical records at individual institutions where we had access to such data (i.e., Columbia University, Montefiore Medical Center, Mount Sinai Health System).

A type of potential selection bias that could have occurred in this study pertains to patients seeking treatment at specific hospitals based on the severity of their illness, even if they live outside the typical catchment area of those hospitals. To account for this, we obtained total hospitalization counts by NYC zip code from the NYC Department of Health and Mental Hygiene.[117] We then repeated all analyses in a subset of the study population that was restricted to zip codes for which at least 40% of the total COVID-19 hospitalizations were included within the INSIGHT-CRN harmonized data repository, with the intent that the restricted population reflected the typical hospital catchment area. The selection of 40% as the cut-off for this restriction enabled an adequate sample size for the restricted analyses while also reducing the potential for selection bias.

To perform a more thorough analysis of selection bias, we used the method, AscRtain, which was developed by Hemani and Palmer.[118,119] This approach uses simulation to characterize the set of selection effects that would have to occur to give rise to the observed effect estimate in a study if the null hypotheses of no effect were true — in other words, the type of selection effects that would have to occur to observe the RRs seen in our study in the setting of air pollutant exposures having no actual effect on COVID-19 outcomes. In considering the plausibility of these selection effects, one can begin to estimate how vulnerable the results of a study are to selection bias.

The AscRtain method requires a number of user-defined inputs to conduct these simulations. First, we assumed that our sample represented approximately 11% of the overall target population. We derived this measure by using existing data indicating that 26.6% of COVID-19 cases were hospitalized during Phase 1 of the pandemic in NYC,[120] and we used estimates only from areas for which we were confident that our sample accounted for at least 40% of the total inpatient population (26.6% × .40 ≈ 11%). Because the assumptions specific to the analysis package require a binary exposure variable, we used the highest quartile of pollutant exposure as our "exposed" group. (As previously described, the quartiles used in our study were based on data for the entire population of NYC rather than only our analytic sample.) We used a COVID-19 prevalence of 5% based on estimates made during Phase 1 of the pandemic.[120] We allowed the selection effects to vary differentially in either direction, meaning that we could have greater selection based on exposure and outcome (i.e., more people with higher air pollutant exposures and adverse outcomes in our population than in the target population) or lower selection risk than baseline (i.e., fewer people with higher air pollution exposures and adverse outcomes than in the target population). We allowed for the interaction between exposure and outcome to affect the risk of selection by an amount varying by 10% in either direction, or allowed the baseline probability of selection to range from 0% to 20%. We simulated approximately 5.7 million parameter combinations.

Selection bias could also arise in our results because not all individuals were tested for COVID-19, and access to testing varied spatially. We stratified the data by zip code-level testing rates as reported by the NYC Department of Health and Mental Hygiene and then repeated length-of-stay analyses within each stratum, given the greater statistical power available for these analyses. Because COVID-19 testing data were available only for a time period that overlapped with Phases 2 and 3, we performed this sensitivity analysis only for these phases of the pandemic.

Statistical Software

The statistical analyses were performed using R statistical software, version 4.1.2 (R Foundation for Statistical Computing), including the packages raster, version 3.5.2, and SF, version 1.0.3, to estimate historical air pollutant exposures; AscRtain, version 0.0.0.9, along with the corresponding SHINY application for the sensitivity analyses; and Diggitty, version 0.3.1, for analyses of confounding and effect modification. We also used ArcGIS Pro, version 3.3.1 software (ESRI, Inc.), along with R for the excess mortality analysis.

RESULTS

POPULATION AND PANDEMIC CHARACTERISTICS

The study population of hospitalized patients with a COVID-19 diagnostic code assigned between March 1, 2020, and February 28, 2021, and a NYC zip code of residence, as recorded in data extracted from the harmonized INSIGHT-CRN repository, is summarized overall and with stratification by phase of the pandemic in **Table 1**. The study population was older than the overall population of NYC, but was representative of the city's racial and ethnic diversity. Hospitalized patients diagnosed with COVID-19 during Phase 1 of the pandemic were more likely to be male, of Black race, and to experience COVID-19–related morbidity (other than pneumonia) or fatality, compared to such patients diagnosed with COVID-19 in Phases 2 and 3. By contrast, a diagnosis of pneumonia was more common among hospitalized patients diagnosed with COVID-19 during Phases 2 and 3 of the pandemic rather than during Phase 1. The numbers of patients hospitalized for COVID-19 are plotted by outcome and date of admission in **Figure 1**. These data extracted from the INSIGHT-CRN repository reflect the temporal trends observed in NYC more broadly, with the initial and largest peak in COVID-19 hospitalizations occurring in Phase 1, followed by a smaller number of hospitalizations during Phase 2 as lockdown measures were initially lifted, and then a smaller peak in Phase 3 that was attributed to the alpha variant of SARS-CoV-2.

Table 1. Demographic and Health Characteristics of Hospitalized Patients with a COVID-19 Diagnostic Code Assigned Between March 1, 2020–February 28, 2021, and a Zip Code of Residence in New York City, Overall and by Phase[a] of the COVID-19 Pandemic[b]

	Overall (*N* = 20,318)	Phase 1 Total Population (*n* = 11,652)	Phase 1 Catchment Area Subgroup[c] (*n* = 7,487)	Phase 2/3 Total Population (*n* = 8,666)	Phase 2/3 Catchment Area Subgroup[c] (*n* = 5,600)
Age, years[d]	**64.2 (17.8)**	**63.9 (17.3)**	**65.1 (17.1)**	**64.5 (18.5)**	**66.0 (18.0)**
Sex[d]					
Male	10,673 (52.5)	6,365 (54.6)	4,065 (54.3)	4,308 (49.7)	2,813 (50.2)
Female	9,645 (47.5)	5,287 (45.4)	3,422 (45.7)	4,358 (50.3)	2,787 (49.8)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Race[d]					
White	5,485 (27.0)	2,876 (24.7)	1,537 (20.5)	2,609 (30.1)	1,442 (25.8)
Black	4,602 (22.6)	2,947 (25.3)	2,025 (27.0)	1,655 (19.1)	1,108 (19.8)
Asian	1,233 (6.1)	538 (4.6)	289 (3.9)	695 (8.0)	487 (8.7)
American Indian & Alaskan Native	58 (0.3)	29 (0.2)	21 (0.3)	29 (0.3)	17 (0.3)
Native Hawaiian & Pacific Islander	47 (0.2)	28 (0.2)	17 (0.2)	19 (0.2)	13 (0.2)
Other	6,738 (33.2)	3,877 (33.3)	2,706 (36.1)	2,861 (33.0)	2,050 (36.6)
Missing	2,155 (10.6)	1,357 (11.6)	892 (11.9)	798 (9.2)	483 (8.6)
Ethnicity[d]					
Non-Hispanic	11,307 (55.7)	6,303 (54.1)	3,708 (49.5)	5,004 (57.7)	3,002 (53.6)
Hispanic	7,123 (35.1)	4,112 (35.3)	2,970 (39.7)	3,011 (34.7)	2,191 (39.1)
Missing	1,888 (9.3)	1,237 (10.6)	809 (10.8)	651 (7.5)	407 (7.3)
BMI[d]					
Underweight (<18.5)	919 (4.5)	569 (4.9)	329 (4.4)	350 (4.0)	248 (4.4)
Normal weight (≥18.5 to 24)	4,718 (23.2)	2,670 (22.9)	1,750 (23.4)	2,048 (23.6)	1,336 (23.9)
Overweight (≥25 to 29)	6,681 (32.9)	3,784 (32.5)	2,427 (32.4)	2,897 (33.4)	1,866 (33.3)
Obesity class I (≥30 to 34)	4,381 (21.6)	2,527 (21.7)	1,620 (21.6)	1,854 (21.4)	1,192 (21.3)
Obesity class II (≥35 to 39)	2,028 (10.0)	1,198 (10.3)	775 (10.4)	830 (9.6)	517 (9.2)
Obesity class III (≥40)	1,591 (7.8)	904 (7.8)	586 (7.8)	687 (7.9)	441 (7.9)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoking status[d]					
Never smoked	17,976 (88.5)	10,290 (88.3)	6,436 (86.0)	7,686 (88.7)	4,838 (86.4)
Ever smoked	2,342 (11.5)	1,362 (11.7)	1,051 (14.0)	980 (11.3)	762 (13.6)
Asthma[d]					
No	16,862 (83.0)	9,702 (83.3)	6,159 (82.3)	7,160 (82.6)	4,565 (81.5)
Yes	3,456 (17.0)	1,950 (16.7)	1,328 (17.7)	1,506 (17.4)	1,035 (18.5)

continued next page

Table 1. (*continued*)

	Overall (N = 20,318)	Phase 1 Total Population (n = 11,652)	Phase 1 Catchment Area Subgroup[c] (n = 7,487)	Phase 2/3 Total Population (n = 8,666)	Phase 2/3 Catchment Area Subgroup[c] (n = 5,600)
Diabetes[d]					
No	11,021 (54.2)	6,124 (52.6)	3,718 (49.7)	4,897 (56.5)	2,999 (53.6)
Yes	9,297 (45.8)	5,528 (47.4)	3,769 (50.3)	3,769 (43.5)	2,601 (46.4)
Hypertension[d]					
No	5,821 (28.6)	3,238 (27.8)	1,854 (24.8)	2,583 (29.8)	1,481 (26.4)
Yes	14,497 (71.4)	8,414 (72.2)	5,633 (75.2)	6,083 (70.2)	4,119 (73.6)
ARDS[d]					
No	17,497 (86.1)	9,756 (83.7)	6,287 (84.0)	7,741 (89.3)	4,948 (88.4)
Yes	2,821 (13.9)	1,896 (16.3)	1,200 (16.0)	925 (10.7)	652 (11.6)
Pneumonia[d]					
No	15,341 (75.5)	10,527 (90.3)	6,997 (93.5)	4,814 (55.6)	2,923 (52.2)
Yes	4,977 (24.5)	1,125 (9.7)	490 (6.5)	3,852 (44.4)	2,677 (47.8)
Dialysis[d,e]					
No	20,037 (98.6)	11,442 (98.2)	7,380 (98.6)	8,457 (99.2)	5,560 (99.3)
Yes	281 (1.4)	210 (1.8)	107 (1.4)	71 (0.8)	40 (0.7)
Ventilation[d]					
No	17,782 (87.5)	9,814 (84.2)	6,191 (82.7)	7,968 (91.9)	5,065 (90.4)
Yes	2,536 (12.5)	1,838 (15.8)	1,296 (17.3)	698 (8.1)	535 (9.6)
Deceased[d]					
No	16,866 (83.0)	9,168 (78.7)	5,702 (76.2)	7,698 (88.8)	4,865 (86.9)
Yes	3,452 (17.0)	2,484 (21.3)	1,785 (23.8)	968 (11.2)	735 (13.1)
Pollutants[f]					
BC	1.1 (0.9–1.2)	1.1 (0.9–1.2)	1.1 (1.0–1.1)	1.1 (0.9–1.2)	1.1 (1.0–1.2)
$PM_{2.5}$	9.0 (8.5–9.3)	8.9 (8.5–9.3)	9.1 (8.6–9.3)	9.0 (8.5–9.4)	9.1 (8.6–9.3)
NO_2	21.0 (19.0–23.2)	20.8 (19.0–23.0)	20.7 (18.6–22.1)	21.1 (19.0–23.2)	20.8 (19.0–23.0)
O_3	30.4 (30.0–31.4)	30.4 (29.8–31.4)	30.4 (30.0–31.4)	30.4 (29.6–31.6)	30.4 (29.1–31.4)

ARDS = acute respiratory distress syndrome; BC = black carbon; BMI = body mass index. Adapted from *Kannoth et al. 2025*; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

[a] Phase 1 (March 2020–June 2020); Phase 2 (July 2020–October 2020); Phase 3 (November 2020–February 2021).
[b] Data were extracted from the INSIGHT Clinical Research Network harmonized data repository of electronic health records obtained from five healthcare systems in the New York City metropolitan area.
[c] The hospital catchment area subgroup is a subset of the total study population restricted to zip codes for which ≥40% of the total hospitalized COVID-19 cases were included in the INSIGHT Clinical Research Network harmonized data repository.
[d] Age is reported as mean (standard deviation); categorical variables are reported as *n* (%).
[e] The dialysis outcome is defined as first-time use of dialysis after the COVID-19 diagnosis. Individuals who received dialysis before COVID-19 diagnosis were excluded from analyses where COVID-related dialysis was the outcome.
[f] Ambient air pollutant concentrations are reported as median (interquartile range). Units for BC, $PM_{2.5}$, NO_2, and O_3 are absorbance units, $\mu g/m^3$, parts per billion, and parts per billion, respectively.

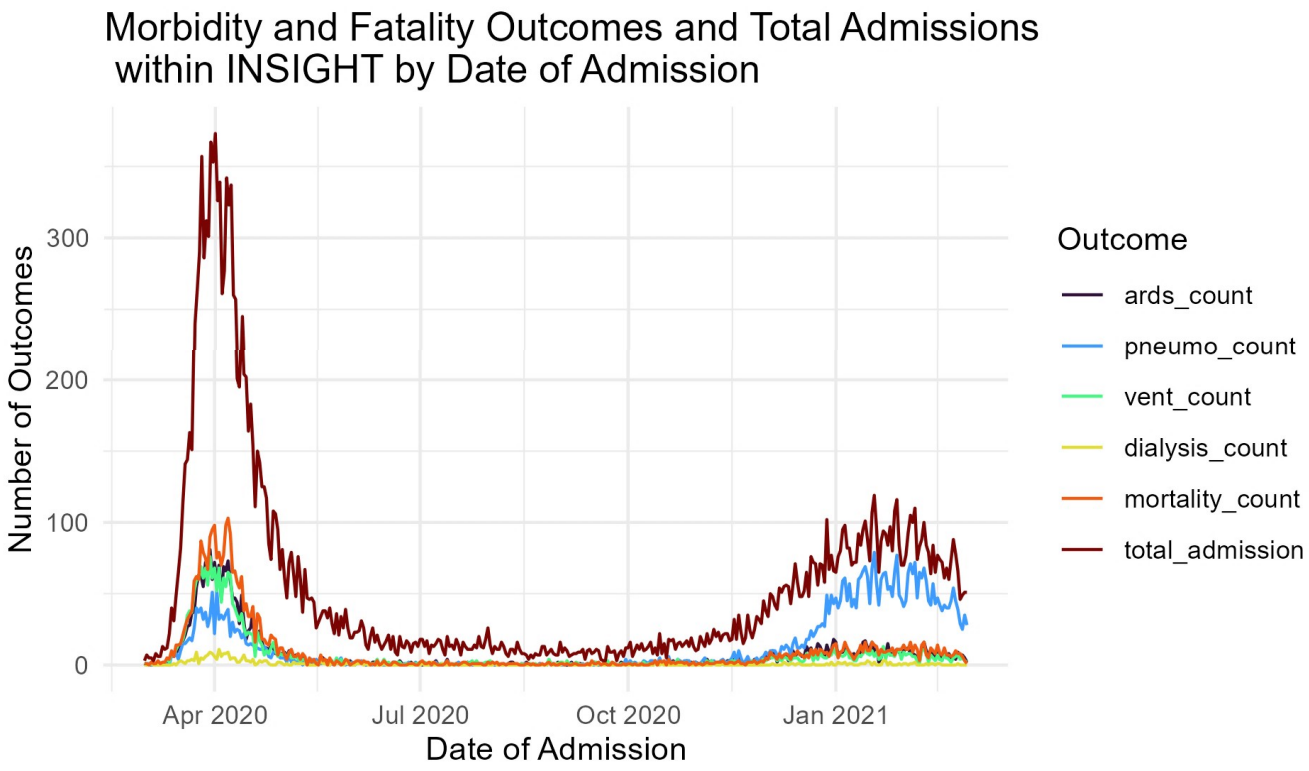

Figure 1. Temporal distribution of numbers of patients hospitalized for COVID-19 and outcomes, by date of admission, March 2020–February 2021. The graph presents the numbers of hospitalized patients with COVID-19 and selected morbidity and fatality outcomes based on data extracted from the INSIGHT Clinical Research Network data repository. ARDS = acute respiratory distress syndrome.

SPATIAL DISTRIBUTION OF AIR POLLUTION AND NEVI METRICS

The spatial distributions of air pollutant concentrations and NEVI scores by zip code throughout NYC are shown in **Figures 2** and **3**, respectively, demonstrating the variability of pollutant exposures and social and structural vulnerabilities across the city. Concentrations of BC, $PM_{2.5,}$ and NO_2 were highly correlated with one another (**Table 2**). Consistently, concentrations of O_3 were inversely correlated with concentrations of the other pollutants, with correlation coefficients ranging from −0.83 to −0.87. Correlations between air pollutant concentrations and both the overall and domain-specific NEVI scores tended to be low, with Spearman correlation coefficients of 0.3 or less, except for the Residential Domain (Table 2).

Hospitalized patients in the study population overall were more likely to reside in neighborhoods with zip codes with higher vulnerability indices. The study subpopulation restricted to hospitalized patients residing in the catchment area of the INSIGHT-CRN hospitals was generally similar to the total study population, most notably concerning the spatial distribution of air pollutant exposures.

VIABILITY OF INSIGHT-CRN DATA

Comparisons of extracts of EHR data received directly from selected individual institutions (Appendix Table A2) did not demonstrate marked differences in the prevalence or distribution of missing data when compared to data in INSIGHT-CRN, as presented in Table 1, suggesting that it was appropriate to proceed with analyzing the harmonized data obtained from the INSIGHT-CRN.

SPATIAL VARIABILITY OF THE PANDEMIC IN NYC

Figure 4 depicts the spatial distribution of the study population of hospitalized patients diagnosed with COVID-19 by residential NYC zip code and stratified by the three pre-COVID-19 vaccination phases of the pandemic. Data in this figure represent total hospitalized patients by zip code and are not normalized to the size of the residential population in each zip code. The number of hospitalized patients per zip code was generally highest in Phase 1, although the spatial distribution of patients did not change dramatically from Phase 1 to Phase 3. Areas of the Bronx, Northern Manhattan, parts of Lower Manhattan and Eastern Manhattan, and South Brooklyn accounted for the largest numbers of hospitalized COVID-19 patients in both Phase 1 and Phase 3. Hospitalization counts were

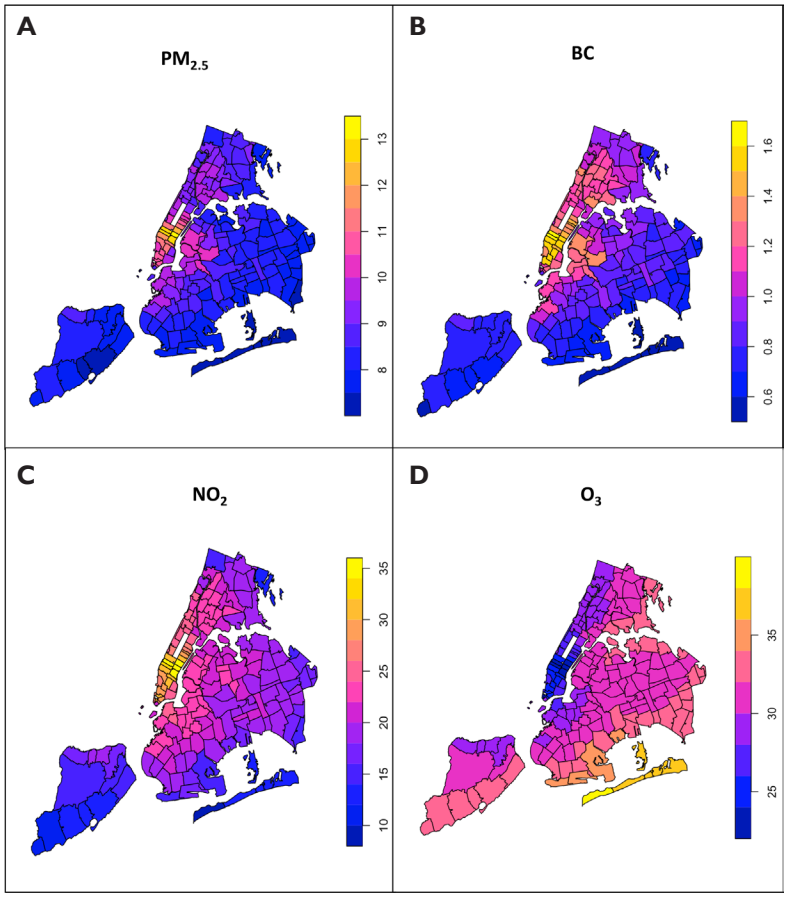

Figure 2. Spatial distribution of 11-year (2009–2019) average concentrations of four air pollutants in New York City, by zip code. Pollutant concentrations are presented for $PM_{2.5}$, expressed in μg/m³ (**A**); BC, expressed in absorbance units (**B**); NO_2, expressed in parts per billion (**C**); and O_3, expressed in parts per billion (**D**). BC = black carbon. Adapted from *Kannoth et al. 2025*; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

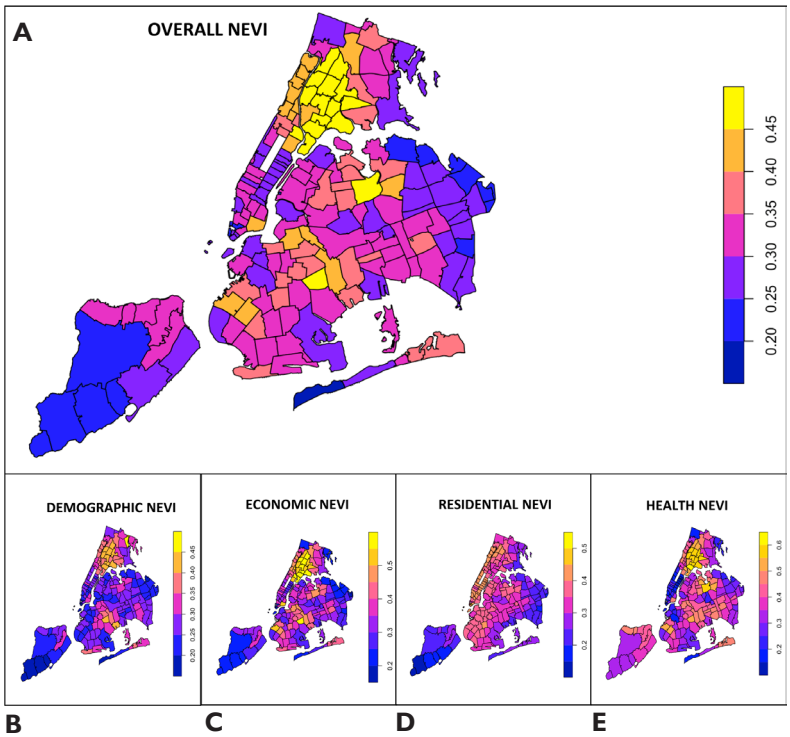

Figure 3. Spatial distribution of NEVI scores overall and for individual NEVI domains, by zip code in New York City. Distributions are presented for overall NEVI scores (**A**) and for scores on four primary NEVI domains specific to demographic (**B**), economic (**C**), residential (**D**), and health-related (**E**) factors. Data sources used to develop the NEVI were the 2015–2019 American Community Survey conducted by the US Census Bureau and the 2020 PLACES project of the US Centers for Disease Control and Prevention. NEVI = neighborhood environmental vulnerability index. Adapted from *Kannoth et al. 2025*; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

Table 2. Correlations[a] Between Neighborhood-Level Environmental Vulnerability Metrics[b] and Air Pollutant Concentrations[c] in New York City

	NEVI	Demographic NEVI	Economic NEVI	Residential NEVI	Health-Related NEVI	$PM_{2.5}$	BC	NO_2	O_3
NEVI	1.00	0.83	0.98	0.37	0.82	0.23	0.27	0.24	–0.13
Demographic NEVI		1.00	0.80	0.25	0.61	0.17	0.22	0.13	–0.07
Economic NEVI			1.00	0.40	0.78	0.29	0.31	0.30	–0.18
Residential NEVI				1.00	–0.11	0.80	0.76	0.83	–0.78
Health-Related NEVI					1.00	–0.19	–0.13	–0.17	0.26
$PM_{2.5}$						1.00	0.96	0.92	–0.86
BC							1.00	0.89	–0.83
NO_2								1.00	–0.87
O_3									1.00

BC = black carbon; NEVI = neighborhood environmental vulnerability index. Adapted from *Kannoth et al. 2025*; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

[a] The presented data are Spearman correlation coefficients.
[b] Neighborhood-level environmental vulnerability metrics include the overall NEVI score and scores on individual NEVI domains.
[c] Air pollutant data are zip code–level, 11-year averages based on data from the 2009–2019 New York City Community Air Survey.

consistently lower during Phase 2. Spatial distributions for several different severe outcomes of COVID generally displayed similar patterns (Appendix Figure A2).

ANALYSES SUPPORTING CONSTRUCTION OF THE FINAL MODEL

No differences in results were observed across analyses using measures based on these three different methods of aggregation for air pollution metrics, so analyses were conducted with the 11-year averages. Categorical analyses of the EHR data extracted from the INSIGHT-CRN did not reveal considerable departures from linearity; therefore, we used continuous variables to represent air pollutant concentrations in all analyses, as previously described in the study methods (Appendix Table A3a–d). Additionally, results of analyses that included domain-specific NEVI data were consistent with the results from analyses using the overall NEVI score, except for the results specific to the residential NEVI domain which were slightly further from the null for pneumonia outcomes during Phase 1 (Appendix Table A4a–d); thus, we used the overall NEVI score rather than the domain-specific NEVI scores in all subsequent models. Generally, we did not observe large differences between the results of unadjusted models vs models adjusted by the full adjustment set (Appendix Table A5). Similarly, constructing two-pollutant models for BC, NO_2, and $PM_{2.5}$, each adjusted for concentrations of O_3 (Appendix Table A6), did not yield results that differed consistently from the results of single-pollutant models, except for results specific to the outcome of mechanical ventilation. Interpollutant correlations with correlation coefficients greater than 0.9 precluded examining the co-pollutant effects between BC, NO_2, and $PM_{2.5}$.

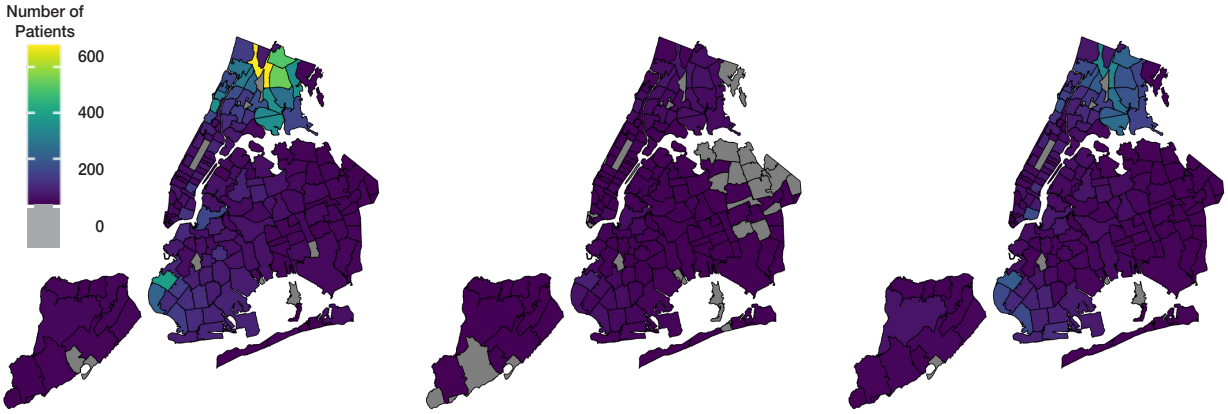

Figure 4. Spatial distribution of hospitalized patients with a COVID-19 diagnosis documented in the INSIGHT Clinical Research Network data repository, by residential New York City zip code and stratified by three phases of the COVID-19 pandemic. The spatial distribution maps are presented, from left to right, in temporal order of the phases of the pandemic: Phase 1 (March 2020–June 2020), Phase 2 (July 2020–October 2020), and Phase 3 (November 2020–February 2021).

FATALITY AND MORTALITY OUTCOMES

Fatality in the Primary INSIGHT-CRN Study Population

Figure 5 and Appendix Table A5 present the hazard ratios (HRs) for death among hospitalized patients diagnosed with COVID-19, by phase of the pandemic and within the full study population and the hospital catchment subset of the study population. Both overall adjusted estimates and adjusted estimates within each tertile of NEVI score are presented. The unadjusted (i.e., crude) and adjusted findings did not differ substantially (Appendix Table A5). Overall, results for the adjusted hazard of fatality among patients suggested that the risk of fatality was inversely associated with exposure to $PM_{2.5}$, NO_2, and BC across the three phases of the pandemic for both the full study population and within the hospital catchment subset. The opposite was true for exposure to O_3, with the risk of fatality increasing with greater O_3 concentrations. Statistically significant effect modification by NEVI score on the association between air pollutant exposures and fatality was observed only in the full study population in Phases 2 and 3 of the pandemic. Stratum-specific estimates revealed that inverse (for $PM_{2.5}$, NO_2, and BC) and positive (for O_3) associations between the hazard of fatality and greater pollutant exposures were primarily observed in areas with the highest vulnerability, with associations between air pollution and fatality being null in areas of lowest vulnerability. These associations did not differ by age, race, ethnicity, or pre-existing chronic disease.

Excess All-Cause Mortality in Public Health Data

Figure 6, which depicts the results of the analysis of excess deaths in the public health dataset, supplements the findings of the fatality analysis that are presented in Figure

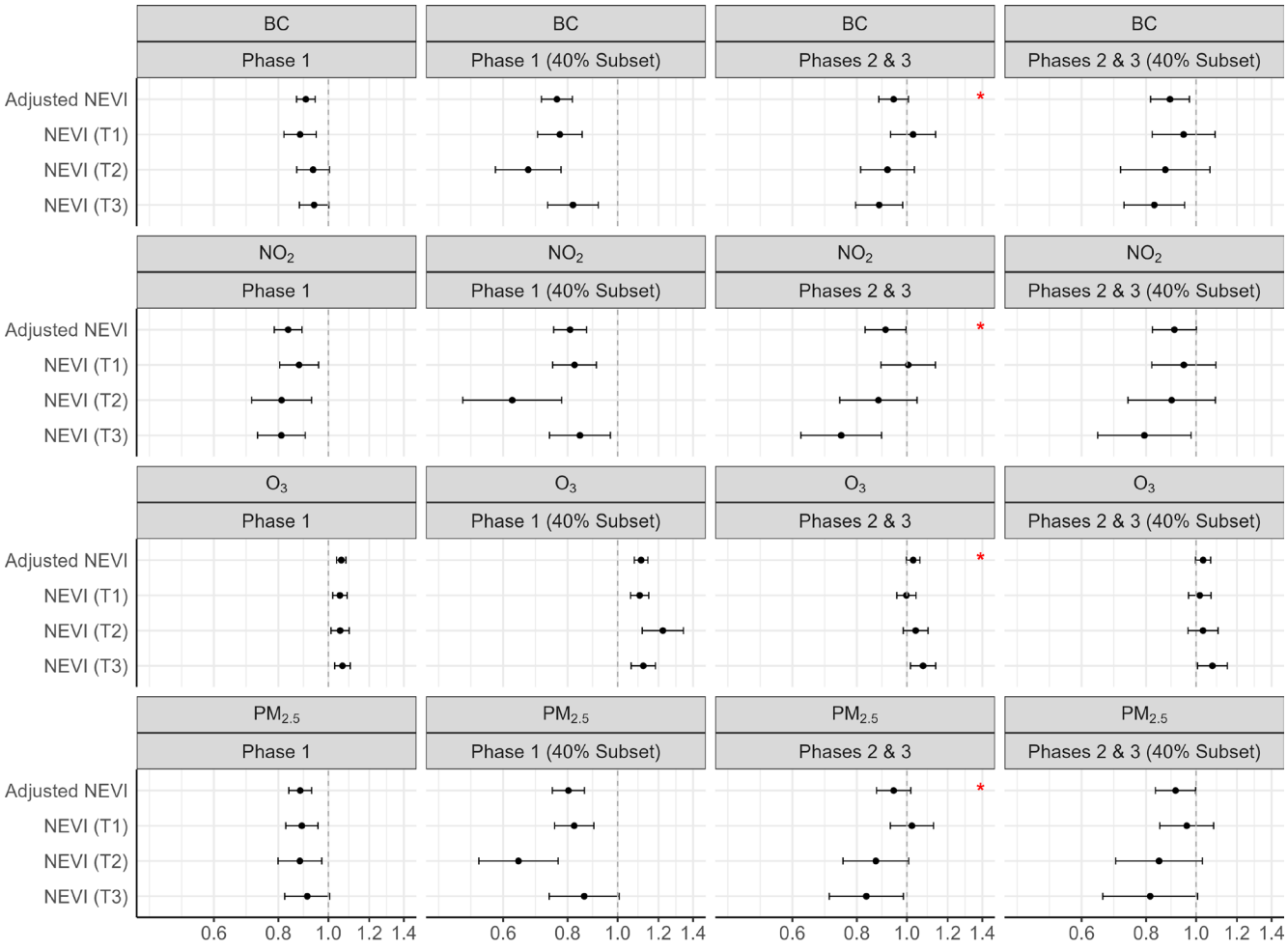

Figure 5. Adjusted and NEVI-stratified hazard ratios and 95% confidence intervals for COVID-19 fatality associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Statistically significant effect modification is indicated by a red asterisk. BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Reprinted from *Azan et al. 2025*; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

5. The inset map (Figure 6B) shows areas of NYC that correspond to each of the nine air pollutant–NEVI strata (i.e., from low pollutant–low NEVI tertile to high pollutant–high NEVI tertile), with the different colors having the same definitions in both the map and the graph. Appendix Figure A3 provides an example of a graph that can be used to identify time periods in which all-cause mortality exceeded the calculated baseline for the period 2015–2020. In this study, excess mortality was not observed in areas of NYC with higher air pollutant concentrations (Figure 6A). The greatest excess mortality was observed in areas with low air pollutant concentrations and high levels of social and structural vulnerability, followed by areas with moderate air pollutant concentrations and high NEVI scores. Figure 6C, 6D, and 6E show that, across all strata of neighborhood-level $PM_{2.5}$ concentrations, the greatest excess mortality was observed in areas with higher social and structural vulnerability.

MORBIDITY OUTCOMES

Length of Stay

Figure 7 shows the HRs for discharge (i.e., hospital length of stay) for each pollutant by phase of the pandemic and among both the full study population and the hospital catchment subset of the study population. Because the Cox proportional hazards model modeled the risk of discharge, an HR greater than 1 indicates a shorter length of stay (i.e., higher hazard of discharge), and an HR less than 1 indicates a longer length of stay. The results in Phase 1 of the pandemic were generally null; however, there was evidence of effect modification for O_3, with shorter length of stay being associated with higher exposure to O_3 only in areas of high vulnerability. In Phases 2 and 3, there was evidence of shorter lengths of stay being associated with higher exposure to $PM_{2.5}$, NO_2, and BC, and with lower exposure to O_3. Significant effect modification by NEVI score was observed for NO_2 and $PM_{2.5}$ in Phases 2 and 3, with shorter lengths of stay being associated with higher air pollutant exposures only in areas with higher levels of social and structural vulnerability and not in areas within the lowest tertile of NEVI scores. In analyses restricted to patients 65 years of age or older among the hospital catchment subset of the study population, there was evidence of longer length of stay (i.e., discharge HRs <1) being associated with higher exposures to $PM_{2.5}$, NO_2, and BC and shorter length of stay being associated with higher exposure to O_3 in Phase 1 of the pandemic (Appendix Table A7),

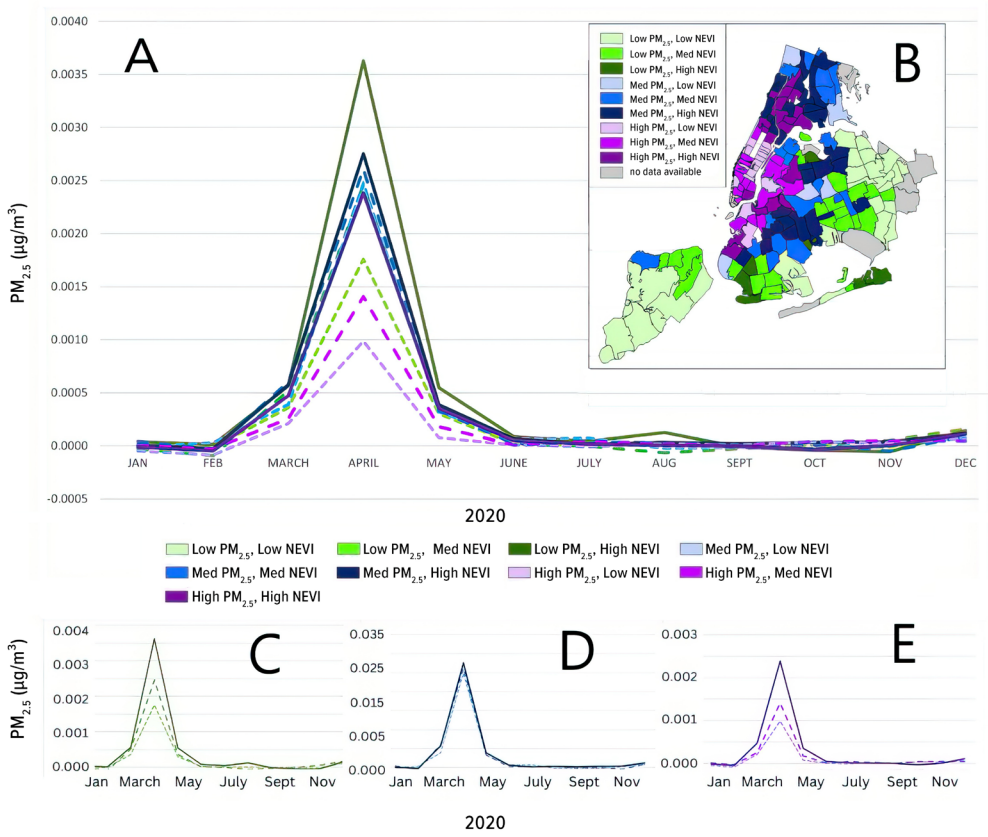

Figure 6. Monthly excess all-cause mortality in 2020 across nine exposure strata based on $PM_{2.5}$ concentration and tertile of the overall NEVI score. The main graph shows excess mortality per month in 2020 for each of nine $PM_{2.5}$/NEVI strata (**A**). The inset map shows the spatial distribution of the nine $PM_{2.5}$/NEVI strata, by zip code in New York City (**B**). The smaller graphs show excess mortality by NEVI tertile for each tertile of $PM_{2.5}$ concentration, including the lowest $PM_{2.5}$ tertile of 7.1 to <8.3 µg/m³ (**C**), the middle $PM_{2.5}$ tertile of 8.3 to <9.2 µg/m³ (**D**), and the highest $PM_{2.5}$ tertile of 9.2–13.0 µg/m³ (**E**). Estimates were obtained using time-series periodic regression as outlined in the methods section. NEVI = neighborhood environmental vulnerability index. Reprinted from *Azan et al. 2025*; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

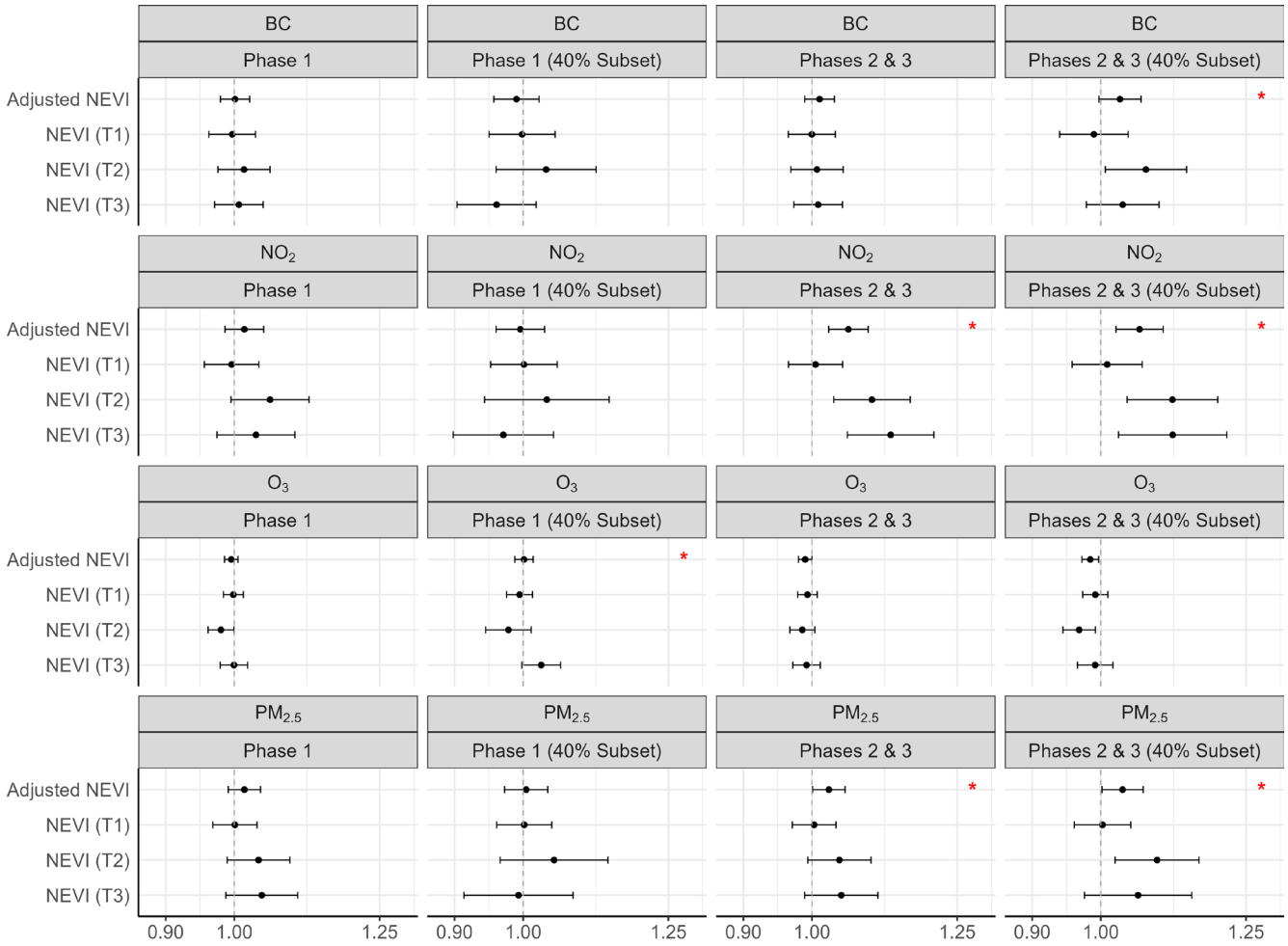

Figure 7. Adjusted and NEVI-stratified hazard ratios and 95% confidence intervals for risk of discharge (hospital length of stay) associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Effect estimates were obtained using Cox proportional hazards models. Statistically significant effect modification is indicated by a red asterisk. BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Reprinted from *Kannoth et al.* 2025; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

although these associations were only marginally statistically significant. These differences did not persist later in the pandemic. Associations between pollutant exposures and hospital length of stay did not differ significantly by race/ethnicity or pre-existing chronic disease.

ARDS

The RRs for a diagnosis of ARDS associated with greater estimated air pollutant exposures are presented in **Figure 8**. During Phase 1 of the pandemic, NO_2 exposure was positively associated with the risk of ARDS among the full study population. In the hospital catchment subset of the study population, the risk of ARDS was positively associated with exposures to NO_2, $PM_{2.5}$, and BC, with the associations with NO_2 and $PM_{2.5}$ showing significant effect modification by NEVI score. The findings stratified by NEVI tertile suggested that the risk of ARDS was positively associated with air pollutant exposures in areas of higher vulnerability. By contrast, the findings were the opposite for O_3, with exposure to O_3 being inversely associated with the risk of ARDS. In Phases 2 and 3 of the pandemic, the associations between pollutant exposures and ARDS were either not statistically significant or demonstrated the reverse of the RRs observed in Phase 1, with exposures to certain pollutants, such as black carbon, being inversely associated with the risk of ARDS, and largely no evidence of effect modification by NEVI tertile.

The associations between pollutant exposures and risk of ARDS did not differ by race or ethnicity but varied

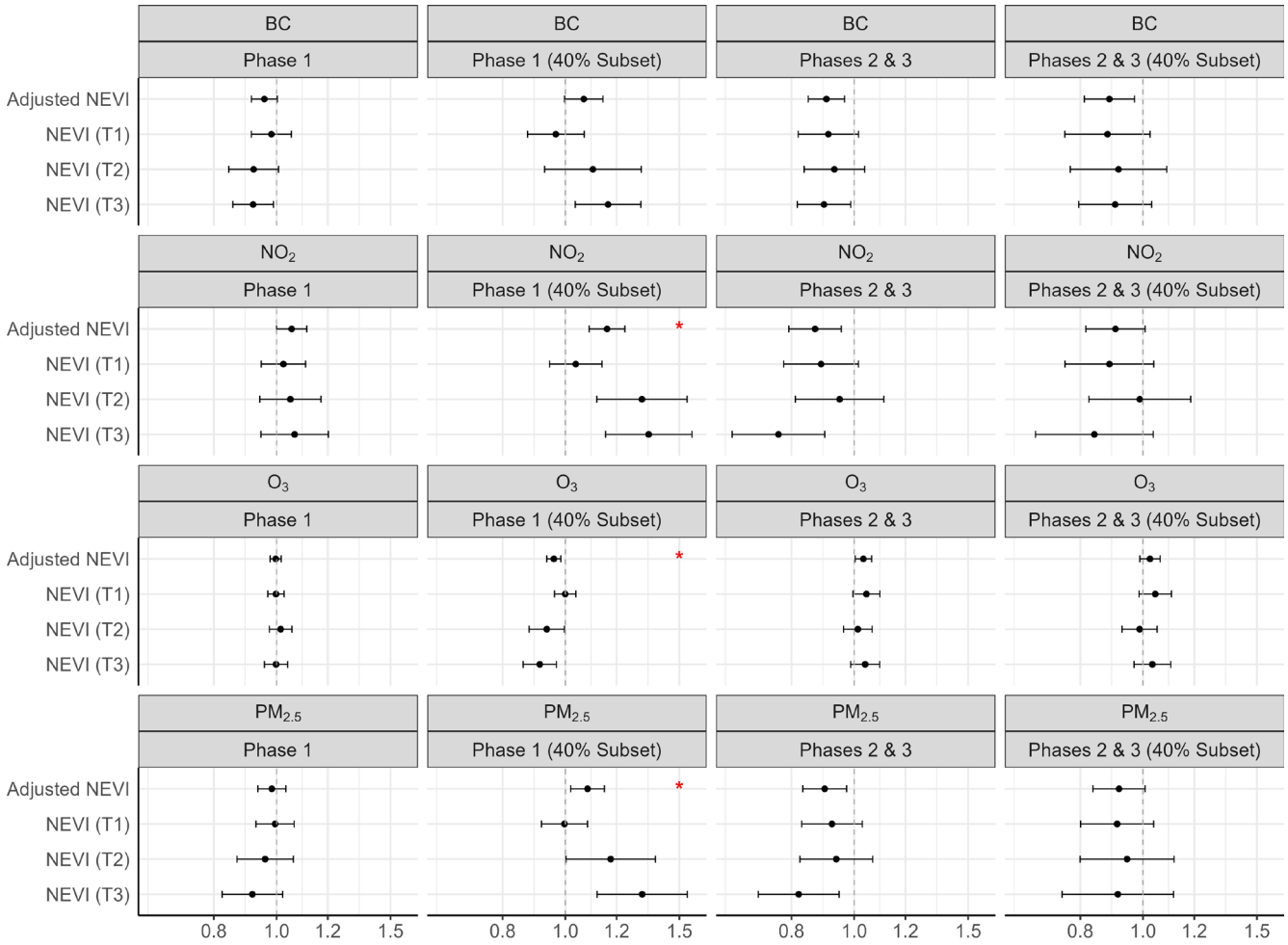

Figure 8. Adjusted and NEVI-stratified RRs and 95% confidence intervals for risk of ARDS (during COVID-19 hospitalization) associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Effect estimates were obtained using modified Poisson models with robust standard errors. Statistically significant effect modification is indicated by a red asterisk. ARDS = acute respiratory distress syndrome; BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Reprinted from *Kannoth et al.* 2025; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

by pre-existing diabetes status. The RR for a diagnosis of ARDS in patients with diabetes and a higher level of NO_2 exposure was 1.73 (95% CI: 1.51, 1.99), as compared to the risk among those without diabetes and a lower exposure to NO_2 exposure; similarly the RR among patients without diabetes and the higher level of NO_2 exposure was 1.08 (95% CI: 0.98, 1.20), with a calculated RERI of 0.23 (95% CI: 0.05, 0.41). The joint effects of NO_2 exposure and diabetes were strongest within the highest NEVI tertile (RR: 2.12; 95% CI: 1.63, 2.75), although the smaller sample size limited precision of the calculated RERI (0.16; 95% CI: −0.40, 0.73) (Appendix Table A8).

Pneumonia

Similar to the findings for ARDS, during Phase 1 of the pandemic, NO_2 exposure was positively associated with the risk of pneumonia among the total study population. In the subset of the study population restricted to the hospital catchment area, the risk of pneumonia was positively associated with exposures to NO_2 as well as $PM_{2.5}$ and BC (**Figure 9**). Also, there was significant effect modification by NEVI tertile, with the highest RRs for positive associations between pollutant exposures and risk of pneumonia occurring in areas of higher vulnerability. For example, the RR for pneumonia that was associated with a 5-unit increase in NO_2 concentration in areas with NEVI scores in the first tertile among the population subset in the hospital catchment area was 1.13 (95% CI: 1.02, 1.25), compared to a RR of 6.36 (95% CI: 4.71, 8.60) in areas with NEVI scores in the highest tertile. We again observed the pattern of opposite results for O_3: exposure to O_3 was inversely associated with the risk of pneumonia in Phase 1 of the

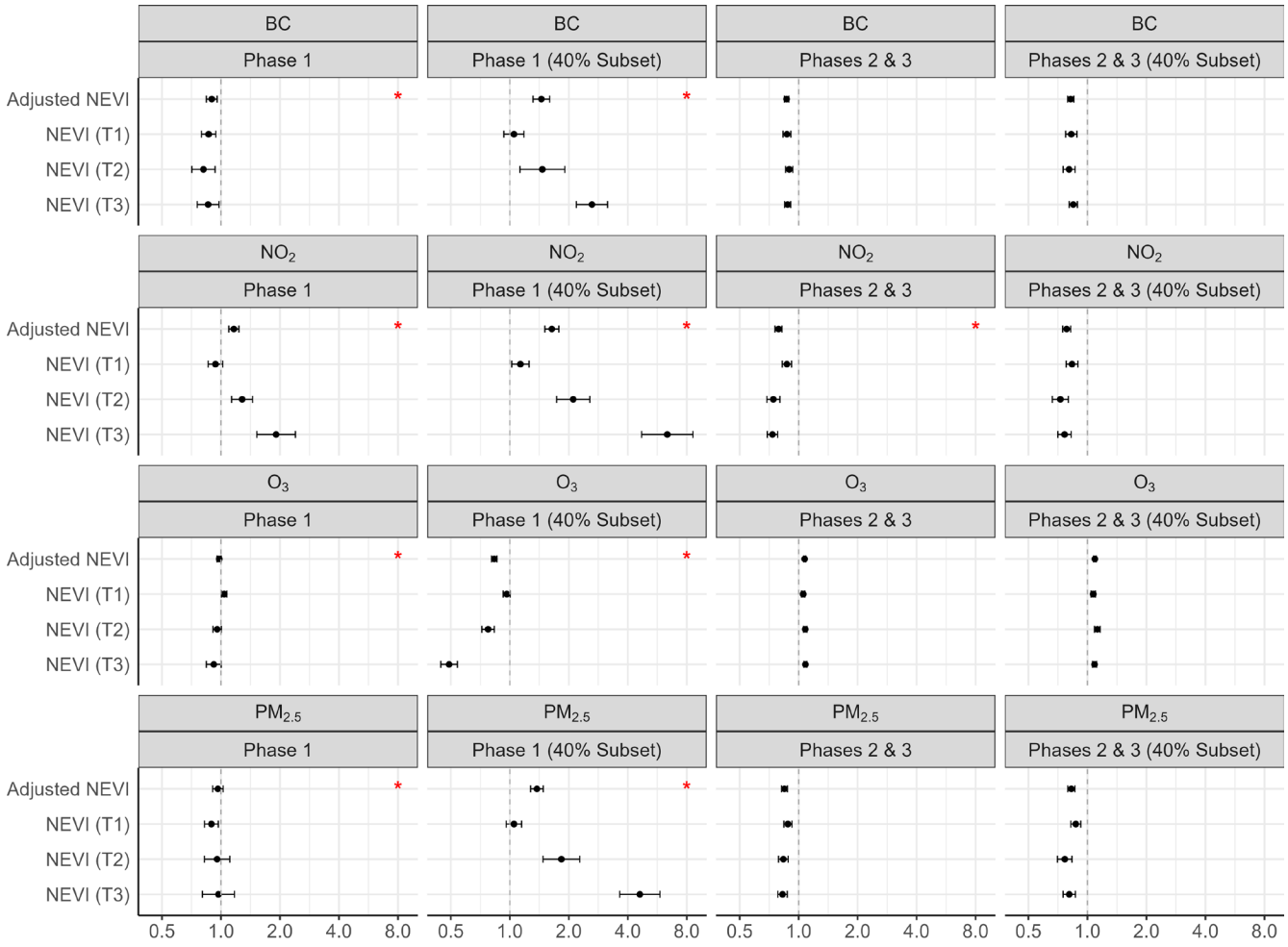

Figure 9. Adjusted and NEVI-stratified RRs and 95% confidence intervals for risk of pneumonia (during COVID-19 hospitalization) associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Effect estimates were obtained using modified Poisson models with robust standard errors. Statistically significant effect modification is indicated by a red asterisk. BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Reprinted from *Kannoth et al.* 2025; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

pandemic, and all associations between pollutant exposures and pneumonia during Phases 2 and 3 had RRs that were the reverse of those seen in Phase 1, with positive associations becoming inverse associations and vice versa.

We also observed racial disparities in the positive associations between pollutant exposures and risk of pneumonia, with both Black and Hispanic populations having higher RRs, even after adjusting for NEVI score. Analyses of effect modification comparing Black and White populations demonstrated statistically significant differences for all pollutants. Tests of effect modification involving Hispanic ethnicity revealed similar results, with significant interaction seen with all pollutants except BC; among Hispanic populations, the greatest statistically significant RRs for pneumonia were associated with exposures to NO_2 and $PM_{2.5}$ (Appendix Table A7). The RRs for a diagnosis of pneumonia were of greater magnitude among patients with asthma, although the calculated RERIs were not statistically significant (RERI for a higher level of NO_2 exposure: 0.28; 95% CI: –0.05, 0.62). Again, joint effects of NO_2 exposure and asthma were strongest in the highest NEVI tertile (RR: 6.53; 95% CI: 3.23, 13.2), but the calculated RERI was very imprecise (RERI: –0.08; 95% CI: –4.83, 4.67) given the small sample sizes within the NEVI strata (Appendix Table A8).

Mechanical Ventilation

Results related to the use of mechanical ventilation were similar to those for the fatality outcomes, with the risk of ventilation being inversely associated with greater estimated exposure to NO_2, BC, and $PM_{2.5}$ and positively associated with greater estimated exposure to O_3 (**Figure 10**). Results

were generally consistent across all phases of the pandemic and in both the full study population and the hospital catchment area subgroup, with effect estimates of greater magnitude observed in Phases 2 and 3. Significant effect modification by NEVI score was observed only for NO_2 exposure in the full study population during Phases 2 and 3, and stratum-specific estimates showed smaller effects in areas of lower NEVI strata. Stratum-specific results within the hospital catchment area subgroup during Phase 1 of the pandemic showed that associations between NO_2, BC, and $PM_{2.5}$ were null in areas of high vulnerability. Associations between pollutant exposures and risk of ventilation did not differ by race, ethnicity, or pre-existing chronic disease. In two-pollutant models that adjusted the effects of NO_2, BC, and $PM_{2.5}$ exposures for the concentration of O_3, effect estimates for the use of mechanical ventilation shifted to the other side of the null during Phase 1. This was most notable for NO_2, with the adjusted risk of use of mechanical ventilation increasing with greater exposure to this pollutant after adjustment for O_3 (RR: 1.33; 95% CI: 1.11, 1.60) (Appendix Table A6). Given the high negative correlation between NO_2 and O_3 (~ −0.8), however, this result should be interpreted with caution.

Dialysis

The RRs for the use of dialysis (among patients with no prior documented use of dialysis) during COVID-19 hospitalization are presented in **Figure 11**. Patterns were similar to those seen in the RRs for ARDS and pneumonia, with elevated risk of dialysis during Phase 1 of the pandemic being associated with NO_2 exposure in the full

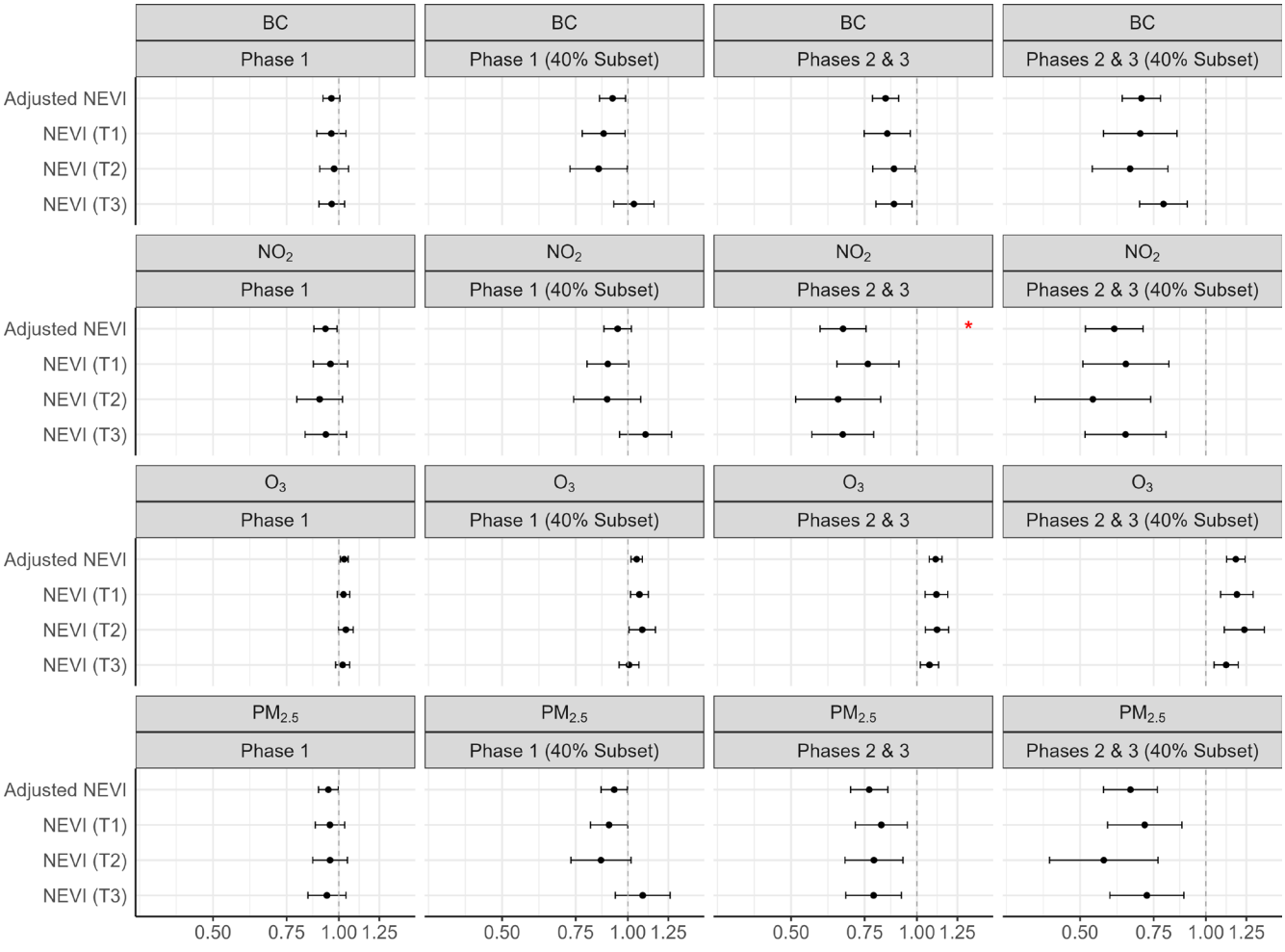

Figure 10. Adjusted and NEVI-stratified RRs and 95% confidence intervals for risk of mechanical ventilation use (during COVID-19 hospitalization) associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Effect estimates were obtained using modified Poisson models with robust standard errors. Statistically significant effect modification is indicated by a red asterisk. BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Reprinted from *Kannoth et al.* 2025; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

study population and with exposures to NO_2, BC, and $PM_{2.5}$ in the hospital catchment area subgroup. Elevated RRs for dialysis associated with exposures to NO_2, BC, and $PM_{2.5}$ were also seen among the hospital catchment subgroup in Phases 2 and 3, although the associated confidence intervals (CIs) were wide. Additionally, the magnitudes of the RRs for dialysis were generally larger than those for other outcomes. Significant effect modification by NEVI score was seen in the associations for all pollutant exposures in Phase 1 as well as Phases 2 and 3 of the pandemic, with elevated (or reduced, for O_3 exposure) risks of dialysis seen exclusively in areas with higher levels of NEVI vulnerability, although the associated CIs were extremely wide as a result of small sample sizes. During Phase 1, RRs for dialysis were of greater magnitude among Black patients compared with White patients (Appendix Table A7). Formal tests of effect modification revealed statistically significant effect modification between air pollutant exposures and race, with *P* values ranging from 0.01 to 0.08. We also observed strong departures from additivity in the joint effects of NO_2 exposure and pre-existing diabetes on the risk of dialysis, with a calculated RERI of 1.37 (95% CI: 0.37, 2.37), although stratification by NEVI tertile was not possible because of small sample sizes (Appendix Table A8).

RISK OF HOSPITAL ADMISSION AMONG ED PATIENTS

Figure 12 presents the results of analyses aimed at estimating the risk of hospital admission among ED patients with COVID-19. For these estimations, the anal-

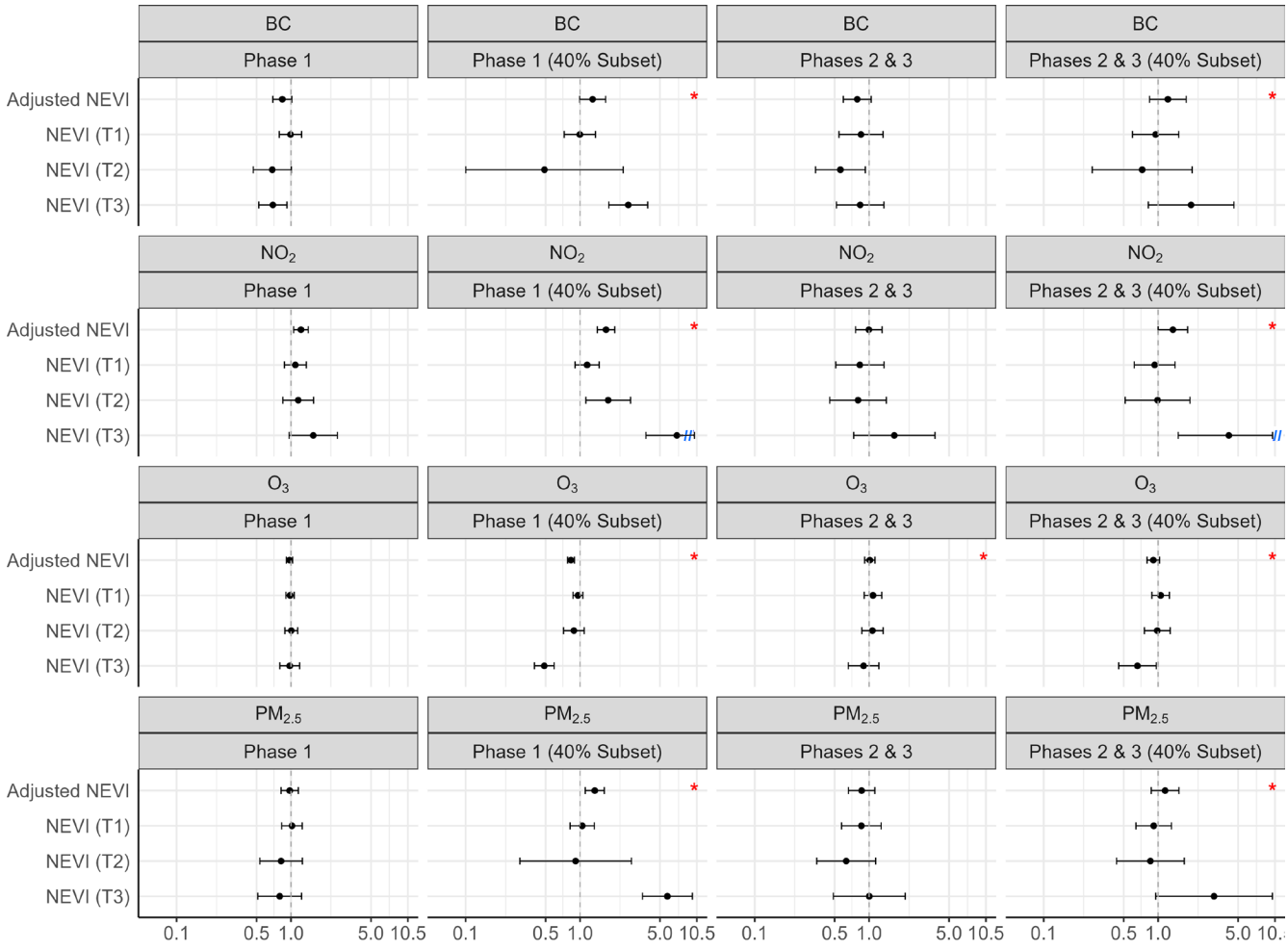

Figure 11. Adjusted and NEVI-stratified RRs and 95% confidence intervals for risk of dialysis (during COVID-19 hospitalization) associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Effect estimates were obtained using modified Poisson models with robust standard errors. The analysis population was restricted to patients with no dialysis documented in the INSIGHT Clinical Research Network data repository within the prior 11 years. Statistically significant effect modification is indicated by a red asterisk. Blue // indicates truncation of the confidence interval. BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Reprinted from *Kannoth et al.* 2025; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

ysis population included all individuals with ED records in the INSIGHT-CRN data repository that documented a diagnosis of COVID-19. The analyses examined the association between long-term exposure to ambient air pollutants and the risk of hospitalization for COVID-19. Results demonstrated that higher estimated concentrations of $PM_{2.5}$, NO_2, and BC were consistently associated with an elevated risk of hospitalization among ED patients with COVID-19. Similar to other analyses in this study, the findings demonstrated the opposite relationship between estimated O_3 exposure and risk of hospitalization, with higher concentrations of O_3 being associated with a reduced risk of hospital admission. For all pollutants, we consistently observed effect modification by NEVI score in both the full study population and the subset of the population residing in the hospital catchment area. Among ED patients with COVID-19, the largest RRs for hospitalization in association with air pollutant exposure were observed in those residing in areas of high vulnerability, although RRs were also elevated in areas of lower vulnerability. Similar results were seen in Phases 2 and 3 of the pandemic, with effect estimates being slightly greater than those in Phase 1. We also observed evidence of effect modification by race and ethnicity, with statistically significant differences in RRs for hospital admission associated with greater pollutant exposure among both Black and Hispanic patients compared to White and non-Hispanic patients, respectively (Appendix Table A7).

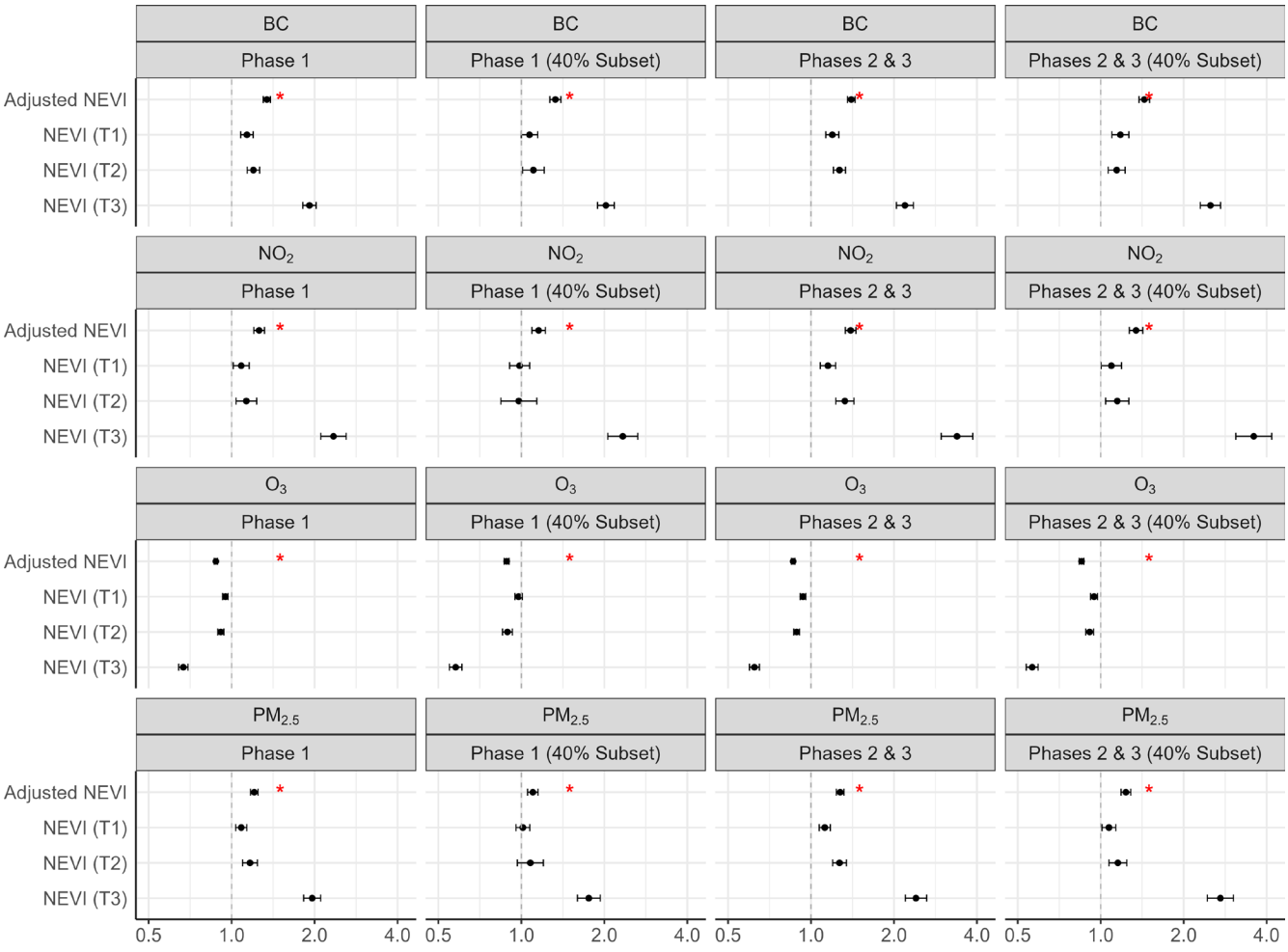

Figure 12. Adjusted and NEVI-stratified RRs and 95% confidence intervals for risk of hospitalization in emergency department patients that was associated with exposure to each of four air pollutants, by phase of the COVID-19 pandemic, among the total study population and the subgroup of patients residing in the hospital catchment area. Effect estimates were obtained using modified Poisson models with robust standard errors. Statistically significant effect modification is indicated by a red asterisk. BC = black carbon; NEVI = neighborhood environmental vulnerability index; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3.

SENSITIVITY ANALYSES FOR SELECTION BIAS

As previously described in the Methods section of this report, we assessed the range of selection factors that would need to exist to explain our observed results if there were no association between air pollutant exposures and COVID-19 outcomes. For this analysis, we used an RR ratio of 1.5, which was between the estimates observed in relationships between NO_2 exposure and a diagnosis of ARDS (RR 1.16), dialysis (RR 1.69), and pneumonia (RR 1.64).

Figure 13 is a two-dimensional plot that depicts the parameter space defined by the selection effects (where β_A is the differential probability of selection based on exposure, and β_Y is the differential probability of selection based on outcome), with dots indicating the values of selection that could plausibly explain the target estimate of 1.5. Of note, the selection bias of concern pertains to the use of a hospitalized cohort and how that cohort differs from the underlying target population of individuals with COVID-19. The x-axis shows selection differential based on exposure, and the y-axis shows selection differential based on outcome. A value of 0 on the x-axis indicates no difference in likelihood of selection into the population, based on exposure status; values greater than 0 indicate that exposed individuals were more likely to be selected into the population, and values less than 0 indicate that exposed individuals were less likely to be selected into the population. Values on the y-axis have similar interpretations based on outcome rather than exposure status. The colors of the dots represent the third selection parameter (i.e., baseline selection into the sample or general risk of being hospitalized, which we allowed to vary from 0% to 20%).

Approximately 22% (22,953 of 104,161) of the total possible parameter combinations could explain the result of an RR of 1.5 as a result of selection effects, even if there were no actual relationship between NO_2 exposure and a given COVID-19 outcome. It is not plausible that individuals diagnosed with a severe outcome would be less likely to be hospitalized than individuals not diagnosed; therefore, our focus is on the two upper quadrants of the graph. As shown in the plotting, however, the plausible combinations of selection effects that could produce the observed estimate occur mainly when the probability of selection into the sample among the exposed is lower than the probability of selection at baseline (i.e., β_A is negative). In other words, if individuals residing in areas with high NO_2 exposure were generally less likely to be hospitalized than were individuals residing in areas with lower NO_2 exposure, selection bias could be a plausible explanation for our result. Our findings among the population of ED patients do not support this hospitalization differential, as patients with greater exposure to air pollutants who presented to the ED were more likely to be admitted to the hospital after their presentation. Increasing the target RR to align with the values that we observed for the outcome of a pneumonia diagnosis or use of dialysis results in a smaller percentage of parameter combinations that may plausibly explain our results, although the probable combinations continue to be those in which the probability of selection among those exposed to air pollutants is considerably lower than the probability of selection at baseline.

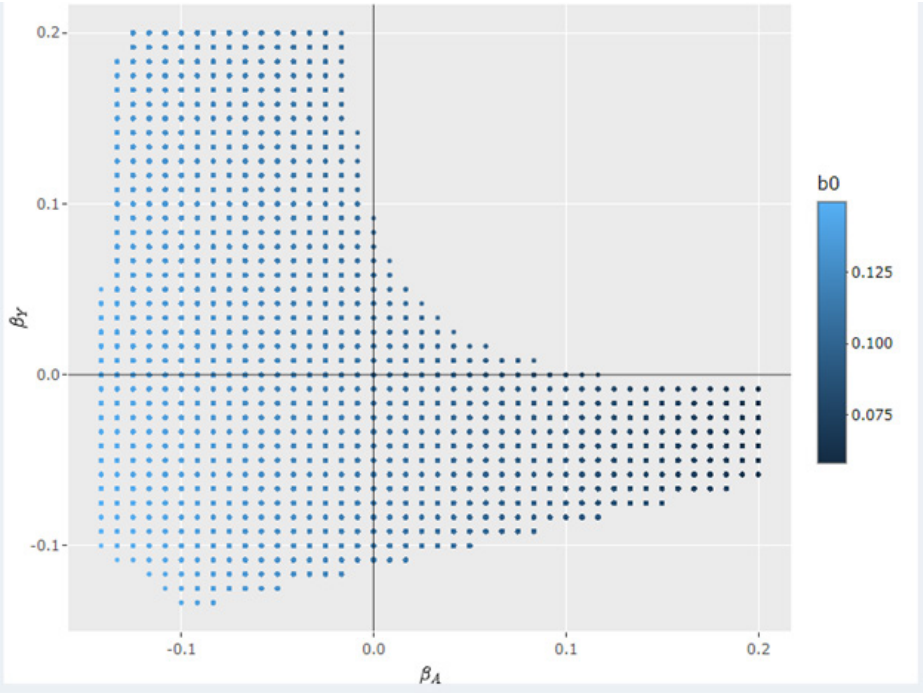

Figure 13. Selection effects that could result in the observed RR for the risk of an ARDS diagnosis associated with exposure to NO_2. The figure presents a graphical depiction of results from simulations designed to determine the selection factors that could explain the observed effect estimate for the association between NO_2 exposure and a diagnosis of ARDS. The graph was created using the AscRtain package in R and the SHINY app. The location of each dot indicates values of selection factors that could plausibly explain the observed results. The lack of dots in the upper right quadrant of the plotting suggests that selection bias is a less likely explanation of the observed results if the likelihood of selection of the exposed population (i.e., patients with higher air pollutant exposures) into hospitalization exceeded the baseline risk of hospitalization in the population. ARDS = acute respiratory distress syndrome; b0 = baseline probability of selection; β_A = differential probability of selection based on exposure; β_Y = differential probability of selection based on outcome. Reprinted from *Kannoth et al.* 2025; Creative Commons license CC BY 4.0 (*https://creativecommons.org/licenses/by/4.0/*).

Sensitivity Analyses Based on COVID-19 Testing

We stratified the population by the prevalence of testing for COVID-19 in the zip code of residence and then reran a subset of the length-of-stay analyses for Phases 2 and 3 of the pandemic. The HRs for length of stay, stratified by tertile of COVID-19 testing, did not differ significantly from the HRs in the original length-of-stay analysis (Appendix Table A9). Rates of testing for COVID-19 were not significantly correlated with average air pollution metrics for NYC zip codes, with Spearman correlation coefficients ranging from –0.2 for O_3 concentrations to 0.2 for $PM_{2.5}$ concentrations.

DISCUSSION AND CONCLUSIONS

The REACH-OUT (Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes) study provides a comprehensive examination of COVID-19–related outcomes among patients hospitalized at five major medical centers in NYC from March 1, 2020, through February 28, 2021, spanning a period that includes both the initial peak in COVID-19 cases and subsequent months before the widespread introduction of vaccination against COVID-19. Overall, we observed mixed results, with higher estimated chronic exposure to the air pollutants NO_2, $PM_{2.5}$, and BC being positively associated with the risks of outcomes such as ARDS, pneumonia, and dialysis but inversely associated with the risks of fatality and use of mechanical ventilation among hospitalized patients with COVID-19. Additionally, chronic exposure to these air pollutants was associated with an increased risk of hospitalization among individuals presenting to the ED who had a COVID-19 diagnosis. By contrast, opposite results were consistently observed for O_3, with a reversal of the positive or inverse associations demonstrated between exposure to NO_2, $PM_{2.5}$, or BC and the studied COVID-19–related outcomes, possibly due to the strong negative correlations between O_3 and these other pollutants.

For many of the observed outcomes with statistically significant findings of multiplicative interaction (i.e., effect modification) between air pollution and the NEVI metric, effect estimates associated with air pollutant exposures were of greater magnitude among individuals who resided in areas with higher neighborhood-level social and structural vulnerability. In analyses of the risk of pneumonia among hospitalized patients with COVID-19 and the risk of hospitalization among ED patients with COVID-19, racial disparities in the effects of air pollution persisted even after adjusting for pre-existing chronic disease as well as neighborhood social and structural vulnerability. Results from our analysis of excess mortality, which used all-cause mortality data for the entire NYC population, were consistent with the findings of our fatality analysis among hospitalized patients with COVID-19, both demonstrating an inverse relationship between air pollutant concentrations and excess mortality. Furthermore, positive associations between air pollutant exposures and COVID-19 outcomes were primarily observed during the initial 4 months of the pandemic, except for associations with the risk of dialysis among hospitalized patients and the risk of hospitalization among ED patients, which were observed during both the initial and subsequent phases of the pandemic.

The results of this study are consistent with the prior literature on positive associations between air pollution and risks of hospitalization and COVID-19 morbidity, but conflict with previous research demonstrating positive associations between air pollution and COVID-19–related fatality and mortality. For example, studies conducted in cohorts in California, England, and Denmark have shown increased risks of hospitalization and mortality among persons with higher levels of chronic exposure to air pollutants.[42,52,121,122] Unlike our study, some of these investigations were population-based and used national registries or were conducted in well-defined cohorts not restricted to records from specific hospitals. In theory, these distinctions would make these studies less susceptible to selection bias, compared to our analyses. Another study conducted in NYC demonstrated an increased risk of fatality associated with chronic air pollution, but only after implementing a complex adjustment strategy. The unadjusted results in that study were consistent with those observed in our study, with a reduced risk of fatality being associated with exposure to air pollution during the initial phase of the pandemic.[31]

Additionally, in the present study, we observed inverse relationships between $PM_{2.5}$ concentrations and excess mortality in an analysis that was unaffected by selection bias that would occur with using a study population of hospitalized patients. Consistent with our results, an ecological study of COVID-19–related mortality at the zip-code level in NYC used models with generalized propensity score weighting to adjust for relevant covariates and found an inverse association between $PM_{2.5}$ and mortality, although this finding was not statistically significant.[123]

The mechanism underlying the observed inverse relationship between these pollutant exposures and risk of fatality in our study is unclear, particularly given that we also demonstrated that higher levels of pollutant exposures were associated with increased risk of some morbidity outcomes, such as diagnoses of ARDS or pneumonia, and the use of dialysis during hospitalization. We observed similar negative relationships between pollutant exposures and the use of mechanical ventilation. It has been documented that many higher-income individuals who were residing in NYC moved out of the city at the start of the COVID-19 pandemic.[124] These individuals who fled NYC were more likely to live in areas with high levels of air pollution and low NEVI metrics.[124] It is possible that if these individuals contracted COVID-19 after leaving NYC, they would have

visited hospitals outside the city and would thus not be represented in either the hospitalized patient population or the all-cause mortality data used in this study. It is also possible that the lack of standard treatment protocols early in the pandemic would have more greatly influenced the results of such studies conducted in a place like NYC, where the majority of COVID-19 cases occurred early in the course of the pandemic and overwhelmed hospital capacity.

Many of the prior studies did not examine the initial phase of the COVID-19 pandemic, or, as in a study in Denmark,[52] did not identify associations between air pollution and fatality or mortality during the early period. These factors limit the opportunities for comparison with our study, in which most of the observed positive associations involved the first phase of the pandemic, which included the initial peak of cases. Additionally, our study population was based in NYC, which experienced an early peak in cases that was among the most severe peaks of COVID-19, followed by a drop in cases during the summer and early fall of 2020 and then a subsequent but smaller second peak in the winter of that year. Previous research has established that the COVID-19 trends observed in NYC differed from those elsewhere in the United States — particularly California, where much of the earlier COVID-19 research in the United States was performed.[125]Also, the temporal plotting of COVID-19 hospitalizations in the present study differs starkly from a similar type of plotting presented in a recent HEI report from Denmark, which showed a much larger peak during a period that coincided with Phase 3 of the pandemic in our study.[83] Pei and colleagues estimated that the population of NYC had a lower level of COVID-19 susceptibility, compared with the rest of the United States, after the initial peak in cases,[125] which may explain some of the discrepancies with our Phases 2 and 3 findings. It should be noted that the results of our analysis of the risk of hospitalization among ED patients with COVID-19 were consistent with these prior investigations, showing that higher levels of air pollution were associated with an increased risk of hospitalization.

Overall, our findings suggest that analyses of the effects of air pollution on COVID-19 outcomes should both adjust for area-level vulnerability due to social and structural factors and examine whether relationships between air pollution and COVID-19 morbidities are modified by such factors. A large body of literature demonstrates that social and structural factors can modify the effects of air pollution on health.[126] Specifically, prior research conducted in NYC using NYCCAS pollution data and hospitalization data has demonstrated that social factors can modify the associations between air pollution and both asthma and cardiovascular outcomes.[103,127] Sharma and colleagues found that the largest effects of pollution were observed in areas of lower deprivation,[127] whereas Clougherty and colleagues reported stronger associations between pollutant exposure and excess cardiovascular disease risk in areas with higher levels of deprivation or crime.[103] Within the context of COVID-19, our results are consistent with the analysis of a national database with records on US veterans with COVID-19.[30] Bowe and colleagues reported a positive association between $PM_{2.5}$ exposure and risk of hospitalization for COVID-19, with a larger risk observed among individuals living in counties with higher deprivation metrics. Similar to our results, their findings also demonstrated that racial disparities in these effects persisted even after accounting for area deprivation and individual pre-existing comorbidities.[30]

The persistence of racial and ethnic disparities in the positive associations between air pollutant concentrations and the risks of pneumonia, hospitalization, and dialysis during a COVID-19 hospitalization was a notable finding of the present study. Formal tests of effect modification showed that greater $PM_{2.5}$, NO_2, and BC exposures were associated with larger RRs for pneumonia among Black and Hispanic patients, with these results generally being statistically significant. Our analyses of the use of dialysis during hospitalization also demonstrated larger RRs associated with greater BC and NO_2 exposures among Black patients. We also observed statistically significant differences between Black and White patients with regard to the positive relationship between air pollutant concentrations and risk of hospitalization. These findings could be attributed to several issues, including racial differences in chronic disease control that are not captured by controlling for a prior diagnosis of such conditions,[128-130] racial differences in treatment before and during hospitalization,[131] and factors related to the effects of racism that remained unmeasured despite our inclusion of an index of neighborhood social and structural factors.[132,133] We strongly encourage researchers conducting future large-scale studies using harmonized data across hospital systems to explicitly focus on examining the multiway interactions between race, social and structural factors at the neighborhood level, chronic disease, air pollution, and COVID-19 outcomes to further elucidate the racial disparities observed during the COVID-19 pandemic.

In this study, analyses examining associations with O_3 exposure consistently demonstrated relationships that were the opposite of those observed for the three other pollutants. Other studies have found similar patterns, both in COVID-19–related research and in investigations of other outcomes associated with air pollution.[52,103] In NYC, chronic O_3 exposure is strongly and negatively correlated with chronic exposure to other pollutants.[103] Using citywide data for NYC, we estimated negative Spearman correlation coefficients for correlations between O_3 and the other pollutants, each of a magnitude larger than −0.8; by contrast, the other pollutants ($PM_{2.5}$, NO_2, and BC) were strongly and positively correlated with each other, with correlation coefficients greater than 0.9. Thus, it is unclear whether our findings of associations observed with exposure to O_3, such as increased risk of fatality, rep-

resent actual relationships or structural artifacts related to correlations between pollutants. Adjusting models for O_3 concentrations did not markedly change the estimates of effects related to $PM_{2.5}$, NO_2, and BC. Given the extremely high correlations that exist between these broad, area-level measures of air pollution, our study was unable to disentangle these effects and draw strong conclusions.

All interpretations of the findings of this research should be tempered with thorough consideration of the limitations of the data. The analyses in this study were primarily restricted to hospitalized patients, thus introducing the potential for selection bias due to several factors. First, the five academic medical centers whose patient medical records composed our study population may tend to attract the more severe cases from neighborhoods outside their typical catchment areas. To mitigate this potential bias, however, we restricted several analyses to the population of patients residing in areas where at least 40% of total COVID-19 hospitalizations were documented in the INSIGHT-CRN data repository. We did observe differences in the results of these analyses in the restricted study population; however, stronger effect estimates were generally noted in the restricted study population, suggesting that the inclusion of patients outside the hospital catchment area biased our results toward the null. The INSIGHT-CRN data repository does not include data from public hospitals. Although all the hospitals that contribute data to the INSIGHT-CRN serve patients from a variety of socioeconomic backgrounds, the average socioeconomic status in our study population was likely higher than that of the NYC population overall. This would influence the generalizability of our results and, as previously mentioned, could induce selection bias if severe cases of COVID-19 in patients residing in areas with either high or low levels of air pollution were routed to specific hospitals. The hospital catchment area subgroup of our study population was designed to reduce this type of selection bias.

Selection bias could also arise from restricting the primary study population to hospitalized patients, essentially conditioning selection on a collider variable if exposure to air pollutants not only increased the risk of adverse outcomes but also increased the risk of COVID-19 incidence.[54,118] This scenario may lead to a selection bias that results from lacking access to data for the full underlying target population and instead relying on either hospitalized cohorts or cohorts of diagnosed cases. The potential effects of this type of selection bias have been highlighted as a primary methodological concern regarding studies of air pollution and COVID-19 outcomes.[134] As suggested by prior literature, we used the AscRtain package in R to address the limitation of using hospitalized patients as our primary study population. We ran a series of simulations to determine the selection factors that could bias our results and then assessed the plausibility of those selection effects in our population.[118,119] Generally, the AscRtain analysis demonstrated that selection bias would have been probable in our study if the risk of hospitalization among those exposed to air pollution was lower than the baseline risk in our cohort. However, our analysis of the population of ED patients provided evidence that the risk of hospitalization was actually greater in areas with higher air pollutant concentrations. Thus, we do not believe that this type of selection bias would fully explain our results, and we encourage researchers conducting other studies in hospitalized populations to use these simulations to appraise the plausibility of bias-inducing selection effects.

In addition to selection bias, the use of data on hospitalized patients is another limitation of the analyses in this study. The EHR data obtained from the INSIGHT-CRN do not include individual measures of socioeconomic status. Although we controlled for a comprehensive index of neighborhood-level social and structural drivers, including socioeconomic conditions, the potential for residual confounding due to individual-level socioeconomic factors still exists, possibly leading to the remaining racial disparities observed in our results. The harmonized EHR data also only included the zip code of residence, which limited the spatial resolution of air pollution estimates that could be used in the analysis. Additionally, NYCCAS data are limited to annual averages at a resolution of 300 m, which may be considered a relatively coarse resolution for assessing intra-urban variation in air pollutant exposures. Thus, assigning exposure status based on the residential address at the time of hospital admission could have led to exposure misclassification and bias in our exposure estimates. Finally, we were unable to account for differences in hospital-based processes during the different phases of the pandemic. For example, given the overwhelming number of hospital admissions and the pandemic-related lockdowns in NYC in Phase 1, very few patients were admitted to the hospital for reasons other than COVID-19. In subsequent phases of the pandemic, individuals initially hospitalized for other primary reasons may subsequently have been diagnosed with COVID-19 during their hospitalization. This may account for some of the discrepancies observed in our results across different phases of the pandemic, as well as the previously described variations in patterns in COVID-19 burden between NYC and other geographic areas.[126] Moreover, race and ethnicity data were missing from the EHR data for approximately 10% to 12% of the study population, with few features that could be used to credibly impute the missing data. In addition, we lacked a sufficient sample size to examine disparities across other smaller racial groups that are known to be especially affected by disparities, including American Indian populations. Lastly, the variation in chronic air pollutant exposures was low, as the study was conducted within a relatively small geographic region; this may have limited our ability to identify strong associations between pollutants and outcomes. Despite these small contrasts in exposures, however, we did observe positive associations between air pollutant exposures and risks of certain outcomes, which is consistent with the broader literature on air pollution and COVID-19.

Despite these limitations, the use of harmonized EHR data across multiple institutions also presents several strengths. The study had a large sample size, which enabled us to directly investigate whether neighborhood-level social and structural factors modified associations with air pollutant exposures and whether racial disparities persisted in the relationship between air pollution and COVID-19 outcomes. The use of data from five different medical centers allowed for greater geographic variability, enabling us to examine more pronounced exposure contrasts than would have been possible by focusing solely on the geographic catchment area of a single hospital. The inclusion of records spanning the previous 11 years also mitigated the risk of potential misclassification of chronic disease diagnoses, as could have occurred if we had relied only on index hospitalization data obtained from the medical records of a single hospital. Furthermore, incorporating historical records maintained in the harmonized data repository facilitated the imputation of data on important confounders, such as BMI and smoking status.[134] Our results from three sensitivity analyses (i.e., an analysis restricted to the hospital catchment area subgroup of the total study population, a complementary analysis of all-cause mortality data, and a simulation-based method to identify the types of selection that would need to exist to explain our results) generally supported our conclusions regarding both the increased risks of ARDS, pneumonia, and use of dialysis among hospitalized patients with COVID-19 and the elevated risk of hospitalization among ED patients with COVID-19; however, the sensitivity analyses reduced to null the risks of fatality among hospitalized patients with COVID-19.

IMPLICATIONS OF FINDINGS

The presence of selection and other biases in this study precludes drawing definitive conclusions based on the results. However, the findings have important implications for future research aimed at addressing unanswered questions regarding the role of air pollution in COVID-19–related health disparities. Notably, our striking findings of positive associations between air pollution and COVID-19 morbidity outcomes, such as pneumonia and the use of dialysis, among hospitalized individuals with COVID-19 and underlying chronic diseases — despite adjustments for a comprehensive environmental vulnerability index based on neighborhood-level social and structural factors — underscore the importance of investigating vulnerabilities within subpopulations as an aspect of pandemic preparedness. To overcome some of the limitations of this study, future research should utilize pooled data that can amass larger sample sizes, thereby improving precision and enabling the investigation of larger exposure contrasts. Additionally, efforts are needed to conduct investigations in cohorts that are less vulnerable to the selection biases inherent in studying hospitalized populations. Future studies should build upon the findings presented in this report. Lastly, there is also a need to design targeted investigations focused on potentially vulnerable subpopulations, with an emphasis on minimizing selection bias and addressing the timely and crucial questions about the potential role of air pollution in future pandemics.

DATA AVAILABILITY STATEMENT

All the main project assets, including the code for analyses, results files, and public data sources (e.g., NYC COVID-19 data, US Census data, PLACES project data), are accessible on GitHub at *https://github.com/jstingone/reach-out*. Individuals interested in obtaining access to the INSIGHT-CRN can visit insightcrn.org to learn about data access procedures. Access to all-cause mortality data can be arranged through the Office of Vital Records at the NYC Department of Health and Mental Hygiene.

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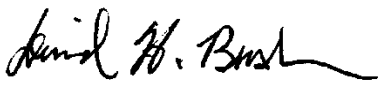
HEI QUALITY ASSURANCE STATEMENT

The conduct of the study "Race, Ethnicity, and Air pollution in COVID-19 Hospitalization OUTcomes (REACH OUT)" was subjected to an independent audit by David Bush and Scott Adamson of Trinity Consultants, Inc. Mr. Bush and Mr. Adamson are experts in quality assurance for air quality monitoring studies and data management.

The audit included a review of data quality for conformance to the study protocol as detailed in the final report and the study's quality assurance plan, reviewing data quality for each of the study components. In April 2025, an off-site audit was conducted via a teleconferencing platform with primary study personnel. The audit concentrated on the study's quality assurance and data management activities and included a review of the overall process utilized to collect new data and to manage and combine the exposure, air quality, epidemiological, and modeling data. Also evaluated were the procedures and measures undertaken to ensure quality and consistency in the processed databases and modeling results. Examples of data and data processing code for the data sets and modeling files were displayed by study personnel and further reviewed in study GitHub directories for consistency, clarity, and completeness.

A written report of the audit was provided to the HEI project manager, who transmitted the findings to the principal investigator. The quality assurance audit demonstrated that the study was conducted by an experienced team with a high concern for data quality. Study personnel were responsive to audit questions and recommendations, providing responses that addressed all audit inquiries. The report appears to be an accurate representation of the study.



David H. Bush, Quality Assurance Officer

SUPPLEMENTARY APPENDIX ON THE HEI WEBSITE

Appendix A contains three figures and nine tables not included in the main report. The appendix is available on the HEI website at *www.healtheffects.org/publications*.

Appendix A. REACH-OUT: Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes

ABOUT THE AUTHORS

Jeanette A. Stingone is an assistant professor of epidemiology at the Mailman School of Public Health at Columbia University. She received her master's degree in community medicine from Mount Sinai School of Medicine in New York City and her PhD in epidemiology from The University of North Carolina at Chapel Hill. Her research focuses on the application of data science techniques to advance research on environmental contributors to perinatal and pediatric health outcomes, including asthma, birth defects, and neurodevelopment. These techniques include the use of machine learning to analyze complex environmental mixtures and the use of semantic technologies to aid in data harmonization and sharing. Stingone is an associate editor at the *Journal of Exposure Science and Environmental Epidemiology*, a section editor for *Environmental Epidemiology at Current Epidemiology Reports*, and an editorial review board member of *Environmental Health Perspectives*.

Stephanie Lovinsky-Desir is an associate professor and chief of the pediatric pulmonary division at Columbia University Vagelos College of Physicians and Surgeons, Morgan Stanley Children's Hospital of New York-Presbyterian. She also holds a secondary appointment in the Department of Environmental Health Sciences of the Mailman School of Public Health at Columbia University. She received her MD from New York Medical College and completed her residency at the Albert Einstein Medical Center in Philadelphia. Her research is focused on understanding how environmental factors affect children with asthma, particularly in urban and minoritized communities. She recently served on the US Environmental Protection Agency's Clean Air Scientific Advisory Committee as a member of the particulate matter panel and is currently serving on the US Environmental Protection Agency's Children's Health Protection Advisory Committee. She is an elected member of the Society for Pediatric Research and is active in the American Thoracic Society, where she is a member of several committees within the Pediatric Assembly and is the vice chair of the Health Equity and Diversity Committee. Lovinsky-Desir is also a spokesperson for the American Lung Association.

Sneha Kannoth is a PhD candidate in the Department of Epidemiology at the Mailman School of Public Health at Columbia University. She received her BS in neuroscience from Carnegie Mellon University and her MPH in chronic disease epidemiology from Yale University. She recently completed predoctoral training in the National Institute of Environmental Health Sciences T32 Environmental Health and Data Science training program. Her research has focused on neighborhood environmental vulnerability and pediatric asthma morbidity in the United States, associations between early COVID-19 testing capacity and later mortality outcomes, the effect of ageism on the health of older persons, and the amplification of ageism on the cost and prevalence of health conditions. She completed a research assistantship in the Department of Epidemiology at the Mailman School of Public Health with Jeanette Stingone, which investigated the relationship between air pollution exposure, neighborhood-level vulnerability to environmental exposures, and COVID-19 mortality and morbidity. Kannoth's research interests include examining how social and physical environmental factors may influence the risk of infectious and chronic disease outcomes.

Mehr Shafiq is a project coordinator in the Department of Epidemiology at the Mailman School of Public Health at Columbia University. She received her BS in biology from Lahore University of Management Sciences and her MPH in epidemiology from Columbia University. With a background in global health research, she has contributed to observational studies and randomized controlled trials in India, Uganda, and South Africa. Her recent research has focused primarily on maternal and child health in resource-limited settings. Previously, Shafiq researched COVID-19 transmission in US childcare settings, exploring health behaviors and practices associated with increased rates of infection and identifying strategies for reducing transmission.

Cong Zhang recently received his MS in biostatistics, with a concentration in public health data science, from Columbia University. He received his BEng in bioengineering from Xi'an Jiaotong University and his BEcon in economics from Peking University. During his time at Columbia University, Zhang was accepted into the Data Science Institute Scholars program, where he conducted research as part of the REACH-OUT study. He is currently a data scientist at CVS Health.

Sandra Albrecht is an assistant professor of epidemiology at the Mailman School of Public Health at Columbia University. She received her BA in philosophy, politics, and economics from the University of Pennsylvania; her MPH from Columbia University; and her PhD in epidemiology from the University of Michigan. She also received postdoctoral training at the Carolina Population Center at The University of North Carolina at Chapel Hill. Her research focuses on the sociocultural and neighborhood-level factors that contribute to a high burden of nutrition-related diseases among immigrants and Latinos in the United States. Past research projects include investigating the social determinants of weight gain in Latino and Chinese immigrants and exploring the role of ethnic enclaves in shaping nutrition-related outcomes. With funding from a National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases K01 award, Albrecht's emerging research seeks to understand the social and behavioral mechanisms underlying the high burden of type 2 diabetes and its complications in diverse groups of Latinos.

Alexander Azan is an assistant professor in the Department of Population Health at NYU Grossman School of Medicine and the Family Health Centers at NYU Langone Health. He received his BS in biology and studio art from Tufts University and his MD from the Perelman School of Medicine at the University of Pennsylvania. He completed his graduate medical training in the Primary Care/Social Internal Medicine residency program at Montefiore Medical Center. Grounded in the tenets of environmental justice, his research examines the impacts of climate-driven extreme weather on health and health equity related to structural and intermediary determinants of health. He employs advanced geospatial and quasi-experimental methods to evaluate the neighborhood-level health impacts of various climate resiliency policies in New York City. Azan's research also focuses on developing and piloting healthcare system climate adaptation initiatives in urban environments. His work is currently supported by the National Institutes of Health and the Smart Surfaces Coalition.

Earle Chambers is the director of the Division of Research and professor of Family and Social Medicine at the Albert Einstein College of Medicine–Montefiore Health System in the Bronx, New York. He received his BS in biology from Duke University, his MPH from the University of Illinois at Chicago, and his PhD in epidemiology from the Graduate School of Public Health at the University of Pittsburgh. He completed his postdoctoral training at the New York Nutrition and Obesity Research Center at Columbia University. His research examines the intersection of the social and built environments on chronic disease risk among historically excluded populations. Chambers also has expertise in diabetes prevention and has conducted research examining the reach and effectiveness of the Diabetes Prevention Program in clinical settings. His research has been supported by the National Institutes of Health, the Robert Wood Johnson Foundation, and the John D. and Catherine T. MacArthur Foundation.

Min Qian is an associate professor of biostatistics at the Mailman School of Public Health at Columbia University. She received her BEcon and BS in economics and mathematics from Wuhan University, her MS in statistics from the University of Toronto, and her PhD in statistics from the University of Michigan. Her primary research interest is in the area of medical decision-making, where the goal is to develop individualized treatment policies that specify which type and intensity of treatment should be offered over time. These treatment policies take patient information — such as demographics, preferences, intermediate response, and adherence — as input and then output treatment decisions at each decision point. Her current research work includes the

design of clinical trials and the development of novel statistical methodologies, which can be used to construct optimal treatment policies. She also has broad interests in applied statistics. Qian has been collaborating with scientists in various areas, including mental health, cardiology, bioinformatics, and epidemiology.

Perry Sheffield is a professor of environmental medicine/climate science and pediatrics at the Icahn School of Medicine at Mount Sinai in New York City, where she codirects the US Environmental Protection Agency Region 2 Pediatric Environmental Health Specialty Unit serving New Jersey, New York, Puerto Rico, and the US Virgin Islands as well as the New York State Department of Health–funded Children's Environmental Health Centers. Her research focuses on climate change–sensitive health outcomes, with current work exploring children's vulnerability to heat. She completed her BS in environmental science at Brown University and her MD at the Medical College of Georgia. Sheffield also completed a pediatrics residency at Johns Hopkins Hospital in Baltimore and a pediatric environmental fellowship at the Icahn School of Medicine at Mount Sinai.

Azure B. Thompson is an assistant professor of community health sciences at SUNY Downstate School of Public Health. She received her DrPH and MPH in sociomedical sciences from Columbia University and a BA in journalism from Howard University. Her areas of expertise include urban health, health disparities, women's health, substance use, and mental health. She was the associate director of policy research and analysis and a research scientist at the National Center on Addiction and Substance Abuse. She has also served as faculty at the Yale School of Medicine at Yale University; a scholar in the National Institutes of Health Office of Research on Women's Health career development program in women's health and addictive behaviors; a National Institute of Mental Health postdoctoral trainee in mental health services at Rutgers University; a National Institute on Drug Abuse predoctoral trainee in drug abuse research at the National Development and Research Institutes; and a W.K. Kellogg Foundation Fellow in Health Policy Research. Thompson is currently working on research projects funded by the National Institutes of Health and the Patient-Centered Outcomes Research Institute in the areas of health disparities, women's health, and mental health.

Jennifer Woo Baidal is a tenured associate professor and associate chair of clinical research in pediatrics at Stanford University School of Medicine. During the time of this study, she was an assistant professor of pediatrics at Columbia University Irving Medical Center. She received her BS from the University of California, Los Angeles, and her MD from Harvard Medical School. She completed a pediatrics internship and residency at Children's Hospital Los Angeles and a fellowship in pediatric gastroenterology at Boston Children's Hospital. She also completed the Harvard-wide Pediatric Health Services Research Fellowship Program and received her MPH from the Harvard T.H. Chan School of Public Health. She is a pediatric weight management provider and health services researcher. Her research focuses on achieving child health equity, with a concentration on reducing racial, ethnic, and socioeconomic disparities in obesity. Woo Baidal's research program translates clinical, community, and epidemiological findings into population-level interventions during pregnancy, infancy, and early childhood to prevent childhood obesity and chronic diseases. As the principal investigator on projects funded by the National Institutes of Health, Patient-Centered Outcomes Research Institute, Robert Wood Johnson Foundation, and Doris Duke Foundation, she leads action-oriented research to prevent early-life risk factors for obesity and its health complications in priority populations.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Azan A, Kannoth S, Zhang C, Shafiq M, Chambers EC, Sheffield PE, et al. 2025. Neighborhood environmental vulnerability factors strongly drove COVID-19 fatality and excess all-cause mortality in New York City, while long-term air pollutant associations were weak and varied. Sci Total Environ 989:179874, *https://doi.org/10.1016/j.scitotenv.2025.179874*.

Kannoth S, Zhang C, Shafiq M, Albrecht SS, Azan A, Chambers EC, et al. 2025. The relationship between chronic air pollution exposure, neighborhood environmental vulnerability, and adverse COVID-19 morbidities among hospitalized New York City residents. Environ Int 202:109660, *https://doi.org/10.1016/j.envint.2025.109660*.

Uong S, Zhou J, Lovinsky-Desir S, Albrecht SS, Azan A, Chambers EC, et al. 2023. Creating a neighborhood environmental vulnerability index for New York City. J Urban Health 100:1007–1023, *https://doi.org/10.1007/s11524-023-00766-3*.

Research Report 230, *Neighborhood Vulnerability, Air Pollution, and Severe COVID-19 Health Outcomes*, by J.A. Stingone et al.

INTRODUCTION

The COVID-19 pandemic created unprecedented conditions that presented a unique opportunity for conducting timely and novel air pollution research aimed at 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 between exposure to air pollution and COVID-19 health outcomes. In particular, HEI was interested in studies that considered whether populations exposed to higher levels of air pollution were at increased risk of mortality from COVID-19 compared with others, and whether these potential effects differed by race, ethnicity, or measures of socioeconomic status.

In response to the request for applications, Dr. Jeanette Stingone of Columbia University submitted a proposal to HEI entitled "Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization Outcomes (REACH OUT)." Dr. Stingone and colleagues proposed to investigate whether the combination of long-term air pollution exposure and neighborhood-level environmental vulnerability affected severe COVID-19–related health outcomes in New York City (NYC*), as indicated by an analysis of emergency department (ED) visits and hospitalizations. The investigators also proposed to calculate the number of excess deaths due to COVID-19, based on all-cause mortality data, and to evaluate whether NYC neighborhoods that experienced higher levels of long-term air pollution exposure had greater numbers of excess deaths. HEI's Research Committee recommended funding Dr. Stingone's study because they thought the proposed research involved several interesting aspects, including (1) a large and socioeconomically diverse patient cohort; (2) the choice of NYC as the study location, potentially facilitating interesting insights for COVID-19–related research, as NYC was among the hardest-hit cities early in the pandemic; (3) the use of single- and two-pollutant models; and (4) construction of a novel neighborhood environmental vulnerability metric for NYC neighborhoods.

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

SCIENTIFIC BACKGROUND

Research from fields such as toxicology, human clinical studies, and epidemiology has linked air pollution exposure with risk of acute lower respiratory infections (i.e., bronchitis, bronchiolitis, and pneumonia), influenza, and respiratory syncytial virus.[1,2] However, research on such respiratory infections is complicated and has shown mixed results regarding the role of air pollution.[3,4]

Several early epidemiological studies suggested potential associations between air pollution and COVID-19,[5-7] but the potential for biased results from these studies was high, partly because early in the pandemic, it was difficult to access reliable data that identified individuals who were infected or seriously ill with COVID-19, and because accuracy and availability of testing varied over space and time. Additionally, estimating potential exposures to ambient air pollution was complicated by the varying degrees of severity and duration of COVID-19 lockdown policies, given the atypical emissions and daily mobility patterns associated with these policies. Results from such early studies were difficult to compare and generalize due to their different study designs, approaches to estimating exposure (i.e., short-term versus long-term exposures), and outcome definitions (e.g., disease incidence, prevalence, severity, and case fatality rates).

Importantly, nearly all of the initial published studies were based on cross-sectional analyses or ecological study designs.[5,8-11] These studies evaluated associations between area-based estimates of pollution (i.e., averaged across counties rather than estimated for each individual) and area-based rates of disease incidence or mortality, for which individual-level risks could not be derived. The need for studies using individual-level data, high-spatial resolution measures of air pollution, and appropriate control for confounding and assessment of effect modification was also highlighted in three early

Dr. Jeanette A. Stingone's 2-year study, "Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes (REACH OUT Study)," began in April 2021. Total expenditures were $481,457. The draft Investigators' Report from Stingone and colleagues was received for review in August 2023. A revised report, received in October 2024, was accepted for publication in December 2024. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and clarify issues in the Investigators' Report and its Commentary. Review Committee member Kiros Berhane was not involved in the review of this report due to working at the same institution as principal investigator Jeanette Stingone.

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

reviews.[12-14] Those reviews all concluded that although early evidence indicated that both short- and long-term exposure to air pollution could affect COVID-19 outcomes, all studies to date had moderate to high risks of bias that precluded their results from providing strong evidence to assess potential causal relationships.

More recent reviews have shown that there is now a stronger body of evidence for an association between short- and long-term air pollution exposures and COVID-19 outcomes.[15-17] However, there remain methodological and statistical limitations (e.g., issues involving data quality or exposure measurement) and gaps in existing knowledge, such as a difficulty in accounting for socioeconomic differences. For example, although population-level health disparities in COVID-19 outcomes have been documented in the United States and globally,[18-20] the understanding of neighborhood social and structural characteristics that might influence such associations is limited.[21]

When Stingone and colleagues initiated their study, there were few studies on the interaction between air pollution, COVID-19, and social and structural vulnerability. Given the many design limitations of the previous studies on this topic, the Stingone study was expected to elucidate whether long-term air pollution exposures and neighborhood-level vulnerability based on social and structural characteristics could explain some of the observed differences in severe COVID-19–related health outcomes among different racial and ethnic groups in NYC.

STUDY OBJECTIVES

The overall aim of Dr. Stingone's study was to estimate the association between long-term air pollution exposure and the risk of severe COVID-19–related health outcomes in NYC and to assess whether these associations varied by neighborhood-level social and structural vulnerability. Separately, the investigators aimed to address limitations due to inadequate reporting of COVID-19 outcomes and potential selection bias by calculating excess all-cause mortality in 2020 across NYC neighborhoods that represented varying levels of long-term air pollution exposures and neighborhood-level vulnerability.

Stingone and colleagues used electronic health record (EHR) data to assemble a cohort of patients in NYC who had been diagnosed with COVID-19 between March 1, 2020, and February 28, 2021. Data collected on the study population of 20,318 hospitalized patients and 19,898 ED patients included individual-level information about demographic and health characteristics. The investigators also compiled public administrative data on monthly all-cause mortality from 2015 through 2020 for NYC zip codes.

The investigators assigned estimates of long-term air pollutant exposures to each patient using zip code–level, 11-year (2009–2019) average concentrations of black carbon (BC), particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) that were obtained from an existing dataset of modeled ambient air pollutant concentrations for NYC. Stingone and colleagues also constructed a novel zip code–level neighborhood environmental vulnerability index (NEVI), using a profiling and clustering approach based on neighborhood social and structural characteristics that included indicators of demographic, economic, residential, and health-related characteristics.

The main statistical analyses used Cox proportional hazards and Poisson regression models to assess the associations of long-term air pollution exposures on the risks of hospital admission with a COVID-19 diagnosis after visiting the ED, length of hospital stay, severe COVID-19 outcomes, and death, as well as the effect of the NEVI score on these associations. Severe COVID-19 outcomes included those indicating adverse respiratory outcomes — such as acute respiratory distress syndrome (ARDS), pneumonia, and the need for mechanical ventilation — and adverse renal outcomes such as the need for dialysis. All analyses of health outcomes were stratified by three phases of the pandemic (defined below).

To evaluate excess all-cause mortality across varying levels of long-term air pollution exposure and neighborhood vulnerability, the team combined zip code–level tertiles of estimated long-term $PM_{2.5}$ exposures and NEVI scores to construct nine categories of combined long-term air pollution exposures and neighborhood vulnerability. The investigators then computed monthly excess all-cause mortality rates by using a time-series periodic regression model previously used to detect infectious disease epidemics. Finally, they compared these rates across the nine categories of air pollution exposures and NEVI scores.

To evaluate the robustness of their main results, Stingone and colleagues conducted additional analyses restricted to zip codes where at least 40% of total COVID-19–related hospitalizations were included in the harmonized EHR data. The purpose of the restricted subset of the study population was to focus the analyses on areas where a proportion of residents sought treatment at hospitals farther from their zip code of residence. To examine the role of additional population-level differences further, the investigators evaluated whether the results were modified by race, ethnicity, or pre-existing chronic disease.

SUMMARY OF METHODS AND STUDY DESIGN

STUDY POPULATION

To identify the study population, the investigators used data from the INSIGHT Clinical Research Network (INSIGHT-CRN). This network, which is the largest clinical data network in the United States, comprises data on more than 12 million unique patients and includes EHR data from five large private healthcare institutions in NYC. The INSIGHT network has information on many individual-level characteristics, including age, gender, race, clinical history, and any pre-existing chronic

diseases, such as asthma, hypertension, and diabetes. The study population included all individuals who lived in NYC and were admitted to the ED or hospitalized with a COVID-19 diagnosis between March 1, 2020, and February 28, 2021.

Based on patient admission date, the cohort was stratified by the three phases of the pandemic: phase 1 (March 2020 through June 2020) comprised the first peak in COVID-19 cases; phase 2 (July 2020 through October 2020) comprised the subsequent period of fewer cases; and phase 3 (November 2020 through February 2021) comprised the second peak. Stingone and colleagues investigated several severe COVID-19 health outcomes, including hospital admission from the ED, length of stay in the hospital, ARDS, pneumonia, need for mechanical ventilation, need for dialysis, and death.

Additionally, for the excess mortality analysis, the investigators used data from the NYC Department of Health and Mental Hygiene's Office of Vital Statistics to determine monthly counts of deaths that occurred from January 1, 2015, through December 31, 2020, for each zip code in NYC.

EXPOSURE ASSESSMENT AND NEIGHBORHOOD VULNERABILITY

Estimates of long-term ambient exposures to BC, $PM_{2.5}$, NO_2, and O_3 were created using data from the NYC Community Air Survey (NYCCAS).[22] The NYCCAS combines monitoring data with land use characteristics in a land use regression model to produce estimates of annual average pollutant concentrations (or summer averages for O_3 concentrations, given large seasonal fluctuations in this pollutant) at a 300-m spatial resolution. To estimate long-term exposures, the investigators calculated 11-year (2009–2019) average annual estimated pollutant concentrations at the zip code level assigned to each patient based on their residence zip code.

To represent neighborhood social and structural vulnerability, the investigators constructed a novel index, the NEVI, by using a statistical profiling and clustering tool called the Toxicological Priority Index.[23] The NEVI was constructed using data on social and structural characteristics (e.g., income, occupation, and quality of housing) that were obtained from the American Community Survey (5-year estimates for 2015–2019) conducted by the US Census Bureau and from the 2020 PLACES project of the US Centers for Disease Control and Prevention. NEVI scores were calculated at the zip code level, using a scale from 0 to 1, with 1 indicating the highest level of neighborhood vulnerability. Each zip code was assigned both an overall score and individual scores for each of four domains: demographic, economic, residential, and health status. Each patient was then assigned an overall NEVI score and domain-specific NEVI scores based on their zip code of residence.

MAIN ANALYSES

The investigators used Cox proportional hazards models to examine associations between estimated long-term ambient air pollution exposures and length of hospital stay or death during COVID-19 hospitalization. Modified Poisson regression models were used to evaluate associations between estimated long-term ambient air pollution exposures and other severe COVID-19 health outcomes (e.g., ARDS and pneumonia). All analyses were stratified by phase of the pandemic, categorized as phase 1 or phases 2/3 combined to gain statistical power, given the relatively low numbers of cases in the later phases. The investigators analyzed the data with and without adjustment for several demographic and health characteristics and the NEVI score. Hazard ratios (HRs) (for Cox proportional hazards models) or RRs (RRs) (for modified Poisson models) and 95% confidence intervals (CIs) were estimated to approximate the interquartile range (IQR) increase in long-term exposure estimates. Effect modification by the NEVI score was assessed on a multiplicative scale, using interaction terms between estimated ambient air pollutant concentrations and NEVI score in the main models and employing models stratified by tertile of NEVI scores within NYC.

In the excess mortality analysis, Stingone and colleagues grouped tertiles of estimates of zip code level long-term $PM_{2.5}$ exposures with tertiles of overall NEVI scores to create nine categories of combined air pollution and neighborhood vulnerability factors (e.g., high $PM_{2.5}$–high NEVI and high $PM_{2.5}$–medium NEVI). The investigators then computed baseline all-cause mortality counts by using a time-series periodic regression model. Monthly population-weighted excess all-cause mortality rates were calculated as deviations from the baseline model for each category and compared against one another.

ADDITIONAL ANALYSES

Stingone and colleagues conducted additional analyses to address potential biases in the study. One such analysis focused on potential selection bias that might have resulted from patients who sought treatment at specific hospitals, regardless of where they lived (i.e., patients who lived outside the hospital's typical catchment area). To address this issue, the investigators repeated their main analyses in a subset of the study population that was restricted to zip codes where at least 40% of all hospitalizations with a COVID-19 diagnosis involved patients who resided within that hospital's typical catchment areas. Additionally, to evaluate effect modification by other population-level differences further, the team evaluated whether the results differed across racial and ethnic groups and among patients with pre-existing chronic disease.

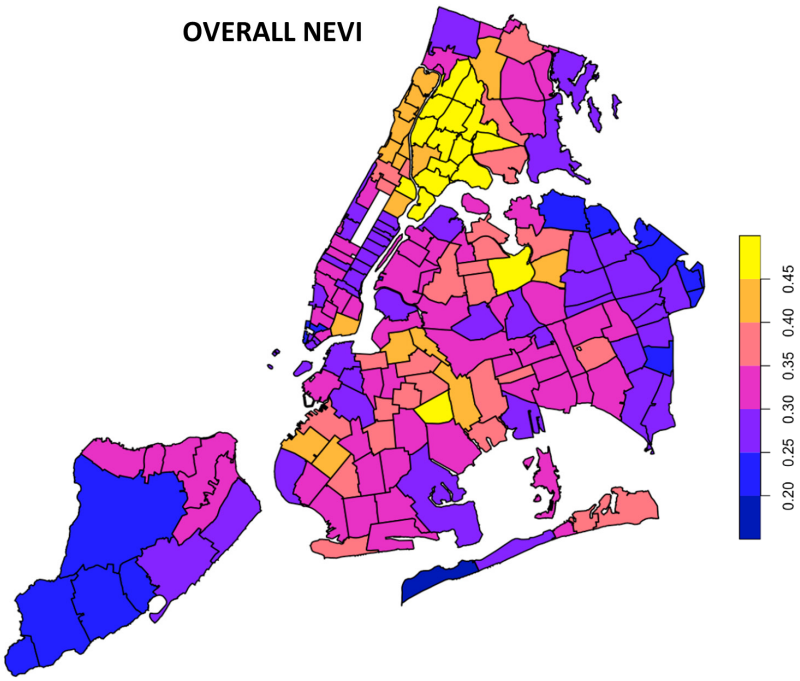
SUMMARY OF KEY RESULTS

STUDY POPULATION AND EXPOSURE CHARACTERISTICS

The study population included 20,318 hospitalized patients and 19,898 ED patients in NYC with a COVID-19

diagnosis. Among the hospitalized population, almost 3,500 patients died in the hospital, nearly 5,000 patients were diagnosed with pneumonia, about 2,800 developed ARDS, about 2,500 required mechanical ventilation, and 281 needed dialysis. Among the ED population, about 4,400 individuals were ultimately admitted to the hospital. Individuals within this study population were predominantly older (mean age, 64 years), male (52.5%), non-Hispanic (55.7%), and identified as a race other than White, Black, Asian, or indigenous (33.2%). The majority of individuals in this cohort had hypertension but did not have asthma or diabetes, and had never smoked. Data collected on body mass index indicated that most patients were overweight (see Investigators' Report Table 1).

Patients in the study population predominantly resided in zip codes with higher overall social and structural vulnerability (i.e., neighborhoods with higher prevalences of characteristics such as social isolation, income inequality, older housing, and lack of health insurance). Across most NYC neighborhoods, NEVI scores were generally between 0.25 and 0.45 (**Commentary Figure 1**). Among individual NEVI domains across NYC zip codes, NEVI scores were higher for the residential and health domains compared to the demographic and economic domains. Overall, neighborhoods with the highest NEVI scores were predominantly found in the Bronx, whereas those with the lowest NEVI scores were largely in certain areas of Manhattan, Queens, and Staten Island.



Commentary Figure 1. Neighborhood environmental vulnerability index (NEVI) scores across NYC neighborhoods at the zip code level. Overall NEVI scores ranged from 0 to 1, with 1 indicating the highest level of vulnerability and 0 indicating the lowest level of vulnerability.

The 11-year median (IQR) annual ambient air pollutant concentrations across NYC zip codes were 1.1 (0.9–1.2) absorbance units for BC, 9.0 (8.5–9.3) $\mu g/m^3$ for $PM_{2.5}$, and 21.0 (19.0–23.2) parts per billion (ppb) for NO_2. The 11-year median (IQR) summer concentration of O_3 was 30.4 (30.0–31.4) ppb. Estimated pollutant concentrations of BC, $PM_{2.5}$, and NO_2 were highly correlated, with Spearman correlation coefficients greater than 0.8. The concentration of O_3 was consistently inversely correlated with the concentrations of other pollutants, with correlation coefficients ranging from –0.83 to –0.87. The correlations between air pollutant concentrations and both the overall and domain-specific NEVI scores were low (correlation coefficients <0.3).

MAIN ANALYSES

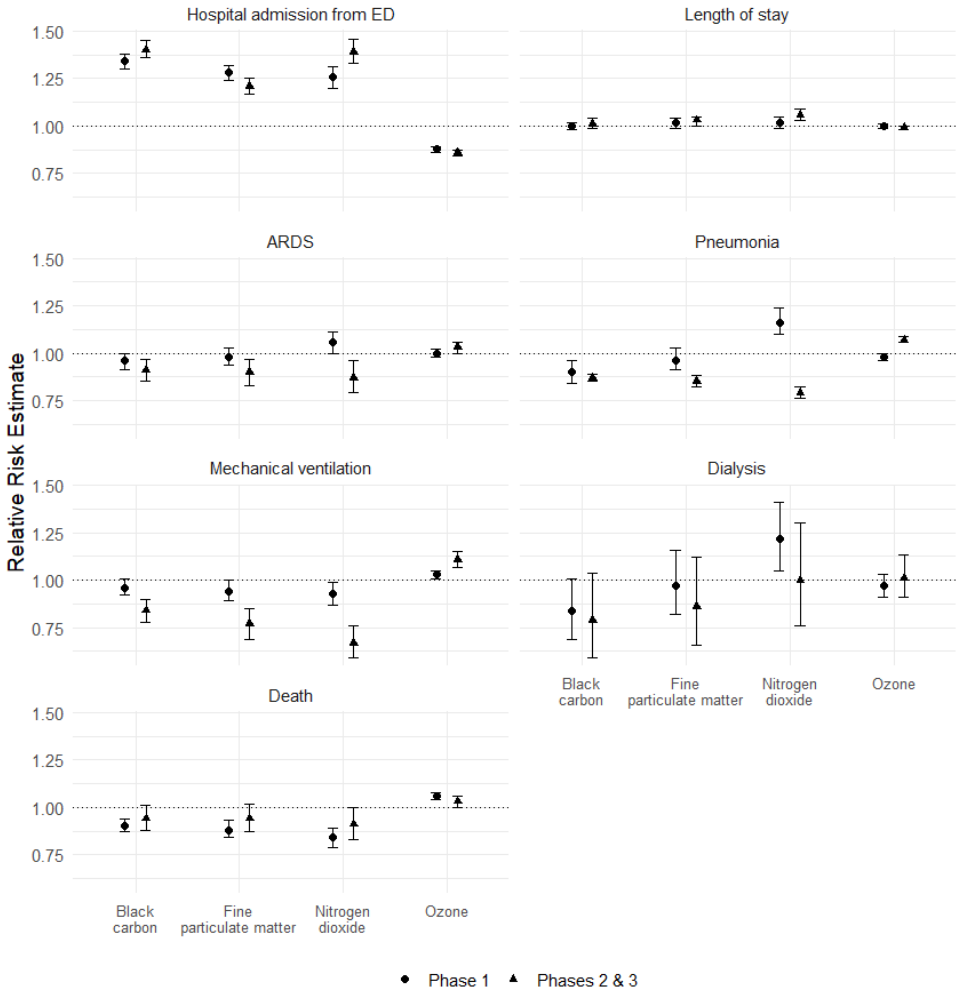
Long-Term Air Pollution and Severe COVID-19 Outcomes

In general, models that adjusted for NEVI scores and other confounders revealed that associations between estimated long-term exposures to ambient air pollution and severe COVID-19 health outcomes varied in direction and strength, depending on the health outcome, pollutant, and phase of the pandemic (**Commentary Figure 2**).

Risk of hospital admission from the ED was the only outcome that consistently demonstrated a positive association with higher levels of estimated long-term exposures to BC, $PM_{2.5}$, and NO_2. Higher estimated long-term exposures to BC and NO_2 were particularly associated with large increases in risk of hospitalization in phases 2/3 of the pandemic, with RRs of 1.40 (95% CI: 1.36, 1.44) and 1.39 (95% CI: 1.33, 1.46), respectively.

By contrast and unexpectedly, higher estimated concentrations of all ambient air pollutants (except O_3) were associated with a decreased risk of death during COVID-19 hospitalization. Across all phases of the pandemic, analyses demonstrated moderate (up to 16%) decreases in the risk of death per IQR increase in estimated long-term exposures to BC, $PM_{2.5}$, and NO_2.

Across the remaining severe COVID-19 outcomes examined in this study, associations between higher estimated long-term ambient air pollution exposures varied by pollutant, outcome, and phase of the pandemic. For length of hospital stay, ARDS, pneumonia, and need for mechanical ventilation, the investigators largely observed that higher estimated long-term exposures to ambient air pollutants were associated with various magnitudes of decreased risk for these outcomes in phases 2 and 3 of the pandemic. For example, the RR for ARDS associated with exposure to BC was 0.91 (95% CI: 0.85, 0.97),



Commentary Figure 2. Associations between estimated long-term (11-year average) ambient air pollutant concentrations and severe COVID-19 health outcomes among the study population. Results for length of hospital stay and death are HRs and 95% CIs from Cox proportional hazards models. Results for risk of hospital admission from the ED, ARDS, pneumonia, mechanical ventilation, and dialysis are RRs and 95% CIs from modified Poisson regression models. Results were estimated per IQR increase in exposure estimates: 0.2 absorbance unit for BC, 1 μg/m^3 for $PM_{2.5}$, 5 ppb for NO_2, and 1 ppb for O_3. (Source: Investigators' Report Appendix Table 5.)

and the RR for need for mechanical ventilation associated with NO_2 exposure was 0.67 (95% CI: 0.59, 0.76). In contrast, associations between these outcomes and estimated long-term exposures to ambient air pollutants were more mixed in phase 1 of the pandemic. Generally, in all phases of the pandemic, there were no positive associations between estimated long-term exposures to any ambient air pollutant and the risk of needing dialysis during hospitalization for COVID-19 (except for an elevated risk of dialysis associated with NO_2 exposure, which was seen in phase 1).

Associations between O_3 exposure and all severe COVID-19 outcomes examined in this study were consistently in the opposite direction of the associations observed for exposures to BC, $PM_{2.5}$, or NO_2. For example, for all phases of the pandemic, the investigators reported that higher estimated long-term O_3 exposure was associated with an increased risk of death during COVID-19 hospitalization and a decreased risk of hospital admission from the ED.

Stingone and colleagues also used stratified models to investigate associations between estimated long-term ambient air pollution exposures and severe COVID-19 outcomes across tertiles of NEVI scores. As with the main models, results from these stratified models varied across pollutants, health outcomes, and phases of the pandemic (**Commentary Table**).

In all phases of the pandemic, associations between estimated long-term exposures to BC, $PM_{2.5}$, and NO_2 and risk of hospital admission from the ED were consistently elevated across all tertiles of NEVI scores, with the strongest risk estimates observed in the highest NEVI tertile (i.e., among patients

Commentary Table. Associations Between Estimated Long-Term Air Pollution Exposures and Severe COVID-19 Outcomes, By Tertile of NEVI Score[a]

		Ambient Air Pollutant							
		BC		$PM_{2.5}$		NO_2		O_3	
Severe COVID-19 Outcome	NEVI Tertile	Pandemic Phase 1	Pandemic Phases 2 and 3	Pandemic Phase 1	Pandemic Phases 2 and 3	Pandemic Phase 1	Pandemic Phases 2 and 3	Pandemic Phase 1	Pandemic Phases 2 and 3
Hospital admission from ED	NEVI T1	1.14 (1.08, 1.20)	1.19 (1.13, 1.26)	1.08 (1.03, 1.17)	1.12 (1.07, 1.17)	1.08 (1.01, 1.16)	1.15 (1.08, 1.23)	0.95 (0.93, 0.97)	0.94 (0.91, 0.96)
	NEVI T2	1.20 (1.14, 1.26)	1.27 (1.21, 1.33)	1.17 (1.10, 1.24)	1.27 (1.20, 1.34)	1.13 (1.04, 1.23)	1.33 (1.23, 1.43)	0.91 (0.89, 0.94)	0.89 (0.87, 0.91)
	NEVI T3	1.92 (1.81, 2.02)	2.19 (2.04, 2.35)	1.96 (1.83, 2.10)	2.40 (2.20, 2.63)	2.34 (2.11, 2.60)	3.39 (2.97, 3.87)	0.67 (0.64, 0.69)	0.62 (0.60, 0.65)
Length of stay	NEVI T1	1.00 (0.96, 1.03)	1.00 (0.96, 1.04)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)	1.00 (0.95, 1.04)	1.01 (0.96, 1.05)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)
	NEVI T2	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)	1.04 (0.99, 1.09)	1.04 (0.99, 1.09)	1.06 (1.00, 1.12)	1.10 (1.03, 1.16)	0.98 (0.96, 1.00)	0.99 (0.97, 1.00)
	NEVI T3	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)	1.04 (0.99, 1.10)	1.05 (0.99, 1.11)	1.03 (0.97, 1.10)	1.13 (1.06, 1.21)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)
ARDS	NEVI T1	0.98 (0.91, 1.05)	0.91 (0.82, 1.02)	0.99 (0.93, 1.06)	0.92 (0.83, 1.03)	1.02 (0.95, 1.11)	0.89 (0.78, 1.02)	1.00 (0.97, 1.03)	1.04 (1.00, 1.10)
	NEVI T2	0.92 (0.84, 1.01)	0.93 (0.84, 1.04)	0.96 (0.87, 1.06)	0.94 (0.82, 1.07)	1.05 (0.94, 1.17)	0.95 (0.81, 1.11)	1.01 (0.97, 1.06)	1.01 (0.96, 1.07)
	NEVI T3	0.92 (0.86, 0.99)	0.90 (0.82, 0.99)	0.92 (0.82, 1.02)	0.82 (0.71, 0.95)	1.07 (0.95, 1.20)	0.76 (0.65, 0.90)	1.00 (0.96, 1.04)	1.04 (0.99, 1.09)
Pneumonia	NEVI T1	0.86 (0.79, 0.94)	0.87 (0.83, 0.91)	0.89 (0.82, 0.97)	0.88 (0.84, 0.92)	0.94 (0.86, 1.02)	0.87 (0.83, 0.92)	1.04 (1.01, 1.07)	1.05 (1.03, 1.08)
	NEVI T2	0.81 (0.71, 0.93)	0.89 (0.86, 0.93)	0.96 (0.82, 1.11)	0.84 (0.79, 0.88)	1.28 (1.13, 1.45)	0.74 (0.69, 0.80)	0.96 (0.91, 1.00)	1.08 (1.06, 1.10)
	NEVI T3	0.86 (0.76, 0.98)	0.88 (0.85, 0.91)	0.97 (0.80, 1.17)	0.83 (0.78, 0.87)	1.91 (1.52, 2.40)	0.74 (0.69, 0.78)	0.92 (0.84, 1.00)	1.08 (1.06, 1.10)
Dialysis	NEVI T1	0.99 (0.79, 1.24)	0.85 (0.55, 1.32)	1.02 (0.83, 1.25)	0.86 (0.58, 1.27)	1.09 (0.88, 1.36)	0.83 (0.51, 1.35)	0.98 (0.90, 1.07)	1.08 (0.91, 1.29)
	NEVI T2	0.69 (0.47, 1.01)	0.56 (0.34, 0.93)	0.82 (0.53, 1.26)	0.63 (0.35, 1.14)	1.16 (0.85, 1.57)	0.80 (0.45, 1.41)	1.01 (0.88, 1.14)	1.07 (0.86, 1.33)
	NEVI T3	0.69 (0.52, 0.92)	0.84 (0.52, 1.35)	0.80 (0.51, 1.24)	1.00 (0.49, 2.07)	1.56 (0.96, 2.54)	1.66 (0.73, 3.76)	0.97 (0.80, 1.19)	0.90 (0.66, 1.22)
Need for mechanical ventilation	NEVI T1	0.96 (0.89, 1.04)	0.85 (0.75, 0.96)	0.95 (0.88, 1.03)	0.82 (0.71, 0.95)	0.95 (0.87, 1.05)	0.76 (0.64, 0.91)	1.03 (0.99, 1.06)	1.11 (1.05, 1.19)
	NEVI T2	0.97 (0.90, 1.05)	0.88 (0.78, 0.99)	0.95 (0.87, 1.05)	0.79 (0.67, 0.93)	0.90 (0.79, 1.02)	0.65 (0.51, 0.82)	1.04 (1.00, 1.08)	1.12 (1.05, 1.19)
	NEVI T3	0.96 (0.90, 1.03)	0.88 (0.80, 0.97)	0.94 (0.84, 1.04)	0.79 (0.68, 0.92)	0.93 (0.83, 1.04)	0.66 (0.56, 0.79)	1.02 (0.98, 1.06)	1.07 (1.02, 1.13)

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Severe COVID-19 Outcome	NEVI Tertile	Ambient Air Pollutant: BC, Pandemic Phase 1	BC, Pandemic Phases 2 and 3	$PM_{2.5}$, Pandemic Phase 1	$PM_{2.5}$, Pandemic Phases 2 and 3	NO_2, Pandemic Phase 1	NO_2, Pandemic Phases 2 and 3	O_3, Pandemic Phase 1	O_3, Pandemic Phases 2 and 3
Death	NEVI T1	0.88 (0.82, 0.95)	1.03 (0.93, 1.14)	0.89 (0.83, 0.95)	1.02 (0.93, 1.13)	0.88 (0.80, 0.96)	1.01 (0.89, 1.14)	1.05 (1.02, 1.09)	1.00 (0.96, 1.04)
	NEVI T2	0.93 (0.87, 1.01)	0.92 (0.81, 1.03)	0.88 (0.80, 0.97)	0.87 (0.75, 1.01)	0.81 (0.71, 0.93)	0.88 (0.74, 1.05)	1.05 (1.01, 1.10)	1.04 (0.98, 1.1)
	NEVI T3	**0.94 (0.88, 1.00)**	**0.88 (0.80, 0.98)**	**0.91 (0.82, 1.01)**	**0.83 (0.71, 0.98)**	**0.81 (0.73, 0.90)**	**0.75 (0.62, 0.89)**	**1.06 (1.03, 1.10)**	**1.07 (1.02, 1.14)**

[a] Results are reported as RRs and 95% CIs (Source: Investigators' Report Appendix Table A5). Tertile 1 corresponds to NEVI scores 0.198–0.294, Tertile 2 corresponds to NEVI scores 0.294–0.349, and Tertile 3 corresponds to NEVI scores 0.349–0.499.

residing in zip codes with the highest level of neighborhood social and structural vulnerability). Similarly, markedly different associations between higher estimated long-term NO_2 exposures and risk of pneumonia were observed for the two highest tertiles of NEVI scores, with the strongest risk estimate reported for the highest NEVI tertiles (although this pattern was evident only in phase 1 of the pandemic).

The investigators reported that higher estimated long-term exposures to BC, $PM_{2.5}$, and NO_2 were associated with lower risks of death during COVID-19 hospitalization across all tertiles of NEVI scores in stratified models. These findings did not strongly differ across NEVI tertiles in phase 1 of the pandemic. In phases 2 and 3 of the pandemic, larger reductions in risk estimates associated with all pollutant exposures were generally observed in the highest NEVI tertile compared to the lowest tertile. In analyses for phase 1 of the pandemic, estimated long-term exposures to all four ambient air pollutants were not significantly associated with length of hospital stay or risks of ARDS, dialysis, or need for mechanical ventilation, with these findings seen across most NEVI tertiles. In phases 2 and 3 of the pandemic, associations between estimated ambient air pollutant exposures and these outcomes were mixed. Again, patterns of association between these outcomes and exposure to O_3 were generally the reverse of the associations observed for exposures to BC, $PM_{2.5}$, or BC.

Excess Mortality Analysis

In the excess mortality analysis that was conducted to address potential selection bias and limitations in the reporting of COVID-10 outcomes, excess mortality in 2020 was greatest in the lowest tertile of estimated long-term $PM_{2.5}$ exposure with the highest NEVI scores. More broadly, in all tertiles of estimated long-term $PM_{2.5}$ exposure, the greatest excess mortality was observed in zip codes that were also in the highest NEVI tertile.

ADDITIONAL ANALYSES

Restricted Study Population Analyses

The investigators conducted analyses restricted to a subset of the study population that corresponded to hospital catchment areas, thereby limiting the proportion of patients included in these analyses who sought treatment outside their neighborhood. Compared to the full population, associations between long-term air pollution exposures and death during COVID-19 hospitalization (adjusted for the effect of the NEVI score and other confounders) in this restricted population were generally stronger in magnitude (i.e., suggestive of a greater protective effect). However, the CIs were wider, and there were some changes in the direction of the associations for all phases of the pandemic. Results in the restricted population for other outcomes were mixed in terms of the direction of the association compared to the full population, such as those pertaining to ARDS and dialysis. Results by NEVI tertiles were generally similar for the restricted and full populations, except for the outcomes of ARDS, pneumonia, and dialysis. Overall, the magnitude of the observed associations was often larger in the restricted population compared to the full population.

Other Effect Modification Analyses

In analyses that used stratified models to evaluate whether results were modified by race or ethnicity, risk estimates for associations between almost all of the ambient air pollutant exposures examined and both pneumonia and hospital admission from the ED were elevated among Black and Hispanic patients, as compared to White and non-Hispanic patients, respectively. Elevated risk estimates for the associations between all ambient air pollutants (except O_3) and dialysis were also elevated among Black patients compared to White patients, but these associations were not always statistically significant. Associations between all four ambient air pol-

lutant exposures and the risk of death, need for mechanical ventilation, and length of hospital stay did not differ by race or ethnicity.

In analyses that evaluated whether results were modified by patients having a pre-existing chronic disease (e.g., asthma, hypertension, and diabetes), the investigators found that greater estimated long-term exposure to NO_2 was associated with higher risks of ARDS and the need for dialysis among patients with diabetes, as compared to patients without diabetes, with the strongest associations observed in the highest NEVI tertile for ARDS. Additionally, the risk of pneumonia associated with greater chronic exposure to NO_2 was of a larger magnitude among patients with asthma, as compared to those without asthma, but these differences were not statistically significant. Associations between air pollutant exposures and the risk of death, length of hospital stay, or need for mechanical ventilation did not differ on the basis of pre-existing chronic conditions.

REVIEW COMMITTEE'S EVALUATION

EVALUATION OF STUDY DESIGN, DATASETS, AND METHODS

This study evaluated potential associations between estimates of long-term exposures to ambient air pollutants and severe COVID-19–related health outcomes among hospitalized patients with a COVID-19 diagnosis in NYC and ED patients with a COVID-19 diagnosis who were ultimately hospitalized. Specifically, the study focused on neighborhood vulnerability (assessed using the NEVI, a novel index that incorporates a combination of social and structural characteristics) as a potential explanation for observed differences in severe COVID-19 outcomes across categories of race and ethnicity.

In its independent evaluation of the Investigators' Report, the HEI Review Committee commended the investigators for their thoughtful framing of the study in the context of the intersection of social and structural characteristics, ambient air pollutant exposures, and severe COVID-19 outcomes. Stingone and colleagues reported mixed results regarding associations between estimated long-term exposures to BC, $PM_{2.5}$, NO_2, and O_3 and risks of several severe COVID-19–related health outcomes (i.e., length of hospital stay, ARDS, pneumonia, need for dialysis, need for mechanical ventilation, hospital admission from the ED, and death). The investigators reported that higher estimated concentrations of BC, $PM_{2.5}$, and NO_2 were consistently associated with increased risk of hospital admission from the ED. However, the direction and magnitude of associations with the other health outcomes examined in the study varied depending on the outcome, ambient air pollutant, and phase of the pandemic. The effect of neighborhood vulnerability on these associations was consistently observed only for the risk of being admitted to the hospital from the ED, with elevated risk estimates observed for higher BC, $PM_{2.5}$, and NO_2 exposures across all levels of NEVI scores and with marked differences in risk estimates between NEVI tertiles. Specifically, the strongest risk estimates were observed in neighborhoods categorized as being the most vulnerable in terms of social and structural characteristics. Other outcomes were not strongly affected by neighborhood vulnerability.

Overall, the Committee found the study approaches and the quality of the epidemiological and exposure data to be appropriate and was impressed with the multiple analyses conducted to address potential biases in the study. However, some important limitations remain, as described in the following sections.

Study Design Strengths

The Committee identified several strengths of the study design, including the use of a large, diverse study population with detailed information about individual patients and the study location of NYC, a city that reported a high number of COVID-19 cases. The Committee also appreciated the construction of the NEVI, which involved using a novel tool (i.e., the Toxicological Priority Index) that can integrate and visualize data across multiple domains.

The Committee was also impressed with the various analyses used to explore potential biases in the study and to evaluate whether the results were influenced by other population-level differences, such as race, ethnicity, or pre-existing chronic disease. Stingone and colleagues noted that a potential source of selection bias in their study could be that some patients might have sought treatment at specific NYC hospitals located outside their neighborhood. The investigators repeated their analyses in a subset of the study population that was restricted to zip codes where at least 40% of the total hospitalizations with a COVID-19 diagnosis involved patients who resided in the neighborhood. The associations observed in these restricted analyses were similar to the associations seen in the full study population for some outcomes (e.g., death) but were generally stronger in magnitude and with wider CIs. There were also changes in the direction of the association for some outcomes (e.g., ARDS) compared to the associations observed in the full population. Thus, this potential source of selection bias may have affected some of the results, biasing associations toward the null.

The Committee also appreciated that the investigators attempted to address the challenges in assessing COVID-19 health outcomes that result from variations in outcome definitions and varying data quality throughout the pandemic. The investigators' decision to approach those difficulties by conducting an excess mortality analysis was useful, and the results of that analysis supported the findings reported in the main analyses that identified associations between ambient air pollutant exposures and risk of death during COVID-19 hospitalization.

Study Design Limitations

The investigators acknowledged several limitations in the study design that were also noted by the Committee. First, to estimate long-term air pollution concentrations, the team used the NYCCAS dataset (which has a spatial resolution of 300 m) and aggregated these data to the zip code level. Although that approach is an improvement over some previous studies on COVID-19 and ambient air pollution, it remains limited by a spatial scale that is relatively coarse for evaluating a single city. Specifically, air pollutant concentrations can vary within zip codes and within a 300-m radius, thus introducing potential exposure measurement error in the study.

The Committee agreed with Stingone and colleagues that, despite the analysis designed to address selection bias resulting from patients who might have sought treatment further from their location of residence, there remain other important potential sources of selection bias. For example, because the study largely focused on hospitalized patients, its generalizability to individuals who did not become severely ill with COVID-19 and were not hospitalized is limited. Also, given that the INSIGHT dataset does not include data from public hospitals, patients in this study population are likely to be of higher socioeconomic status than the average individual living in NYC.

DISCUSSION OF FINDINGS AND INTERPRETATION

The Committee found the investigators' presentation and discussion of the results to be comprehensive and fair, and their interpretations of the results to be appropriately cautious given the mixed findings. More broadly, the Committee members noted that disentangling the links between air pollution, COVID-19, and neighborhood social and structural characteristics is a challenging task, and they commended Stingone and colleagues for their efforts to address this important but complicated research question.

Nonetheless, some of the results remain difficult to explain. For example, inverse associations were reported between estimated long-term BC, $PM_{2.5}$, and NO_2 exposures and death during COVID-19–related hospitalization, suggesting a protective effect associated with higher long-term exposures to ambient air pollution. Similarly, the excess mortality analysis demonstrated higher mortality rates in areas with the lowest levels of estimated $PM_{2.5}$ concentrations. These results are counterintuitive, given the known link between air pollution and respiratory outcomes, and are also the opposite of the findings of some earlier studies on COVID-19 and air pollution.[24-31] One other study conducted in NYC similarly reported an inverse association between $PM_{2.5}$ concentrations and risk of COVID-19 death, but this association was attenuated after adjustment for individual-level factors and propensity score weighting.[32] Studies that have reported positive associations between air pollution and COVID-19 deaths differ from this study, both in their use of exposure estimates assigned based on ambient air pollution concentrations at the individual rather than zip code level and in their use of study populations derived from population-based cohorts or administrative data. Other outcomes examined in this study, such as the need for mechanical ventilation, also demonstrated the protective effects of ambient air pollution. However, a direct comparison between these results (as well as the findings regarding other severe COVID-19 outcomes examined in this study) and findings of other studies is limited by differences in the air pollutants examined, exposure definitions used, and COVID-19 outcomes of interest evaluated in these studies. For example, many other studies have assessed the outcomes of hospitalization and admission to the intensive care unit.

The investigators speculated that their findings might have been driven by several factors, one notable factor being that the INSIGHT data did not include any individual-level measures of socioeconomic status. Although the NEVI is composed of many social and structural (including socioeconomic) characteristics that reflect neighborhood-level vulnerability, the potential for residual confounding remains. Another factor that could have influenced the results is that areas in NYC with high concentrations of ambient air pollution are typically areas with a higher proportion of individuals of high socioeconomic status, as well as high-income or older residents who left NYC during the pandemic and, therefore, might not be represented in the study population. The investigators also noted that a lack of standard COVID-19 treatment protocols early in the pandemic might have strongly influenced study results in a city like NYC, where the majority of COVID-19 cases occurred early in the pandemic and overwhelmed hospital capacity. Finally, Stingone and colleagues also noted that many earlier studies either did not examine the first phase of the pandemic or did not observe any associations between estimated air pollution exposure and COVID-19 death during this initial phase.[24]

The Committee generally agreed with the investigators' explanations and posited that the mixed results overall might have been driven by model-induced correlations among the ambient air pollutants examined from the underlying exposure model used to produce the NYCCAS dataset. Additionally, as previously mentioned, the use of zip code–level estimates of ambient air pollutant concentrations might be too coarse a spatial scale to reflect variations in exposure accurately.

Related to the overall objective of the study, the Committee wondered whether the results necessarily provided evidence for the role of neighborhood vulnerability in modifying associations between ambient air pollution and severe COVID-19–related health outcomes. The investigators reported that only one outcome (hospital admission from the ED) demonstrated consistent effect modification by the overall NEVI score, with risk estimates being strongly elevated among patients who resided in areas with higher levels of neighborhood social and structural vulnerability. The corresponding results for other outcomes were mixed. Thus, it is unclear whether the NEVI score only partially explains differences in associations between long-term ambient air pollutant exposures and

severe COVID-19 outcomes in NYC. The investigators did not find consistent effect modification by the NEVI score (except in relation to hospital admissions from the ED); however, they did demonstrate elevated risks among Black and Hispanic patients compared to White and non-Hispanic patients, respectively, and among patients with diabetes or asthma, compared to patients without these chronic diseases, even after adjusting for the effect of the NEVI score. Those results indicate increased vulnerability among certain subgroups within the population. Additional research further examining the complex relationships between social and structural vulnerability, air pollution, and COVID-19 outcomes is warranted.

Another HEI-funded study of ambient air pollution and COVID-19 health outcomes reported elevated relative risks of COVID-19 incidence among patients exposed to higher long-term estimated exposures to $PM_{2.5}$ and NO_2 who were also of lower socioeconomic status, as well as those with pre-existing chronic disease (including diabetes).[24] A third HEI-funded study demonstrated elevated relative risks of COVID-19 hospitalization among patients exposed to higher long-term estimated exposures to $PM_{2.5}$ and NO_2 who were also of lower socioeconomic status, but no association among patients with pre-existing chronic disease.[29]

SUMMARY AND CONCLUSIONS

Overall, this study contributes to knowledge about potential associations between long-term exposures to ambient air pollution and severe COVID-19 health outcomes during COVID-19 hospitalization and the effect of neighborhood social and structural vulnerability on those associations. Stingone and colleagues reported mixed findings for associations between estimated long-term air pollution exposures and several severe COVID-19 health outcomes, with results varying by ambient air pollutants and phases of the pandemic. Only the association between certain air pollutant exposures and risk of hospital admission from the ED was consistently modified by neighborhood vulnerability, with elevated risk estimates reported among patients who resided in areas with the highest level of social and structural vulnerability. There was inconsistent evidence that associations between estimated long-term air pollutant exposures and other severe COVID-19 health outcomes were modified by neighborhood vulnerability.

Key strengths of the study design were the use of a large and diverse study population that included several individual characteristics; the decision to conduct the study in NYC, which experienced a high volume of COVID-19 cases early in the pandemic; and the construction of a novel neighborhood social and structural vulnerability index, known as the NEVI. The investigators also conducted multiple analyses to address potential biases in their study and several additional analyses to evaluate the effect modification of associations between estimated long-term air pollutant exposures and severe COVID-19 health outcomes by other population-level differences.

Assessing the intersection between air pollution, COVID-19 outcomes, and social and structural factors is challenging. This study demonstrates the complexity of this relationship and highlights the need for additional research on vulnerability within subpopulations, including multifaceted interactions between population-level characteristics such as race, ethnicity, chronic disease, neighborhood vulnerability, and respiratory infections more broadly.

The results of this study might have been limited by potential selection bias, despite the multiple additional analyses conducted to address such biases. Additionally, the findings are likely not generalizable to the broader US population, as the main study cohort consisted of hospitalized patients, and the hospitalization data did not include data from public hospitals.

This study is the fourth in a series of HEI-funded studies investigating potential associations between air pollution and COVID-19. Generally, this body of work has demonstrated elevated relative risks of COVID-19 severity (e.g., hospitalization and intensive care unit admission) associated with several ambient air pollutants, including BC, $PM_{2.5}$, and NO_2. Several of the other studies have shown increased relative risks of COVID-19 death that were associated with ambient air pollutants such as $PM_{2.5}$ and NO_2. Collectively, the results provide evidence that exposure to air pollution can worsen the outcomes of respiratory infectious diseases.

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ABBREVIATIONS AND OTHER TERMS

ARDS	acute respiratory distress syndrome
b0	baseline probability of selection into the sample
BC	black carbon
BMI	body mass index
β_A	differential probability of selection based on exposure
β_Y	differential probability of selection based on outcome
CI	confidence interval
CPT	Current Procedural Terminology
ED	emergency department
EHR	electronic health record
HR	hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
ICU	intensive care unit
INSIGHT-CRN	INSIGHT Clinical Research Network
NEVI	neighborhood environmental vulnerability index
NO_2	nitrogen dioxide
NYC	New York City
NYCCAS	New York City Community Air Survey
O_3	ozone
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
REACH-OUT	Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization OUTcomes
RERI	relative excess risk due to interaction
RR	risk ratio
T1	tertile 1
T2	tertile 2
T3	tertile 3
ToxPi	Toxicological Priority Index

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