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. This report has not been reviewed by public or private party institutions, including those that support the Health Effects Institute, and may not reflect the views of these parties; thus, no endorsements by them should be inferred.

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

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.

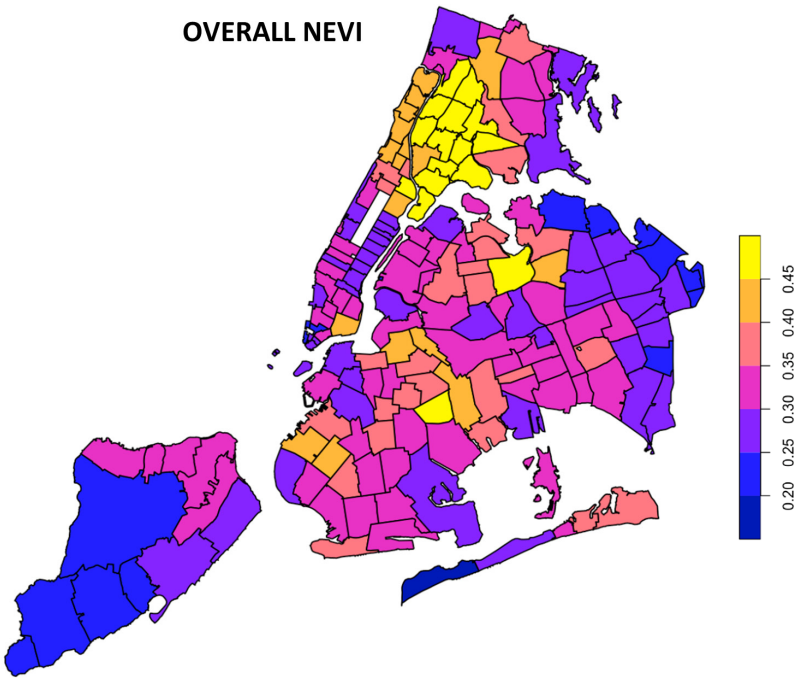
SUMMARY OF KEY RESULTS

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

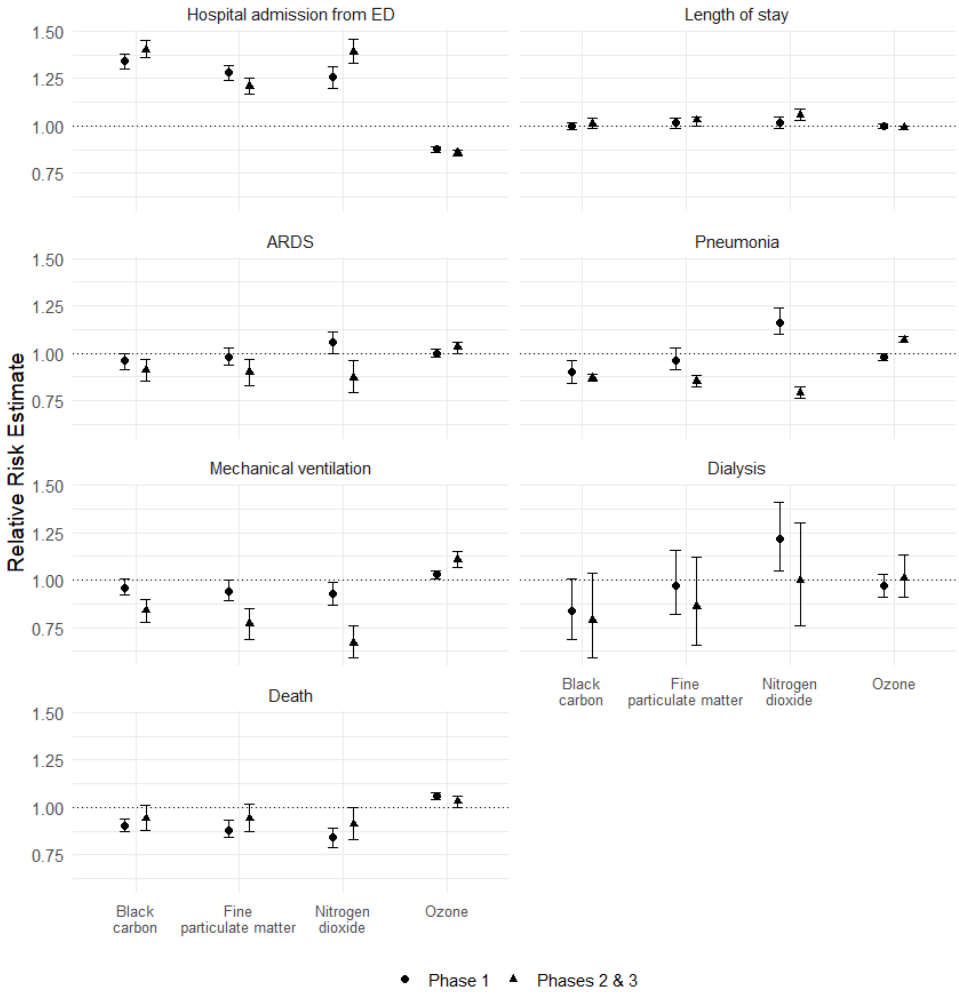
Long-Term Air Pollution and Severe COVID-19 Outcomes

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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REFERENCES

1. Monoson A, Schott E, Ard K, Kilburg-Basnyat B, Tighe RM, Pannu S, et al. 2023. Air pollution and respiratory infections: the past, present, and future. Toxicol Sci 192:3–14; *https://doi.org/10.1093/toxsci/kfad003*.
2. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. 2017. A joint ERS/ATS policy statement: What constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 49; *https://doi.org/10.1183/13993003.00419-2016*.
3. HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution. 2022. Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution. Special Report 23. Boston, MA: Health Effects Institute.
4. Loaiza-Ceballos MC, Marin-Palma D, Zapata W, Hernandez JC. 2022. Viral respiratory infections and air pollut-

ants. Air Qual Atmos Health 15:105–114; *https://doi.org/10.1007/s11869-021-01088-6*.

5. Bashir MF, Ma BJ, Bilal, Komal B, Bashir MA, Farooq TH, et al. 2020. Correlation between environmental pollution indicators and COVID-19 pandemic: a brief study in Californian context. Environ Res 187:109652; *https://doi.org/10.1016/j. envres.2020.109652*.
6. Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. 2021. Links between air pollution and COVID-19 in England. Environ Pollut 268:115859; *https://doi.org/10.1016/j.envpol.2020.115859*.
7. Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. 2020. Air pollution and COVID-19 mortality in the United States: strengths and limitations of an ecological regression analysis. Sci Adv 6:eabd4049; *https://doi.org/10.1126/sciadv.abd4049*.
8. Coker ES, Cavalli L, Fabrizi E, Guastella G, Lippo E, Parisi ML, et al. 2020. The effects of air pollution on COVID-19-related mortality in Northern Italy. Environ Resour Econ (Dordr) 76:611–634; *https://doi.org/10.1007/s10640-020-00486-1*.
9. Cole MA, Ozgen C, Strobl E. 2020. Air pollution exposure and COVID-19 in Dutch municipalities. Environ Resour Econ 76:581–610; *https://doi.org/10.1007/s10640-020-00491-4*.
10. Konstantinoudis G, Padellini T, Bennett J, Davies B, Ezzati M, Blangiardo M. 2021. Long-term exposure to air pollution and COVID-19 mortality in England: a hierarchical spatial analysis. Environ Int 146:106316; *https://doi.org/10.1016/j.envint.2020.106316*.
11. Liang D, Shi L, Zhao J, Liu P, Sarnat JA, Gao S, et al. 2020. Urban air pollution may enhance COVID-19 case fatality and mortality rates in the United States. Innovation (Camb) 1:100047; *https://doi.org/10.1016/j.xinn.2020.100047*.
12. Copat C, Cristaldi A, Fiore M, Grasso A, Zuccarello P, Signorelli SS, et al. 2020. The role of air pollution (PM and NO_2) in COVID-19 spread and lethality: a systematic review. Environ Res 191:110129; *https://doi.org/10.1016/j.envres.2020.110129*.
13. Katoto PDMC, Brand AS, Bakan B, Obadia PM, Kuhangana C, Kayembe-Kitenge T, et al. 2021. Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity, and mortality of COVID-19: a rapid systematic review. Environ Health 20:41; *https://doi.org/10.1186/s12940-021-00714-1*.
14. Villeneuve PJ, Goldberg MS. 2020. Methodological considerations for epidemiological studies of air pollution and the SARS and COVID-19 coronavirus outbreaks. Environ Health Perspect 128:095001; *https://doi.org/10.1289/EHP7411*.
15. Bhaskar A, Chandra J, Hashemi H, Butler K, Bennett L, Cellini J, et al. A literature review of the effects of air pollution on COVID-19 health outcomes worldwide: statistical challenges and data visualization. Ann Rev Pub Health 44:1–20; *https://doi.org/10.1146/annurev-publhealth-071521-120424*.
16. Sheppard N, Carroll M, Gao C, Lane T. 2023. Particulate matter air pollution and COVID-19 infection, severity, and mortality: a systematic review and meta-analysis. Sci Total Environ 880:163272; *https://doi.org/10.1016/j.scitotenv.2023.163272*.
17. Yu K, Zhang Q, Wei Y, Chen R, Kan H. 2023. Global association between air pollution and COVID-19 mortality: a systematic review and meta-analysis. Sci Total Environ 906:167542; *https://doi.org/10.1016/j.scitotenv.2023.167542*.
18. Yaya S, Yeboah H, Charles CH, Otu A, Labonte R. 2020. Ethnic and racial disparities in COVID-19-related deaths: counting the trees, hiding the forest. BMJ Glob Health. 5:e002913; *https://doi.org/10.1136/bmjgh-2020-002913*.
19. Dey T, Dominici F. 2020. COVID-19, air pollution, and racial inequity: connecting the dots. Chem Res Toxicol 34:669–671; *https://doi.org/10.1021/acs.chemrestox.0c0043*.
20. Magesh S, John D, Li WT, Li Y, Mattingly-App A, Jain S, et al. 2021. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status: a systematic review and meta-analysis. JAMA Netw Open 4:e2134147; *https://doi.org/10.1001/jamanetworkopen.2021.34147*.
21. Berkowitz RL, Gao X, Michaels EK, Mujahid MS. 2021. Structurally vulnerable neighborhood environments and racial/ethnic COVID-19 inequities. Cities Health 5:S59–S62; *https://doi.org/10.1080/23748834.2020.1792069*.
22. Clougherty JE, Kheirbek I, Eisl HM, Ross Z, Pezeshki G, Gorczynski JE, et al. 2013. Intra-urban spatial variability in wintertime street-level concentrations of multiple combustion-related air pollutants: the New York City Community Air Survey (NYCCAS). J Expo Sci Environ Epidemiol 23:232–240; *https://doi.org/10.1038/jes.2012.125*.
23. Reif DM, Sypa M, Lock EF, Wright FA, Wilson A, Cathey T, et al. 2013. ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence. Bioinformatics 29:402–403; *https://doi.org/10.1093/bioinformatics/bts686*.
24. Andersen ZJ, Zhang J, Lim Y-L, So R, Jørgensen JT, Mortensen LH, et al. 2023. Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN). Research Report 214. Boston, MA: Health Effects Institute.
25. Chen C, Wang J, Kwong J, Kim J, van Donkelaar A, Martin RV, et al. 2022. Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study. CMAJ 194:E693–700; *https://doi.org/10.1503/cmaj.220068*.
26. Garcia E, Marian B, Chen Z, Li K, Lurmann F, Gilliland F, et al. 2022. Long-term air pollution and COVID-19 mortality rates in California: findings from the Spring/Summer and Winter surges of COVID-19. Environ Pollut 292:118396; *https://doi.org/10.1016/j.envpol.2021.118396*.
27. Hyman S, Zhang J, Andersen ZJ, Cruickshank S, Møller P, Daras K, et al. 2023. Long-term exposure to air pollution and COVID-19 severity: a cohort study in Greater Manchester, United Kingdom. Environ Pollut 327:121594; *https://doi.org/10.1016/j.envpol.2023.121594*.
28. Jerrett M, Nau CL, Young DR, Butler RK, Batteate CM, Su J, et al. 2023. Air pollution and meteorology as risk factors for COVID-19 death in a cohort from Southern California. Environ Int171:107675; *https://doi.org/10.1016/j.envint.2022.107675*.

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

30. Nobile F, Michelozzi P, Ancona C, Cappai G, Cesaroni G, Davoli M, et al. 2022. Air pollution, SARS-CoV-2 incidence and COVID-19 mortality in Rome: a longitudinal study. Eur Respir J 60:2200589; *https://doi.org/10.1183/13993003.00589-2022*.

31. Stafoggia M, Ranzi A, Ancona C, Bauleo L, Bella A, Cattani G, et al.; EpiCovAir Study Group. 2023. Long-term exposure to ambient air pollution and mortality among four million COVID-19 cases in Italy: the EpiCovAir study. Environ Health Perspect 131:057004; *https://doi.org/10.1289/EHP11882*.

32. Bozack A, Pierre S, DeFelice N, Colicino E, Jack D, Chillrud SN, et al. 2022. Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York City. Am J Respir Crit Care Med 205:651–62; *https://doi.org/10.1164/rccm.202104-0845oc*.

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