Research Report 238, *Ambient Air Pollution and COVID-19 in California*, by M. Kleeman et al.

INTRODUCTION

The COVID-19 pandemic led to unprecedented conditions that lent themselves to timely and novel air pollution research exploring important policy-related 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 proposals for research on new and important aspects of the intersection between air pollution exposures and COVID-19 health outcomes. In particular, HEI was interested in studies exploring whether people exposed to higher levels of air pollution were at greater risk of death from COVID-19 than were populations with lower levels of air pollution exposures and whether potential associations between air pollution and COVID-19 outcomes differed by race, ethnicity, or measures of socioeconomic status.

In response to the Request for Applications, Dr. Michael Kleeman of the University of California, Davis, submitted an application to HEI titled "Ambient Air Pollution and COVID-19 in California." Kleeman and colleagues proposed to develop high-resolution estimates of chronic and short-term exposures to ambient air pollution across Southern California and to evaluate the potential associations between air pollution exposures and COVID-19 disease progression, long-term COVID-19 complications, and mortality due to COVID-19 by using electronic health records from the Kaiser Permanente Southern California (KPSC) health system. Additionally, the investigators proposed to examine the association between air pollution exposures and COVID-19 incidence and mortality across neighborhoods in Los Angeles County. HEI's Research Committee recommended funding Kleeman's study because the investigators were proposing methods for answering novel questions, had access to a unique dataset (namely, detailed individual-level data from the KPSC database), and planned to examine various air pollutant exposures (i.e., nitrogen dioxide [NO_2], ozone [O_3], particulate matter [PM] mass concentrations, and major sources and chemical components of PM ≤2.5 µm in aerodynamic diameter [$PM_{2.5}$]).

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

SCIENTIFIC BACKGROUND

Research from toxicological and population health studies has demonstrated an association between air pollution exposure and the risk of acute lower respiratory infections (i.e., bronchitis, bronchiolitis, and pneumonia), influenza, and respiratory syncytial virus.[1,2] Research on such respiratory infections is complicated, however, and has yielded mixed findings regarding the role of air pollution.[3,4]

Several early epidemiological studies suggested possible positive associations between air pollution and COVID-19.[5–7] However, the potential for bias in those results was high, partly because early in the pandemic, it was difficult to obtain reliable data identifying individuals who were infected with the SARS-CoV-2 virus or seriously ill with COVID-19, and because accuracy and availability of testing varied by location and over time. Additionally, estimating ambient air pollution exposures was complicated by the varying degrees of severity and duration of COVID-19 lockdown policies and the atypical levels of pollutant emissions and daily mobility patterns associated with these policies. Results from these early studies were difficult to compare and generalize, given different study designs, approaches to estimating exposure (i.e., short-term versus long-term exposures), and outcome definitions (e.g., disease incidence, prevalence, severity, or case fatality rates).

Importantly, nearly all of the initial published studies in this field were based on cross-sectional analyses or ecological study designs.[5–11] They 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. Three early reviews highlighted the need for studies to use individual-level data and high spatial resolution measures of air pollution, to control for confounding, and to assess effect modification.[12–14] These reviews all concluded that although early evidence indicated that both short- and long-term exposure to air pollution could

Dr. Michael Kleeman's 2-year study, "Ambient Air Pollution and COVID-19 in California," began in April 2021. Total expenditures were $495,122. The draft Investigators' Report was received for review in January 2024. A revised report, received in August 2024, was accepted for publication in September 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 Michael Jerrett did not partake in the review of the report due to a conflict of interest.

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

be associated with COVID-19 outcomes, those studies had moderate to high overall risks of bias that precluded drawing conclusions about potential causal relationships.

At the time Kleeman and colleagues began their study, the available literature included little high-quality evidence, partly due to weaknesses in study designs. Kleeman's study aimed to address several limitations, notably by using a large database of individual-level health records and developing air pollution exposure estimates with high spatial resolution. Additionally, the investigators sought to evaluate questions that had not yet been addressed in the scientific literature on air pollution and COVID-19, such as multistate health effects (i.e., disease progression from one state of health to another, such as from hospitalization to death) and long-term complications of COVID-19 (i.e., long COVID-19).

SUMMARY OF APPROACH AND METHODS

STUDY OBJECTIVES

Kleeman and colleagues aimed to investigate the relationships between ambient air pollution exposures and COVID-19 incidence, progression, and mortality, as well as long COVID-19 outcomes (which pertain to a variety of debilitating symptoms that can occur after serious COVID-19 disease).[15] The specific aims of the study were as follows:

- **Aim 1:** Generate high-resolution air pollution exposure estimates for $PM_{2.5}$ mass and components, ultrafine PM ≤0.1 μm in aerodynamic diameter ($PM_{0.1}$) mass, NO_2, and O_3 at multiple spatial resolutions across Southern California.
- **Aim 2:** Conduct a spatial analysis by Los Angeles County ZIP codes to quantify associations between estimated air pollution concentrations and COVID-19 incidence and mortality across neighborhoods, using high spatial resolution exposure estimates that include $PM_{2.5}$ components.
- **Aim 3:** Examine COVID-19 mortality and multistate health effects in Southern California by assessing the association between air pollution exposures and both mortality and the progression from COVID-19 hospitalization to more severe disease states or recovery among a cohort of patients hospitalized with COVID-19 as documented in the KPSC healthcare database.
- **Aim 4:** Examine long COVID-19 in Southern California by assessing the relationship between ambient air pollutant exposures and diagnosis of conditions associated with long COVID-19 outcomes among the KPSC cohort.

Kleeman and colleagues obtained ZIP code–level counts of COVID-19 cases and deaths in Los Angeles County between June 19, 2020, and January 3, 2021, based on data from the California Department of Public Health (CDPH). For the KPSC cohort, the investigators used electronic health records from the KPSC healthcare system to create a cohort of more than 20,000 adults across Southern California who had been diagnosed with COVID-19 between June 1, 2020, and January 30, 2021, were hospitalized within 21 days of a positive COVID-19 test, and had been KPSC members for at least 1 year.

The investigators generated estimates of daily ambient $PM_{2.5}$, $PM_{2.5}$ components (species and sources), $PM_{0.1}$, NO_2, and O_3 concentrations for 2016, 2019, and 2020 at multiple spatial resolutions using a chemical transport model (CTM) and a land use regression (LUR) model. Chronic (annual average) and short-term (30-day average) exposure estimates for the ambient air pollutants were assigned to the residential address of each patient in the KPSC cohort (or to each ZIP code in the CDPH data).

Kleeman and colleagues used various regression modeling approaches to evaluate associations between both single and multipollutant air pollution exposures and COVID-19 outcomes, as described in further detail in the Methods section. An analysis evaluating whether changes in air quality were associated with COVID-19 incidence, severity, and mortality was originally intended to be conducted alongside the generation of high-resolution ambient air pollution estimates specific to Aim 1. However, low numbers of COVID-19 cases during the lockdown period that affected air pollution patterns in California (i.e., earlier in 2020) resulted in insufficient statistical power to conduct such an analysis.

METHODS AND STUDY DESIGN

Study Population

The CDPH data included counts of COVID-19 cases and COVID-19 deaths that occurred between June 19, 2020, and January 3, 2021, by ZIP code in Los Angeles County. These data included ZIP code–level demographic information on age, sex, and race/ethnicity.

KPSC is a regional entity of Kaiser Permanente, a large integrated healthcare system and one of the oldest and largest not-for-profit health plans in the United States. KPSC has a racially, ethnically, and socioeconomically diverse membership of 4.8 million members across nine counties in Southern California. The KPSC study cohort consisted of adults (aged 18 years or older) in Southern California who had been hospitalized within 21 days of a clinical diagnosis of COVID-19 or a positive COVID-19 test that occurred between June 1, 2020, and January 30, 2021, and who had been KPSC members for at least 1 year. The KPSC data included individual-level information on demographic and health characteristics such as age, sex, race/ethnicity, body mass index (BMI), and level of exercise.

Patient deaths were included in the cohort data for patients who died 90 or fewer days after their initial hospitalization. Patients whose KPSC membership ended within 90 days after hospitalization were excluded from the cohort. In analyses for Aim 3, patients who received treatment outside the

KPSC system were excluded. Additionally, the investigators defined deterioration due to COVID-19 as admission to the intensive care unit (ICU) or the need for ventilation. Analyses for Aim 4 also included patients who were discharged after hospitalization with COVID-19 and who were KPSC members for at least 1 year before and after their COVID-19 diagnosis.

Long COVID-19 was defined using a set of clinically meaningful categories based on 45 diagnostic codes[16] and grouped by organ system. Patients were considered to have long COVID-19 if they had received one or more cardiac, cardiometabolic, pulmonary, or neurological diagnoses within 3 to 12 months after discharge from their COVID-19–related hospitalization.

The investigators linked both the KPSC and CDPH data with area-level characteristics, including data on the Neighborhood Deprivation Index, income, crowding, temperature, relative humidity, and green space. Temperature and relative humidity were daily maximums (using Gridded Surface Meteorological data)[17] and aggregated to monthly means for each patient's residential address during the 1-month period before their COVID-19 hospitalization. An overview of the study populations and health outcomes of interest for each aim, by chapter of the Investigators' Report, is presented in **Commentary Table 1**.

Exposure Estimation

The investigators used a CTM to generate estimates of daily air pollutant exposure for $PM_{0.1}$ (mass), $PM_{2.5}$ (mass and components), NO_2, and O_3 in Southern California. They also used an LUR model to generate estimates of daily air pollutant exposures for $PM_{2.5}$ (mass) and NO_2. Daily estimates were averaged to reflect chronic (annual) and short-term (30-day) exposures, with data for specific pollutants, types of exposure, and years depending on the particular analysis for each aim (Commentary Table 1). Estimates were assigned to the residential address of each patient (in the KPSC cohort) or each ZIP code (in the CDPH data).

Daily $PM_{2.5}$ and NO_2 concentrations were estimated at 100-m resolution for the years 2019 and 2020 with an LUR model that used a deletion/substitution/addition algorithm.[18] Daily concentrations of a large number of pollutants (Commentary Table 1) at 1-km resolution were produced for the years 2016, 2019, and 2020 by using the University of California, Davis/California Institute of Technology (UCD/CIT) air quality model.[19, 20] UCD/CIT is a three-dimensional CTM that simulates the evolution of gas and particle phase pollutants in the atmosphere based on emissions, transport, deposition, chemical reaction, and phase change.

Main Epidemiological Analyses

To assess the associations between various air pollutant exposures (Commentary Table 1) and COVID-19 cases and COVID-19 deaths across Los Angeles County ZIP codes (Aim 2), Kleeman and colleagues used negative binomial regression models. In the single-pollutant models, the investigators adjusted for several ZIP code–level covariates, including demographic variables (e.g., sex, race, age) and socioeconomic and health-related variables (e.g., income, smoking status, obesity). Associations were reported as incidence rate ratios (IRRs) and 95% confidence intervals (CIs), with pollutant exposures standardized by their interquartile range (IQR). The investigators also used two-pollutant models to assess confounding by $PM_{2.5}$, NO_2, and O_3.

To assess the associations between various air pollutant exposures and both COVID-19 mortality and progression to more severe COVID-19 states or recovery (Aim 3), the investigators conducted two analyses. First, they used single- and two-pollutant Cox proportional hazards models to assess associations between various air pollutant exposures and patient deaths in the KPSC cohort. The study team adjusted their models for several individual and community-level covariates, such as BMI, level of exercise, Neighborhood Deprivation Index, temperature, and relative humidity, depending on the ambient air pollutant. Associations were analyzed per IQR increment in ambient air pollutant exposure and reported as hazard ratios (HRs) with 95% CIs.

Second, Kleeman and colleagues used a multistate survival model[21, 22] to assess associations between $PM_{2.5}$, NO_2, and O_3 exposures and patient transitions to recovery or deterioration to more severe COVID-19 states or outcomes (i.e., ICU admission, ventilation, or death). The investigators examined six transition states: (1) hospitalization to deterioration (i.e., ICU admission or need for ventilation), (2) hospitalization to recovery, (3) hospitalization to death, (4) deterioration to recovery, (5) deterioration to death, and (6) recovery to death. It was assumed that the amount of time a patient existed in any given state did not influence their time spent in any other state (i.e., a Markovian assumption). The study team ran single- and two-pollutant models adjusted for both individual- and community-level covariates, and they reported HRs with 95% CIs standardized by the IQR for estimated concentrations of each ambient air pollutant.

To evaluate long COVID-19 outcomes (Aim 4), the investigators used logistic regression to examine the associations between chronic and short-term exposures to various air pollutants before hospital admission and long COVID-19 diagnoses within 3 months after hospital discharge, as well as within 12 months after hospital discharge. The investigators conducted analyses with single-, two-, and three-pollutant models adjusted for both individual- and community-level covariates. Associations were reported as odds ratios (ORs) with 95% CIs per IQR increment increase in exposure to ambient air pollutants.

Additional Analyses

Kleeman and colleagues also evaluated associations between ambient air pollutant exposures and COVID-19 deaths for potential effect modification by temperature

Commentary Table 1. Summary of COVID-19 Outcomes, Pollutant Exposures, and Methods by Study Aim and Chapter of the Investigators' Report

Study Aim, Chapter	Study Population	Health Outcomes	Year	Pollutant Exposures	Methods
Aim 1, Chapter 3	N/A	N/A	2016, 2019, 2020	Chronic (2016, 2019, 2020 annual average) and short-term (30-day average) $PM_{0.1}$, $PM_{2.5}$, $PM_{2.5}$ organic compounds, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ nitrate, $PM_{2.5}$ source tracers, NO_2, O_3	LUR model ($PM_{2.5}$ and NO_2 only) and CTM ($PM_{0.1}$, $PM_{2.5}$, $PM_{2.5}$ components [species and sources], NO_2, O_3)
Aim 2, Chapter 4	*N* = 773,374 cases and *N* = 14,311 deaths in Los Angeles County (CDPH)	COVID-19 cases and deaths	2019	Chronic (2019 annual average) $PM_{0.1}$, $PM_{2.5}$, $PM_{2.5}$ organic compounds, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ nitrate, $PM_{2.5}$ on-road gasoline tracer, NO_2, O_3	Negative binomial regression models with adjustment for sex, race/ethnicity, age >70 yr, median income, mean homeowner occupancy rate, mean prevalence of current smoking status, mean prevalence of obesity
Aim 3, Chapter 5	*N* = 21,415 hospitalized KPSC patients	COVID-19 deaths	2016	Chronic (2016 annual average) $PM_{0.1}$, $PM_{2.5}$, $PM_{2.5}$ organic compounds, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ nitrate, $PM_{2.5}$ on-road gasoline tracer, $PM_{2.5}$ on-road diesel tracer, $PM_{2.5}$ biomass combustion tracer, NO_2 (CTM), O_3	Cox proportional hazard regression models with adjustment for various demographic, socioeconomic, chronic health, and area-level characteristics depending on the ambient air pollutant (Investigators' Report Appendix B Table B1)
Aim 3, Chapter 6	*N* = 15,978 hospitalized KPSC patients	COVID-19 hospitalization, recovery, deterioration, and death	2016	Chronic (2016 annual average) $PM_{2.5}$, NO_2, O_3	Multistate survival regression models with adjustment for various demographic, socioeconomic, chronic health, and area-level characteristics depending on the ambient air pollutant (Investigators' Report Appendix D Table D2)
Aim 4, Chapter 7	*N* = 12,634 hospitalized KPSC patients	Cardiac, cardiometabolic, pulmonary, and neurological long COVID-19 outcomes within 3 months to 12 months after hospital discharge	2019, 2020	Chronic (365-day average before hospitalization) and short-term (30-day average) $PM_{0.1}$, $PM_{2.5}$, $PM_{2.5}$ organic compounds, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ nitrate, $PM_{2.5}$ biomass combustion tracer, NO_2, O_3	Logistic regression models with adjustment for smoking, exercise, BMI, status of MediCal enrollment, and area-level deprivation, proportion of people taking public transit, temperature, relative humidity, and greenspace

BMI = body mass index; CDPH = California Department of Public Health; CTM = chemical transport model; KPSC = Kaiser Permanente Southern California; LUR = land use regression; N/A = not applicable.

and relative humidity in the KPSC cohort. The study team implemented Cox proportional hazard regression models with an interaction term between one ambient air pollutant and one meteorological variable. If the interaction term was significant (i.e., *P* value <0.05), stratified models were run by tertiles of temperature or relative humidity. Analyses of effect modification were conducted for both single- and two-pollutant models, with associations reported as HRs with 95% CIs, standardized by IQR of the ambient air pollutant exposures.

SUMMARY OF KEY FINDINGS

STUDY POPULATION CHARACTERISTICS

The CDPH study population included 773,374 cases of COVID-19 and 14,311 COVID-19 deaths across 308 ZIP codes in Los Angeles County. In this study population, patients diagnosed with COVID-19 were on average predominantly female (54.6%), 70 years of age or older (93.7%), and non-White (69.8%), whereas COVID-19 deaths occurred primarily in patients who were male (57.9%), less than 70 years of age (58.7%), and a race/ethnicity other than White (78.6%).

The KPSC cohort included 21,994 adults hospitalized within 21 days of a COVID-19 diagnosis or positive COVID-19 test; however, the analysis population varied by study aim (Commentary Table 1). Generally, patients in this cohort were primarily older (median age: 64 years), male (57.7%), Hispanic/Latino (56.4%), and had comorbidities (mean Elixhauser index: 3.0). Those who deteriorated (i.e., admitted to the ICU or received ventilation) or died after hospitalization were predominantly 65 years of age or older, male, and Hispanic/Latino. Women were more likely than men to experience long COVID-19 outcomes. Patients diagnosed with long COVID-19 outcomes within 3 months and within 12 months after being discharged from the hospital had lower rates of exercise and higher BMIs compared to those who were not diagnosed with long COVID-19 over these follow-up periods; no other noteworthy differences were observed between these groups.

EXPOSURE ESTIMATION AND ASSESSMENT

The $PM_{2.5}$ and NO_2 exposure estimates generated using LUR and CTM approaches for Aim 1 produced different estimates, which was understandable given the differences in the underlying methods for each model (Investigators' Report Figure 5). For example, both the LUR model and CTM estimated high annual average concentrations of NO_2 around Los Angeles in 2020, but the LUR model estimates were higher than those produced by the CTM. Similarly, the CTM predicted high annual average concentrations of $PM_{2.5}$ around Los Angeles and in the San Joaquin Valley region north of Los Angeles in 2020, whereas the LUR model predicted the highest $PM_{2.5}$ concentrations in the eastern region of the state (i.e., San Bernardino, Riverside, and Imperial counties) in 2020.

The median of estimated chronic exposures to various measures of PM mass and components, NO_2, and O_3 varied across the analyses for each aim (**Commentary Table 2**). The upper range of the median of estimated pollutant concentrations across all study aims was around 13 µg/m³ for $PM_{2.5}$, 22 parts per billion (ppb) for NO_2, and 66 ppb for O_3. The median of short-term (30-day average) estimated exposures was fairly similar to the medians of estimated chronic exposures. Generally, many of the ambient air pollutants were moderately to highly correlated with one another (e.g., $PM_{2.5}$ and $PM_{0.1}$).

Commentary Table 2. Ranges of the Median of Estimated Exposures to Ambient Air Pollutants Across Study Aims[a]

Ambient Air Pollutant	Range of the Median of Estimated Chronic Concentrations	Range of the Median of Estimated Short-Term Concentrations
$PM_{0.1}$	0.91–0.99 µg/m³	0.83 µg/m³
$PM_{2.5}$	9.0–13.1 µg/m³	10.3–12.9 µg/m³
$PM_{2.5}$ elemental carbon	0.47–0.58 µg/m³	0.59 µg/m³
$PM_{2.5}$ organic compounds	2.07–2.53 µg/m³	2.10 µg/m³
$PM_{2.5}$ nitrate	1.60–3.81 µg/m³	1.91 µg/m³
$PM_{2.5}$ on-road gasoline tracer	0.24–0.30 µg/m³	N/A
$PM_{2.5}$ on-road diesel[b]	0.07 µg/m³	N/A
$PM_{2.5}$ biomass combustion	1.01–1.71 µg/m³	0.39 µg/m³
NO_2	13.4–22.0 ppb	14.0–17.0 ppb
O_3	54.5–66.0 ppb	48.0 ppb

N/A = not applicable; ppb = parts per billion.

[a]Chronic exposures were based on annual average air pollutant concentrations across the study cohort. Short-term exposures were based on 30-day average air pollutant concentrations across the study cohort.

[b]Only used in one analysis (Aim 4).

Ozone was the least correlated with the other ambient air pollutants and was inversely correlated with NO_2.

MAIN EPIDEMIOLOGICAL ANALYSES

Associations Between Chronic Exposures to Air Pollutants and COVID-19 Outcomes (Aim 2)

In the CDPH study population, single-pollutant models demonstrated higher risks of COVID-19 incidence and mortality per IQR increment increase in chronic exposure to several ambient air pollutants, including $PM_{0.1}$, $PM_{2.5}$ (mass, elemental carbon, nitrate, and from on-road gasoline vehicles), and O_3 (**Commentary Figure 1**). Generally, the magnitude of the associations was slightly stronger for the risk of COVID-19 death compared to COVID-19 incidence. Estimates of $PM_{2.5}$ produced by the LUR model demonstrated statistically significant associations with both COVID-19 incidence and mortality, whereas the estimates produced by the CTM demonstrated elevated associations with these outcomes but were not statistically significant. Risk estimates ranged in magnitude from 1.02 to 1.27. The strongest risk estimate was observed for COVID-19 death per IQR increase in estimated O_3 concentration (IRR: 1.27; 95% CI: 1.17, 1.37).

The two-pollutant models demonstrated elevated risks of COVID-19 incidence and mortality per IQR increase in estimated NO_2 and $PM_{2.5}$ concentrations, after controlling for O_3, and elevated risks per IQR increase in estimated O_3 concentration, after controlling for $PM_{2.5}$ or NO_2 (Investigators' Report Figure 8). As seen in results from the single-pollutant models, the strongest IRRs were observed for associations between O_3 concentrations and COVID-19 deaths (IRR [controlling for NO_2]: 1.42; 95% CI: 1.23, 1.56 and IRR [controlling for $PM_{2.5}$ (CTM)]: 1.37; 95% CI: 1.26, 1.50). The associations between $PM_{2.5}$ concentrations and both COVID-19 incidence and mortality were generally attenuated after controlling for NO_2. Results were similar regardless of the exposure modeling method (i.e., LUR or CTM) used to estimate $PM_{2.5}$ and NO_2 concentrations, although the associations observed using exposure estimates generated by the LUR model were often larger in magnitude compared to the associations based on CTM-generated exposure estimates.

Associations Between Estimated Chronic Exposures to Air Pollutants and COVID-19 Progression or Death (Aim 3)

In the KPSC cohort, the investigators reported positive associations between COVID-19 deaths and IQR increases in exposures to each of the ambient air pollutants evaluated in single-pollutant models, except for $PM_{2.5}$ organic compounds (although this association was nearly statistically significant), $PM_{2.5}$ from biomass combustion, and O_3 (a finding in contrast to the results observed in Aim 2) (**Commentary Figure 2**). Reported risk estimates were generally moderate in size, and the risk estimates that were strongest in magnitude were observed for $PM_{2.5}$ (estimated by the CTM): HR: 1.12; 95% CI: 1.06, 1.17, $PM_{2.5}$ nitrate: HR: 1.12; 95% CI: 1.07, 1.17, and NO_2: HR: 1.10; 95% CI: 1.04, 1.16. In two-pollutant models, the HRs generally remained elevated for associations between COVID-19 death and $PM_{2.5}$ exposures, as did the association with NO_2 when controlling for O_3, with some fluctuations in magnitude (Investigators' Report Figure 11). However, the association with NO_2 was attenuated in models controlling for $PM_{2.5}$.

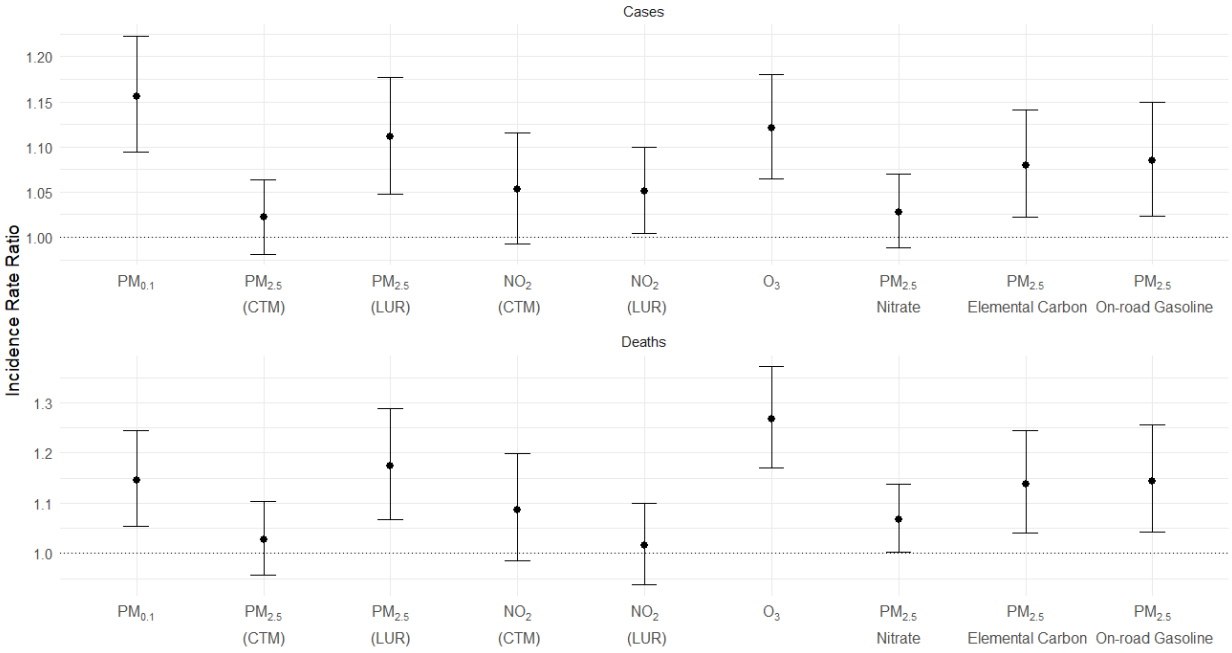
In analyses of the progression to more severe COVID-19 states, Kleeman and colleagues reported elevated HRs in single-pollutant models of the associations between $PM_{2.5}$, NO_2, and O_3 exposures (comparing the highest versus lowest quartiles of exposure) and several COVID-19–related transitional states: the transition from hospitalization to deterioration, the transition from deterioration to death, and the transition from recovery to death (**Commentary Table 3**). For example, HRs for the associations between the highest (versus the lowest) quartile of exposure to each pollutant and the transition from COVID-19 hospitalization to deterioration were 1.16 ($PM_{2.5}$), 1.19 (NO_2), and 1.21(O_3).

In two-pollutant models across multiple combinations of $PM_{2.5}$, NO_2, and O_3 exposures, HRs for the transition from COVID-19 hospitalization to deterioration remained elevated, with small to modest changes in magnitude compared to the HRs from the single-pollutant models (Investigators' Report Table 8). The results from analyses for other transition states demonstrated no clear pattern in the changes in direction or magnitude of the associations across combinations of $PM_{2.5}$, NO_2, and O_3 exposures in the two-pollutant versus single-pollutant models.

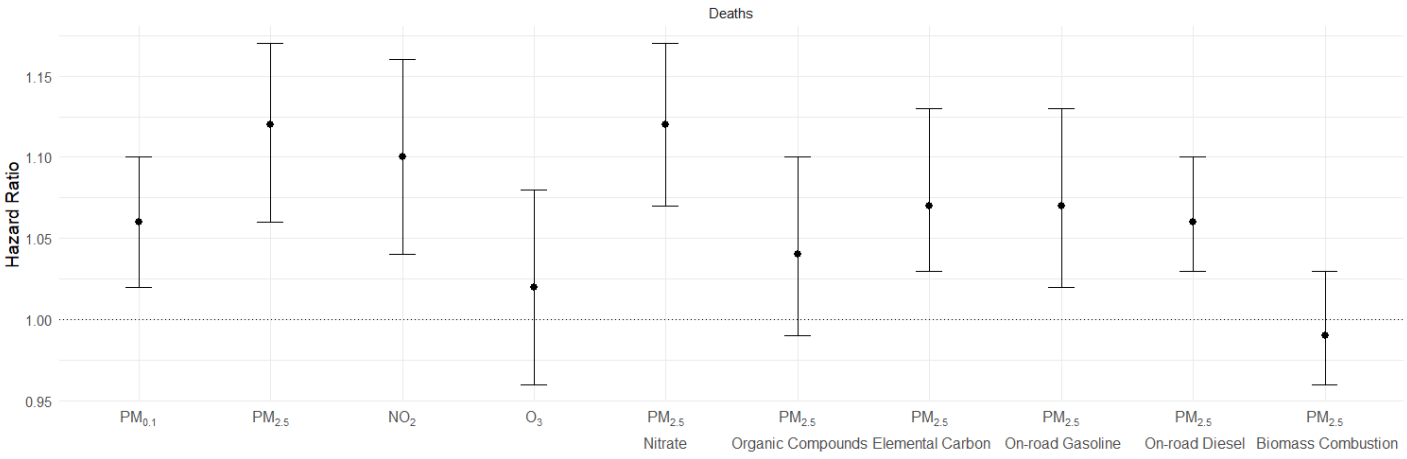
Associations Between Estimated Air Pollutant Exposures and Long COVID-19 (Aim 4)

In analyses of the KPSC cohort, the investigators reported mixed results regarding associations between short-term exposures to different ambient air pollutants and specific types of long COVID-19 outcomes diagnosed within 3 months of hospital discharge (**Commentary Figure 3**). Elevated odds of several long COVID-19 outcomes were reported per IQR increment increase in short-term exposures to $PM_{0.1}$, $PM_{2.5}$ nitrate, and O_3. No statistically significant associations between NO_2 exposure and any long COVID-19 outcome were observed (although the odds ratio for cardiometabolic long COVID-19 was elevated). Additionally, no significant associations between any short-term air pollutant exposures and neurological long COVID-19 were reported. Interestingly, the investigators observed a modest-sized inverse association between estimated $PM_{2.5}$ exposure and pulmonary long COVID-19, although this association was not robust in various sensitivity analyses adjusting for O_3 and $PM_{2.5}$ from biomass combustion (Investigators' Report Table 14).

The observed associations between ambient air pollutant exposures and a diagnosis of long COVID-19 within 12 months after hospital discharge were often in the same direction (i.e., positive or inverse) as — but generally weaker in magnitude



Commentary Figure 1. Associations between estimated chronic pollutant concentrations and COVID-19 incidence and mortality in the California Department of Public Health cohort. Results shown are incidence rate ratios and 95% confidence intervals estimated per interquartile range increase in 2019 annual average pollutant concentrations. The results are from single-pollutant models that included adjustment for neighborhood characteristics (i.e., demographic, socioeconomic, and chronic health factors). CTM = chemical transport model; LUR = land use regression. Source: Adapted from Investigators' Report Figure 7.



Commentary Figure 2. Associations between estimated chronic pollutant concentrations and COVID-19 deaths in the Kaiser Permanente Southern California cohort. Results shown are hazard ratios and 95% confidence intervals estimated per interquartile range increase in 2016 annual average exposures. The results are from single-pollutant models that included adjustment for individual (e.g., body mass index, exercise) and neighborhood (e.g., Neighborhood Deprivation Index) characteristics. Source: Investigators' Report Appendix C Table C3.

Commentary Table 3. Associations Between Estimated Ambient Air Pollutant Concentrations and COVID-19 Transition States, Based on Single-Pollutant and Two-Pollutant Models[a]

	Ambient Air Pollutant					
	$PM_{2.5}$		NO_2		O_3	
Transition State	**Single-Pollutant Model**	**Two-Pollutant Model**	**Single-Pollutant Model**	**Two-Pollutant Model**	**Single-Pollutant Model**	**Two-Pollutant Model**
Hospitalization to deterioration	1.16 (1.12, 1.20)	NO_2: 1.11 (1.05, 1.17) O_3: 1.13 (1.09, 1.17)	1.19 (1.13, 1.24)	$PM_{2.5}$: 1.07 (1.00, 1.14) O_3: 1.21 (1.15, 1.26)	1.21 (1.13, 1.28)	$PM_{2.5}$: 1.13 (1.06, 1.21) NO_2: 1.24 (1.17, 1.32)
Hospitalization to recovery	1.00 (0.97, 1.03)	NO_2: 0.98 (0.94, 1.03) O_3: 1.01 (0.98, 1.03)	1.01 (0.97, 1.04)	$PM_{2.5}$: 1.02 (0.97, 1.08) O_3: 1.00 (0.97, 1.04)	0.96 (0.91, 1.00)	$PM_{2.5}$: 0.96 (0.91, 1.01) NO_2: 0.96 (0.92, 1.01)
Hospitalization to death	0.74 (0.51, 1.08)	NO_2: 1.00 (0.58, 1.73) O_3: 0.67 (0.45, 1.00)	0.60 (0.40, 0.90)	$PM_{2.5}$: 0.62 (0.32, 1.23) O_3: 0.59 (0.38, 0.92)	1.46 (0.87, 2.46)	$PM_{2.5}$: 1.68 (0.98, 2.90) NO_2: 1.39 (0.85, 2.28)
Deterioration to recovery	0.96 (0.92, 1.01)	NO_2: 0.90 (0.84, 0.96) O_3: 0.96 (0.91, 1.01)	1.03 (0.97, 1.09)	$PM_{2.5}$: 1.13 (1.04, 1.24) O_3: 1.03 (0.96, 1.10)	0.98 (0.91, 1.05)	$PM_{2.5}$: 1.00 (0.92, 1.08) NO_2: 0.98 (0.91, 1.05)
Deterioration to death	1.11 (1.04, 1.17)	NO_2: 1.14 (1.04, 1.25) O_3: 1.10 (1.04, 1.17)	1.07 (0.99, 1.16)	$PM_{2.5}$: 0.94 (0.83, 1.06) O_3: 1.08 (1.00, 1.17)	1.08 (0.98, 1.19)	$PM_{2.5}$: 1.03 (0.94, 1.14) NO_2: 1.11 (0.99, 1.23)
Recovery to death	1.10 (0.97, 1.24)	NO_2: 1.21 (0.99, 1.49) O_3: 1.07 (0.93, 1.23)	1.03 (0.86, 1.23)	$PM_{2.5}$: 0.85 (0.64, 1.13) O_3: 1.03 (0.86, 1.23)	1.24 (1.01, 1.51)	$PM_{2.5}$: 1.19 (0.95,1.48) NO_2: 1.27 (0.99, 1.61)

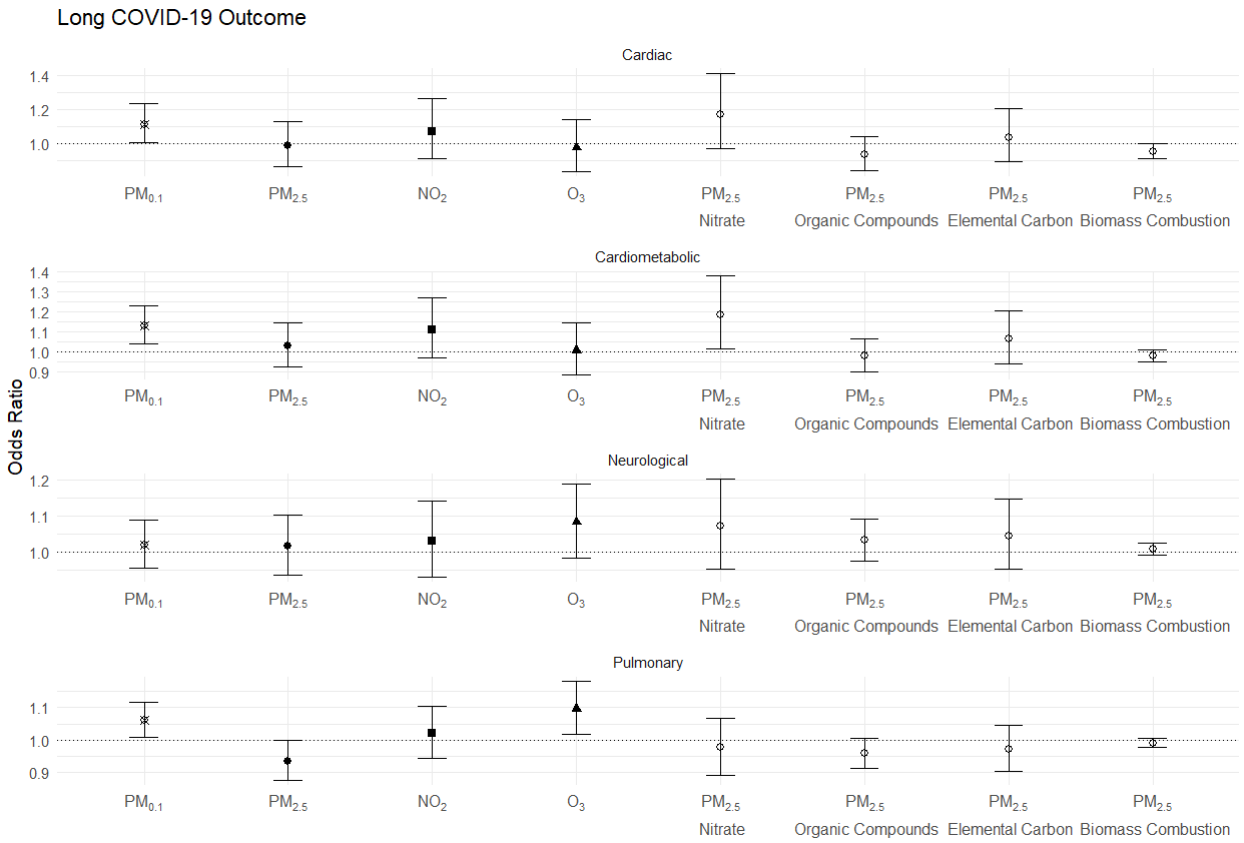
[a]Results shown are hazard ratios and 95% confidence intervals. Source: Investigators' Report Table 8.

than — the reported associations with long COVID-19 diagnosis within 3 months after discharge.

In two- or three-pollutant models, positive associations were only observed between short-term $PM_{0.1}$ exposures and cardiac, cardiometabolic, and pulmonary long COVID-19 outcomes, as well as between short-term O_3 exposures and pulmonary long COVID-19 outcomes, diagnosed within 3 months after hospital discharge. The association between estimated $PM_{2.5}$ exposure and pulmonary long COVID-19 became attenuated when controlling for O_3 exposure in two-pollutant models and when controlling for both O_3 and NO_2 exposure in three-pollutant models.

Additional Analyses

Kleeman and colleagues evaluated the effect modification by temperature and relative humidity on the association between ambient air pollutant exposures and COVID-19 deaths. In models stratified by temperature tertile, elevated risks of death were generally observed in the lower two tertiles of temperature (i.e., among patients exposed to lower mean monthly temperatures over the month before COVID-19 hospitalization), and no association was observed in the highest tertile of temperature (i.e., among patients exposed to the highest mean monthly temperatures over the month before COVID-19 hospitalization). For example, associations between estimated $PM_{2.5}$ exposure and COVID-19 death across tertiles of temperature ranged from an HR > 1.02 for tertile 1 (monthly mean temperatures of 5.90°C to 20.29°C) to an HR < 1.00 in tertile 3 (monthly mean temperatures of 22.20°C to 44.60 °C) (Investigators' Report Figure 12). A similar yet often more pronounced pattern was observed for associations between ambient air pollutant exposures and COVID-19 death across tertiles of relative humidity (Investigators' Report Appendix C Figure C1). These findings collectively



Commentary Figure 3. Associations between estimated short-term pollutant concentrations and long COVID-19 outcomes diagnosed within 3 months after hospital discharge in the Kaiser Permanente Southern California cohort. Results shown are odds ratios and 95% confidence intervals estimated per interquartile range increase in 30-day average pollutant exposures. The results are from single-pollutant models that included adjustment for individual (e.g., body mass index, exercise) and neighborhood (e.g., Neighborhood Deprivation Index) characteristics. Source: Investigators' Report Figure 18.

suggest that higher temperatures and higher relative humidity both weaken the association between ambient air pollutant exposures and COVID-19 death.

HEI REVIEW COMMITTEE'S EVALUATION

Overall, this study provided important contributions to understanding potential associations between chronic and short-term exposures to ambient air pollution and several COVID-19–related health outcomes. Kleeman and colleagues observed elevated risks of COVID-19 incidence and mortality, progression to more severe health states during COVID-19 hospitalization, and long COVID-19 outcomes among patients with elevated estimated exposure to several air pollutants. The investigators also found that both temperature and relative humidity modified associations between air pollutant exposures and COVID-19 mortality, with stronger associations observed at lower temperature and relative humidity and weaker associations observed at higher temperature and relative humidity. Chronic exposures to $PM_{2.5}$, NO_2, and O_3 were all associated with progression to more severe states of COVID-19, whereas short-term exposures to $PM_{0.1}$ were consistently associated with multiple types of long COVID-19 outcomes diagnosed within 3 months after discharge from the hospital.

In its independent evaluation of the Investigators' Report, the HEI Review Committee noted that the comprehensive set of analyses supported by high-resolution exposure estimates and individual-level electronic health records from a large healthcare database was a particular strength of the study. The Committee also thought that the findings were interesting and relevant, especially those related to the progression to more severe states of COVID-19 and long COVID-19 outcomes, which are outcomes that are not susceptible to bias from selective testing and diagnosis, the same way that COVID-19 incidence is.

The Committee commented that the findings were not wholly generalizable, given the population of hospitalized individuals that composed the main study cohort and the widespread immunity to COVID-19 that is now prevalent in the overall population. The Committee also noted that the strength of the investigators' conclusions, highlighting air pollution as a modifiable environmental risk factor that could be altered to improve the prognosis for patients with COVID-

19, might preferably be somewhat tempered in light of some of the limitations of this study. Overall, however, the study has provided valuable insights into the role of air pollution in exacerbating the severity of disease and adverse health outcomes, and these insights might be useful in the context of future infectious respiratory disease outbreaks.

The Committee noted several additional study strengths and limitations, which are highlighted below.

EVALUATION OF STUDY DESIGN, DATASETS, AND ANALYTICAL APPROACHES

The HEI Review Committee acknowledged several strengths of the study design, such as the generation of high-resolution chronic and short-term exposure estimates for multiple ambient air pollutants and the detailed speciated exposure estimates for $PM_{2.5}$ components, which had not been investigated in earlier studies on the effects of air pollution on COVID-19 outcomes. Another strength was assembling a main study cohort based on a large sample of individual-level electronic health records from a large integrated healthcare database that included data on all aspects of patient care, as well as many patient-specific demographic and clinical characteristics. The Committee also appreciated the exploration of the multistate COVID-19 health outcomes, long COVID-19 outcomes, and effect modification of observed associations by meteorology, all of which had not previously been rigorously explored in relation to air pollution and COVID-19 outcomes. In general, the Committee was impressed with the thorough examination of each aim, which was accomplished by conducting a strategically designed series of analyses.

The Committee noted a few limitations related to exposure assignment and some analytical approaches. The Committee thought that the use of different exposure models (i.e., LUR modeling versus CTM approaches) to provide a quality check on the epidemiological results was sensible, although the influences of the differing exposure estimates on COVID-19 outcomes were explored only in the analysis of CDPH data for Los Angeles County (Aim 2). It would have also been interesting to explore the impact of modeling differences in some of the analyses of the KPSC cohort.

The Committee also wondered whether the differences in temporality across analyses might have influenced the results; specifically, chronic exposures were defined using average annual exposure estimates for 2016 in some analyses but for 2019 in other analyses. Similarly, Committee members wondered whether average exposures during the 30 days before hospitalization were the most appropriate length of time to define short-term exposures in the analyses of long COVID-19 outcomes. Other studies evaluating other COVID-19 outcomes, such as incidence, hospitalization, and death,[22–24] also have used 30-day average estimates of ambient air pollutant concentrations to represent short-term exposures, although it is unclear whether this choice was based on biological mechanisms or some other reason. Future work in this area could benefit from including additional sensitivity analyses to explore the effects of such nuances in defining short-term exposures, as well as the choice of the year for the annual averages used to represent chronic or long-term exposures.

Regarding some of the analytical methods used in this study, the Committee remained somewhat skeptical of the use of the Markovian assumption in the analysis of associations between air pollutant exposures and multistate health effects of COVID-19. This assumption presumes that the amount of time that a patient exists in any given state (e.g., hospitalization, deterioration to more severe COVID-19 states) does not influence their time spent in any other state. However, the Committee noted that it might be more reasonable to assume that, for example, a patient's progression from hospitalization to ICU admission and from ICU admission to death is, in fact, partially influenced by their time spent in prior states. They were curious about how the use of an alternative assumption or relaxation of the Markovian assumption (e.g., the use of a semi-Markov model in which the hazard depends on the time spent in the current state and thus affects the likelihood of transitioning to another state)[25,26] might have changed the results of this analysis. Although the investigators acknowledged this point, they noted that they were unable to characterize how time spent in one state would influence subsequent transitions, thus choosing to make the simplifying Markovian assumption.

The Committee noted that the investigators' choice of terminology at times created confusion in interpreting the study's findings. For instance, the term "effect" was used in a way that could imply causality, despite being intended as a measure of association.[27] Similarly, in analyzing associations between air pollutant exposures and COVID-19 incidence and deaths in Los Angeles County, the investigators used the word "synergy" to describe an independent effect rather than an interaction while also referring to synergy in the context of a statistical method for assessing multiplicative interactions on an additive scale.

EVALUATION OF FINDINGS AND INTERPRETATION

The Committee generally agreed with the presentation and interpretation of the findings in this study. Kleeman and colleagues reported positive associations between chronic air pollutant exposures and COVID-19 incidence, progression to more severe states of COVID-19 during hospitalization, and death. They also reported positive associations between chronic and short-term air pollutant exposures and several long COVID-19 outcomes (i.e., cardiac, cardiometabolic, and pulmonary conditions). The elevated risks of COVID-19 incidence and mortality demonstrated by the investigators are largely consistent with the findings of other studies using the KPSC database.[22,23] Other HEI-funded studies using individual-level data from Denmark[28] and Spain[29] also have demonstrated elevated risks of COVID-19 mortality associated with $PM_{2.5}$ and NO_2; however, those studies both reported inverse associations between COVID-19 mortality

and O_3, whereas this study reported a positive association for this relationship in the CDPH cohort and no association in the KPSC cohort. The Committee noted that the inconsistency in the findings on the association between O_3 exposure and COVID-19 mortality in the CDPH data versus the KPSC cohort was unexpected, especially given the strength of the reported associations between O_3 exposure and other COVID-19 outcomes examined in this study. This inconsistency might be due to differences in the spatial scale of the data (i.e., ZIP code–level data in the CDPH data versus individual-level data in the KPSC cohort). Interestingly, another study using the KPSC database also found no association between long-term O_3 exposure and COVID-19 mortality,[23] and a different study that analyzed KPSC data reported a positive association between long-term O_3 exposure and COVID-19 incidence.[24] However, differences in the specific air pollutants, exposure definitions, and COVID-19 outcomes examined across such studies limit the ability to directly compare their results.

Looking beyond the COVID-19 pandemic, the investigators noted that their findings have broader implications for future infectious disease outbreaks. They indicated that their results suggest that reducing air pollution exposures could lead to decreased incidence of infections, less severe outcomes, and, potentially, a reduction in the development of post-acute conditions. The Committee agreed that the findings provide useful insights into the role of air pollution in adverse health outcomes; furthermore, the Committee concurred that their insights can be applied to future outbreaks involving novel infectious respiratory diseases and contribute useful information regarding both the progression of such diseases to more severe states of illness and the development of post-acute conditions. The Committee noted that the results of this study are most relevant for severe COVID-19 outcomes, as many of the analyses were conducted using a cohort of hospitalized patients (i.e., those severely ill with COVID-19) — a limitation that was appropriately acknowledged by the investigators. Additionally, the Committee wondered how the findings might translate to the current general population that is either largely vaccinated against COVID-19 or has obtained natural immunity through prior disease. Kleeman and colleagues also discussed the generalizability of their findings to the current population, which has much lower rates of severe disease, as an area that merits further research. Nonetheless, the Committee generally thought that the results might be relevant and applicable in the setting of a new respiratory disease to which the population has no immunity.

The investigators also referred to vaccine hesitancy among certain populations and in some locations as a motivation for studying modifiable environmental risk factors (e.g., air pollution). Throughout the report, they noted the importance of preventive measures that target such modifiable exposures. The Committee agreed that studying the complex interplay between air pollution and COVID-19 is worthwhile. However, the role of air pollution and other environmental risk factors should be viewed as one component that can be targeted alongside multiple other public health and preventive measures pertinent to future infectious respiratory disease outbreaks, but likely not as a solution to address vaccine hesitancy.

The Committee had additional thoughts on some other specific results of this study. The Committee appreciated the exploration of effect modification by temperature and relative humidity on the association between air pollutant exposures and COVID-19 mortality, which remains understudied in the context of air pollution and COVID-19. Kleeman and colleagues reported that both higher temperature and higher relative humidity weakened the associations between exposures to most of the examined air pollutants and risk of death due to COVID-19. The investigators further posited that this finding might be biologically plausible if cooler and less humid conditions interfere with viral defenses in the human nose. The Committee noted that these results could partially reflect seasonality (i.e., the variations in infectious disease that coincide with seasonal patterns throughout the year), which the investigators acknowledged might have generally affected their findings in this analysis. Although focused on transmission and infection, some studies in China that have explored the relationship between meteorology, air pollution, and seasonal influenza have also shown effect modification by temperature and humidity, with higher temperature and higher humidity being associated with decreased risk of influenza transmission and infection.[30,31]

In analyses of air pollutant exposures and multistate COVID-19 health effects, Kleeman and colleagues found that exposure to air pollution was positively associated with progression to more severe states or outcomes, such as admission to the ICU, death after deterioration to more severe states, and death after recovery and discharge from the hospital (only for chronic exposure to O_3). The investigators noted that these results corroborate their earlier findings regarding COVID-19 deaths and further underscore that the results imply that air pollution could affect both COVID-19 severity and a healthy recovery among patients discharged from the hospital. Although the Committee generally found these conclusions to be reasonable and commended the investigators on their exploration of multistate COVID-19 outcomes, the Committee wondered how greatly the use of a Markovian assumption (as previously described) influenced the direction and magnitude of the observed associations.

The Committee found the analyses of associations between air pollutant exposures and long COVID-19 outcomes especially interesting. Kleeman and colleagues highlighted their results on long COVID-19 as potentially the most important findings of their study and noted that long COVID-19 continues to affect more than 6% of the US population, with implications for individuals and the public health system more broadly.[32–34] Indeed, in a recent review, researchers described the difficulties in studying and managing long COVID-19, given the range and severity of health impacts and the ongoing questions related to biological mechanisms, treatment efficacy, and susceptibility.[35] Other research has

demonstrated that long COVID-19 outcomes might be associated with the severity of COVID-19 and the recurrence of infection.[36] The current study provides additional evidence that both the incidence and severity of long COVID-19 might be positively associated with air pollution.

The investigators reported elevated risks of cardiac, cardiometabolic, and pulmonary long COVID-19 outcomes associated with exposures to several air pollutants ($PM_{0.1}$, $PM_{2.5}$ nitrate, and O_3). Other studies assessing the relationship between air pollution and long COVID-19 have also found positive associations between several air pollutants and long COVID-19.[37-39] Whereas those other studies all reported positive associations between $PM_{2.5}$ and long COVID-19, Kleeman and colleagues observed no or inverse (for pulmonary long COVID-19 outcomes) associations between estimated $PM_{2.5}$ exposure and long COVID-19; after sensitivity analyses, however, the observed inverse association between estimated $PM_{2.5}$ exposure and pulmonary long COVID-19 outcomes was found to be null. The investigators suggested several areas for future research in this context, including the exploration of common biological mechanisms between air pollution health effects and long COVID-19, examination of these relationships in populations with different profiles of air pollution exposure, and evaluation of longer-term and ongoing air pollution exposures.

CONCLUSIONS

Overall, Kleeman and colleagues have provided evidence of associations between chronic and short-term exposures to air pollution and COVID-19 incidence and mortality, progression to more severe states of COVID-19, and long COVID-19 outcomes. The use of individual-level electronic health records from a large healthcare database and fine-scale exposure assessment were particular strengths of the study. Additionally, the investigators conducted novel analyses of associations between air pollutant exposures and multistate COVID-19 health effects and long COVID-19 outcomes and evaluated effect modification by temperature and relative humidity on associations between exposure to ambient air pollution and COVID-19 mortality.

Kleeman and colleagues reported elevated risks of COVID-19 incidence and mortality associated with exposures to $PM_{0.1}$, $PM_{2.5}$, some $PM_{2.5}$ components, and O_3 across neighborhoods in Los Angeles County based on data from the California Department of Public Health. Using a study cohort based on a large healthcare database, the investigators also reported elevated risks of COVID-19 mortality associated with all ambient air pollutants examined in the study, except for O_3 and some PM components, across Southern California. Furthermore, $PM_{2.5}$, NO_2, and O_3 exposures were all found to significantly affect the progression from hospitalization to more severe COVID-19 states (i.e., admission to the ICU or need for ventilation), whereas exposure to $PM_{0.1}$ was most consistently associated with long COVID-19 outcomes. Certain methodological choices, such as the use of a Markovian assumption in the multistate health effects model, might have affected some of the reported findings.

Ultimately, this study presents findings from a comprehensive set of analyses that contribute both new and corroborating evidence of associations between air pollution and COVID-19 health outcomes. The study is the fifth and final in a series of HEI-funded studies investigating the association between air pollution and COVID-19. The designs of these studies differ with regard to the assessed exposures, the COVID-19 outcomes investigated, and the analytical approaches. Nonetheless, the resulting body of work published thus far generally demonstrates elevated risks of COVID-19 mortality associated with several ambient air pollutants, including $PM_{2.5}$ and NO_2. Although the results of this study by Kleeman and colleagues might not be generalizable to the broader US population because the current general population has now gained some form of natural or vaccine-induced immunity to COVID-19, the findings provide valuable insights into the potential role of air pollution in the risk of adverse health outcomes that might be relevant to future infectious respiratory disease outbreaks. However, although air pollution is an important modifiable environmental risk factor, efforts to improve air quality as a strategy for reducing health risks should be viewed as one part of a compendium of public health and preventive measures targeting future outbreaks.

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