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Ambient Air Pollution and COVID-19 in California

Michael Kleeman, Claudia Nau, Jason Su, Deborah R. Young, Rebecca Butler, Lin-Syuan Yang, Christina Batteate, Sarah Eng, Richard T. Burnett, and Michael Jerrett

INCLUDES A COMMENTARY BY THE INSTITUTE'S REVIEW COMMITTEE

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with a Commentary by the HEI Review Committee

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ABOUT HEI

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

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

HEI typically receives balanced funding from the US Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 390 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 275 comprehensive reports published by HEI, as well as in more than 2,500 articles in peer-reviewed literature.

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

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

ABOUT THIS REPORT

Research Report 238, *Ambient Air Pollution and COVID-19 in California*, presents a research project funded by the Health Effects Institute and conducted by Dr. Michael Kleeman at the University of California, Davis, and colleagues. The report contains three main sections:

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

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

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

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

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

PREFACE

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

INTRODUCTION

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

Although there has been an enormous cost to this pandemic, both human and economic, it created unprecedented conditions that lent themselves to timely and novel air pollution research aimed at exploring policy-relevant topics, including key factors that contributed to changing patterns of air pollution over space and time, potential benefits to human health associated with such changes in exposures, and relationships between past or current exposures to air pollution and susceptibility to the effects of COVID-19 infections (Boogaard et al. 2021).

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

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

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

   The observed changes in air quality presented a unique opportunity for accountability research on this "natural experiment." HEI acknowledged that it could be difficult for investigators to find control populations not affected by the interventions; in addition, interventions in various locations occurred during different periods. Moreover, there would be challenges related to the major reorientating of healthcare systems to deal with COVID-19 and accompanying challenges in estimating comparable hospitalization rates and other health outcomes at a time when utilization of healthcare was changed and diagnostic criteria for COVID-19 and respiratory outcomes were also variable across time and space. Studies investigating health effects are needed to account for those kinds of changes.
2. **Susceptibility Factors:** Are individuals or populations who have been chronically or acutely exposed to higher levels of air pollution at greater risk of mortality from COVID-19 compared to those exposed to lower levels of air pollution? Do the potential effects differ by race or ethnicity or by measures of socioeconomic status?

   Limited evidence from the 2002–2004 SARS outbreak indicated a possible association between higher air pollution concentrations and higher-than-expected

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

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

STUDY SELECTION

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

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

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

Zorana Andersen of the University of Copenhagen and colleagues used a population-based nationwide cohort of 3.7 million Danish adults to investigate whether long-term exposure to air pollution is associated with increased risk of COVID-19-related morbidity and mortality and to identify the most susceptible groups by age, sex, socioeconomic status, ethnicity, and comorbidity (Andersen et al. 2023).

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

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

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

Cathryn Tonne of ISGlobal and colleagues are assessing whether long-term exposure to air pollution increased the risk of COVID-19 hospitalization and mortality in the general population of 5 million people in Catalonia, Spain, and whether short-term exposure to air pollution increased the risk of COVID-19 hospitalization after visiting the emergency department and mortality among the 300,000 people who tested positive for SARS-COV-2 during the study period (Tonne et al. 2024).

PROTOCOLS AND FUTURE DIRECTIONS

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

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

Investigator (institution)	Study or Report Title	Location	Study Design and Population	Theme	Final Report Published
Zorana Andersen (University of Copenhagen)	Long-Term Exposure to Air Pollution and COVID-19 Mortality and Morbidity in Denmark: Who Is Most Susceptible?	Denmark	Cohort Study: Population-based nationwide cohort of all Danes 40 years or older (N > 3 million)	Susceptibility	HEI Research Report 214, 2023
Kai Chen (Yale University)	Effect of Air Pollution Reductions on Mortality During the COVID-19 Lockdowns in Early 2020	China, Germany, Italy, and the United States	Time Series Study: Populations in 4 countries: China (Jiangsu Province), Italy, Germany, and the US (California)	Accountability	HEI Research Report 224, 2025
Michael Kleeman (University of California Davis)	Ambient Air Pollution and COVID-19 in California	California, United States	Cohort Study: Population-based cohort using a medical records database in Southern California from Kaiser Permanente	Susceptibility	HEI Research Report 238, 2026
Jeanette Stingone (Columbia University)	Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization Outcomes (REACH OUT Study)	New York City, United States	Cohort Study: Population-based cohort using harmonized electronic health records in NYC	Susceptibility	HEI Research Report 230, 2025
Cathryn Tonne (ISGlobal)	Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain	Catalonia, Spain	Cohort Study: Population-based regionwide cohort of 6 million residents of Catalonia, Spain	Susceptibility	HEI Research Report 220, 2024

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HEI STATEMENT

Synopsis of Research Report 238

Ambient Air Pollution and COVID-19 in Southern California

BACKGROUND

Exposure to air pollution has been linked with increased risks of influenza, respiratory syncytial virus, and other types of respiratory infection. Some epidemiological studies conducted early in the COVID-19 pandemic reported that rates of COVID-19 death were higher in areas with greater levels of air pollution, suggesting a possible association between air pollution and risk of death or poor health outcomes due to COVID-19. The early studies, however, had notable methodological shortcomings (e.g., a lack of high-resolution estimates of exposure or detailed information on individuals, such as socioeconomic status) and thus had a high potential for biased results. To investigate the potential associations between air pollution, COVID-19, and human health further, HEI funded five studies in various countries in the fall of 2020. This Statement highlights a study conducted by Dr Michael Kleeman and colleagues at the University of California, Davis.

APPROACH

The investigators used two sources of health data, one from the California Department of Public Health (CDPH) and the other from the Kaiser Permanente Southern California (KPSC) healthcare system, from June 2020 through January 2021. The CDPH data included information on about 773,000 COVID-19 cases and 14,000 deaths due to COVID-19 across 308 ZIP codes in Los Angeles County. The KPSC cohort consisted of more than 20,000 adult patients in Southern California who were diagnosed with COVID-19 and hospitalized within 21 days of a positive COVID-19 diagnosis or test, and this dataset contained detailed information on patient characteristics and all aspects of patient care.

Two different approaches were used to estimate outdoor air pollutant concentrations. The investigators used both an advanced chemical transport model and a land use regression sta-

What This Study Adds

- This study evaluated associations between estimated outdoor air pollution concentrations and risk of COVID-19 disease, COVID-19 disease progression or recovery, deaths due to COVID-19, and long COVID-19 conditions among a study population in Southern California.
- The study used administrative data from the state of California and a cohort of hospitalized patients with COVID-19 from a large healthcare system, combined with high-resolution estimates of outdoor air pollution concentrations calculated using chemical transport and statistical land use regression models.
- Kleeman and colleagues found that increased risk of COVID-19 death was associated with estimated annual average exposures to ultrafine particulate matter, fine particulate matter, and several specific components of fine particulate matter; however, their findings on associations between ozone exposure and COVID-19 death in the administrative and healthcare system datasets were inconsistent.
- Exposures to several pollutants were also associated with progression from hospitalization to more severe COVID-19 illness and with several long COVID-19 outcomes.
- The findings from this study provide useful insights into how air pollution might contribute to adverse COVID-19 health outcomes, and these insights might apply to future respiratory infectious disease pandemics. However, the findings reported here likely only apply to individuals who become severely ill, requiring hospitalization.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Michael Kleeman at the University of California, Davis, and colleagues. Research Report 238 contains the detailed Investigators' Report and a Commentary on the study prepared by the HEI Review Committee.

tistical model to produce highly refined estimates of daily outdoor concentrations of ultrafine particulate matter, fine particulate matter, fine particulate matter components, nitrogen dioxide, and ozone at multiple spatial resolutions for 2016, 2019, and 2020. Average long-term (annual) and short-term (30-day) exposure estimates were linked to ZIP codes for the CDPH data and patients' residential addresses in the KPSC cohort.

Kleeman and colleagues used various regression modeling approaches to evaluate associations between both single- and multipollutant air pollution exposures and COVID-19 outcomes. To analyze outcomes regarding COVID-19 cases and deaths in the CDPH data, the investigators used negative binomial models with adjustment for ZIP code-level demographic and socioeconomic factors. For the KPSC cohort, they used Cox proportional hazards models to analyze outcomes of patient deaths and multistate survival modeling to analyze outcomes related to patients transitioning to recovery or more severe states of illness (i.e., admission to intensive care, needing ventilation, or death). The investigators also evaluated whether weather (temperature and relative humidity) influenced the effect of long-term outdoor air pollution exposures on the risk of COVID-19 death. Additionally, they used logistic regression to analyze long COVID-19 outcomes 3 months and 12 months after discharge from the hospital in the KPSC cohort.

KEY RESULTS

Air Pollution Exposure Estimated outdoor air pollution exposures varied across the different types of analyses and statistical methods used in the study. The range of estimated average long-term (annual) air pollutant exposures in Southern California was around 9–13 μg/m^3 for fine particulate matter, 13–22 parts per billion for nitrogen dioxide, and 55–66 parts per billion for ozone. In general, the statistical model produced higher estimates of nitrogen dioxide exposure around Los Angeles than did the chemical transport model; these models also produced different estimates of where exposures to fine particulate matter were highest in southern California. For most of the analyses in this study, the investigators used outdoor air pollution concentrations estimated using the chemical transport model.

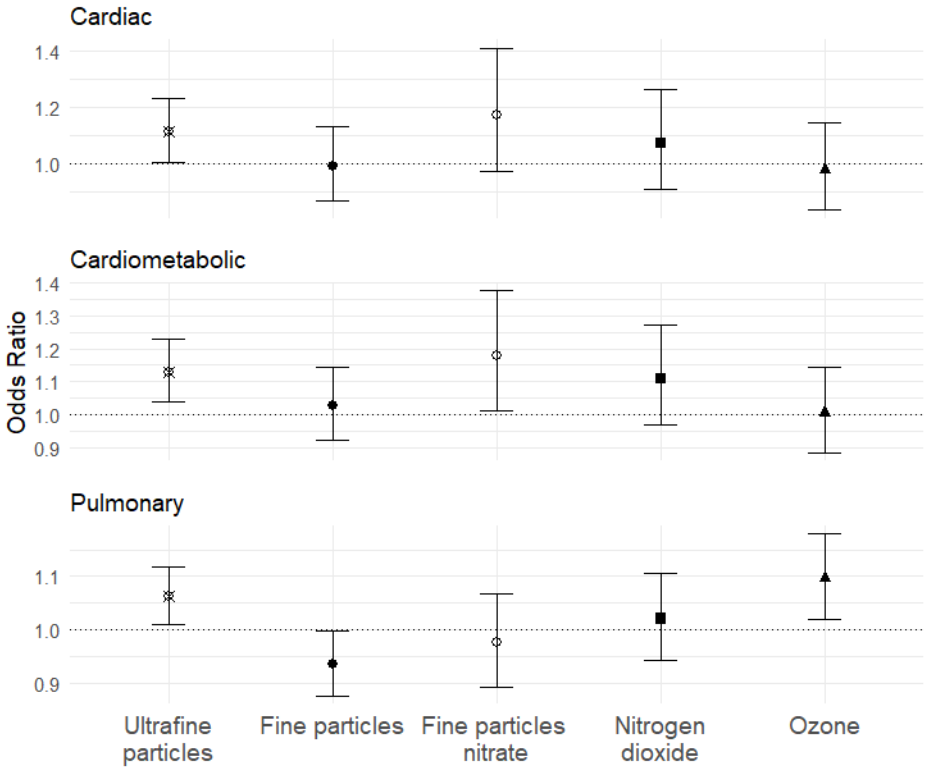
COVID-19 Cases and Deaths In the CDPH dataset, Kleeman and colleagues observed that higher estimated exposures to ultrafine particulate matter, fine particulate matter, and some of its components, and ozone were associated with elevated risks of COVID-19 incidence and death, with the strongest risks being associated with ozone concentrations. The two-pollutant models showed slightly elevated risks of both COVID-19 incidence and death associated with most combinations of these pollutants. In the KPSC cohort, the investigators observed that elevated risks of COVID-19 death were associated with exposures to most particulate matter pollutants and nitrogen dioxide but not with ozone; the risk estimates for fine particulate matter and nitrogen dioxide generally remained elevated in two-pollutant models. The investigators found that higher temperatures and higher relative humidity levels weakened the associations between long-term air pollutant exposures and risk of COVID-19 death.

Transition to More Severe COVID-19 States Greater estimated long-term exposures to fine particulate matter, nitrogen dioxide, and ozone were associated with higher risks of progressing to more severe COVID-19 illness. Greater estimated long-term exposures to fine particulate matter were also associated with higher risks of progressing from more severe COVID-19 illness to death. Across these three pollutants, the risk of deterioration (defined as a patient progressing from hospitalization to needing ventilation or intensive care) associated with the highest (versus the lowest) level of exposure increased by as much as 16% to 21%, depending on the pollutant. Among the analyzed associations between pollutant exposures and risk of transition to adverse COVID-19 outcomes, the strongest risk estimate was observed for the association between ozone exposure and transitioning from recovery after COVID-19 hospitalization to death. The two-pollutant models also demonstrated that exposures to fine particulate matter, nitrogen dioxide, and ozone were generally associated with elevated risks of transitioning from COVID-19 hospitalization to deterioration.

Long COVID-19 Higher estimated short-term exposures to ultrafine particulate matter, fine particulate matter nitrate, and ozone were associated with increased risks for long COVID-19 outcomes in the 3 months following discharge from the hospital (**Statement Figure**), including pulmonary, cardiometabolic, and cardiac outcomes, but not neurological outcomes. The strongest risk estimate per unit increase in estimated pollutant exposure was observed for the association between short-term particulate matter nitrate exposure and cardiometabolic long COVID-19. In two- or three-pollutant models, risk estimates for short-term ultrafine particulate matter exposures and long COVID-19 outcomes remained elevated (as did the risk estimate for short-term ozone exposure and pulmonary long COVID-19). Fewer positive associations were observed between short-term air pollution exposures and long COVID-19 outcomes in the 12 months following discharge from the hospital.

INTERPRETATION AND CONCLUSIONS

In its independent evaluation of the Investigators' Report on this study, the HEI Review Committee concluded that the study improved the level of understanding about associations between exposures to outdoor air pollution and adverse health outcomes of COVID-19. Specifically, the study demonstrated



Statement Figure. Associations between short-term air pollutant exposures and long COVID-19 outcomes occurring within 3 months after hospital discharge in the Kaiser Permanente Southern California cohort. These results from single-pollutant models show odds ratios and 95% confidence intervals estimated per interquartile range increases in pollutant exposure (estimated from the chemical transport model). Source: Adapted from Investigators' Report Figure 18.

that multiple air pollutants were associated with increased risks of COVID-19 incidence, death due to COVID-19, progression to more severe illness after a COVID-19 diagnosis, and long COVID-19 outcomes. The Committee especially appreciated that Kleeman and colleagues explored factors that had not previously been investigated in earlier studies, such as COVID-19 health outcomes specific to multiple different health states and long COVID-19 conditions, as well as the effect of weather on the outcomes of interest. The Committee also valued the use of individual-level health information obtained from a large healthcare system and the calculation of highly refined estimates of long-term and short-term exposures to multiple outdoor air pollutants, including specific components of fine particulate matter.

This study provided further evidence of an association between fine particulate matter, as well as nitrogen dioxide (only in the KPSC cohort), and an increased risk of death due to COVID-19. The findings contributed new information indicating that long-term exposures to fine particulate matter, nitrogen dioxide, and ozone each were associated with transitioning from COVID-19 hospitalization to deterioration to more severe illness, whereas short-term exposures to ultrafine particulate matter, fine particulate matter nitrate, and ozone were associated with several long COVID-19 outcomes. However, the ability to generalize the findings of this study to the broader population may be limited because the current population has now gained some form of natural or vaccine-induced immunity to COVID-19.

Overall, this study offers both additional evidence and new contributions that enable a better understanding of the relationship between outdoor air pollution and adverse health outcomes of COVID-19, thus providing valuable insights that might be relevant to future outbreaks of other infectious respiratory diseases. Importantly, although air pollution is an important modifiable environmental risk factor, efforts to improve air quality as a means of reducing health risks should be viewed as part of a broader collection of public health and prevention measures aimed at reducing the adverse health effects of future outbreaks.

INVESTIGATORS' REPORT

Ambient Air Pollution and COVID-19 in California

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ABSTRACT

Introduction As of December 2023, more than 6.9 million people globally had died from COVID-19, including more than 1.165 million deaths in the United States. It is estimated that approximately 18.8 million people in the United States have experienced post-acute COVID-19 conditions, also known as post-acute sequelae of SARS-CoV-2 (PASC) or long COVID, in the first 3 years after the pandemic. Although some initial cases of long COVID have resolved, with the ongoing incidence of COVID-19, roughly 17.8 million persons in the United States continue to suffer from long COVID at the time of this writing.[1–3] Preliminary evidence early in the COVID-19 pandemic suggested that exposure to air pollution increased the likelihood of contracting COVID-19 and worsened outcomes for those who became ill. The validity of these findings was uncertain, however, as few studies used highly accurate exposure models incorporating individual-level data on patient characteristics and risk factors. Although the COVID-19 public health emergency has ended, the disease continues to pose substantial risks to individual and population health. At the time of this writing, nearly 35,000 individuals per week are hospitalized with COVID-19 in the United States, and the weekly number of COVID-19–related deaths ranges from 900 to 1,400.[4]

Methods In this study, we investigated relationships between ambient air pollution and COVID-19-related outcomes, including incidence, severity, mortality, and long COVID conditions. We used advanced models to estimate exposures, incorporating numerous air pollutants, particle species, and wildfire emissions. We used administrative COVID-19 data and several cohorts of patients from a large health system, and each was formed to evaluate different hypotheses.

Daily air pollution exposures for Southern California were estimated with high spatial and chemical resolution, using a combination of land use regression and chemical transport models for the years 2016, 2019, and 2020. Exposure variables included ozone (O_3*), nitrogen dioxide (NO_2), fine particulate matter (PM) ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$mass), ultrafine PM ≤0.1 µm in aerodynamic diameter ($PM_{0.1}$), and major sources or chemical components of PM in each size fraction. Exposures for multiple study populations were investigated using statistical analysis methods to test for associations with COVID-19–related outcomes, including the following:

- COVID-19 cases (N = 773,374) and deaths (N = 14,311), by age, race, and sex, for 308 ZIP codes in Los Angeles County between June 19 and January 3, 2021. A negative binomial regression was performed for both individual and multiple ambient air pollutants to evaluate their associations with COVID-19 incidence and mortality.
- Patients with COVID-19 who were admitted to Kaiser Permanente Southern California (KPSC) hospitals between June 1, 2020, and January 30, 2021 (N = 21,415). Cox proportional hazards models were used to evaluate associations between ambient air pollutant exposure and COVID-19 mortality. A subset was of KPSC patients with COVID-19 who received care exclusively in KPSC hospitals (N = 15,978). A multistate survival model was used to examine how air pollution affects the transition to recovery or deterioration to more severe COVID-19 states (e.g., intensive care admission or death). A subset was of KPSC patients with COVID-19 who maintained membership with KPSC for 1 year after hospital discharge (N = 12,634). We combined a set of 45 diagnoses of post-acute sequelae of SARS-CoV-2 (PASC) into categories based on organ systems and then studied a subset of these PASC categories that could be affected by air pollution, including cardiac, cardiometabolic, pulmonary, and neurological conditions. Logistic regression was used to evaluate associations

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

between 30-day air pollution exposure before hospital admission and PASC conditions diagnosed at 3 months and 12 months post-discharge.

Results $PM_{0.1}$, O_3, NO_2, and $PM_{2.5}$ elemental carbon exposures were identified as risk factors for COVID-19 incidence and mortality in the general population of Los Angeles County. Air pollution exposures were also significantly associated with COVID-19 mortality in the cohort of hospitalized KPSC patients, controlling for other individual health risks. Incremental increases equivalent to the interquartile range for several pollution exposure concentrations were significantly associated with increased mortality, including $PM_{2.5}$ mass (hazard ratio [HR], 1.12), $PM_{0.1}$(HR, 1.06), $PM_{2.5}$ nitrate (HR, 1.12), $PM_{2.5}$ elemental carbon (HR, 1.07), $PM_{2.5}$ on-road diesel (HR, 1.06), and $PM_{2.5}$ on-road gasoline (HR, 1.07). Humidity and temperature in the month of diagnosis were significant negative predictors of COVID-19 mortality and negative modifiers of the air pollution effects. Results of the multistate analysis were consistent with these findings and further suggested that O_3, NO_2, and $PM_{2.5}$ each were associated with deteriorating health states. Increased $PM_{2.5}$ concentration was associated with increased risk of deterioration to both intensive care admission (HR, 1.16) and death (HR = 1.11). Effects of O_3 were similar to those of $PM_{2.5}$, but O_3 also affected the transition from recovery to death (HR, 1.24). Several air pollutants — particularly O_3, $PM_{0.1}$, and $PM_{2.5}$ nitrate — were significantly associated with several long COVID outcomes, including cardiac, cardiometabolic, and pulmonary conditions.

Conclusions Broadly, we concluded that several common air pollutants are associated with COVID-19 incidence, mortality, and progression to more severe states of illness, including long COVID conditions. Air pollution is a modifiable environmental risk factor that could be altered to improve the prognosis of COVID-19, thereby also reducing the public health impacts of coronaviruses now and in the future. This is particularly important for preventing long COVID, as evidence suggests that PASC conditions can occur even in vaccinated individuals. Given that 10% to 30% of individuals with COVID-19 will experience some form of PASC, which can have lifelong debilitating effects,[5] the importance of addressing modifiable environmental risk factors, such as air pollution, cannot be underestimated. A recent *Lancet* editorial noted that societal investment in understanding the pathogenesis of long COVID and preventive measures has lagged well behind the levels needed to effectively treat and mitigate this complex disease.[6] Our research focused mostly on hospitalized patients, but it also included one study on the general population effects. The results of both analyses were generally concordant, although our most important findings likely apply only to patients hospitalized with COVID-19.

CHAPTER 1: INTRODUCTION AND OUTLINE

The COVID-19 pandemic represents one of the largest threats to population health in more than a century. As of December 2023, more than 690 million people worldwide had been diagnosed with COVID-19, resulting in more than 6.9 million deaths.[7] As of 2023, nearly 35,000 individuals per week are hospitalized with COVID-19 in the United States, and the weekly number of COVID-19–related deaths ranges from 900 to 1,400.[160] Moreover, many of those affected will experience post-acute sequalae of SARS-CoV-2(PASCs), also known as long COVID, a condition that affects approximately 10% to 30% of patients with COVID-19.[5] Earlier conservative estimates suggested that roughly 65 million people globally suffer from long COVID,[5] and the most recent research indicates that long COVID has affected some 18.8 million people in the United States alone.[1,2] In addition, more than 25% of those with long COVID experience activity limitations, which can affect their ability to work.[8,9] Due to inconsistent testing and various other factors, estimating the likely number of cases of long COVID is complicated. Despite a lack of accurate estimates of the number of cases of COVID-19, even a conservative calculation based on a 10% to 30% incidence of long COVID among hospitalized cases alone would indicate that 3,500–10,500 new cases of long COVID occur per week in the United States.

Although researchers have extensively investigated the etiology of acute COVID-19, there remain considerable uncertainties about how potential risk factors influence the incidence and severity of the disease, mortality, and the development of PASC conditions. Recent evidence from North America, Asia, and Europe implicates air pollution as a risk factor that affects the incidence, prognosis, and mortality rate of COVID-19.[10–23] Limited evidence based on small studies from Sweden and Saudi Arabia suggests that air pollution is a risk factor for developing long COVID; however, these studies were conducted in environments with very high or low exposure to air pollutants, raising questions about their generalizability.[140, 141]

Biologically plausible mechanisms suggest that exposure to air pollution may render people more susceptible to contracting COVID-19 and, furthermore, that once infection occurs, greater exposure to air pollution may worsen the prognosis.[24–28] For example, nitrogen dioxide (NO_2), a marker of traffic-related air pollution,[29,30] probably increases the risk of lung infections by impairing the function of alveolar macrophages and epithelial cells in the lungs.[31] Findings from epidemiological and toxicological studies align with a large body of research linking air pollution to risk of viral and bacterial respiratory infections,[17,32] chronic respiratory morbidities (e.g., asthma, chronic obstructive pulmonary disease, lung cancer),[33–35] hospitalizations,[31] and mortality.[36–38]

Our review of the literature on air pollution exposure and COVID-19 outcomes identified a limited number of studies that used individual-level data, controlling for potential confounders, to evaluate outcomes related to disease severity or mortality.[21,38–41] These studies were focused on the early phases of the pandemic, possibly resulting in lower statistical power due to a relatively small number of deaths. Some of the mortality studies used high-quality exposure estimates, but none assessed the contribution of particle sources or ultrafine particle concentrations. Also, none of these studies examined interactions between air pollution and meteorological variables, such as temperature and humidity.

This study makes several contributions to the literature. Specifically, we expanded the evidence base by using a large sample of individual data, a longer study period than found in existing studies, exposure models capable of assessing particle species and sources, and meteorological variables (Chapter 5). We also employed a multistate model (Chapter 6). No previous studies have used a multistate model to examine the progression to more severe states of disease and the likelihood of recovery from acute COVID-19 during and after hospitalization. Moreover, only limited evidence on potential associations between air pollution exposures and long COVID exists; as previously described, the two existing well-conducted studies have several limitations (e.g., small sample size, inaccurate characterization of exposures, and questionable representativeness of the high and low exposure profiles), highlighting the need for further research on this disease that poses a large threat to public health. Here we address such limitations in existing studies on long COVID by incorporating a larger sample from an area with air pollution exposures more typical of those observed in the United States and Europe, a speciated exposure model, and specific time windows of exposure (Chapter 7). More generally, few existing studies of COVID-19 severity or mortality or long COVID have attempted to comprehensively estimate air pollution exposures that incorporate different particle physicochemical species and sources.

In this context, we addressed several central research objectives. Firstly, we assessed whether greater air pollution exposures led to increased risk of COVID-19 incidence and death among confirmed COVID-19 cases in a population sample from Southern California. This study is built on previous evidence[42] but expanded the analysis with speciated and source-specific particle estimates using individual-level health data. Secondly, we assessed associations between a wide array of air pollution estimates and mortality among patients in the Kaiser Permanente Southern California (KPSC) health system (which has an excellent electronic health records [EHR] system) who were hospitalized with COVID-19 across Southern California. In a novel addition to previous research, we also investigated the impact of temperature and humidity as both a direct risk factor and a modifying influence on the health effects of air pollution. We extended this analysis with a multistate investigation of how air pollution influenced the progression of COVID-19 to recovery, more

severe states of illness (i.e., admission to an intensive care unit), and death, as well as the progression from recovery to death. Lastly, we investigated the relationship between air pollution exposure and long COVID in a subcohort of the KPSC data.

CHAPTER 2: SPECIFIC AIMS AND GENERAL APPROACH

Stated generally, we hypothesized that air pollution exposures could increase the risk of COVID-19 infection, progression from COVID-19 to more severe states of illness, and death due to COVID-19. We also hypothesized that air pollution would increase the risk of developing PASC conditions, or long COVID.

Beyond the introductory chapters (Chapters 1 and 2), this report is organized into the following sections: exposure modeling (Chapter 3), population health impacts of air pollution on COVID-19 incidence and mortality in Los Angeles (Chapter 4), associations between air pollutants, meteorology, and COVID-19 mortality (Chapter 5), multistate analysis of the relationship between air pollution exposure and progression from COVID-19 to more severe states of illness (Chapter 6), long COVID in relation to air pollution exposures (Chapter 7), and a concluding chapter synthesizing important findings and emphasizing public health implications (Chapter 8). Except for Chapter 8, all chapters are written as stand-alone components of the study to enhance readability. Our central aims and hypotheses are outlined below.

AIM 1: DEVELOP CHRONIC AND SUBCHRONIC AIR POLLUTION EXPOSURE FIELDS

Exposure fields were developed for periods before the COVID-19 pandemic (2016 and 2019) to analyze the effects of chronic air pollution and for a period during the pandemic (2020) to analyze the effects of shorter-term (subchronic, 30-day) changes in air pollution concentrations. The subchronic exposure fields accounted for both modified behavior patterns (traffic, air travel, restaurant dining) during the pandemic and the exceptionally severe wildfire season in 2020. Our original intention was to test whether any of the air quality changes were associated with COVID-19 incidence, severity, and mortality. The majority of cases of COVID-19, however, occurred late in the year, when air pollution patterns had largely returned to their historical norms. The low case count during periods of altered air pollution reduced the statistical power and caused other artifacts in the statistical analysis. Therefore, we had no testable hypotheses related to Aim 1, although the exposure fields associated with this aim are used in the subsequent aims.

AIM 2: HIGH-RESOLUTION SPATIAL ANALYSIS

The strength of the association between air pollution and COVID-19 outcomes can be artificially weakened by incomplete exposure estimates and inconsistent reporting of health outcomes across different jurisdictions nationwide. County-level estimates, for example, may reflect substantial errors regarding exposure, as air pollution can vary considerably within counties. Analyses that are specific to a smaller geographical area with a large population, consistent health reporting practices, and accurate pollution exposure estimates are more likely to detect an association between air pollution and COVID-19 incidence or mortality with greater precision than analyses specific to larger spatial units. Earlier studies in Los Angeles reported positive associations but lacked individual health data as well as data on particle species and sources. In this project, we quantified associations between air pollution and COVID-19 incidence and mortality by using high-resolution (e.g., 30-m to 1-km) spatial modeling of exposures to analyze data for 308 out of 584 ZIP codes in Los Angeles County that represented approximately 10 million residents, 773,374 cases of COVID-19, and 14,311 deaths due to COVID-19. This aim had one associated hypothesis:

- **Hypothesis 1:** Studies using high-quality data to assess air pollution and COVID-19 within small neighborhoods will detect associations more accurately than will national or statewide analyses, which would be subject to substantial case-ascertainment bias and exposure misclassification.

AIM 3: MORTALITY AND MULTISTATE HEALTH EFFECTS OF CHRONIC AIR POLLUTION EXPOSURE

We studied questions about mortality and progression to either more severe illness states or recovery in a cohort of patients with confirmed COVID-19 who were members of the KPSC health system. The EHRs for KPSC patients contain detailed demographic and health information for each patient. Multiple exposure models were used to cover a broad range of potentially relevant pollutants. This aim was associated with two hypotheses:

- **Hypothesis 2A**: Patients living in areas with higher chronic and subchronic air pollution exposures who are hospitalized with COVID-19 will be more likely to progress to serious illness requiring admission to the intensive care unit (ICU) or death than those living in lower pollution areas.
- **Hypothesis 2B**: Patients living in areas with higher chronic and subchronic air pollution exposures who were hospitalized with COVID-19 will be less likely to transition toward recovery and more likely to die than those living in lower pollution areas.

AIM 4: LONG COVID

Preliminary findings suggest that patients who recover from the acute effects of COVID-19 may experience PASC conditions known as long COVID. We studied the relationship between air pollution exposure and increased incidence of PASC conditions at 3 months and 12 months after discharge from the hospital. PASC conditions were defined as a set of 45 diagnoses described in detail by Tartof and colleagues.[43] We collaborated with a KPSC hospitalist to create clinically meaningful categories that group these 45 diagnostic codes by organ system. This aim had one associated hypothesis:

- **Hypothesis 3:** Exposure to air pollution will increase the risk of developing long COVID, or PASC conditions, in patients who have recovered from the acute effects of COVID-19.

Many of the aims and research hypotheses evolved as new information became available during the study. Most notably, because of very low case counts, we were unable to fully test hypotheses related to modified air pollution exposure during lockdown periods in the initial stages of the pandemic. By contrast, we were able to greatly expand the sophistication of the long COVID analysis by incorporating the outcomes of work performed at KPSC to define PASC conditions. Overall, the research summarized in this report was adapted to the dynamic environment of the COVID-19 pandemic to answer the most important research questions within the confines of the time and resources available for the project.

Research Roadmap[a]

Research Aim	Description of Methods
Aim 1: Generate exposure fields	
• Generate land use regression exposure fields	**Chapter 3:** Development of Chronic and Subchronic Exposure Fields / Methods / Land Use Regression Model
• Generate chemical transport model exposure fields	**Chapter 3:** Development of Chronic and Subchronic Exposure Fields / Methods / Chemical Transport Model **Appendix A. Supplemental Information for Chapter 3:** Development of Chronic and Subchronic Exposure Fields **Appendix E. Supplemental Information for Chapter 7:** Association Between Air Pollution and Post-Acute Sequelae of SARS-CoV-2
Aim 2: High-resolution spatial analysis	**Chapter 4:** Risks of Species-Specific Air Pollution for COVID-19 Incidence and Mortality in Los Angeles / Study Design and Methods
Aim 3: Multistate health effects of chronic and subchronic air pollution	**Chapter 5:** Air Pollution and Meteorology as Risk Factors for COVID-19 Mortality in Southern California / Materials and Methods **Chapter 6:** Air Pollution and Sequelae of COVID-19: A Multistate Analysis / Methods
Aim 4: Long COVID-19	**Chapter 7:** Association Between Air Pollution and Post-Acute Sequelae of SARS-CoV-2 (PASC)

[a]The term "synergy" refers to a joint effect that exceeds the additive effect expected from the individual items.[44] We use "synergism" to explain the cumulative risk index findings in Chapter 4. When the cumulative risk index is greater than the sum of the individual relative risks for single pollutants, we call this "synergism between pollutants." We use the term "interaction" to describe the influence of other meteorological variables on the slope of the concentration–response function for given air pollutants. The term "effect modification" is reserved for subgroup analyses in which the air pollution concentration-response function differs across certain subgroups, such as patients with obesity and patients with normal body weight. The terms "long COVID" and "PASC" are used interchangeably in the literature. In Chapter 7, after a general introduction that clarifies this interchangeability, we have largely used the term "PASC" as the predominant term in this report.

CHAPTER 3: DEVELOPMENT OF CHRONIC AND SUBCHRONIC EXPOSURE FIELDS

INTRODUCTION

Air pollution exposure fields can be estimated using ground-based monitoring data,[45] land use regression (LUR) models,[46] satellite observations,[47] chemical transport models (CTMs),[48] or data fusion techniques that combine these methods of estimation.[49] Each technique has strengths and weaknesses, depending on the nature of the target pollutant. Some pollutants have sharp spatial gradients and/or random time variability, whereas other pollutants are more uniformly distributed in space and time. Some pollutants are routinely measured at numerous locations, and others are measured only in the context of special studies. This complex exposure landscape involving various pollutants requires a combination of methods to span the full range of exposure variables that may be of interest in studying associations between air pollution and COVID-19.

In the present study, we generated air pollution exposure fields by using both LUR models to achieve high spatial resolution for traditional pollutants and CTMs to span a broad range of chemical species, particle size fractions, and source tracers. Each exposure field was produced with the maximum possible spatial resolution for that model for the entire KPSC service area and with daily time resolution for the years 2016, 2019, and 2020. The basic methods used to generate the exposure fields are summarized in the following sections. Additionally, this chapter presents the time-averaged results from the LUR model and CTM and compares overlapping pollutant-specific exposures predicted by both the LUR and CTM modeling approaches.

METHODS

LAND USE REGRESSION MODEL

In the land use regression (LUR) model, exposure fields for daily concentrations of NO_2 and fine particulate matter (PM) ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$mass) were developed using the deletion/substitution/addition algorithm.[46,50] This algorithm is an aggressive model search algorithm that iteratively generates polynomial generalized linear models based on the existing terms in the current "best" model and the following three steps: (1) a deletion step that removes a term from the model, (2) a substitution step replacing one term with another, and (3) an addition step that adds a term to the model. The search for the "best" estimator starts with the base model specified by "formula," which is typically the intercept model, unless the user requires a number of terms to be forced into the final model. Before searching through the statistical model space of polynomial functions, the datasets for a specific year and specific type (e.g., saturation or government continuous monitoring) are randomly assigned into v folds (or groups) of roughly equal numbers of observations in each fold. Data in one fold are used for validation, and data in the remaining folds are used for prediction or model training. This process is repeated v times, until all folds are used for validation. The polynomial within the search space that minimizes the cross-validated risk is selected as the prediction algorithm. The use of v-fold randomization out-of-sample cross-validation helped avoid model overfitting. We limited the predictors to linear terms (i.e., the maximum sum of powers in each variable was 1) and disallowed any interaction. Further, we modeled the repeated measures in our annual models to account for the fact that measurements for a given site could be taken multiple times during the training period.

CHEMICAL TRANSPORT MODEL

Chemical transport models (CTMs) predict pollutant concentration fields using fundamental equations based on conservation of mass, fluid mechanics, chemical kinetics, and thermodynamic equilibrium. The University of California, Davis/California Institute of Technology (UCD/CIT) airshed model used in this project was a reactive three-dimensional CTM predicting the evolution of gas- and particle-phase pollutants in the atmosphere in the presence of emissions, transport, deposition, chemical reaction, and phase change, as represented by **Equation 1**.

$$\frac{\partial C_i}{\partial t} + \nabla u \times C_i = \nabla K \nabla C_i + E_i - S_i + R_i^{gas}(C) + R_i^{part}(C) \cdot$$

(**Equation 1**)

where C_i is the concentration of gas- or particle-phase species i at a particular location as a function of time t; $\boldsymbol{u}$ is the wind vector; K is the turbulent eddy diffusivity; E_i is the emissions rate; S_i is the loss rate; R_i^{gas} is the change in concentration due to gas-phase reactions; R_i^{part} is the change in concentration due to particle-phase reactions; and R_i^{phase} is the change in concentration due to phase change.[51] Loss rates include both dry and wet deposition. Phase change for inorganic species occurs using a kinetic treatment for gas-particle conversion[52] driven toward the point of thermodynamic equilibrium.[53] Phase change for organic species is treated as a kinetic process, with vapor pressures of semivolatile organics calculated using the two-product model.[54]

The basic capabilities of the UCD/CIT model are similar to those of the Community Multiscale Air Quality model maintained by the US Environmental Protection Agency (EPA); however, the UCD/CIT model has several source apportionment features and higher particle size resolution, making it attractive for this project. The UCD/CIT model explicitly tracks the mass and number concentrations of particles in 15 discrete size bins, ranging from 10-nm to 10-μm, with tracer species used to quantify source contributions to the primary particle mass in each bin.

Further details of the UCD/CIT model, including the meteorological fields and emissions inventories used to drive the model, are provided in Appendix A. *Note: Appendices are available on the HEI website.*

Statistical Bias Correction The accuracy of CTM exposure fields is typically determined by the accuracy of the input data used to drive the CTM calculations and/or the completeness of the model formulation. Random errors and systematic errors that change with time and location are often present in concentration fields predicted by CTMs. Measurements can be combined with CTM predictions to improve the accuracy of the pollutant concentration fields while retaining the rich information describing multiple pollutants and source apportionment information that is inherent in CTM predictions. This fusion of measurements and model predictions can be especially valuable in the setting of wildfire events, which often produce extremely high exposure concentrations over limited periods of time. The statistical bias correction performed for the years 2016, 2019, and 2020 is described further below:

- **Year 2016:** For the exposure fields developed for 2016, the bias in CTM predictions at each monitoring location was combined with the CTM predictions for concentrations of both primary particles emitted from nine different source categories and secondary nitrate and sulfate PM to form a time series that was analyzed using multiple linear regression (MLR) based on **Equation 2**. An intercept was not considered in the regression equation, given the assumption that any constant bias introduced by abnormally high boundary conditions or underpredicted wind speeds would manifest as overpredictions in the indicated particle metrics. An intercept (i.e., constant bias) could potentially introduce overlap or "double counting" in the regression model formulation.

$$Bias = a1 \times Tracer1 + a2 \times Tracer2 + \cdots + a9 \times Tracer9 + a10 \times Nitrate + a11 \times Sulfate + a12 \times Ammonium$$

(**Equation 2**)

Here a_i represents regression coefficients; nitrate, sulfate, and ammonium are the concentrations of these chemical components in fine particles; and $Tracer_1$ represents the concentrations of primary fine particles emitted from (1) on-road gasoline vehicles, (2) off-road gasoline vehicles, (3) on-road diesel vehicles, (4) off-road diesel vehicles, (5) biomass combustion, (6) food cooking, (7) aircraft, (8) natural gas combustion, and (9) all other sources.

The time series from all 40 sites included in the study were combined into a single dataset with 452 data points to support the 12 independent variables in the regression analysis. Multiple MLR models were explored, with nonzero coefficients eventually selected for the source tracers for off-road gasoline vehicles, on-road diesel vehicles, biomass combustion, food cooking, and all other sources, as well as inorganic ions. A single set of regression coefficients was able to explain the bias, with an $R^2 = 0.82$ and a regression slope of 0.92.

The MLR bias equation (**Equation 3**) was applied to each CTM grid cell to predict the bias in CTM concentrations. The baseline CTM concentrations were then adjusted using the equation

$$Cbias_{corr} = Cbaseline \times \left(1 - \frac{bias}{Cbaseline}\right)$$

(**Equation 3**)

where $Cbias_{corr}$ is the bias predicted by the MLR Equation 2, and $Cbaseline$ is the original CTM prediction.

The corrected $PM_{2.5}$ mass concentrations had a mean fractional bias of 0.181, significantly improving the accuracy of the exposure fields in 2016. Further details of the improvements to CTM exposure fields for the year 2016 are presented in Appendix A.

- **Years 2019 and 2020:** In recent years, techniques such as data fusion and machine learning have been used to improve predictions of air quality. In this study, a random forest regression (RFR) technique was used to reduce bias in the $PM_{2.5}$ concentration predicted by the UCD/CIT source-oriented CTM for the years 2019 and 2020. RFR is a powerful statistical machine learning approach that has advantages over traditional methods, such as bias correction and MLR.[55–58]

Four major support elements were used in the current RFR approach: surface monitoring data from the US EPA and Purple Air, Moderate Resolution Imaging Spectroradiometer (MODIS) aerosol optical depth retrievals, meteorology data from the Weather Research and Forecasting model, and CTM results from the UCD/CIT model. The fractional bias values between UCD/CIT $PM_{2.5}$ variables and EPA daily average observations were calculated as training targets in the RFR approach. (Fractional bias is defined in Appendix Table E1.) Models for each month of the year were trained independently. The correction factor (*CF*) that can be applied to the $PM_{2.5}mass$ predicted by the UCD/CIT model is calculated in **Equation 4** as

$$CF_{PM_{2.5}mass} = (2 + FB_{PM_{2.5}mass}) / (2 - FB_{PM_{2.5}mass})$$

(**Equation 4**)

where *FB* is the fractional bias.

This training process used for $PM_{2.5}$ mass was also applied to five additional predicted concentrations, including $PM_{2.5}$ organic compounds (OC), $PM_{2.5}$ elemental carbon (EC), $PM_{2.5}$ ammonium, $PM_{2.5}$ nitrate, and $PM_{2.5}$ sulfate. Some of these species also appear as training support variables in Appendix Table E2. In these cases, the RFR training procedure was modified to remove the target variable from the list of training support variables. The final step of the RFR method involved calculating the mean correction factor based on the weighted fraction average of the correction factor values derived from the six sets of RFR training. This approach optimized improvements across all PM

variables. Further details of the improvements to CTM exposure fields for the years 2019 and 2020 are presented in Appendix E.

RESULTS

Both LUR and CTM exposure fields were produced with daily time resolution for the years 2016, 2019, and 2020. All exposure fields are available for download, as described in the Data Availability Statement. The following sections summarize some of the major spatial and temporal trends inherent in each exposure field. These fields were subsequently used for the epidemiological analyses conducted in this project.

LAND USE REGRESSION MODELS

Figures 1 and 2 show The seasonal average variation in LUR model predictions for exposure fields regarding NO_2 and $PM_{2.5}$ mass in Southern California, with 100-m spatial resolution in 2020. Predicted NO_2 concentrations were highest along transportation corridors, reflecting the predominance of emissions from mobile sources. By contrast, LUR model predictions for $PM_{2.5}$ mass concentrations were more uniform, peaking outside Los Angeles. Supporting information regarding the LUR model is provided in Appendix A.

CHEMICAL TRANSPORT MODELS

Figure 3 displays the annual average concentrations predicted by the CTM calculations for the year 2020, with 1-km spatial resolution. $PM_{2.5}$ mass concentrations peaked in the urban areas of Southern California and in the San Joaquin Valley surrounding Bakersfield to the north. Ultrafine PM ≤0.1 μm in aerodynamic diameter ($PM_{0.1}$) concentrations had sharper spatial gradients around major sources of emissions. Notably, predicted $PM_{0.1}$ mass concentrations peaked around military bases using aviation fuel with a higher sulfur content than that of commercial aviation fuel. The accuracy of these $PM_{0.1}$ concentration peaks has not been verified with ground-based measurements. As the population size in the affected zones is small relative to that of the major cities, however, the uncertainty regarding exposure in these zones is not expected to significantly influence the results of the epidemiological analysis. $PM_{2.5}$ EC is a primary pollutant that is mainly associated with diesel engines, and concentrations of this pollutant were predicted to be highest in urban centers with major transportation corridors. Spatial gradients for $PM_{2.5}$ EC were relatively sharp. $PM_{2.5}$ nitrate is a secondary pollutant with smoother spatial gradients. Predicted $PM_{2.5}$ nitrate concentrations were highest in the San Joaquin Valley north of Southern California, reflecting the high concentrations of precursor ammonia and oxides of nitrogen (NO_x). Predicted NO_2 concentrations were highest in urban centers and agricultural regions, where fertilized soils can emit NO_x. Ozone (O_3) concentrations predicted by the CTM were highest downwind of major urban centers, where diluted concentrations of NO_x and volatile organic compounds (VOCs) mix with biogenic VOCs, resulting in a VOC/NO_x ratio with maximum efficiency for forming O_3.

DISCUSSION AND CONCLUSION

$PM_{2.5}$ mass and NO_2 exposure fields were predicted using both LUR models and the CTM. The two independent approaches understandably produced different estimates. Both models predicted significant NO_2 concentrations over the city of Los Angeles, but the LUR model predicted higher concentrations than did the CTM. Given that statistical bias corrections were not applied to gas-phase species in the CTM calculations and that the monitoring network for NO_2 is quite dense in urban locations, the fine-grained details of NO_2 concentrations in urban Los Angeles are likely better represented by the LUR model. Regionally, the CTM predicted enhanced NO_2 concentrations in areas with significant agricultural activities. Fertilized soils release NO_x into the atmosphere, which can significantly increase concentrations of NO_2.[59] The CTM calculations included soil NO_x emissions, enhancing the predicted NO_2 concentrations in the San Joaquin Valley and the Imperial Valley. Fertilized soils were not a predictor of NO_2 concentrations in the LUR models.

$PM_{2.5}$ mass concentrations predicted by the LUR model peaked in the arid regions in the eastern portion of California, presumably reflecting the prevalence of windblown dust. By contrast, $PM_{2.5}$ mass concentrations predicted by the CTM peaked most strongly over Los Angeles and in the San Joaquin Valley north of Los Angeles. Predicted $PM_{2.5}$ concentrations from the CTM also showed hotspots corresponding to wildfire locations during the simulation period. The LUR model indirectly accounted for wildfires by incorporating satellite-observed aerosol optical depth as a predictor. The CTM used estimates of wildfire emissions from the Global Fire Emissions Database, which contains data based on satellite observations of burned areas. The degree to which plumes of wildfire emissions mix vertically varied in each model, leading to different estimates of the effect of wildfires on ground-level concentrations.

Overall, the level of agreement between exposure fields generated by the LUR model and the CTM model provides a quality control/quality assurance check on the results of epidemiological analyses conducted using those fields. Epidemiological results that are consistent across different exposure estimates are considered extremely robust, whereas epidemiological results that change depending on the method used to generate the exposure fields should be evaluated with additional sensitivity analyses to build confidence in the findings.

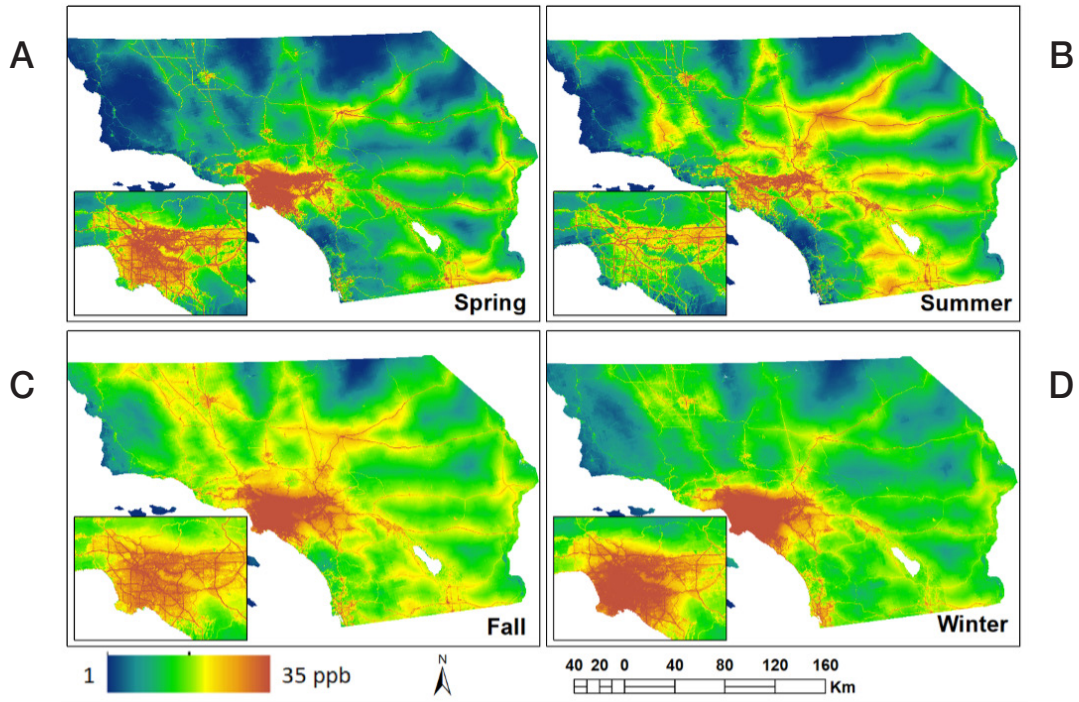


Figure 1. Seasonal average variation in NO_2 exposure fields predicted using the LUR model for Southern California, 2020. Exposure fields are presented for the spring (A), summer (B), fall (C), and winter (D). ppb = parts per billion.

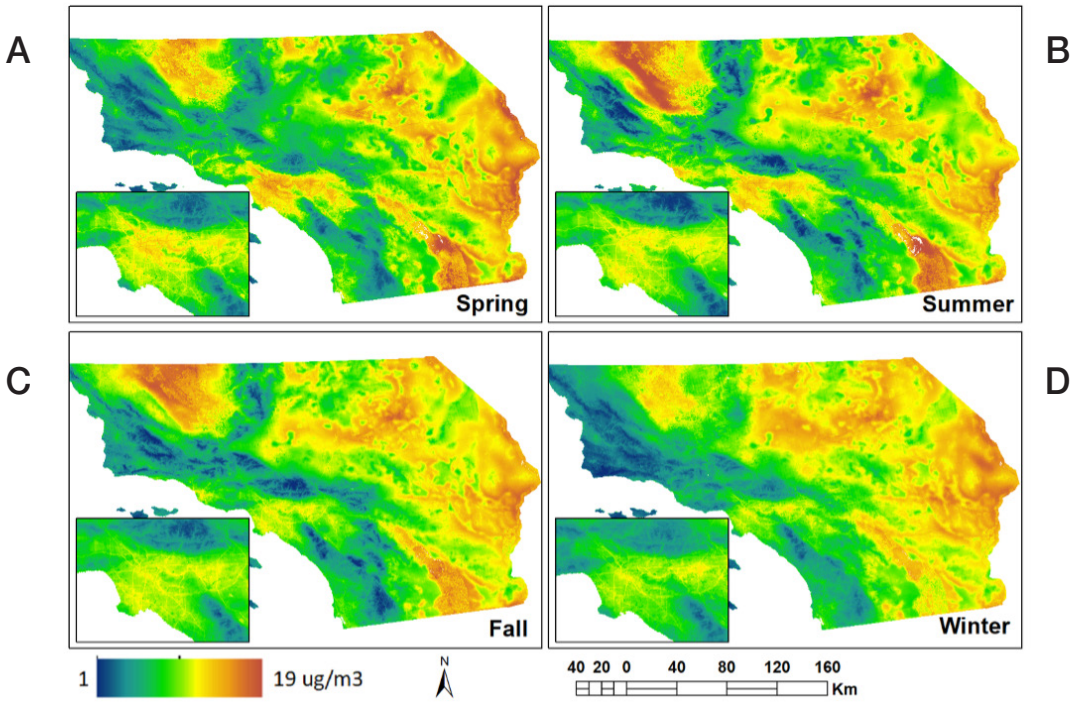


Figure 2. Seasonal average variation in $PM_{2.5}$ mass exposure fields predicted using the LUR model for Southern California, 2020. Exposure fields are presented for the spring (A), summer (B), fall (C), and winter (D).

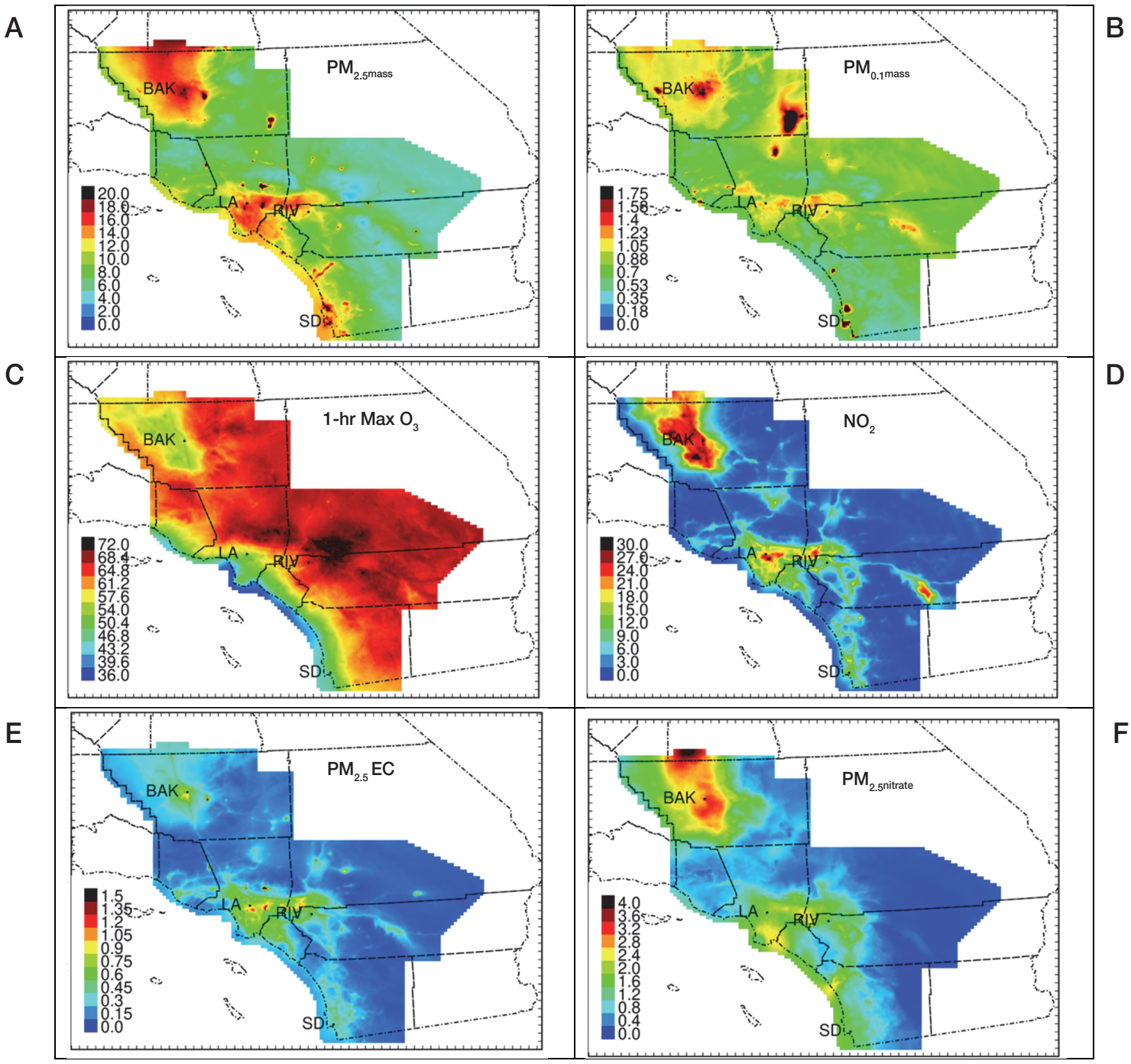


Figure 3. Annual average pollutant concentrations predicted by the CTM for Southern California, 2020. Concentrations are presented for $PM_{2.5}$ mass (A), $PM_{0.1}$ mass (B), 1-hour maximum O_3 (C), NO_2 (D), $PM_{2.5}$ elemental carbon (E), and $PM_{2.5}$ nitrate (F). All particulate matter species have units of $\mu g/m^3$, and all gas species have units of ppb. ppb = parts per billion.

CHAPTER 4: SPECIES-SPECIFIC AIR POLLUTION AS A RISK FACTOR FOR COVID-19 INCIDENCE AND MORTALITY IN LOS ANGELES

INTRODUCTION

COVID-19 caused over 6.9 million deaths worldwide during the period from the initial detection of the etiologic virus, SARS-CoV-2, in December 2019 to mid-2023.[60] These deaths associated with the COVID-19 pandemic occurred against a background of other disease-related burdens, including air pollution, which causes approximately 7 million excess deaths each year and was the fifth leading cause of global mortality in 2015.[47] Possible synergistic relationships between air pollutants and viral infection have been demonstrated in both ex vivo and in vitro studies, supporting the biological plausibility of interactions between air pollution and host defenses against viral infections.[61] For example, $PM_{2.5}$ penetrates deep into the respiratory system, where it can irritate the lung alveoli.[62] These injury pathways align with extensive evidence from epidemiological studies demonstrating associations between air pollution and risk of respiratory conditions, including asthma, pneumonia, chronic obstructive pulmonary disease (COPD), nasopharyngeal cancer, and lung cancer.[63–65] Additionally, a review of multiple cohort studies indicated that the excess risks of all-cause mortality per additional 10-μg/m^3 increment in long-term exposure to $PM_{2.5}$ and NO_2 were 6% and 5%, respectively.[66]

Ecological studies suggest that chronic exposure to air pollution exacerbates risks of COVID-19 incidence, severity, and mortality. Previous work has found that residential exposure to NO_2 was significantly associated with COVID-19 incidence, mortality, and fatality in Los Angeles.[67] In Italy, researchers identified significant correlations between COVID-19 case counts and 3-year (2017–2019) average levels of $PM_{2.5}$, PM ≤10 μm in aerodynamic diameter (PM_{10}), and NO_2 as well as the number of days exceeding the regulatory limits for O_3.[68] At the county level in the United States, COVID-19 mortality in 2020 increased by 8% per 1-μg/m^3 increase in $PM_{2.5}$.[69] Two studies involving hospitalized KPSC patients reaffirmed significant associations between both COVID-19 prognosis and mortality and long-term exposure to air pollutants, such as $PM_{0.1}$, $PM_{2.5}$ mass, and $PM_{2.5}$ on-road gasoline and diesel.[70]

Quantifying associations between air pollution exposures and COVID-19 outcomes is a complex task. Statistical models must adjust for confounding factors, including demographics, meteorological conditions, and socioeconomic status. Higher maximum daily temperature and relative humidity have been reported to modify associations between PM concentrations and death due to COVID-19.[70] Confounding effects of race, ethnicity, and income status on the relationship between air pollutants and COVID-19 outcomes also have been reported. A meta-analysis of 68 studies indicated that racial/ethnic minority populations with lower socioeconomic status had higher incidence rates and severity of COVID-19.[71] People of color and low-income communities are disproportionately exposed to $PM_{2.5}$ and NO_2 emissions from transportation and industrial sources.[63,72,73] Additionally, successive variants of SARS-CoV-2 have demonstrated different rates of transmissibility and mortality. For example, the Delta variant was approximately 60% more transmissible than the Alpha variant, which was considered highly infectious. In Scotland, the rise of the Delta variant of SARS-CoV-2 in late 2020 contributed to a higher risk of hospitalization for COVID-19, compared to the corresponding risk associated with the Alpha variant from April to May 2021.[74]

Although the relationship between criteria air pollutants (e.g., PM, NO_2, O_3) and COVID-19 outcomes has been widely discussed, there has been little study of associations between COVID-19 and specific air pollutant species at a fine spatial resolution (e.g., at the census tract or ZIP code level). In this study, we assessed the spatial and temporal associations between $PM_{0.1}$, $PM_{2.5}$ mass, $PM_{2.5}$ EC, $PM_{2.5}$ on-road gasoline and diesel vehicles, NO_2, and O_3 at the ZIP code level and the outcomes of COVID-19 incidence and mortality among the general population in Los Angeles County.

STUDY DESIGN AND METHODS

COVID-19 OUTCOME DATA

Daily numbers of COVID-19 cases and deaths in Los Angeles County were obtained from the California Department of Public Health (CDPH). To ensure consistency across SARS-CoV-2 variants, we targeted the period when the Delta variant was dominant. From June 19 to December 19, 2020, the Delta variant accounted for more than 50% of the COVID-19 cases in California.[70] Given the assumptions of a typical incubation period of COVID-19 and the majority of COVID-19–related deaths occurring 2 weeks after infection, we added a 2-week buffer after the period dominated by the Delta variant. Thus, the study period spanned from June 19, 2020, to January 3, 2021. Before its release by the CDPH, the COVID-19 dataset was initially aggregated by ZIP code and stratified by sex, age categorized by 10-year age groups, and race and ethnicity (including non-Latino White, non-Latino Black, non-Latino Asian, Latino/Hispanic, and other racial/ethnic groups). In accordance with the CDPH data use agreement safeguarding confidentiality, data for any ZIP code with a cumulative count less than 10 were suppressed. The

final dataset used for analysis included a total of 773,374 COVID-19 cases and 14,311 deaths that occurred during the study period in Los Angeles County.

EXPOSURE ASSESSMENT USING ANNUAL EXPOSURE FIELDS FOR 2019

Exposure fields for air pollutant concentrations across Southern California were simulated using the UCD/CIT CTM UCD/CIT, which predicts gaseous and particulate pollutant concentrations in the atmosphere on the basis of emissions, transport, deposition, chemical reactions, and phase changes.[75,76] The model calculations incorporate the emissions from nine major source categories to provide source apportionment estimates in the exposure fields. The CTM exposure fields of air pollutant concentrations for 2019 were estimated using a 1-km scale. The model calculates concentrations of all photochemical pollutants and incorporates explicit tracers for major pollutant sources, such as traffic. The daily exposure data, including 1-hour maximums for O_3 and daily averages for all other pollutants, were aggregated to an annual scale in the present study.

We used the 2019 annual mean pollutant concentrations as indicators to examine the relationship between chronic exposure to air pollution and COVID-19 cases and deaths that occurred during the ensuing study period. Pollutants analyzed in the study included $PM_{0.1}$, $PM_{2.5}$ mass, $PM_{2.5}$ nitrate, $PM_{2.5}$ EC, $PM_{2.5}$ on-road gasoline vehicles, NO_2, and 1-hour maximum O_3. $PM_{2.5}$ on-road gasoline vehicles, which is used to track contributions from gasoline-powered mobile sources, was assigned to emissions from the California Air Resources Board inventory that uses the on-road gasoline vehicle PM profile. PM concentrations were estimated in micrograms per cubic meter ($\mu g/m^3$), and gaseous pollutants were estimated in parts per million by volume (ppm).

To specify the difference in associations attributed to exposure modeling methodologies, we also generated exposure fields of air pollutant concentrations using an LUR for the 2019 annual mean concentrations of $PM_{2.5}$ ($\mu g/m^3$) and NO_2 (ppm). The LUR model applied the deletion/substitution/addition machine learning algorithm to account for approximately 600 covariates, such as traffic, land cover, and distance to roadways at different Euclidean buffers around pollution monitors to predict annual NO_2 concentrations in California at a spatial resolution of 100 m.[77] For comparison with results from the CTM, the LUR data were initially aggregated to a spatial resolution of 1 km. In the following sections, the two estimates of $PM_{2.5}/NO_2$ generated by different modeling methodologies are denoted as $PM_{2.5}/NO_2$ (CTM) and $PM_{2.5}/NO_2$ (LUR).

Individual panels in **Figure 4** show unique geospatial layers for residential areas, ZIP code boundaries, and raw $PM_{2.5}$ mass concentrations, which were combined to estimate pollution levels for residential areas by ZIP code in Los Angeles. All exposure fields were cut to the residential areas to estimate the annual mean exposure to air pollutants during 2019. Data on residential land use in Los Angeles were obtained from the California statewide parcel boundary dataset.[78] Mean residential exposure data for each ZIP code within the county were then extracted using the ZIP code boundary polygon obtained from the City of Los Angeles GeoHub open data portal.[79] The city of Avalon (ZIP code 90704) was excluded from the analysis, given its location on Santa Catalina Island, which is situated off the coast of Southern California. Thus, a total of 308 ZIP codes were analyzed in this study.

STATISTICAL ANALYSIS

A negative binomial regression was performed for each air pollutant to evaluate associations with COVID-19. Poisson models were also used to evaluate the outcomes of COVID-19 cases and deaths, and dispersion tests were conducted using the AER package in R.[80] The null hypothesis for the AER dispersion test assumes equidispersion in a Poisson model, whereas the alternative hypothesis assumes either overdispersion or underdispersion. Additionally, as no zeros were observed in the cumulative outcomes throughout the study period, we concluded that there were no issues involving zero-inflation in the models. After testing for overdispersion and zero-inflation in the Poisson models for COVID-19 cases and deaths, we determined that negative binomial models would be more appropriate than Poisson models.

To account for potential confounding factors, all models were adjusted for covariates, including demographic variables (e.g., sex, non-White race, advanced age), socioeconomic factors (e.g., median income, mean homeowner occupancy rate), and factors pertaining to chronic health conditions (e.g., mean prevalence of current smoking status and obesity). The older adult population in this study was defined as individuals who were 70 years of age or older, as the raw data were categorized by 10-year age groups. ZIP code-level data on total population, median income, and homeowner occupancy rate were obtained from the US Census Bureau's American Community Survey 1-year estimates for 2020.[81] Data on mean prevalence of current smoking status and obesity were downloaded from the 2020 release of ZIP Code Tabulation Area–level estimates provided by the Centers for Disease Control and Prevention.[82] Total population in each ZIP code was used as an offset in the NB models to calculate the incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for COVID-19 incidence and mortality associated with pollutant concentrations standardized by the interquartile range (IQR).

Two-pollutant NB models were also used to differentiate between the effects of $PM_{2.5}$, NO_2, and O_3. An additive effect of two or more items is considered the baseline for

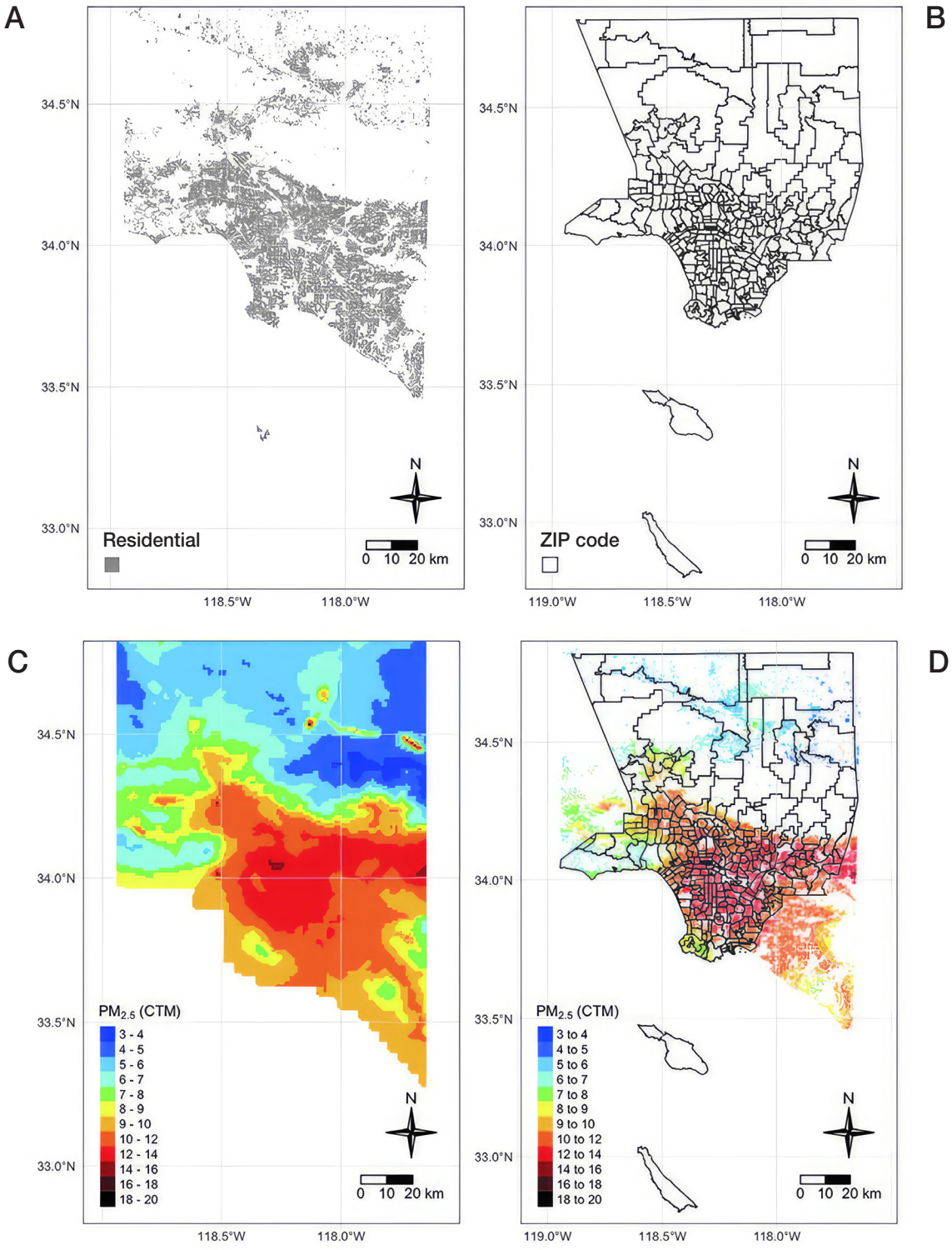


Figure 4. Geospatial data for Los Angeles County, California, 2019. The panels present residential areas (A), boundaries for 308 ZIP codes in Los Angeles County (B), the exposure field for the 2019 annual mean $PM_{2.5}$ mass concentrations (μg/m³) predicted using the CTM (C), and the final geospatial data representing residential exposure to 2019 annual mean $PM_{2.5}$ mass concentrations (μg/m³) by ZIP code (D).

the detection of synergy.[44] The joint effects of two pollutants were assessed by comparing the individual IRRs derived from one-pollutant models for each pollutant to the multiplied product of the IRRs from the two-pollutant model.

Additionally, we utilized the Global Moran's *I* test to determine the spatial pattern in the distribution of COVID-19 cases and deaths. This test provides a statistical measure for assessing spatial autocorrelation, which refers to the degree of similarity or clustering in spatial data. Both COVID-19 cases and deaths showed a clustered distribution, as the Global Moran's I statistics ($P < 2.2e^{-16}$ for both distributions) exceeded the range of random spatial autocorrelation. Hence, using the CARBayes package in R,[83] we utilized a spatial generalized linear mixed model with a binomial distribution to adjust for potential residual spatial autocorrelation among COVID-19 cases and deaths. The CARBayes package applies random effects with a conditional autoregressive (CAR) prior distribution to model the spatial autocorrelation.[83] Additionally, a Spearman rank correlation matrix was applied to the non-normally distributed pollutant concentrations, using the stats package in R.[84] All analyses and figure generation were implemented in R Studio version 4.2.2.

DESCRIPTIVE SUMMARY

Descriptive statistics for COVID-19 incidence and mortality, as well as the 2019 annual mean pollutant concentrations for ZIP codes in Los Angeles, are presented in **Table 1**. During the study period, the median total number of COVID-19 cases and deaths across ZIP codes was 1,753 and 40, respectively. Among the 308 ZIP codes in Los Angeles County, 17 were excluded from the analysis of COVID-19 incidence, and 40 were excluded from the analysis of COVID-19 mortality, per the CDPH protocol for data suppression.

The spatial distributions of the 2019 annual mean residential exposure to $PM_{2.5}$ (CTM/LUR), NO_2 (CTM/LUR), and O_3 are illustrated in **Figure 5**. Although the estimated statistical distributions of pollutants across different modeling methodologies were similar, the spatial patterns differed notably. **Figure 6** shows a stable trend in COVID-19 incidence and mortality over time, with relatively low numbers of COVID-19 cases and deaths occurring from June 19, 2020, to the middle of November 2020. COVID-19 cases and deaths escalated sharply from mid-November 2020 until peaking in late January 2021.

A correlation matrix for pollutants is presented in **Table 2**. Most particle-phase species were moderately to highly correlated with each other and with NO_2. By contrast, O_3 was negatively correlated with all other pollutants. The correlation coefficients between CTM and LUR model predictions for $PM_{2.5}$ and NO_2 were r = 0.78 and r = 0.81, respectively (data not shown), indicating strong agreement despite notable variation between the two methodologies.

ONE-POLLUTANT NEGATIVE BINOMIAL MODEL

The risk plots in **Figure 7** display the IRRs for COVID-19 incidence and mortality per additional IQR increment based on the single-pollutant models. Certain pollutants were found to be associated with higher risks for both COVID-19 incidence and mortality, including $PM_{0.1}$ (incidence IRR, 1.156; mortality IRR, 1.145), $PM_{2.5}$ (LUR) (incidence IRR, 1.111; mortality IRR, 1.173), $PM_{2.5}$ EC (incidence IRR, 1.08; mortality IRR, 1.137), $PM_{2.5}$ tracer 1 (incidence IRR, 1.085; mortality IRR, 1.144), and O_3 (incidence IRR, 1.121; mortality IRR, 1.268). Other pollutants were significantly associated with only one outcome in the single-pollutant models. For example, NO_2 (LUR) was only positively associated with COVID-19 incidence, whereas $PM_{2.5}$ nitrate was only positively associated with COVID-19 mortality. Furthermore, the statistical significance of risks regarding COVID-19 varied by exposure modeling methodology in the single-pollutant models. Although the CTM estimates for $PM_{2.5}$ mass demonstrated no significant risks associated with COVID-19, the LUR model estimate for this pollutant showed significant risks for both COVID-19 incidence and mortality. Similarly, the significance of COVID-19 risks associated with NO_2 differed across modeling methods and outcomes. All IRRs and corresponding 95% CIs derived from the single-pollutant models are available in Appendix B.

TWO-POLLUTANT NEGATIVE BINOMIAL MODEL

The two-pollutant models focused on combinations between O_3 and CTM/LUR modeling of $PM_{2.5}$ and NO_2 (**Figure 8**). Significantly elevated risks of COVID-19 incidence and mortality were found per additional IQR increment in both NO_2 (CTM/LUR) and $PM_{2.5}$ (CTM/LUR), after controlling for O_3. Likewise, risks of COVID-19 incidence and mortality were slightly increased per additional IQR increment in O_3, after controlling for either $PM_{2.5}$ (CTM/LUR) or NO_2 (CTM/LUR). These results were consistent with the negative correlations between O_3 and other pollutants (Table 2). The IRRs of $PM_{2.5}$ generally declined with controlling for NO_2, suggesting that the effects of $PM_{2.5}$ on COVID-19 outcomes were cancelled out by NO_2, regardless of the modeling methodology.

The joint effect of two pollutants on risks of COVID-19 outcomes refers to the product of each IRR in the two-pollutant model. For example, the joint effect of NO_2 (CTM) and $PM_{2.5}$ (CTM) on COVID-19 incidence was 1.13 × 0.947 = 1.07 (Appendix B), which was greater than the individual effect of either pollutant (NO_2 IRR, 1.053; $PM_{2.5}$ IRR, 1.022). This suggests that NO_2 (CTM) and $PM_{2.5}$ (CTM) have a synergistic effect on COVID-19 incidence. This process was repeated for each two-pollutant model. Synergistic effects of two pollutants on COVID-19 incidence and mortality were found for most combinations of O_3 and CTM/LUR modeling of $PM_{2.5}$ or NO_2. No synergistic effects were found for combinations of NO_2 (LUR) and $PM_{2.5}$ (LUR).

Table 1. Descriptive Statistics for (a) COVID-19 Incidence and Mortality and (b) 2019 Annual Mean Pollutant Concentrations for Particulate Matter (μg/m^3) and Gaseous Pollutants (ppb) by ZIP Code in Los Angeles County

(a) COVID-19 Incidence and Mortality by ZIP Code

		Min	Mean (SD)	Median (IQR)	Max	NA
Cases	Total count [a]	1	2,658 (2,655)	1,753 (852–3,574)	14,965	17
	Male (%) [b]		46.3 (7.5)	45.6 (44.1–47.3)		17
	Older adults (%) [c]		92.3 (4.3)	93.2 (90.3–95.2)		17
	Non-White (%) [d]		59.5 (20)	64.6 (42.9–75)		17
Deaths	Total count [a]	3	53 (44)	40 (19–74)	235	40
	Male (%) [b]		54.6 (17.8)	58.8 (49.8–64.7)		40
	Older adults (%) [c]		42.8 (23.4)	39.5 (27.6–52.1)		40
	Non-White (%) [d]		67.8 (30.3)	73.7 (45.7–100)		40

(b) 2019 Annual Mean Pollutant Concentrations by ZIP Code

	Pollutant	Min	Mean (SD)	Median (IQR)	Max	NA
(CTM)	$PM_{0.1}$ (μg/m^3)	0.51	0.91 (0.14)	0.91 (0.84–1.02)	1.20	0
	$PM_{2.5}$ nitrate (μg/m^3)	0.32	1.5 (0.35)	1.6 (1.37–1.74)	2.17	0
	$PM_{2.5}$ mass (μg/m^3)	4.24	11.12 (2.18)	11.77 (10.52–12.65)	15.02	0
	$PM_{2.5}$ EC (μg/m^3)	0.06	0.51 (0.2)	0.54 (0.4–0.65)	1.01	0
	$PM_{2.5}$ on-road gasoline(μg/m^3)	0.02	0.23 (0.1)	0.24 (0.17–0.3)	0.45	0
	O_3 (ppb)	39.35	54.62 (6.66)	54.52 (49.67–59.42)	69.92	0
	NO_2 (ppb)	0.90	14.68 (6.38)	15.87 (10.34–18.81)	29.49	0
(LUR)	$PM_{2.5}$ mass (μg/m^3)	3.87	8.76 (1.77)	9.0 (7.67–9.89)	14.47	6
	NO_2 (ppb)	4.50	14.78 (4.04)	15.3 (12.98–17.35)	26.02	6
	NO_2 (ppb)	4.50	14.78 (4.04)	15.3 (12.98–17.35)	26.02	6

Max = maximum; Min = minimum; NA = not available.
Total numbers of COVID-19 cases and deaths were 773,374 and 14,311, respectively.
The numbers of males among the COVID-19 cases and deaths were 351,409 and 8,292, respectively.
The numbers of older adults (aged ≥70 yr) among the COVID-19 cases and deaths were 724,628 and 5,913, respectively.
The numbers of individuals of non-White race/ethnicity among the COVID-19 cases and deaths were 540,196 and 11,245, respectively.

SPATIAL CONDITIONAL AUTOREGRESSIVE MODEL

The spatial conditional autoregressive (CAR) model demonstrated a divergent relationship between COVID-19 outcomes and $PM_{2.5}$ estimated by different exposure modeling methodologies. Elevated risks of COVID-19 incidence and mortality were observed for most pollutants, except for $PM_{2.5}$ nitrate, ozone, and NO_2 (LUR) as shown in **Table 3**. $PM_{2.5}$ (CTM) showed a significant positive association with COVID-19 incidence and mortality. The narrow CIs for several pollutants resulted from employing the Markov Chain Monte Carlo (MCMC) simulation; specifically, we configured the model to generate 10,000 MCMC samples in each chain.

DISCUSSION

This study used negative binomial and spatial CAR models to explore associations between species or source-specific PM, gaseous pollutants, and COVID-19 outcomes. The NB models were used to estimate the effect of predictors on COVID-19 outcomes (counts of cases and deaths), whereas the spatial CAR models specifically addressed spatial dependencies by including a spatial random effect. In both models, we found elevated risks of COVID-19 incidence and mortality with higher levels of $PM_{0.1}$, O_3, and markers of combustion sources, including NO_2 and $PM_{2.5}$ EC. Generally, the effect estimates for

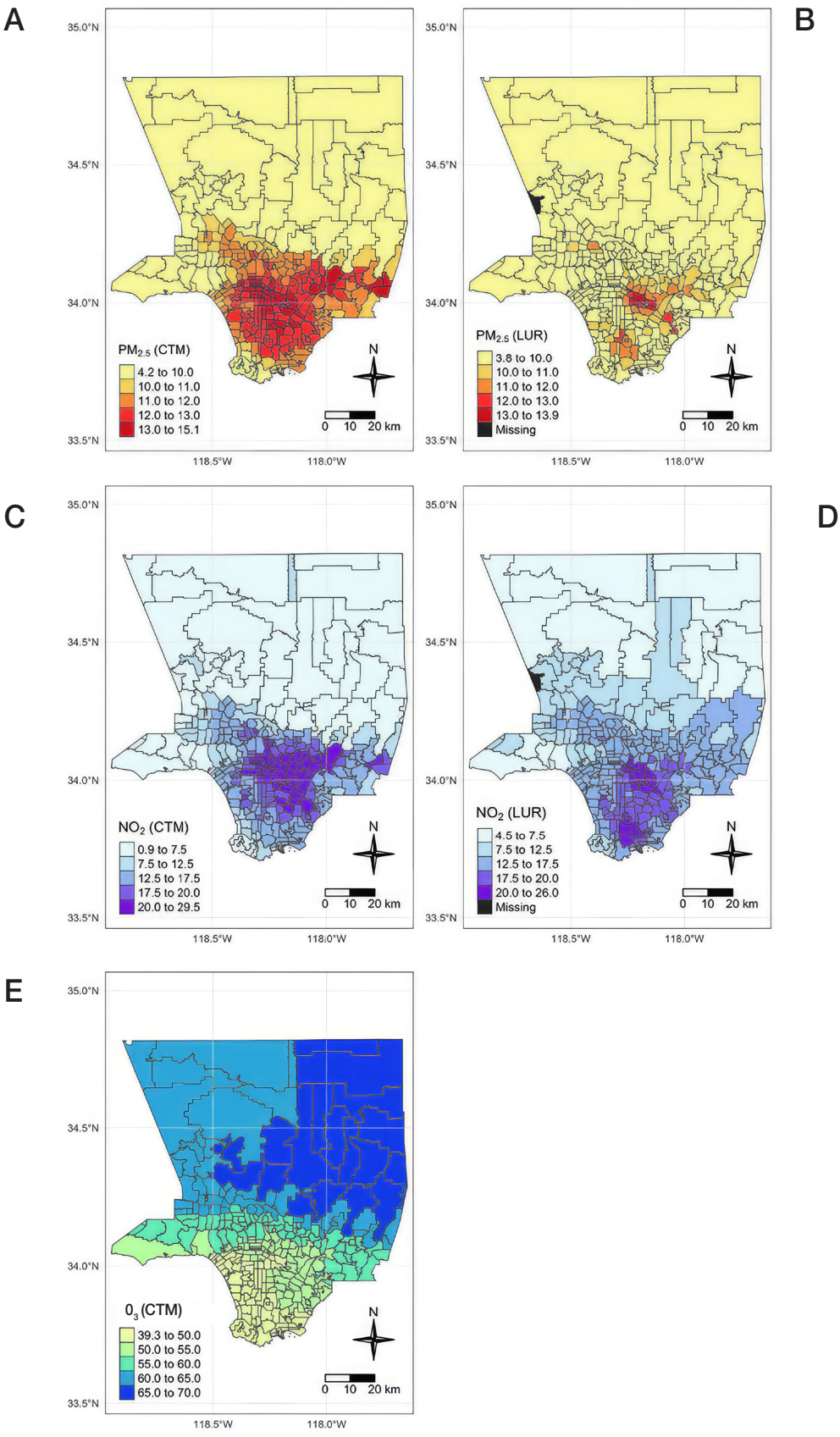


Figure 5. Spatial distribution of 2019 annual mean residential pollutant exposures in Los Angeles County, California. Pollutant exposure data are presented for $PM_{2.5}$ predicted using the CTM (A), $PM_{2.5}$ predicted using the LUR model (B), NO_2 predicted using the CTM (C), NO_2 predicted using the LUR model (D), and O_3 (E).

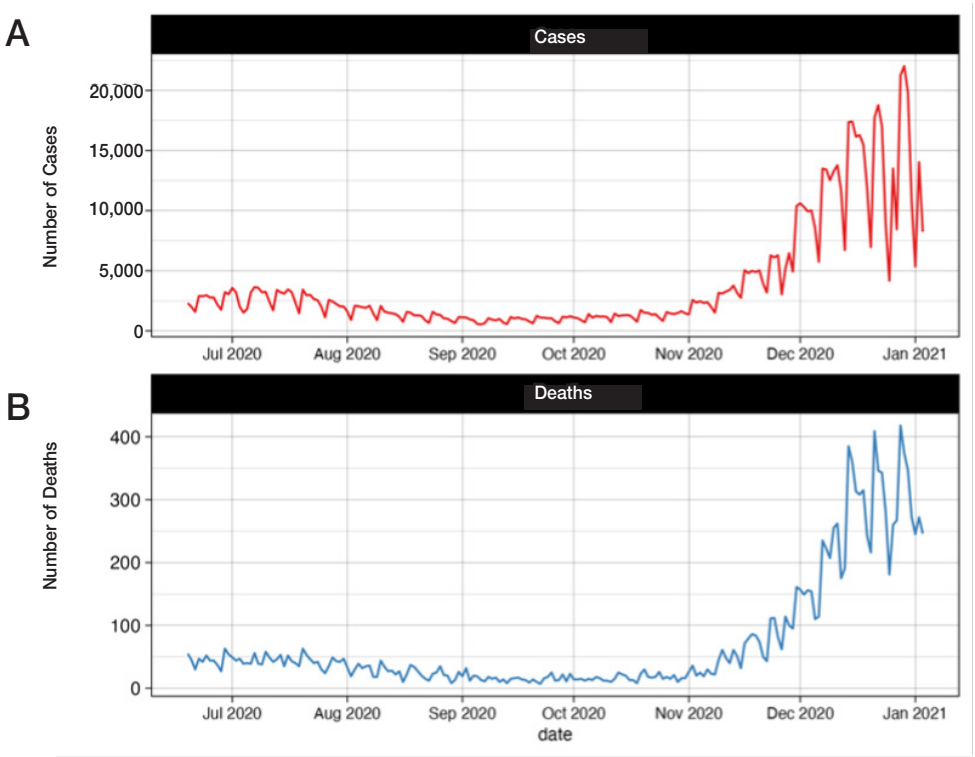


Figure 6. Time series of COVID-19 cases (A) and deaths (B) in Los Angeles County, California from June 19, 2020, to January 3, 2021.

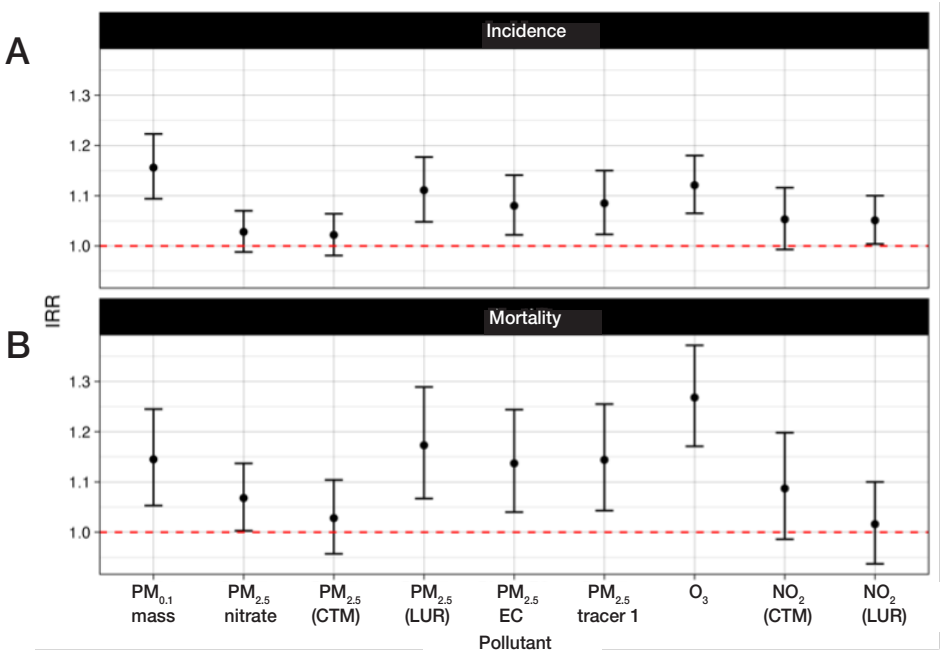
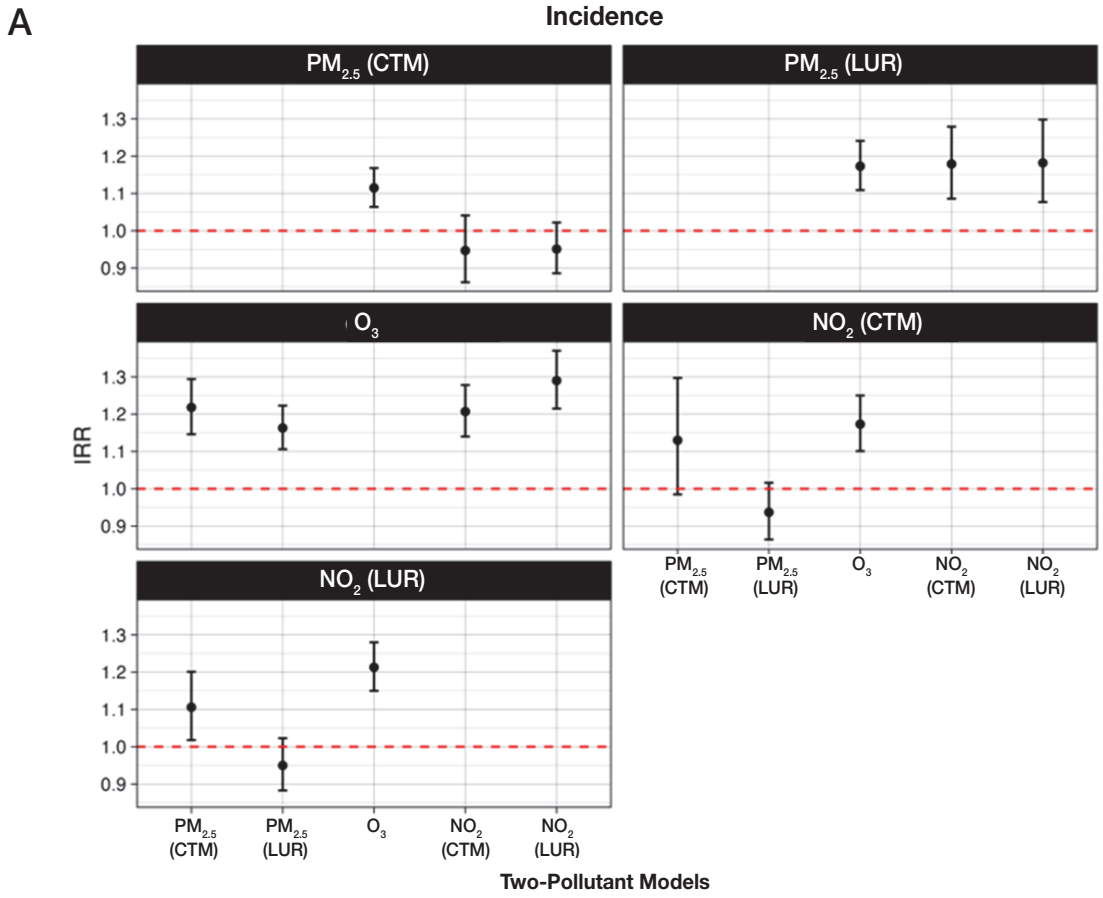


Figure 7. Plot of incident rate ratios for COVID-19 incidence (A) and mortality (B) per additional IQR increment in air pollutant exposures in Los Angeles County, California from June 19, 2020, to January 3, 2021. Data are based on the results of single-pollutant models.

COVID-19 incidence from the CAR model were slightly lower than those from the negative binomial model, suggesting that spatial dependence influenced the health effects of air pollutants in the negative binomial models.[70,85–88] The negative association between $PM_{2.5}$ nitrate and the incidence of COVID-19 in the CAR model may be attributed to the role of this pollutant as a subset of $PM_{2.5}$ mass as well as the availability of both NO_x and ammonia. Furthermore, both O_3 and $PM_{2.5}$ nitrate are products of a common atmospheric photochemical reaction system. We ran a two-pollutant CAR model and confirmed that the association between $PM_{2.5}$ nitrate and COVID-19 incidence changed from negative (IRR, 0.986) to positive (IRR, 1.055) after incorporating O_3 into the CAR model. Isolating the effect of $PM_{2.5}$ nitrate is more complex, and the CAR model did not account for confounding from other pollutants. Except the negative association between $PM_{2.5}$ nitrate and COVID-19 incidence, our findings are consistent with several previous studies that also found positive associations between air pollutants and COVID-19 incidence and mortality, specifically for $PM_{2.5}$, NO_2, and O_3.[70,85–88] Additionally, the large sample size used in the CAR model may increase the statistical power to detect effects, leading to smaller CIs for some pollutants.

The CTM and LUR modeling approaches used in this study yielded somewhat different results due to differences in data source, methods, and spatial resolution. These differences also reflect the assumptions underlying each approach. The CTM calculated pollutant concentrations based on fundamental equations conserving mass and energy, combined with rate equations predicting chemical transformations. By contrast, the LUR model used statistical methods to estimate the relationship



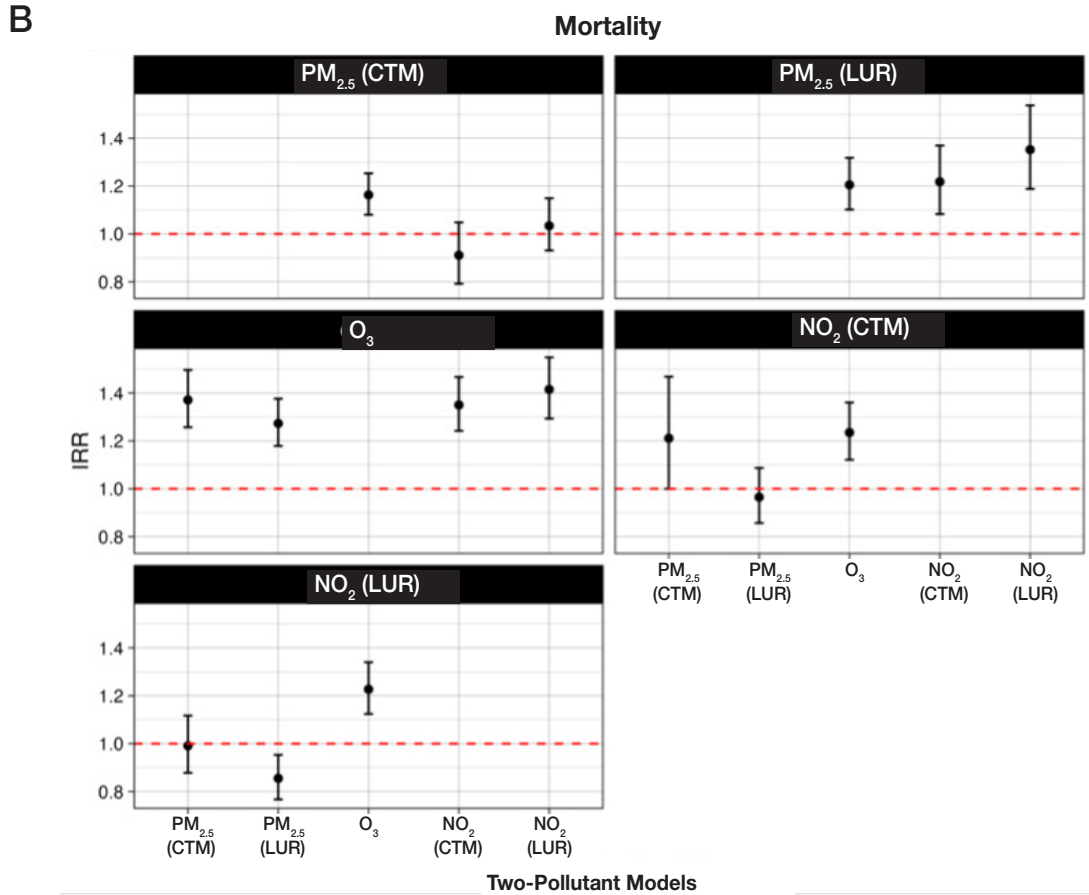


Figure 8. Plot of incident rate ratios for COVID-19 incidence (A) and mortality (B) per additional IQR increment in $PM_{2.5}$, NO_2, and O_3 exposures in Los Angeles County, California from June 19, 2020, to January 3, 2021. Data are based on the results of two-pollutant models controlling for sex, age, race, income, homeowner occupancy rate, and prevalences of current smoking and obesity.

Table 2. Pearson Correlations Between Air Pollutants

CTM									LUR	
Pollutant		**$PM_{0.1}$**	**$PM_{2.5}$ nitrate**	**$PM_{2.5}$ mass**	**$PM_{2.5}$ EC**	**$PM_{2.5}$ On-Road Gasoline**	**NO_2**	**O_3**	**$PM_{2.5}$ mass**	**NO_2**
CTM	$PM_{0.1}$	1	0.18	0.70	0.77	0.71	0.71	–0.04		
	$PM_{2.5}$ nitrate		1	0.56	0.49	0.49	0.49	–0.22		
	$PM_{2.5}$ mass			1	0.94	0.90	0.90	–0.51		
	$PM_{2.5}$ EC				1	0.98	0.79	–0.36		
	$PM_{2.5}$ on-road gasoline					1	0.98	–0.30		
	NO_2						1	–0.42		
	O_3							1		
LUR	$PM_{2.5}$ mass								1	0.83
	NO_2									1

Table 3. Spatial Conditional Autoregressive Model for Each Air Pollutant

COVID-19 Outcome	IRR	95% CI	Pollutant
Incidence	1.211	(1.2–1.22)	$PM_{0.1}$
	0.968	(0.968–0.968)	$PM_{2.5}$ nitrate
	1.003	(1.003–1.003)	$PM_{2.5}$ (CTM)
	1.224	(1.201–1.253)	$PM_{2.5}$ (LUR)
	1.076	(1.071–1.079)	$PM_{2.5}$ EC
	1.043	(1.043–1.043)	$PM_{2.5}$ on-road gasoline
	1.271	(1.271–1.271)	O_3
	1.034	(1.034–1.034)	NO_2 (CTM)
	1.107	(1.107–1.107)	NO_2 (LUR)
Mortality	1.172	(1.055–1.305)	$PM_{0.1}$
	1.108	(0.985–1.305)	$PM_{2.5}$ nitrate
	1.194	(1.052–1.373)	$PM_{2.5}$ (CTM)
	1.128	(1.006–1.261)	$PM_{2.5}$ (LUR)
	1.226	(1.076–1.392)	$PM_{2.5}$ EC
	1.239	(1.09–1.403)	$PM_{2.5}$ on-road gasoline
	1.132	(0.83–1.411)	O_3
	1.21	(1.044–1.372)	NO_2 (CTM)
	1.095	(0.969–1.213)	NO_2 (LUR)

between pollutant concentrations and land use, physical geography, and transportation factors. The LUR method captures less of the regional pattern but is more influenced at the neighborhood level by traffic and land use data. Additionally, the CTM involves estimates of NO_2 and $PM_{2.5}$ exposure that rely extensively on field monitoring data for cross-validation or bias correction.

Synergy refers to a joint effect that exceeds the additive effects expected from the individual items.[44] We found synergistic effects on COVID-19 incidence and mortality with most of the two-pollutant combinations among O_3, $PM_{2.5}$ (CTM/LUR), and NO_2 (CTM/LUR). These findings align with the results of a study that investigated the synergistic effects of $PM_{2.5}$ and O_3 on the risk of preterm birth, which found that interactions between high levels of $PM_{2.5}$ and O_3 increased the risk of preterm birth by 230% compared to the expected outcome based on the sum of the effects of each pollutant; similarly, the authors reported that the joint effect of high levels of NO_2 and O_3 contributed to a 181% excess risk of preterm birth.[89] The influence of confounding due to other pollutants, however, cannot be distinguished from the combined effect. Source-specific types of PM were excluded from the two-pollutant models, as the total mass, by definition, includes some of the source- or species-specific components. Pollutants with exposure estimates derived from different methods also were not combined in the same two-pollutant model to avoid introducing uncertainty about whether observed differences resulted from actual effects or differences in the specifications of the exposure models.

To minimize the potential for bias due to changes in transmissibility and disease severity associated with different variants of SARS-CoV-2, our study focused on the period in which the Delta variant accounted for more than 50% of confirmed COVID-19 cases, as indicated by a previous study of patients hospitalized for COVID-19 in Southern California.[70] Vaccination status was not considered in the data analysis, as the study period was focused on the latter half of 2020, when vaccines were not readily available. A study in Israel that used multivariate linear regression with controlling for demographic characteristics and vaccination rates proposed the presence of positive associations between the Delta variant–dominated wave of COVID-19 that occurred in the summer of 2021 and long-term exposure to PM_{10}, $PM_{2.5}$, NO_2, carbon monoxide, and sulfur dioxide.[90]

A strength of our study was the estimation of exposure in residential areas to pollutants. Rather than computing the overall mean concentrations of pollutants for each ZIP code, we more realistically considered residential exposure by extracting exposure fields from only the residential areas within each unit. Though individual-level data were not attainable in this study, we were able to adjust for demographic factors by using COVID-19 data from the CDPH, which provided proportions by sex, race/ethnicity, and age categories, aggregated by ZIP code. Additionally, the use of source and species-specific PM helped identify the independent effects of these pollutants as contributors to elevated risks of COVID-19 outcomes.

This study offers several improvements compared to a previous analysis of the association between air pollution and COVID-19 outcomes in Los Angeles.[67] A prior study utilizing individual-level data found no significant interactions among variables representing various sociodemographic, lifestyle, and health-related factors.[85] Firstly, the present study used ZIP code–level data on COVID-19 incidence and mortality, with the numbers of cases and deaths stratified by sex, race/ethnicity, and age category, whereas the previous study used neighborhood-level data for the numbers of COVID-19 cases and deaths. Secondly, this study assessed exposures on the basis of 2019 data for LUR modeling of NO_2 and $PM_{2.5}$ as well as 2019 data for CTM-based estimates of species-specific $PM_{2.5}$, NO_2, and O_3; by contrast, the prior study used 2016 data for LUR modeling of NO_2. Furthermore, our analysis specifically focused on the period in which the Delta variant of SARS-CoV-2 was predominant. These methodological advancements reduced uncertainty and provided a better understanding of the relationship between air pollution and COVID-19 outcomes.

This study also has a few limitations that warrant consideration. First, several ZIP codes were suppressed because of concerns about confidentiality. Second, annual mean pollutant concentrations were used as a proxy for chronic exposure, but the acute effects of air pollution were not considered. Third, data on COVID-19 outcomes were aggregated at the ZIP code level, as individual-level data with residential information were inaccessible. Lastly, occupation, which can alter the risks of both exposure to and incidence of COVID-19, was not accounted for in the study. In addition, although our model incorporated several covariates, including age, sex, race/ethnicity, and socioeconomic status, environmental factors other than air pollution were not taken into consideration. Some environmental factors may influence both air pollution levels and COVID-19 outcomes. For example, meteorological factors affect the dispersion and concentration of air pollutants, yet lower temperatures and lower levels of humidity have been demonstrated to be favorable for the transmission of COVID-19 in China.[91] The risk of COVID-19 mortality was found to be 47% lower in areas of India with the highest versus the lowest district-level scores on the normalized difference vegetation index (NDVI), a measure of greenness.[92] Although meteorological variables were not directly incorporated in the statistical analysis in the present study, the CTM uses meteorological conditions, including temperature, relative humidity, wind speed, wind direction, total solar radiation, and ultraviolet solar radiation, as inputs in simulating the transport, transformation, deposition, and formation of air pollutants.[93]

CONCLUSION

This study adds to the growing body of evidence suggesting that air pollution affects the risks of COVID-19 incidence and mortality. The findings presented here also provide critical insights into the spatial associations between source and species-specific air pollutants and COVID-19 incidence and mortality, adjusted for demographic characteristics, socioeconomic status, and some chronic conditions (such as smoking and obesity). Future studies can benefit from integrating short-term exposure data and daily individual-level data on COVID-19 outcomes to clarify the relationship between air pollution and COVID-19, particularly among both racial/ethnic minority populations and people with pre-existing conditions.

CHAPTER 5: AIR POLLUTION AND METEOROLOGY AS RISK FACTORS FOR COVID-19 MORTALITY IN SOUTHERN CALIFORNIA

INTRODUCTION

The COVID-19 pandemic represents one of the largest threats to population health in more than a century. As of December 2023, more than 690 million people worldwide have been diagnosed with COVID-19, resulting in more than 6.9 million deaths.[7] Although researchers have extensively investigated the etiology of COVID-19, there remain considerable uncertainties about how potential risk factors may influence the incidence and severity of the disease as well as resulting mortality. Recent evidence from North America, Asia, and Europe implicates air pollution as a risk factor that affects the incidence, prognosis, and mortality rate of COVID-19.[10–23]

Biologically plausible mechanisms suggest that exposure to air pollution may render people more susceptible to contracting COVID-19, and that once infection occurs, greater exposure to air pollution may worsen the prognosis of the disease.[24–28] For example, NO_2, a marker for traffic-related air pollution,[29,30] likely increases the risk of lung infections by impairing the function of alveolar macrophages and epithelial cells in the lung.[31] Findings from epidemiological and toxicological studies align with a large body of research linking air pollution to risk of viral and bacterial respiratory infections,[17,32] chronic respiratory morbidities (e.g., asthma, chronic obstructive pulmonary disease, lung cancer),[33–35] hospitalizations,[31] and mortality.[36–38]

Our review of the growing literature on air pollution exposure and COVID-19 outcomes identified only five other mortality studies that have used individual-level data and controlled for potential confounders.[21,38–41] These studies were focused on the early phases of the pandemic, possibly resulting in lower statistical power due to a relatively small number of deaths. Some of these studies used high-quality exposure estimates, but none assessed particle source contributions or ultrafine particle concentrations. Also, none of these studies examined interactions between air pollution and meteorological variables such as temperature and humidity.

In the present study, we expanded the evidence base by using a large sample of individual-level data, a longer study period, exposure models capable of assessing particle species and sources, and meteorological variables. In this context, we addressed two research objectives. Firstly, we assessed whether greater air pollution exposures led to increased risk of death among patients with confirmed COVID-19 who were members of the KPSC healthcare system. Secondly, we investigated whether meteorological variables influenced the risk of death due to COVID-19 or modified associations between air pollution and COVID-19 mortality.

MATERIALS AND METHODS

KPSC COHORT AND HEALTH DATA

KPSC is a large integrated healthcare system with a racially, ethnically, and socioeconomically diverse membership of 4.7 million people residing across nine Southern California counties. The KPSC membership, described elsewhere in further detail,[94] approximately represents the overall population of the second-largest urban region in the United States. KPSC maintains an integrated Electronic Health Record (EHR) data system that captures all aspects of patient care, including diagnoses, inpatient and outpatient visits, pharmacy encounters, and laboratory tests.

Clinical care changed rapidly during the first months of the COVID-19 pandemic. Thus, the observation period for this study began on June 1, 2020, by which time new standards of care for COVID-19, such as placing patients in the prone position, had become more common. We identified KPSC patients with a positive COVID-19 molecular diagnostic test and/or diagnosis (ICD-10 codes B34.2, B97.29, J12.89, J20.8, J22, J80, or U07.1) that occurred from June 1, 2020, to January 30, 2021. We included both COVID-19 diagnoses and tests because patients could have received a COVID-19 test outside of the KPSC health system and subsequently been diagnosed with COVID-19 at a KPSC facility, without being retested. The selected ICD-10 codes were those that have been used to identify COVID-19 in other research. We also worked with KPSC hospitalists to identify appropriate ICD-10 codes for this study.

The study cohort comprised patients who were 18 years of age or older at the time of their positive COVID-19 test or diagnosis. To reliably assess comorbidities, the population sample was limited to patients who had been KPSC members for at least 1 year before being diagnosed with or testing positive for COVID-19. We defined COVID-19–related hospitalizations as those occurring within 21 days of the patient's COVID-19 diagnosis or positive test (N = 316,224).[95] Less severe (i.e., nonhospitalized) cases were excluded, which limits the generalizability of our results to more severely ill (i.e., hospitalized) cases. We limited the study population to hospitalized patients rather than all patients with a positive COVID-19 test, as testing could have occurred after contact with an individual with SARS-CoV-2 or upon hospital admission after the onset of severe illness. Such timing would lead to uncertainty about the window of time within which testing could have occurred

in different patients, thereby introducing substantial errors in the study follow-up times and thus leading to biased results in the statistical models. Restricting the study population to hospitalized patients removed any uncertainty about the timing of hospitalization and thus also eliminated the related potential errors and bias. Patients who died up to 90 days after their initial hospitalization were included in the study cohort. (Further details on the ascertainment of death data are provided in Appendix C.) Patients whose KPSC membership ended during the 90-day observation window and patients hospitalized for childbirth were excluded from the study. After application of the eligibility and exclusion criteria, the cohort used for data analysis consisted of 21,415 patients. This study was approved by the Kaiser Permanente Institutional Review Board.

The KPSC EHR includes information on patient age and sex. Member race/ethnicity categories have been created using a validated algorithm that uses multiple data sources.[95]

Five broad comorbidity categories used in prior COVID-19 research were created to identify comorbidities that may increase an individual's risk of severe COVID-19 outcomes.[95,97] We used Elixhauser disease categories to define specific disease categories that are relevant to COVID-19 (Appendix C).

We collected data on four individual-level confounders that were considered in the analysis: body mass index (BMI), smoking status, Exercise Vital Sign (EVS) value, and MediCalstatus (low income). BMI is an important risk factor for COVID-19 mortality.[96] The most recent BMI value available in the patient EHR was used to represent this potential confounder.[96] BMI data were cleaned using validated algorithms to delete biologically implausible values. In the KPSC health system, smoking status and EVS data (coded as min/wk of moderate to vigorous exercise) are collected during each in-person outpatient healthcare encounter. Smoking status (ever-smoker vs. never-smoker) was coded based on information provided during the patient's last encounter before their COVID-19 test or diagnosis, dating back up to 4 years. All EVS data for the past 4 years were identified for every patient. The median number of minutes of exercise per week was calculated for use in the analysis.[98] We used enrollment at KPSC via MediCal to identify patients with very low income.

We queried vaccination status and found that only 33 patients in the study cohort were vaccinated against COVID-19 prior to hospitalization. Thus, approximately 99.85% of the cohort was unvaccinated during the study period.

In accordance with common practices in analyzing EHR data, we added predictors of community-level socioeconomic status (SES) to serve as a proxy for individual SES and to adjust for community-level effects of social determinants of health.[99–101] Community-level predictors at the census block group level were obtained from the 2018 American Community Survey, including a validated Neighborhood Deprivation Index (NDI), a measure of crowding (the proportion of households with more than one occupant per home), and the proportion of workers aged 16 years or older who commute to work via public transportation.[102]

GridMET meteorological data are high–spatial resolution (approximately 4-km) surface meteorological data covering the contiguous United States. We acquired GridMET daily maximum temperature and relative humidity data for the entire study period by using Google Earth Engine.[103] The GridMET data for the home address of each study participant were aggregated to monthly means for the period up to the month of hospitalization for COVID-19.

EXPOSURE ASSESSMENT: CHEMICAL TRANSPORT MODEL

Exposure simulations were carried out across California using the UCD/CIT source-oriented, three-dimensional, reactive chemical transport model (CTM).[104] The UCD/CIT model predicts the evolution of gas- and particle-phase pollutants in the atmosphere in the presence of emissions, transport, deposition, chemical reaction, and phase change. The pressing timeline for conducting this study during an ongoing public health crisis necessitated leveraging past efforts that had prepared and validated CTM inputs. We previously reported CTM exposure fields with 4-km resolution over California for the years 2000–2016.[105] The most recent year in this time range (i.e., 2016) was selected as the starting point for characterizing chronic exposure in the present study. Meteorology and emissions inputs for the year 2016 were downscaled to improve spatial resolution to 1 km. Bias in the raw CTM output fields was removed using a constrained regression model based on source apportionment tags and the difference between predicted and measured concentrations. Appendix Figure A13 illustrates the stability of the exposure fields for O_3 and $PM_{2.5}$ across the years 2016, 2019, and 2020. Although factors such as wildfires, behavioral changes associated with COVID-19, and weather patterns driven by El Niño-Southern Oscillation cause some year-to-year variation, the major spatial patterns for these and other exposures are stable over time (Appendix A).

CTM predictions include a wide range of pollutants. For our study area, we estimated $PM_{2.5}$ mass, $PM_{2.5}$ nitrate, $PM_{2.5}$ OC, $PM_{2.5}$ EC, $PM_{0.1}$, NO_2, and O_3. We also extracted PM source tracers for on-road diesel, on-road gasoline, and biomass combustion. These exposure fields were assigned to the geocoded home addresses of the patients in the study cohort. Although the exposure fields were restricted to 2016, we accounted for population mobility

by assigning exposures to each address for any patient in the cohort who had moved within the past 5 years. We then performed time-weighted averaging of the exposures to account for mobility effects for those who had moved during the preceding 5 years.

STATISTICAL ANALYSIS

We used Cox proportional hazards models with adjustment for potential individual- and neighborhood-level confounders. All models were stratified at baseline by age, sex, and race/ethnicity. Age was categorized by 5-year age groups. We controlled for potential nonindependence at the census tract level by using a sandwich estimator, which allowed for robust variance estimation. All statistical analyses were performed using the R version 4.0.4.[84]

The Cox model estimates the instantaneous hazard of dying during follow-up as

$$h_{ij}(t) = h_{0s}(t)\exp(\beta P_{ij} + \delta X_{ij} + \zeta Z_{ij} + fW_{itj}) \quad \textbf{(Equation 5)}$$

$$CF_{PM_{2.5}mass} = (2 + FB_{PM_{2.5}mass}) / (2 - FB_{PM_{2.5}mass})$$

where $h_{ij}(t)$ is the hazard function for the ith subject in the jth census tract neighborhood; $h_{0s}(t)$ is the baseline hazard function for stratum s (i.e., age, race, and sex); P_{ij} is the air pollution exposure metric of interest (e.g., $PM_{2.5}$) standardized to the IQR for individual i in census tract j; X_{ij} represents individual-level risk factors (i.e., smoking status, exercise, BMI, poverty) for individual i in census tract j; Z_{ij} represents neighborhood-level risk factors (i.e., deprivation index, proportion of workers aged 16 or older taking public transit, crowding) for individual i in census tract j; W_{itj} represents weather conditions (i.e., maximum temperature and humidity) for individual i at the t^{th} month of admission in census tract j; and β,δ,ζ,f: are regression coefficients.

Equation 5 above represents the general form of the model. Confounders were selected for each pollutant, according to the following procedure: We ran unadjusted models stratified by age, race/ethnicity, and sex for each pollutant exposure. We tested every possible confounder (BMI, smoking status, etc.) one at a time with each pollution estimate. We included any confounder that changed the unadjusted pollution coefficient by at least 10%. We subsequently ran the adjusted models for all pollution exposures that included variables meeting the 10% criterion. Exposures were standardized for comparison across pollutants by dividing each by their respective IQR. For pollutants with statistically significant effects at conventional levels ($P < 0.05$) after adjustment, we then conducted stratified analyses on variables that could modify the association between air pollution and COVID-19 mortality, including race/ethnicity, sex, age, and number of chronic disease categories.

We also tested for interaction by running models with a multiplicative term involving one pollutant and one meteorological variable. When statistically significant interactions were present based on the P value of the interaction term, we stratified the HR estimates for the pollutant by tertile of the meteorological variable.

We examined two-pollutant models (i.e., O_3 and NO_2, NO_2 and $PM_{2.5}$ mass, and O_3 and $PM_{2.5}$ mass). We also explored the concentration–response functions for each pollutant that had a significant individual effect in a fully adjusted model. The concentration–response functions were estimated using the pspline function in the gam package in R.

We also investigated the potential influence of different SARS-CoV-2 variants by performing sensitivity analyses restricted to periods in which the Delta variant was dominant. The CDPH has performed retrospective genomic analyses on specimens from all stages of the COVID-19 pandemic (*https://data.chhs.ca.gov/dataset/covid-19-variant-data*). Early in the present study, five different variants of SARS-CoV-2 were circulating. The Delta variant was dominant throughout much of the study period, although the Omicron variant became dominant approximately during the last 1 month of the study. It is likely, however, that many of the hospitalizations that occurred over the last weeks to months of the study were due to infections with the Delta variant, given the latency period of the infection and the time required for a person to become ill enough to require hospitalization.

Sensitivity analyses focused on the period from June 19, 2020, to January 3, 2021. The start date of this period corresponds to the initial date on which the Delta variant accounted for more than 50% of the COVID-19 cases. The Delta variant lost dominance (i.e., accounting for less than 50% of COVID-19 cases) as of December 19, 2020. We added a 2-week buffer to the end date of the period of Delta-dominant cases, given the assumption that it would have taken at least 2 weeks after the onset of infection for many of the Delta-related hospitalizations and deaths to occur. Thus, we conservatively used January 3, 2021, as the end date of the period included in the sensitivity analysis. We also reran the analyses for $PM_{2.5}$ using this restricted time period to enable comparison of the results with those from the main analysis.

RESULTS

DESCRIPTIVE STATISTICS

Table 4 displays the demographic and clinical characteristics of the cohort of 21,415 KPSC patients hospitalized with COVID-19, of whom 4,815 died within 90 days after hospitalization. The median age of patients was 64 years (IQR, 52–75), and 58% were male. Among patients in the cohort, 56% were of Hispanic origin, 23% were White,

Table 4. Demographic and Clinical Characteristics of Hospitalized Patients with COVID-19, by Outcome

Characteristic	Total (*N* = 21,415) *n* (%)	Outcome Within 90 Days	
		Alive (*N* = 16,600) *n* (%)	Deceased (*N* = 4,815) *n* (%)
Age at diagnosis (yr)[a]	64 (52–75)	61 (50–72)	74 (64–83)
Race/ethnicity			
White	4,861 (23%)	3,550 (21%)	1,311 (27%)
Asian/Pacific Islander	2,281 (11%)	1,801 (11%)	480 (10.0%)
Black	1,851 (8.6%)	1,444 (8.7%)	407 (8.5%)
Hispanic	12,077 (56%)	9,541 (57%)	2,536 (53%)
Other/multiple/unknown	345 (1.6%)	264 (1.6%)	81 (1.7%)
Sex			
Female	9,067 (42%)	7,284 (44%)	1,783 (37%)
Male	12,348 (58%)	9,316 (56%)	3,032 (63%)
Smoking status			
Never-smoker	13,392 (63%)	10,825 (65%)	2,567 (53%)
Ever-smoker	7,738 (36%)	5,542 (33%)	2,196 (46%)
Unknown	285 (1%)	233 (1%)	52 (1%)
BMI[a]	31 (27–36)	31 (27–36)	29 (25–35)
Unknown	608 (3%)	502 (3%)	106 (2%)
Medicaid			
No	18,722 (87%)	14,596 (88%)	4,126 (86%)
Yes	2,693 (13%)	2,004 (12%)	689 (14%)
Exercise Vital Sign[a]	0 (0–90)	0 (0–100)	0 (0–65)
Unknown	748 (4%)	625 (4%)	123 (3%)
Percentage of housing units with >1 occupant/room[a]	0.09 (0.03–0.18)	0.09 (0.03–0.18)	0.08 (0.03–0.18)
Unknown	598 (3%)	466 (3%)	132 (3%)
NDI[a]	0.42 (–0.28 to 1.25)	0.43 (–0.27 to 1.25)	0.40 (–0.30 to 1.26)
Unknown	6 (0%)	5 (0%)	1 (0%)
Percentage of workers aged ≥16 yr commuting by public transportation[a]	0.02 (0.00–0.05)	0.02 (0.00–0.05)	0.02 (0.00–0.05)
Unknown	599 (3%)	465 (3%)	134 (3%)
BMI category			
Normal weight	2,777 (13%)	1,876 (11%)	901 (19%)
Overweight	5,933 (28%)	4,468 (27%)	1,465 (30%)
Obesity, class 1	5,669 (26%)	4,543 (27%)	1,126 (23%)
Obesity, class 2/3	6,193 (29%)	5,075 (31%)	1,118 (23%)
Underweight	235 (1.1%)	136 (0.8%)	99 (2.1%)
Unknown	608 (3%)	502 (3%)	106 (2%)
Frailty (*Lancet* index)[a]	5 (2–12)	5 (2–10)	9 (4–18)
Unknown	4,608 (22%)	4,008 (24%)	600 (12%)

Continues next page

Table 4. (*continued*)

Characteristic	Total (*N* = 21,415) *n* (%)	Outcome Within 90 Days: Alive (*N* = 16,600) *n* (%)	Outcome Within 90 Days: Deceased (*N* = 4,815) *n* (%)
Elixhauser Comorbidity Index[a]	3.0 (1.0–5.0)	2.0 (1.0–5.0)	5.0 (2.0–7.0)
Cardiovascular disease	8,637 (40%)	5,625 (34%)	3,012 (63%)
Unknown	410 (2%)	349 (2%)	61 (1%)
Hypertension	12,369 (58%)	8,738 (53%)	3,631 (75%)
Unknown	410 (2%)	349 (2%)	61 (1%)
COPD	4,519 (21%)	3,276 (20%)	1,243 (26%)
Unknown	410 (2%)	349 (2%)	61 (1%)
Diabetes	9,524 (44%)	6,887 (41%)	2,637 (55%)
Unknown	410 (2%)	349 (2%)	61 (1%)
Other Elixhauser diagnosis	13,627 (64%)	9,878 (60%)	3,749 (78%)
Unknown	410 (2%)	349 (2%)	61 (1%)
Skilled nursing facility flag	293 (1.4%)	136 (0.8%)	157 (3.3%)
County of residence			
Kern	543 (2.5%)	435 (2.6%)	108 (2.2%)
Los Angeles	10,580 (49%)	8,226 (50%)	2,354 (49%)
Orange	2,142 (10%)	1,744 (11%)	398 (8.3%)
Riverside	2,372 (11%)	1,755 (11%)	617 (13%)
San Bernardino	2,890 (13%)	2,131 (13%)	759 (16%)
San Diego	1,874 (8.8%)	1,512 (9.1%)	362 (7.5%)
Ventura	423 (2.0%)	338 (2.0%)	85 (1.8%)
Unknown	591 (3%)	459 (3%)	132 (3%)
COVID-19 surge–related case (first hospital admission after Nov 16, 2020)	15,090 (70%)	11,378 (69%)	3,712 (77%)
Days of follow-up[a]	7 (4–16)	6 (4–11)	17 (10–27)

[a]Median (IQR).

11% were Asian/Pacific Islanders, 8.6% were Black, and 1.6% were of other or unknown race/ethnicity. Approximately 37% of patients had ever been smokers, and 13% of patients had health insurance through MediCal, a government health program for low-income persons.

The distribution of hospital admission dates for all patients in the study cohort is presented in **Figure 9**, which shows a large surge in admissions from November 2020 to the end of the study period. Most hospitalized patients were overweight or obese, with 29% meeting the criteria for overweight, 27% having class 1 obesity, and 30% having class 2 or higher obesity. Comorbidities identified in the patients' medical histories included cardiovascular disease (41%), hypertension (59%), COPD (22%), diabetes (45%), and other chronic conditions (65%), as summarized in Table 4.

Patients who died within 90 days after their first hospitalization were older (median age, 74 years vs. 61 years), more likely to be male (63% vs. 56%), and more likely to have ever been smokers (46% vs. 34%), compared to those who remained alive during this period. Additionally, patients who died had more comorbidities (median Elixhauser Comorbidity Index, 5.0 vs. 2.0) and a greater prevalence of chronic diseases, including cardiovascular disease (63% vs. 35%), hypertension (76% vs. 54%), diabetes (55% vs. 42%), and COPD (26% vs. 20%).

Descriptive statistics for pollutant exposures among the patients in the study cohort are shown in **Table 5**. Many of the pollutants were moderately to highly correlated with one another (**Table 6**). For example, $PM_{2.5}$ mass and $PM_{2.5}$ nitrate were strongly correlated (r = 0.9). O_3 was the least correlated with the other pollutants and, as expected, had

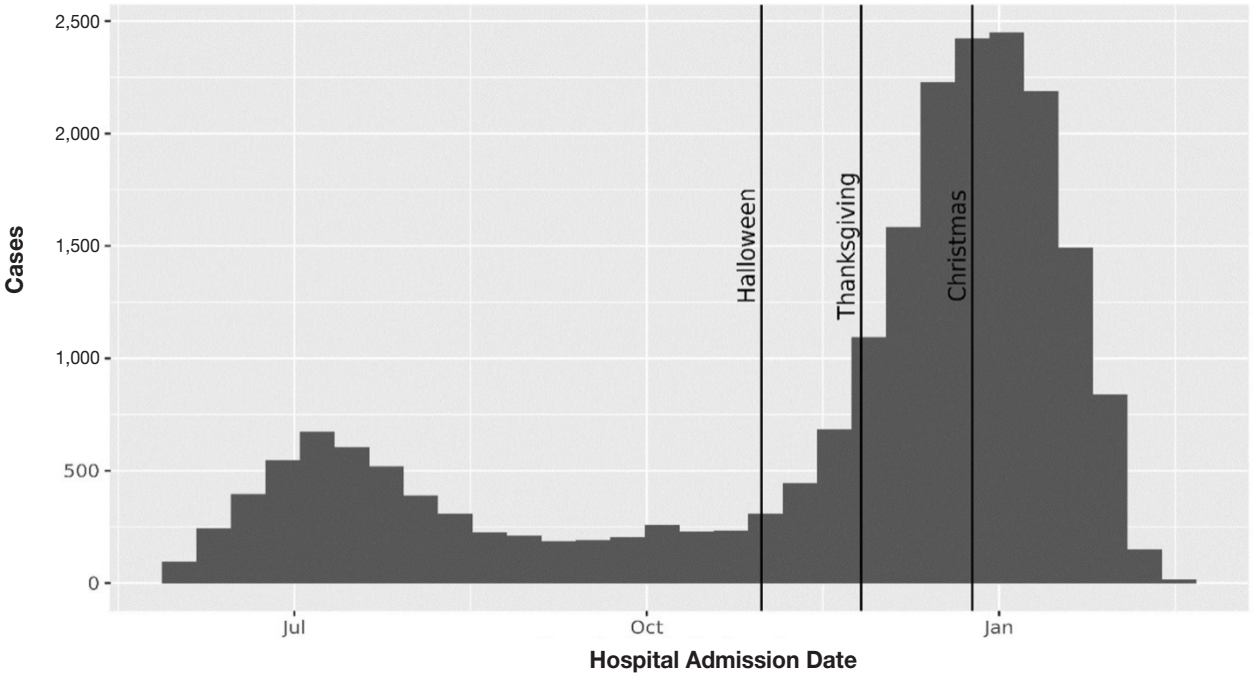


Figure 9. Hospital admission dates in 2020–2021 among the study cohort of patients hospitalized with COVID-19 in Southern California.

Table 5. Descriptive Statistics for Pollutant Exposures Among Hospitalized Patients with COVID-19, by Outcome

Characteristic	Total (*N* = 21,415)	Outcome Within 90 Days	
		Alive (*N* = 16,600)	Deceased (*N* = 4,815)
NO_2 (ppb)			
Median (IQR)	21 (13, 25)	21 (13, 25)	20 (14, 25)
Mean (SD)	19 (7)	19 (7)	19 (7)
Range	1, 39	1, 39	2, 36
O_3 maximum (ppb)			
Median (IQR)	66 (60, 72)	66 (60, 72)	67 (60, 73)
Mean (SD)	66 (8)	66 (8)	66 (8)
Range	40, 84	40, 84	43, 83
$PM_{2.5}$ mass (µg/m_3)			
Median (IQR)	12.30 (10.50, 14.00)	12.30 (10.50, 14.00)	12.40 (10.60, 14.00)
Mean (SD)	12.34 (2.40)	12.33 (2.39)	12.39 (2.44)
Range	5.77, 27.70	5.77, 27.70	6.05, 23.80
$PM_{2.5}$ nitrate (µg/m^3)			
Median (IQR)	3.81 (2.88, 4.54)	3.80 (2.86, 4.53)	3.84 (2.93, 4.56)
Mean (SD)	3.64 (1.18)	3.63 (1.17)	3.67 (1.20)
Range	0.19, 7.16	0.19, 7.16	0.26, 7.02

Continues next page

Table 5. (*continued*)

Characteristic	Total (*N* = 21,415)	Outcome Within 90 Days	
		Alive (*N* = 16,600)	Deceased (*N* = 4,815)
$PM_{2.5}$ organic compounds (μg/m³)			
Median (IQR)	2.07 (1.56, 2.60)	2.08 (1.56, 2.60)	2.05 (1.57, 2.56)
Mean (SD)	2.08 (0.69)	2.08 (0.69)	2.07 (0.68)
Range	0.31, 8.24	0.31, 8.24	0.32, 7.59
$PM_{0.1}$ (μg/m³)			
Median (IQR)	0.90 (0.72, 1.07)	0.90 (0.72, 1.07)	0.91 (0.74, 1.06)
Mean (SD)	0.89 (0.29)	0.89 (0.29)	0.90 (0.29)
Range	0.22, 6.63	0.26, 6.63	0.22, 4.20
$PM_{2.5}$ elemental carbon (μg/m³)			
Median (IQR)	0.47 (0.33, 0.59)	0.47 (0.33, 0.60)	0.46 (0.34, 0.58)
Mean (SD)	0.47 (0.19)	0.47 (0.19)	0.47 (0.19)
Range	0.05, 1.53	0.06, 1.52	0.05, 1.53
On-road diesel $PM_{2.5}$ (μg/m³)			
Median (IQR)	0.30 (0.19, 0.41)	0.30 (0.19, 0.41)	0.29 (0.20, 0.40)
Mean (SD)	0.32 (0.18)	0.32 (0.18)	0.32 (0.18)
Range	0.01, 1.78	0.01, 1.76	0.02, 1.78
On-road gasoline $PM_{2.5}$ (μg/m³)			
Median (IQR)	0.071 (0.052, 0.093)	0.072 (0.052, 0.094)	0.071 (0.052, 0.091)
Mean (SD)	0.073 (0.029)	0.073 (0.030)	0.072 (0.029)
Range	0.003, 0.213	0.003, 0.213	0.003, 0.194
Biomass combustion $PM_{2.5}$ (μg/m³)			
Median (IQR)	1.01 (0.73, 1.26)	1.01 (0.73, 1.27)	0.99 (0.72, 1.25)
Mean (SD)	1.02 (0.46)	1.02 (0.45)	1.02 (0.49)
Range	0.01, 9.93	0.01, 9.93	0.01, 9.03
Relative humidity (%)			
Median (IQR)	70 (58, 82)	71 (59, 82)	67 (57, 79)
Mean (SD)	70 (14)	70 (14)	68 (14)
Range	25, 99	25, 99	31, 98
Unknown	6	6	0
Temperature (°C)			
Median (IQR)	21.1 (20.0, 25.0)	21.1 (20.0, 25.9)	20.8 (19.9, 22.5)
Mean (SD)	22.9 (5.2)	23.1 (5.2)	22.3 (4.9)
Range	5.9, 44.6	5.9, 44.5	7.2, 44.6
Unknown	6	6	0

Table 6. Correlations Between Pollutants and Meteorological Variables

	NO_2	O_3 Maximum	$PM_{2.5}$ Mass	$PM_{2.5}$ Nitrate	$PM_{2.5}$ Organic Compounds	$PM_{0.1}$	$PM_{2.5}$ Elemental Carbon	On-Road Diesel $PM_{2.5}$	On-Road Gasoline $PM_{2.5}$	Biomass Combustion $PM_{2.5}$	Relative Humidity	Temperature
NO_2	1.000	–0.255	0.715	0.615	0.843	0.691	0.849	0.731	0.842	0.522	0.232	0.077
O_3 maximum	–0.255	1.000	0.263	0.304	–0.286	0.090	–0.066	0.090	–0.175	–0.291	–0.584	0.093
$PM_{2.5}$ mass	0.715	0.263	1.000	0.898	0.683	0.839	0.885	0.893	0.804	0.253	–0.021	0.114
$PM_{2.5}$ nitrate	0.615	0.304	0.898	1.000	0.519	0.659	0.728	0.705	0.693	0.095	–0.002	0.125
$PM_{2.5}$ organic compounds	0.843	–0.286	0.683	0.519	1.000	0.797	0.857	0.742	0.847	0.793	0.248	0.047
$PM_{0.1}$	0.691	0.090	0.839	0.659	0.797	1.000	0.817	0.751	0.716	0.464	–0.032	0.062
$PM_{2.5}$ elemental carbon	0.849	–0.066	0.885	0.728	0.857	0.817	1.000	0.929	0.933	0.414	0.154	0.089
On-road diesel $PM_{2.5}$	0.731	0.090	0.893	0.705	0.742	0.751	0.929	1.000	0.866	0.352	0.046	0.081
On-road gasoline $PM_{2.5}$	0.842	–0.175	0.804	0.693	0.847	0.716	0.933	0.866	1.000	0.449	0.270	0.076
Biomass combustion $PM_{2.5}$	0.522	–.291	0.253	0.095	0.793	0.464	0.414	0.352	0.449	1.000	0.193	-0.006
Relative humidity	0.232	–0.584	–0.021	–0.002	0.248	–0.032	0.154	0.046	0.270	0.193	1.000	0.237
Temperature	0.077	0.093	0.114	0.125	0.047	0.062	0.089	0.081	0.076	-0.006	0.237	1.000

negative associations with NO_2 (r = 0.26) and some of the particle species or source tracers.

Figure 10 displays the spatial distributions of several pollutants across Southern California in 2016, including $PM_{2.5}$ mass, $PM_{2.5}$ nitrate, $PM_{2.5}$ EC, and $PM_{0.1,}$ as well as $PM_{2.5}$ on-road gasoline and diesel. The spatial patterns differed substantially among several pollutants. For example, $PM_{2.5}$ on-road gasoline displayed variation consistent with highways that carry large volumes of traffic, whereas $PM_{2.5}$ mass and $PM_{2.5}$ nitrate had relatively consistent exposures across the region, likely because secondary formation of these particles in the atmosphere contributed a large portion of the mass. All pollutants had relatively higher concentrations in the inland areas of San Bernardino and Riverside.

RESULTS FROM ADJUSTED MODELS

The confounders selected for each pollutant in the adjusted models are shown in Appendix Table C1. The main results regarding associations between air pollution and COVID-19–related death are presented in **Figure 11** and Appendix Table C3. After adjustment for confounding, several air pollutants were significantly associated with dying among hospitalized patients with COVID-19, including $PM_{2.5}$ mass (hazard ratio [HR], 1.12; 95% CI, 1.06–1.17), $PM_{2.5}$ nitrate (HR, 1.12; 95% CI, 1.07–1.17), $PM_{2.5}$ EC (HR, 1.07; 95% CI, 1.03–1.13), $PM_{0.1}$ (HR, 1.06; 95% CI, 1.02–1.10), $PM_{2.5}$ on-road diesel (HR, 1.06; 95% CI, 1.03–1.10), and $PM_{2.5}$ on-road gasoline (HR, 1.07; 95% CI, 1.02–1.13). The effects of $PM_{2.5}$ mass were partly confounded by NO_2 in the two-pollutant models but remained significantly associated with an increased risk of death (Figure 11). During the period in which the Delta variant of SARS-CoV-2 was dominant, the findings on associations between $PM_{2.5}$ mass and COVID-19–related death were similar to results from the main model (HR, 1.13; 95% CI, 1.07–1.20).

The effects of gaseous species were sensitive to adjustment for co-pollutants. In particular, NO_2 was significantly associated with the risk of death (HR, 1.10; 95% CI, 1.04–1.16), whereas exposure to O_3 had a positive but nonsignificant effect on mortality risk (HR, 1.02; 95% CI, 0.96–1.08). Because inverse spatial patterns can lead to positive confounding,[22] we also ran co-pollutant models that included O_3 and NO_2. In those models, NO_2 exposure remained significantly associated with an elevated risk of death, but O_3 exposure showed no significant effects. When

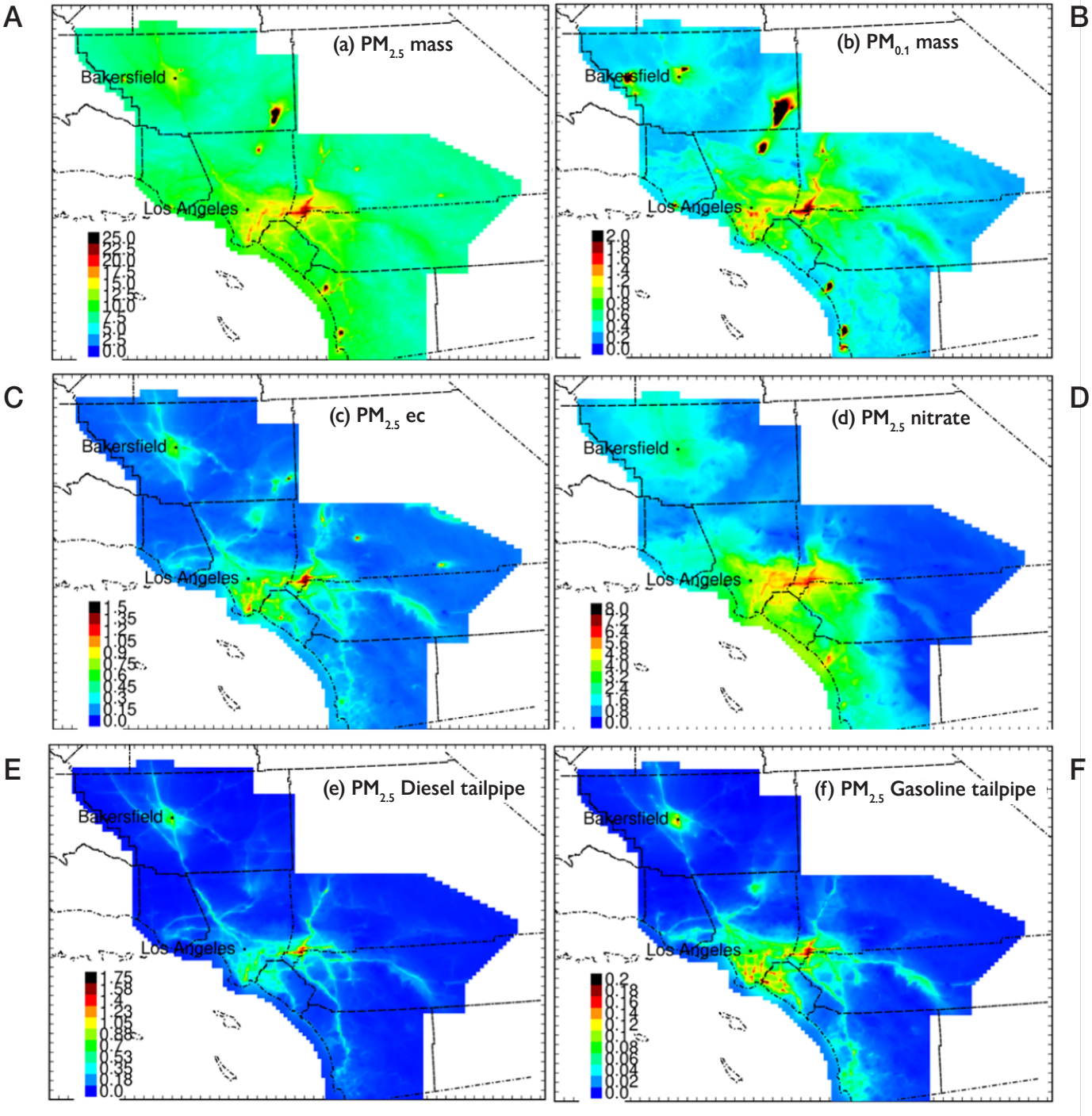


Figure 10. Spatial distributions of the predicted exposure fields for specific particulate matter air pollutants in Southern California, 2016. Data are presented for $PM_{2.5}$ mass (A), $PM_{0.1}$ (B), $PM_{2.5}$ elemental carbon (C), $PM_{2.5}$ nitrate (D), $PM_{2.5}$ on-road diesel (E), and $PM_{2.5}$ on-road gasoline (F). All units are $\mu g/m^3$.

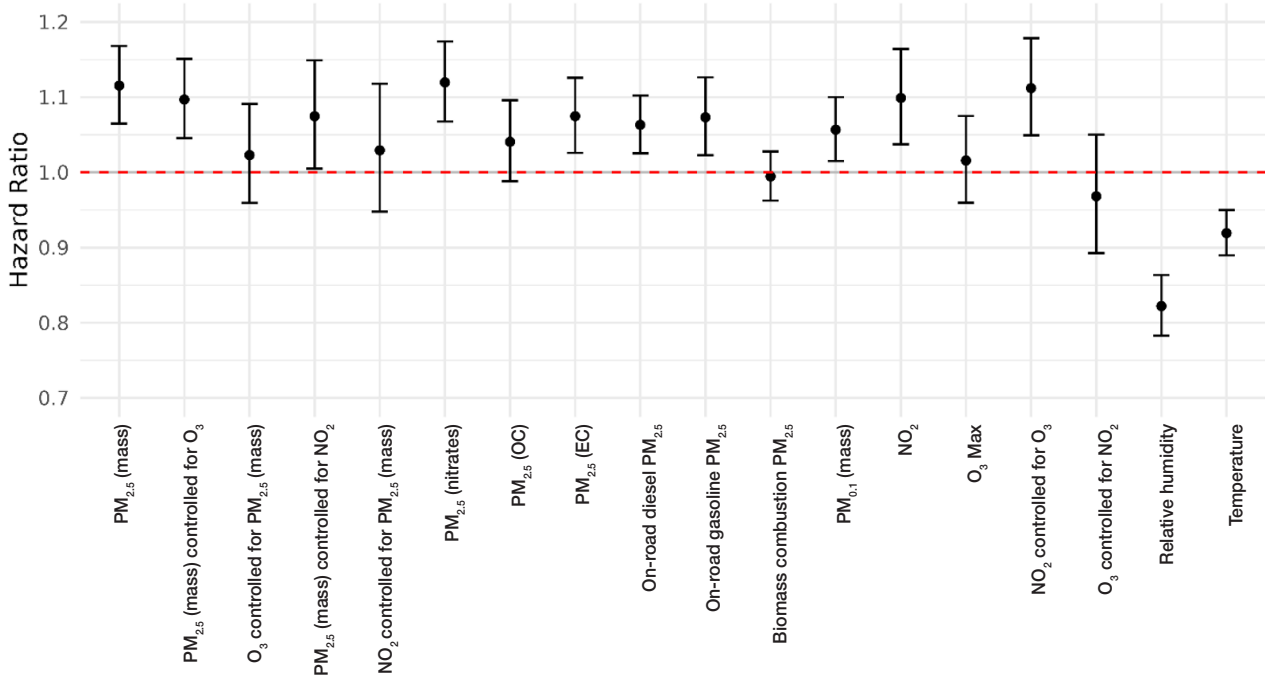


Figure 11. Risk plots showing hazard ratios for COVID-19 mortality per additional IQR increment in air pollutant exposures among patients hospitalized with COVID-19 in Southern California. Data are based on results from adjusted models controlling for confounders.

both $PM_{2.5}$ and NO_2 were included in the same model, adjustment for the confounding effect of $PM_{2.5}$ reduced the effect of NO_2 to the null (Figure 11).

Higher temperatures (HR, 0.92; 95% CI, 0.89–0.95) and higher humidity (HR, 0.82; 95% CI, 0.78–0.86) during the month in which a patient was diagnosed with COVID-19 were significantly associated with a lower risk of death.

STRATIFICATION ANALYSES

All variables included in the subgroup analyses demonstrated no significant impact on the relationship between air pollution concentrations and death among hospitalized patients with COVID-19, with statistical significance based on the Q statistic for each analysis (Appendix Tables C4 and C6).

INTERACTION MODELS WITH METEOROLOGICAL VARIABLES

After determining that temperature and humidity significantly modified the effects of air pollution on risk of death among hospitalized patients with COVID-19, we ran analyses that stratified by tertile for these variables to visualize the effect modification of the association between $PM_{2.5}$ and risk of death (**Figure 12**). Effect modification by strata of temperature and humidity in the analyses for other pollutants is displayed in Appendix Figure C1. For most of the pollutants, an elevated risk of death was seen only in the two lower tertiles of temperature. Effect modification was particularly pronounced for humidity, with the effects of most pollutants showing a graded decline with increased humidity. Overall, most effects of exposure to pollutants were present only in the two lower tertiles of humidity.

CONCENTRATION–RESPONSE ANALYSIS

Concentration–response curves are shown in **Figure 13**. For most of the pollutants, we observed fairly linear curves if sufficient data were available to support the spline derivation. Some pollutants, such as $PM_{2.5}$ EC and $PM_{2.5}$ on-road diesel, displayed a supralinear response, with a steeper response curve at low levels of exposure to the pollutant. This type of supralinear function has been observed in many studies of air pollution and mortality.[106] Humidity displayed a clear linear negative association with the risk of death in hospitalized patients with COVID-19. Temperature demonstrated a U-shaped curve, with risk of death appearing to be higher at lower temperatures, although there were insufficient data to support the spline derivation; the inverse curve appeared linear.

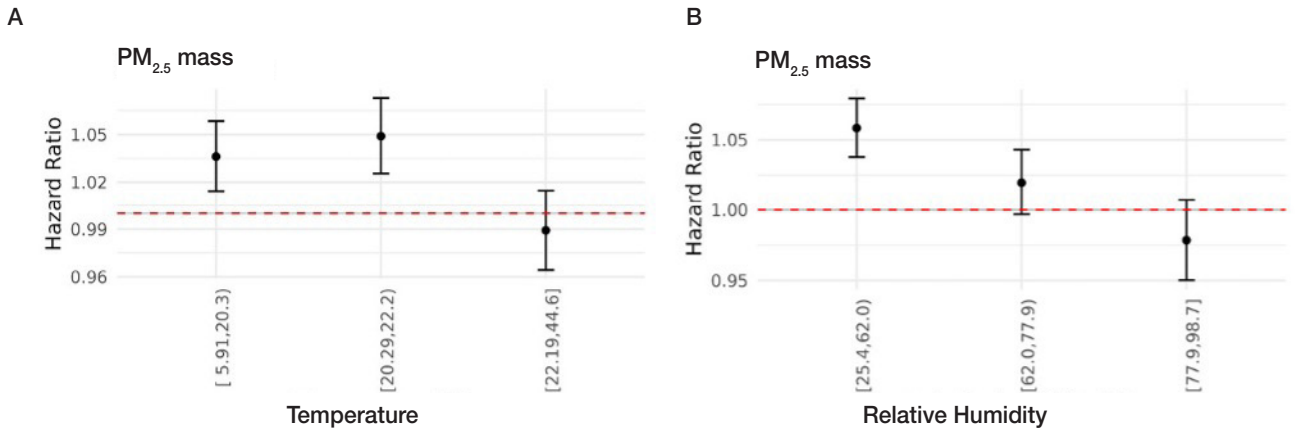


Figure 12. Risk plots of hazard ratios for COVID-19 mortality per additional IQR increment in $PM_{2.5}$ mass exposure, stratified by tertile of maximum temperature (A) and relative humidity (B) during the month of diagnosis, among patients hospitalized with COVID-19 in Southern California. Stratified risk plots for other pollutants are presented in Appendix C.

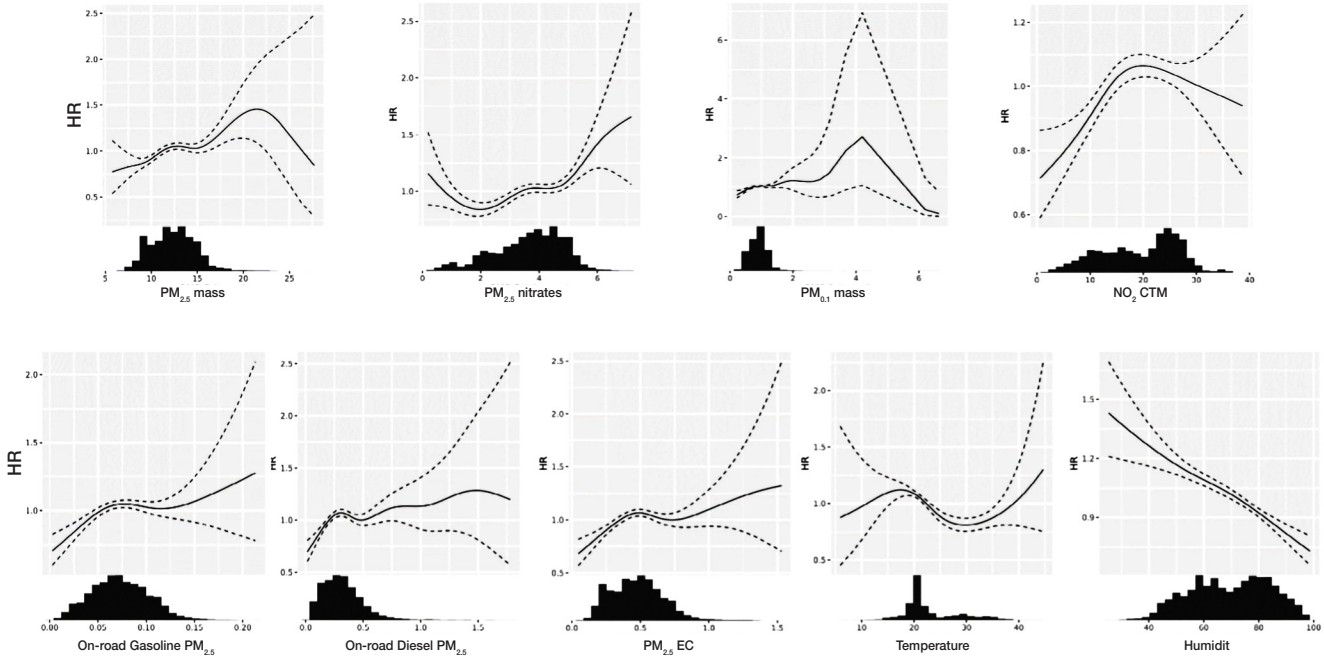


Figure 13. Concentration-response functions for pollutants and meteorological variables. Units of measurement are μg/m³ for all pollutant concentrations, degrees Celsius for temperature, and percentage for relative humidity.

DISCUSSION AND CONCLUSION

In this study, we evaluated whether chronic exposure to air pollution and meteorological factors at the time of diagnosis affected the risk of death in patients hospitalized with COVID-19. We found that the risk of death after COVID-19–related hospitalization was significantly associated with exposure to $PM_{2.5}$ mass, $PM_{0.1}$, and several of the particle species or source tracers. The effects associated with $PM_{2.5}$ mass were reduced, but remained significantly elevated, in a model that included NO_2; however, the effect of NO_2 was reduced to a nonsignificant level in the two-pollutant model. Some species, such as $PM_{2.5}$ OC, demonstrated elevated yet statistically nonsignificant relative risks; the association between the $PM_{2.5}$ biomass combustion and risk of death was not statistically significant. During late summer and early fall, wildfires are the predominant source of biomass combustion, which produces significant organic carbon (Chapter 7). Most of the recent wildfires, however, occurred months before the large surge in COVID-19 cases and deaths that occurred from late October 2020 to early January 2021.

Meteorology is associated with the transmission of COVID-19,[107] and recent studies have shown that meteorological conditions likely affected COVID-19 mortality rates in Europe.[27] These researchers proposed that humidity may interfere with both the viral defenses of the nasal mucosa and the sputum deeper in the airway, resulting in more severe infection and subsequently contributing to a poor prognosis after the virus becomes established in the respiratory tract, particularly in the nose.[27,108] Temperature and humidity can also affect the size of viral droplets and persistence of the virus in ambient air, although the extent to which these effects could affect disease severity is unknown.[109] Our study demonstrated significant negative associations between both temperature and humidity and the risk of death in hospitalized patients with COVID-19. We also found significant effect modification of the associations between air pollution and mortality, with lower temperature and humidity generally associated with larger air pollution effects. If viral defenses are indeed influenced by meteorology, this lends biological plausibility to both the direct effects of humidity and temperature and their effect modification of the association between air pollution and COVID-19 mortality.

Comparing the results of our study to the findings of other mortality studies provides several relevant insights. Chen and colleagues[21] investigated the effect of air pollution on COVID-19 severity and mortality, using data on KPSC members and a California Line Source Dispersion Model (CALINE) that estimated traffic exposures (freeway and nonfreeway) using NO_x concentrations. For each standard deviation increase in the level of nonfreeway NO_x, the odds of ICU admission were 1.11 (95% CI, 1.04–1.19), and the odds of death were 1.10 (95% CI, 1.03–1.18). Exposure to several other freeway pollutants, however, had protective effects.[21] Including regional $PM_{2.5}$ and NO_2 as confounders attenuated the effects by 19% to 26%; after this adjustment for confounding, exposure to freeway NO_x demonstrated a significantly protective effect on mortality (ORR, 0.94; 95% CI, 0.88–1.01). Exposure measurement error may have been present in this study, given the inability of the CALINE dispersion model to handle complex traffic, terrain, and meteorological conditions, all of which exist in Southern California.[110,111] The present study had a longer follow-up period (with about 4.5 times as many deaths) than did the study by Chen and colleagues, which also may have contributed to differences in the findings.

Additionally, a follow-up to this study, which used the same health data but relied on inverse-distance averaging to interpolate data from government monitors, identified significant chronic effects associated with $PM_{2.5}$ exposure and subchronic effects of exposure to NO_2.[41] This follow-up study, however, also had a high probability of exposure measurement error, given the spatial variation in these pollutants and the sparse data support available from the relatively few government monitors, each covering thousands of square kilometers.[41]

Another study from the United Kingdom relied on UK Biobank data and used an agnostic exposomic approach to evaluate many risk factors for COVID-19 incidence and mortality.[39] Although mild associations with $PM_{2.5}$ exposure were present in univariate models, these associations were eliminated in multivariate models, leading the authors to conclude there was little evidence of an independent association between air pollution and COVID-19 mortality. This study, however, involved relatively few deaths and may have lacked power to detect subtle effects of air pollution.

A study using data from hospitalized patients in New York City reported an association between each 1-μg/m^3 increase in $PM_{2.5}$ exposure and risk of mortality (risk ratio, 1.11; 95% CI, 1.02–1.21).[38] Given the reported IQR of 0.7 μg/m^3, the rate ratio would be approximately 1.08. Neither black carbon nor NO_2 exposure was significantly associated with COVID-19 mortality. Notably, this study also found that Hispanic ethnicity significantly modified the association between air pollution and risk of COVID-19–related death; these results differ from our finding of no significant effect modification by racial/ethnic subgroups. This study lacked individual data on certain potential risk factors for COVID-19 mortality, including obesity and smoking; consequently, residual confounding in the results cannot be ruled out.

A study involving a large administrative cohort from Rome, Italy, identified significant associations between both NO_2 and $PM_{2.5}$ exposure and COVID-19 mortality.[40] The associations in that study were somewhat smaller than those found in our study, although there is overlap between the CIs for both studies.[40] The range of $PM_{2.5}$ exposures in the Italian cohort was much smaller than what we observed in Southern California, which may partly explain the smaller effects observed in Rome.

The present study has several limitations. For instance, although we controlled for several individual confounders (e.g., smoking status and obesity), the data from the KPSC health system did not include potentially important confounding variables, such as occupational status. Nascent research suggests that some occupational groups in California have an increased risk of mortality from COVID-19, particularly in the farming, material moving, transportation, and construction sectors, all of which may involve elevated occupational exposure to air pollution.[112] It is possible that the lack of data on occupational status could have biased our results, although it is important to consider that there are numerous complexities involved in analyzing and interpreting data on COVID-19 mortality risk in different occupational groups.[112,113]

An additional limitation of the present study involves the temporal mismatch between the exposure fields from 2016, which predated the study by roughly 3 years, and other more current sources of data. Overall spatial pat-

terns of exposure are unlikely to have changed over this intervening period. Some portions of our study period, however, overlapped with the COVID-19–related lockdown period, during which traffic emissions were lower.[114] Therefore, patients in the study cohort may have experienced lower exposures to air pollution than they would have under normal conditions; we did not account for this factor in our exposure or statistical models. The impact of this limitation would have resulted in overestimating the near-source traffic exposures of patients, which may have biased some results toward the null hypothesis. In our study, the risks of COVID-19 mortality associated with exposure to near-road pollutants, such as $PM_{2.5}$ EC, $PM_{0.1}$, $PM_{2.5}$ on-road diesel, and $PM_{2.5}$ on-road gasoline, were lower than the risks associated with $PM_{2.5}$ mass and $PM_{2.5}$ nitrate exposures; these findings may reflect the lack of capacity in our exposure model to account for potential effects of the COVID-19 lockdown. Despite this limitation, our study still demonstrated significant associations between several near-source pollutants and COVID-19 mortality. We were also unable to account for the acute effects of air pollution that may have contributed to the risks of COVID-19 mortality. Currently, we are extending the CTM to derive contemporaneous estimates of acute and chronic exposure to pollutants.

Another concern with observational studies of COVID-19 and resulting mortality pertains to the different SARS-CoV-2 variants that emerged and gained dominance during the course of the pandemic. If certain variants were more virulent than others, as appears likely,[115] and these virulent variants coincidentally emerged during periods with high levels of air pollution, the associations between air pollution exposure and COVID-19 mortality could be confounded by the virulence of the SARS-CoV-2 variants. In this study, the Delta variant was dominant during the majority of the study period. We performed sensitivity tests on the $PM_{2.5}$ model by restricting the analysis to periods when Delta was the dominant variant; the results from the restricted analysis were virtually the same as those from the full analysis. Given the similarity in these findings, we concluded that our results were not likely confounded by differing levels of virulence among SARS-CoV-2 variants.

We used data on time-to-event after hospitalization to avoid bias in our follow-up periods, which could have varied considerably if we had used the date of COVID-19 diagnosis as the starting point for each patient in the study. A more general concern about collider bias has been raised regarding studies of COVID-19 and hospitalization. If the tracking of COVID-19 begins at the point of infection, hospitalization can be a collider variable, as both COVID-19 and air pollution exposure could increase the risk of hospitalization. As a follow-up, our study began at the point of hospitalization; however, the hospitalization event is not a collider variable. Nevertheless, restricting the study population to hospitalized patients likely reduced the generalizability of our results to hospitalized individuals rather than the general population.

Other environmental variables, including wind speed and ultraviolet radiation, have also been implicated in the spread and severity of COVID-19. Both of these variables were purposefully included in our CTM for exposures. Wind speed, in particular, has a major impact on ambient concentrations of several pollutants, and we were concerned that including wind speed as a distinct variable would induce collinearity into the model. In reviewing the literature on wind speed, we also found that most of the influence of this meteorological parameter affects the transmission of COVID-19 but not the severity of symptoms or risk of death.[108,109] Ultraviolet B (UVB) radiation potentially influences COVID-19 outcomes via its relationship to vitamin D deficiency, which has been identified as a risk factor for more severe COVID-19 outcomes.[116] We visually explored the 1-km UVB fields used as inputs in the CTM used in this study. UVB levels were higher inland and lower near the Pacific coastline, likely due to fog and cloud cover. Recent UVB exposure modeling, however, estimates that personal behavior and occupation are much more important predictors of UVB exposure than ambient levels alone, which often account for little of the explained variation in objectively measured UVB.[117,118] Therefore, ambient levels of UVB are unlikely to be reasonable proxies for UVB exposure and subsequent deficiency.

Additionally, we queried our database to identify patients with vitamin D deficiency and performed stratified analyses to assess whether air pollution contributed to worse outcomes in these patients. Of the patients in the study cohort, 4,142 (19.34%) had a laboratory vitamin D test within 1 year before their COVID test date; among those who had a vitamin D test, 1,524 (7.13% of the total cohort) were deficient in vitamin D (i.e., 25-hydroxyvitamin D laboratory result <30 ng/mL) based on their most recent vitamin D laboratory result before hospitalization. As this subgroup of patients with vitamin D deficiency is a relatively small proportion of the entire cohort (and likely represents an underestimate of the actual size of the subgroup), we were unable to stratify the analysis.

Virucidal activity also decreases in the presence of higher levels of UVB radiation,[108,109] although this effect would be more likely to influence viral transmission and not disease severity. Furthermore, most of the COVID-19 cases likely occurred as a result of exposure to SARS-CoV-2 in an indoor environment, where ambient UVB radiation would likely have minimal impact on virucidal activity.[108] Future research is nevertheless needed to determine whether vitamin D deficiency modifies the effects of air pollution exposure on COVID-19 severity.

Saturation of ICU capacity, another possible factor affecting survival in COVID-19 patients, may have acted as a confounder in this study. Internal data and consultations with attending physicians revealed, however, that despite the described surge in COVID-19 cases (Figure 9), the KPSC ICUs were never saturated beyond capacity during this period. The health system did not run out of ventilators

or physical space for admitting seriously ill patients with COVID-19. An overflow facility that could have accepted KPSC patients was never used. Thus, saturation of the ICU is unlikely to have confounded our results.

The observational nature of this study precludes causal interpretation of the results. Our findings nevertheless enable us to conclude that chronic exposure to air pollution in Southern California is associated with increased risk of death from COVID-19. Better knowledge about environmental factors, such as air pollution and meteorology, could be used by communities and local governments to target neighborhoods with higher risks of COVID-19 mortality. Such information could also be used by healthcare systems to assist clinicians in better estimating the likely severity of disease in patients residing in areas with high levels of air pollution. Minimizing transmission and reducing the severity of COVID-19 through nonpharmaceutical interventions, such as masking and economic shutdowns, remains problematic over the longer term,[119] given the social and environmental costs of such approaches. Furthermore, modeling suggests that nonpharmaceutical measures have the potential to increase the severity of other respiratory viral outbreaks in the future.[120] Pharmaceutical measures like vaccines continue to have mixed results, partly because of vaccine hesitancy in some locations and population groups.[121] By contrast, air pollution is a modifiable environmental risk factor that could affect disease severity across the entire population. Reducing air pollution may thus provide a more sustainable means of reducing COVID-19 severity, thereby yielding substantial population benefits. Mitigating air pollution may also lessen the risks of catastrophic outcomes due to future pandemics fueled by novel viruses, while also beneficially affecting a wide array of other health endpoints.

CHAPTER 6: AIR POLLUTION AND PROGRESSION OF COVID-19: A MULTISTATE ANALYSIS

INTRODUCTION

Although vaccines are critically important in reducing the severity of COVID-19 infections, vaccination against COVID-19 has demonstrated mixed results as a strategy for disease control, partly because of vaccine hesitancy in some population groups and geographic locales.[121] The limitations of such pharmaceutical interventions have prompted interest in the modification of environmental risk as a potential approach to reducing the severity of COVID-19 after infection occurs.

Air pollution is a pervasive yet modifiable environmental exposure. Studies using individual-level data have revealed that air pollution can lead to increased risk of hospitalization, ICU admission, and death.[21,38–41,122–124] To date, no studies have investigated how air pollution affects patients' progression from hospital admission for COVID-19 to outcomes such as admission to the ICU, death, or recovery. Increasing the body of knowledge about how air pollution may influence the progression of COVID-19 through possible states of severity or recovery or both can help strengthen understanding of how this ubiquitous environmental exposure affects prognosis in COVID-19. Such information would provide another strategy for mitigating the severity of COVID-19 while circumventing debates about vaccine efficacy and safety.

In this study, we used a unified multistate survival model to investigate how air pollution affects transitions between different states of health that can occur after hospitalization with COVID-19. We hypothesized that 1) patients living in areas with higher chronic exposure to air pollution who are hospitalized with COVID-19 are more likely to progress toward serious illness requiring ICU admission or death than are patients with less exposure to air pollution, and 2) patients living in areas with higher chronic exposure to air pollution who are hospitalized with COVID-19 will be less likely than those living in areas with less chronic air pollution exposure to transition toward sustained recovery.

METHODS

KPSC COHORT AND HEALTH DATA

The KPSC membership of 4.7 million people broadly represents the overall population of Southern California.[94] KPSC maintains an EHR in an integrated system that captures all aspects of patient care, including diagnoses, inpatient and outpatient encounters, pharmacy encounters, and laboratory tests.

We identified KPSC patients with a positive COVID-19 molecular diagnostic test and/or diagnosis of COVID-19 based on prior testing (ICD-10 codes B34.2, B97.29, J12.89, J20.8, J22, J80, or U07.1) that occurred from June 1, 2020, to January 30, 2021. Given that rapid changes in clinical care occurred over the first months of the pandemic, we chose to begin the observation period for this study on June 1, 2020, by which time new standards of care for COVID were more widely implemented.

The study cohort included patients aged 18 years or older at the time of their COVID-19 diagnosis or positive COVID-19 test. To reliably assess comorbidities, we restricted eligibility to those who had been KPSC members for at least 1 year before their COVID-19 diagnosis or positive test or both. COVID-19–related hospitalizations were defined as those that occurred within 21 days of a patient's COVID-19 diagnosis or positive test (N = 316,224).[95] The study cohort comprised only hospitalized patients rather than all those who tested positive for COVID-19, as testing may have occurred after contact with an infected person or upon hospital admission after the onset of severe illness. Such timing could lead to uncertainty about the window of time within which testing could have occurred in different patients, thereby introducing substantial errors in the study follow-up times and thus leading to biased results in the statistical models. Limiting the study to hospitalized patients eliminated these concerns, as there was no uncertainty about the date of hospitalization. Approximately one-quarter of patients included in the initial sample were ineligible because they received treatment outside the KPSC system, making it unfeasible to reliably ascertain their course of treatment. Patients whose KPSC membership ended during the 90-day observation window or who were hospitalized for childbirth were excluded from the study. Patients who died up to 90 days after either their initial hospitalization or a readmission after discharge were included in the study cohort. (Further details on the ascertainment of death data are provided in Appendix D.) The final cohort used for data analysis consisted of 15,978 patients with complete medical records. A flow chart depicting the selection criteria for the study population is presented in **Figure 14**. This study was approved by the Kaiser Permanente Institutional Review Board.

DEMOGRAPHICS AND COVARIATES

The EHR in the KPSC health system includes information on patient age, sex, and race/ethnicity.[95] The most recent BMI value available in the patient EHR was used to represent this potential confounder.[96] BMI data were cleaned using validation algorithms to delete biologically implausible values. In the HPSC health

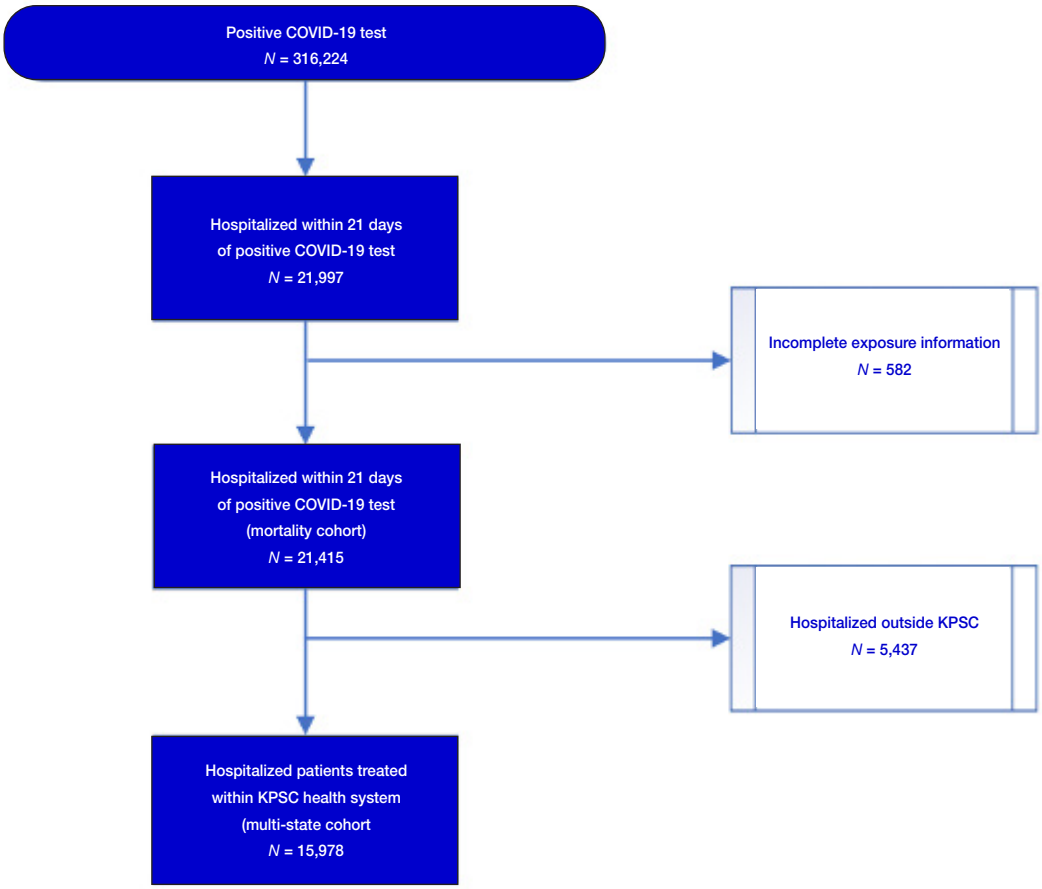


Figure 14. Flow chart depicting selection of the study cohort used in the multistate survival model.

system, smoking status and EVS data (coded as min/wk of moderate to vigorous exercise) are collected during each in-person outpatient healthcare encounter,[98] and we used data on these factors as potential confounders. Smoking status (ever-smoker or never-smoker) was coded based on the information provided during the patient's last encounter before their COVID-19 test or diagnosis, dating back up to 4 years. Patients who were enrolled at KPSC via MediCal (i.e., state-sponsored medical care for patients in poverty) were classified as having a very low income. We did not include COVID-19 vaccination status in the analysis, as COVID-19 vaccines were not yet widely available by the end of the study period. (A total of 19 patients in the study cohort had been vaccinated against COVID-19 before hospitalization.) In summary, four individual-level confounders were considered in the analysis: smoking status (ever-smoker vs. never-smoker), BMI and BMI^2, MediCal enrollment (as a proxy for poverty), and EVS data (as an estimation of the usual number of minutes per week of moderate to vigorous exercise).

CONTEXTUAL VARIABLES

We added predictors of community-level SES to the proxy for individual SES and adjusted for community-level effects of social determinants of health.[99–101] Community-level predictors at the census block group level were obtained from the 2018 American Community Survey.[102] These predictors included the previously validated NDI, a measure of crowding (the percentage of households with more than one occupant per home) that was used as a proxy for poor housing quality, and the percentage of workers aged 16 years or older who commute to work via public transportation (which is associated with low income in Southern California).[17]

Because previous research has indicated that meteorological conditions can affect the severity of COVID-19,[8] we obtained GridMET surface meteorological data (with approximately 4-km resolution) to estimate daily maximum temperature and relative humidity for the entire study period by using Google Earth Engine.[103] GridMET data for the home address of every study participant were aggregated to monthly means for the month of hospitalization with COVID-19.

Although the evidence is mixed, some research indicates that tree canopy and green cover can have a beneficial effect on respiratory health outcomes.[125] Emerging evidence from county-level analyses in the United States also indicates that green space may be associated with COVID-19 mortality.[126] We therefore included as a potential confounder a high-resolution metric of green space based on satellite retrievals compiled by the National Agriculture Imagery Program.[127]

EXPOSURE ASSESSMENT: CHEMICAL TRANSPORT MODEL

Exposure simulations were carried out across California, using the UCD/CIT source-oriented, three-dimensional, reactive chemical transport model (CTM).[104] The UCD/CIT model predicts the evolution of gas- and particle-phase pollutants in the atmosphere in the presence of emissions, transport, deposition, chemical reaction, and phase change. The pressing timeline for conducting this study during an ongoing public health crisis necessitated leveraging past efforts that had prepared and validated CTM inputs. We previously reported CTM exposure fields with 4-km resolution over California for the years 2000–2016.[105] We re-estimated exposures for 2016 at 1-km resolution. Meteorology and emission inputs for the year 2016 were downscaled to improve spatial resolution to 1 km. Bias in the raw CTM output fields was minimized using a constrained regression model based on source apportionment tags and the difference between predicted and measured concentrations. (Further details on methods used for the CTM are available in Appendix A.)

In this study, we estimated $PM_{2.5}$ mass, NO_2, and O_3. Subchronic exposure fields were assigned to the geocoded home address of the cohort members. The exposure fields were intended to account for spatial patterns of chronic exposure, which are relatively stable over the 4–5 years that ensued between the exposure modeling and formation of the study cohort. We accounted for residential mobility of patients by using a weighted average of exposures based on time spent at each residential address.

STATISTICAL ANALYSIS

We implemented a multistate survival model, using the mstate package in R.[128] These models used a time-to-event process to evaluate the instantaneous hazard of transitioning from one health state to another (e.g., from the ICU to death). The six health event states used in the model, along with the number of patients for each state and transition event, are presented in **Figure 15**. The multistate models essentially represent an extension of the Cox proportional hazards model to more than two states (e.g., alive or dead), allowing for efficient modeling of all predefined transition states. Compared to conventional Cox models for time-to-event processes, multistate models can simultaneously model dynamic transitions between multiple events, avoiding a loss of statistical power that can result from dividing the states into smaller samples, potentially leading to false-negative findings. Including multiple health states can also lead to novel insights about the

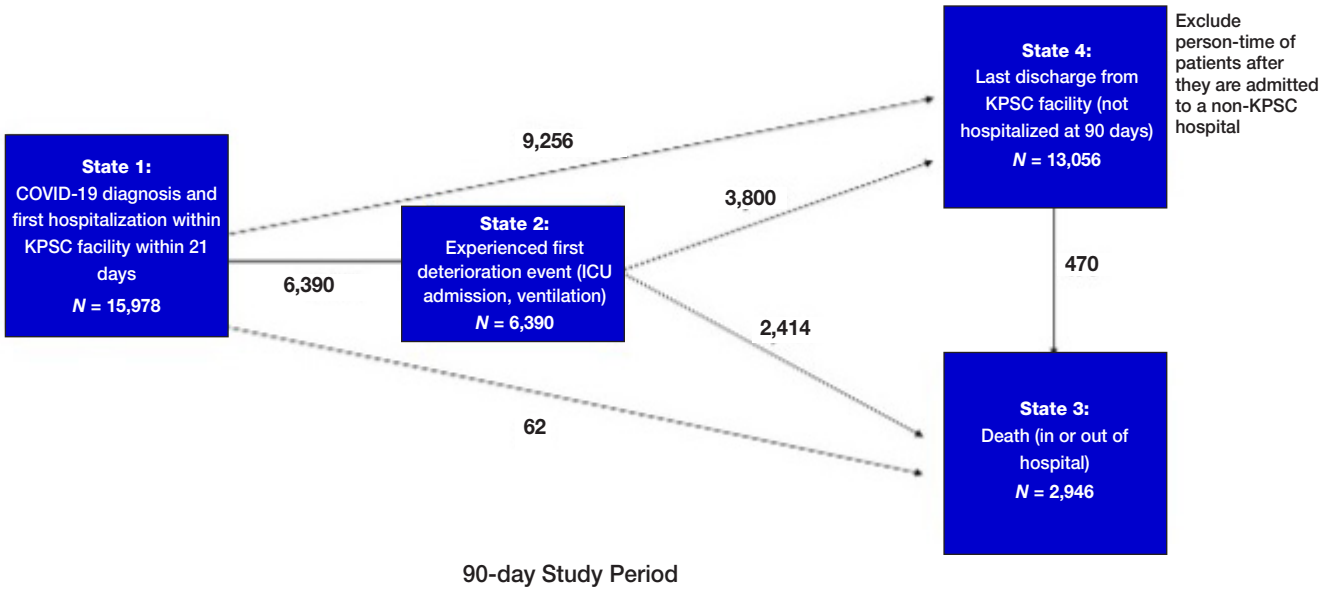


Figure 15. Health states and transition events between states in a multistate survival model, with number of patients by state and transition event. In the study cohort, 270 patients with COVID-19 who entered the hospital experienced no transition events but remained hospitalized for the entire study period.

relationship between intermediate endpoints and death (e.g., ICU to death).[129] We assumed that time spent in any given state did not influence the time spent in any other state (i.e., Markov assumption); this assumption effectively resets the follow-up time to zero once a patient enters a given state.

For a sensitivity analysis, we also ran Cox proportional hazards models to examine how air pollution exposure influences time between health states, by constructing a dataset consisting of patients who entered one health state and then transitioned to another state. We applied the same rules as those used in the multistate model. (Technical details on definitions of the states depicted in Figure 15 are available in Appendix D.) Confounders were included in the model if they changed the pollution coefficient by 10% or more in the Cox models. Confounders were selected separately for each of the transition events. (Further information on the included confounders is presented in Appendix Tables D2–D4.) In conducting a sensitivity analysis, we also included all possible individual confounders along with most of the contextual variables (i.e., temperature, humidity, green space, and neighborhood deprivations) while excluding the proportion of housing units with more than one occupant per room and the proportion of workers aged 16 or older using public transit, as these factors were collinear with neighborhood deprivation. We included age and sex as stratification variables in the baseline hazard. Confounders were included as linear terms or categorical variables, as shown in Appendix Tables D2–D4.

We also ran a series of two-pollutant models, including models for $PM_{2.5}$ and NO_2, $PM_{2.5}$ and O_3, and NO_2 and O_3.

RESULTS

Demographic and clinical characteristics of patients in the study cohort, stratified by major health event states, are presented in **Table 7**. Patients who experienced deterioration events after hospitalization (defined as admission to the ICU or use of intensive oxygen therapy) were older than those who did not progress to more severe states of health. Among hospitalized patients, the rate of deterioration was higher among Hispanic patients than among patients in other racial/ethnic groups. White patients experienced a higher rate of death compared to patients of other races or ethnicities. Rates of hospitalization, deterioration, and death were much higher among men than among women, and men had a lower rate of recovery than did women. Patients who deteriorated or died had higher rates of chronic disease, compared to those who recovered. Patients who experienced deterioration or died had slightly higher $PM_{2.5}$ and O_3 exposures, on average, than did all patients who were hospitalized or those who recovered; whereas, NO_2 exposures were generally similar across each of the health event transitions, with very slightly less exposure among patients who died. Similarly, patients who experienced deterioration or died generally resided in areas with lower ambient temperatures and humidity levels during the month in which they were diagnosed, compared to all hospitalized patients or those who recovered.

The possible transition events between health states, as well as the numbers and proportions of patients who experienced each health state event, are presented in Appendix Tables D6 and D7 and depicted in Figure 15. Many of the hospitalized patients experienced deterioration, with most deaths occurring in patients who first deteriorated.

The multistate model results for $PM_{2.5}$ exposure are shown in **Table 8** and **Figure 16**. Most of the transitions between events had the expected sign on the coefficients. Comparing the lowest quartile to the highest quartile of $PM_{2.5}$ exposure, the HR for experiencing the transition from hospitalization to a deterioration event was 1.16 (95% CI, 1.12–1.20). Similarly, comparing these quartiles of $PM_{2.5}$ exposure, the HR for transitioning from deterioration to death was 1.11 (95% CI, 1.04–1.17). The level of $PM_{2.5}$ exposure was not significantly associated with the risk of experiencing other transition events except, notably, the transition from recovery to death, for which the HR was 1.10 (95% CI, 0.97–1.25).

Results for O_3 were largely consistent with those for $PM_{2.5}$ (Table 8 and Figure 16). Comparing the lowest quartile to the highest quartile of O_3 exposure, the HR for transitioning from hospitalization to deterioration was 1.21 (95% CI, 1.13–1.28). The HR for transitioning from hospitalization to recovery was 0.96 (95% CI, 0.91–1.00), suggesting that those living in areas with lower O_3 exposure were more likely to recover than those living in areas with higher levels of O_3. The point estimate of the HR for transitioning from hospitalization to death was elevated, although this association with O_3 exposure was not statistically significant. Comparing the lowest vs. highest quartile of O_3 exposure, the HR for transitioning from deterioration to death was 1.08 (95% CI, 0.98–1.19), which was of borderline significance. The strongest association with O_3 was seen for the transition from recovery to death, with an HR of 1.24 (95% CI, 1.01–1.51), implying that those who lived in areas with greater O_3 exposure were more likely to die after discharge from the hospital than those in areas with lower levels of O_3.

Effects of NO_2 exposure (i.e., lowest vs. highest quartile) were somewhat weaker than those for O_3 or $PM_{2.5}$ (Table 8 and Figure 16). The HR for transitioning from hospitalization to deterioration was 1.19 (95% CI, 1.13–1.24). Unexpectedly, based on a small group of 62 patients, the HR for transitioning directly from hospitalization to death was 0.60 (95% CI, 0.40–0.90). The HR for the transition from deterioration to death was elevated, but the association was not statistically significant (HR, 1.07; 95% CI, 0.99–1.16).

The sensitivity analysis that included all patients and most of the contextual confounders of the effects of pollutant exposure largely supported all of the main results,

Table 7. Demographic and Clinical Characteristics and $PM_{2.5}$, NO_2, and O_3 Exposures of Patients Hospitalized with COVID-19, by Health Event

Characteristic	All Hospitalized (*N* = 15,978)	Ever Deteriorated (*N* = 6,390)	Ever Recovered/ Discharged (*N* = 13,056)	Died (*N* = 2,946)
Deterioration date indicator 0/1[a]	6,390 (40.0%)	6,390 (100.0%)	3,800 (29.1%)	2,572 (87.3%)
Died indicator 0/1[a]	2,946 (18.4%)	2,572 (40.3%)	470 (3.60%)	2,946 (100.0%)
Recovery indicator 0/1[a]	13,056 (81.7%)	3,800 (59.5%)	13,056 (100.0%)	470 (16.0%)
Age index				
Median (IQR)	63 (51, 74)	65 (55, 75)	61 (50, 72)	73 (63, 82)
Mean (SD)	62 (16)	64 (15)	60 (16)	72 (13)
Range	18, 105	18, 102	18, 105	18, 105
Race/ethnicity[a]				
Asian/Pacific Islander	1,810 (11.3%)	743 (11.6%)	1,492 (11.4%)	311 (10.6%)
Black	1,342 (8.40%)	477 (7.46%)	1,107 (8.48%)	241 (8.18%)
Hispanic	9,538 (59.7%)	4,037 (63.2%)	7,788 (59.7%)	1,702 (57.8%)
White	3,143 (19.7%)	1,082 (16.9%)	2,550 (19.5%)	666 (22.6%)
Other/multiple/unknown	145 (0.91%)	51 (0.80%)	119 (0.91%)	26 (0.88%)
Sex[a]				
Female	6,700 (41.9%)	2,288 (35.8%)	5,715 (43.8%)	1,041 (35.3%)
Male	9,278 (58.1%)	4,102 (64.2%)	7,341 (56.2%)	1,905 (64.7%)
Medicaid[a]				
No	13,961 (87.4%)	5,545 (86.8%)	11,482 (87.9%)	2,515 (85.4%)
Yes	2,017 (12.6%)	845 (13.2%)	1,574 (12.1%)	431 (14.6%)
Exercise Vital Sign				
Median (IQR)	0 (0, 95)	0 (0, 90)	0 (0, 100)	0 (0, 75)
Mean (SD)	62 (97)	57 (90)	65 (100)	47 (82)
Range	0, 1,050	0, 1,050	0, 1,050	0, 1,050
Unknown	529 (3.31%)	224 (3.51%)	452 (3.46%)	68 (2.31%)
Housing units with >1 occupant/room (%)				
Median (IQR)	0.10 (0.03, 0.19)	0.10 (0.03, 0.20)	0.09 (0.03, 0.19)	0.10 (0.03, 0.19)
Mean (SD)	0.12 (0.12)	0.13 (0.12)	0.12 (0.12)	0.12 (0.11)
Range	0.00, 0.78	0.00, 0.71	0.00, 0.78	0.00, 0.71
Unknown	384 (2.40%)	153 (2.39%)	322 (2.47%)	67 (2.27%)
Neighborhood Deprivation Index				
Median (IQR)	0.45 (−0.24 to 1.28)	0.52 (−0.19 to 1.36)	0.45 (−0.25 to 1.28)	0.46 (−0.25 to 1.33)
Mean (SD)	0.58 (1.03)	0.64 (1.03)	0.57 (1.03)	0.59 (1.04)
Range	−1.56 to 5.28	−1.56 to 5.28	−1.51 to 5.28	−1.56 to 4.08
Unknown	4 (0.03%)	2 (0.03%)	3 (0.02%)	1 (0.03%)

Continues next page

Table 7. (*continued*)

Characteristic	All Hospitalized (*N* = 15,978)	Ever Deteriorated (*N* = 6,390)	Ever Recovered/ Discharged (*N* = 13,056)	Died (*N* = 2,946)
Workers aged ≥16 yr commuting by public transportation (%)				
Median (IQR)	0.02 (0.00, 0.06)	0.02 (0.00, 0.06)	0.02 (0.00, 0.06)	0.02 (0.00, 0.05)
Mean (SD)	0.04 (0.06)	0.04 (0.06)	0.04 (0.06)	0.04 (0.06)
Range	0.00, 0.83	0.00, 0.58	0.00, 0.83	0.00, 0.58
Unknown	383 (2.40%)	153 (2.39%)	321 (2.46%)	67 (2.27%)
BMI (kg/m²)				
Median (IQR)	31 (27, 36)	32 (28, 37)	31 (27, 36)	30 (26, 35)
Mean (SD)	32 (8)	33 (8)	32 (8)	31 (8)
Range	13, 88	14, 88	13, 87	13, 88
Unknown	429 (2.68%)	189 (2.96%)	362 (2.77%)	60 (2.04%)
Elixhauser comorbidities				
Median (IQR)	2.00 (1.00, 5.00)	3.00 (1.00, 5.00)	2.00 (1.00, 4.00)	4.0 (2.0, 6.0)
Mean (SD)	3.08 (2.88)	3.26 (2.92)	2.82 (2.76)	4.4 (3.1)
Range	0.00, 18.00	0.00, 17.00	0.00, 18.00	0.0, 16.0
Elixhauser, combined CVD[a]	5,570 (34.9%)	2,375 (37.2%)	4,037 (30.9%)	1,630 (55.3%)
Unknown	391 (2.45%)	156 (2.44%)	332 (2.54%)	56 (1.90%)
Elixhauser, combined hypertension[a]	8,651 (54.1%)	3,722 (58.2%)	6,595 (50.5%)	2,106 (71.5%)
Unknown	391 (2.45%)	156 (2.44%)	332 (2.54%)	56 (1.90%)
Elixhauser, combined pulmonary disease[a]	3,013 (18.9%)	1,260 (19.7%)	2,346 (18.0%)	682 (23.2%)
Unknown	391 (2.45%)	156 (2.44%)	332 (2.54%)	56 (1.90%)
Elixhauser, combined diabetes[a]	6,882 (43.1%)	3,114 (48.7%)	5,265 (40.3%)	1,598 (54.2%)
Unknown	391 (2.45%)	156 (2.44%)	332 (2.54%)	56 (1.90%)
Elixhauser, combined other[a]	9,406 (58.9%)	3,817 (59.7%)	7,331 (56.2%)	2,142 (72.7%)
Unknown	391 (2.45%)	156 (2.44%)	332 (2.54%)	56 (1.90%)
Relative Humidity (%)				
Median (IQR)	72 (59, 82)	70 (58, 80)	73 (60, 82)	68 (58, 79)
Mean (SD)	71 (14)	69 (14)	71 (14)	68 (13)
Range	33, 99	33, 99	33, 98	33, 98
Temperature (°C)				
Median (IQR)	21.1 (20.1, 25.3)	21.0 (20.0, 23.5)	21.2 (20.2, 25.9)	20.9 (20.0, 22.7)
Mean (SD)	23.1 (4.8)	22.7 (4.6)	23.2 (4.8)	22.4 (4.4)
Range	5.9, 38.5	8.7, 38.5	5.9, 38.0	10.5, 38.5
Smoking status[a]				
Never-smoker	10,246 (64.1%)	3,890 (60.9%)	8,655 (66.3%)	1,598 (54.2%)
Ever-smoker	5,543 (34.7%)	2,421 (37.9%%)	4,241 (32.5%)	1,323 (44.9%)
Unknown	189 (1.18%)	79 (1.24%)	160 (1.23%)	25 (0.85%)

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Table 7. (*continued*)

Characteristic	All Hospitalized (*N* = 15,978)	Ever Deteriorated (*N* = 6,390)	Ever Recovered/ Discharged (*N* = 13,056)	Died (*N* = 2,946)
$PM_{2.5}$ mass (μg/m³)				
Median (IQR)	12.60 (11.00, 14.20)	12.80 (11.30, 14.40)	12.60 (10.90, 14.20)	12.80 (11.20, 14.40)
Mean (SD)	12.63 (2.36)	12.87 (2.33)	12.58 (2.34)	12.84 (2.44)
Range	6.12, 27.70	6.53, 26.30	6.12, 27.70	6.50, 23.80
NO_2 (ppb)				
Median (IQR)	22 (15, 25)	22 (16, 25)	22 (14, 25)	21 (15, 25)
Mean (SD)	20 (7)	20 (6)	20 (7)	20 (7)
Range	1, 34	1, 33	1, 34	2, 33
O_3 maximum (ppb)				
Median (IQR)	66 (60, 73)	67 (61, 74)	66 (60, 72)	67 (61, 74)
Mean (SD)	66 (8)	67 (8)	66 (8)	67 (8)
Range	40, 84	43, 84	42, 84	43, 83

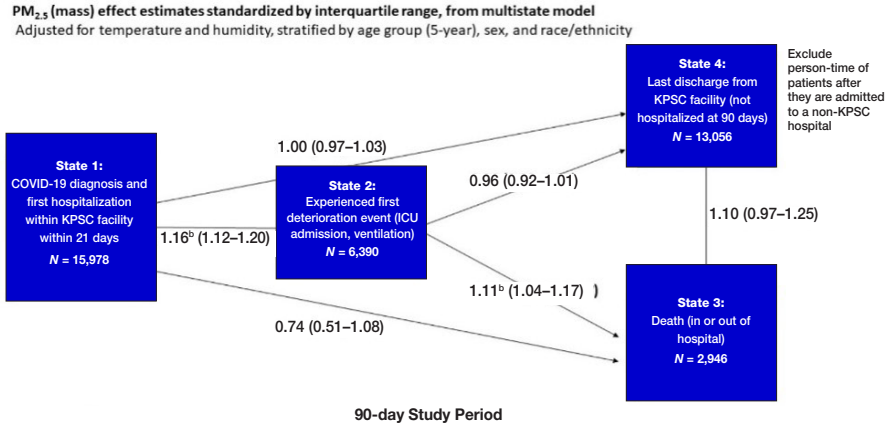
CVD = cardiovascular disease.
[a]Presented data are *n* (%).

Table 8. Effects of Pollutant Exposure on Transitions Between COVID-19–Related Health States[a]: Results of Single- and Multipollutant Models

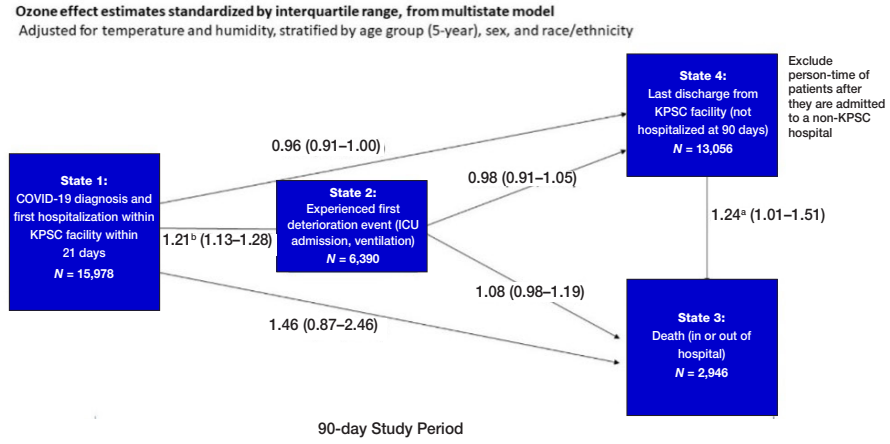
	Hospitalization to Deterioration		Hospitalization to Recovery		Hospitalization to Death		Deterioration to Recovery		Deterioration to Death		Recovery to Death	
Single Pollutant	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
$PM_{2.5}$ mass	1.16	1.12, 1.20	1.00	0.97, 1.03	0.74	0.51, 1.08	0.96	0.92, 1.01	1.11	1.04, 1.17	1.1	0.97, 1.25
O_3 maximum[b]	1.21	1.13, 1.28	0.96	0.91, 1.00	1.46	0.87, 2.46	0.98	0.91, 1.05	1.08	0.98, 1.19	1.24	1.01, 1.51
NO_2	1.19	1.13, 1.24	1.01	0.97, 1.04	0.60	0.40, 0.90	1.03	0.97, 1.09	1.07	0.99, 1.16	1.03	0.86, 1.23
Two Pollutants												
$PM_{2.5}$ mass	1.13	1.09, 1.17	1.01	0.98, 1.03	0.67	0.45, 1.00	0.96	0.91, 1.01	1.10	1.04, 1.17	1.07	0.93, 1.23
O_3 maximum	1.13	1.06, 1.21	0.96	0.91, 1.01	1.68	0.98, 2.90	1.00	0.92, 1.08	1.03	0.94, 1.14	1.19	0.95, 1.48
O_3 maximum	1.24	1.17, 1.32	0.96	0.92, 1.01	1.39	0.85, 2.28	0.98	0.91, 1.05	1.11	0.99, 1.23	1.27	0.99, 1.61
NO_2	1.21	1.15, 1.26	1.00	0.97, 1.04	0.59	0.38, 0.92	1.03	0.96, 1.10	1.08	1.00, 1.17	1.03	0.86, 1.23
$PM_{2.5}$ mass	1.11	1.05, 1.17	0.98	0.94, 1.03	1.00	0.58, 1.73	0.90	0.84, 0.96	1.14	1.04, 1.25	1.21	0.99, 1.49
NO_2	1.07	1.00, 1.14	1.02	0.97, 1.08	0.62	0.32, 1.23	1.13	1.04, 1.24	0.94	0.83, 1.06	0.85	0.64, 1.13

[a]Transitions between COVID-19–related states of health are depicted by arrows in Figure 15.
[b]Daily maximum 1-hr average O_3 concentration.

(A) $PM_{2.5}$ mass effect estimates



(B) O_3 effect estimates



(C) NO_2 effect estimates

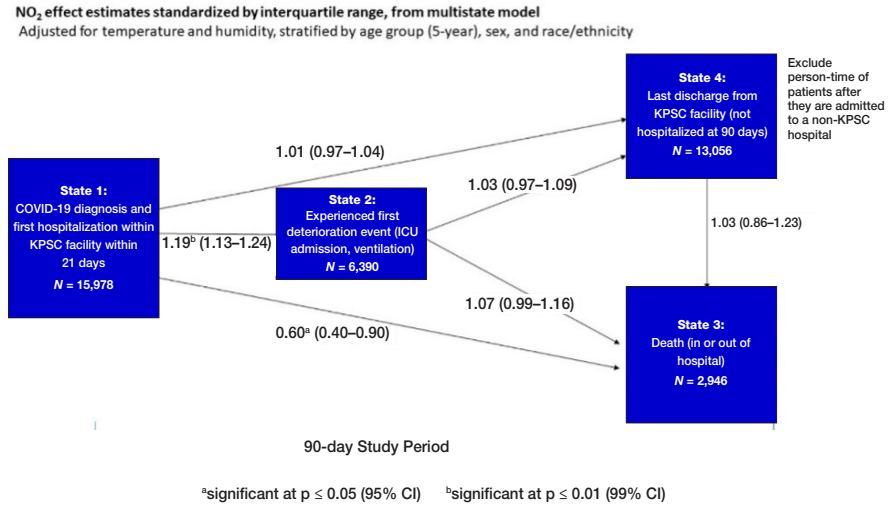


Figure 16. Effect estimates for select pollutants in a multistate survival model. Hazard ratios (95% CIs) are presented for exposure effects of $PM_{2.5}$ mass (**A**), O_3 (**B**), and NO_2 (**C**). Results are adjusted for temperature and relative humidity as confounders, stratified by age group (5-year), sex, and race/ethnicity. aP ≤ 0.05. bP ≤ 0.01 (99% CIs).

except for a slightly lower effect of O_3 exposure on the risk of transitioning from hospitalization to ICU admission (Appendix Table D9).

We also ran two-pollutant models for all possible combinations (Table 8). The effect of $PM_{2.5}$ exposure on the risk of transitioning from hospitalization to deterioration remained significantly elevated but was attenuated when NO_2 was included in the model. For the transition from deterioration to recovery, the effects of $PM_{2.5}$ exposure became larger and statistically significant when NO_2 was included in the model, indicating that patients living in less polluted areas were more likely to recover than those living in more polluted places. Effects of $PM_{2.5}$ exposure on both the transitions from deterioration to death and from recovery to death became stronger in the model including $PM_{2.5}$ and NO_2, with the association for the latter transition approaching statistical significance in the two-pollutant model.

Most of the effects of NO_2 were attenuated and not statistically significant in the two-pollutant models with $PM_{2.5}$, although the risk of transitioning from hospitalization to deterioration remained elevated and nearly significant. In the two-pollutant models with NO_2 and $PM_{2.5}$, some of the effects of NO_2 changed direction, with NO_2 exposure becoming negatively associated (although not significantly) with both transitioning from deterioration to death and from recovery to death. In the model with $PM_{2.5}$, the association between NO_2 exposure and the transition from deterioration to recovery became statistically significant, meaning that patients living in areas with higher NO_2 exposure were more likely to recover after a deterioration event — an unlikely result that probably reflects instability in the estimation that is due to collinearity between the two pollutants.

When NO_2 was included in the two-pollutant models, the effect of O_3 exposure on the risk of transitioning from hospitalization to deterioration remained of similar size and remained statistically significant, and the effect on the transition from hospitalization to recovery was attenuated and of borderline significance. Other results continued to display similar patterns but were mildly attenuated in size and significance.

With $PM_{2.5}$ in the two-pollutant model, the effects of O_3 exposure were mixed, and only the association with transitioning from hospitalization to deterioration remained statistically significant. When $PM_{2.5}$ was included in the model, the HR for the effect of O_3 exposure on the transition from hospitalization to death became higher and borderline significant. The two-pollutant model revealed that $PM_{2.5}$ confounded the effect of O_3 exposure on the transition from deterioration to death, with the adjusted effects being two-thirds smaller than in the single-pollutant model.

Results for the Cox model are also shown in Appendix Table D8. The directions of the associations between pollutant exposure and the transitions between health event states were mostly as expected, and the results were remarkably similar to those from the multistate model.

DISCUSSION AND CONCLUSION

We hypothesized that greater exposure to air pollution would relate to increased risk of deterioration events and death among patients hospitalized with COVID-19. We also hypothesized that air pollution would affect the pathways to recovery, with those living in areas with higher levels of air pollution being less likely to recover from COVID-19. The results of this study generally confirmed both hypotheses.

All studied pollutants significantly affected the transition from hospitalization to deterioration. Although $PM_{2.5}$ was the only pollutant that significantly affected the transition from deterioration to death, there was evidence that exposure to O_3 and, to a lesser extent, NO_2 elevated the risk of this transition. Exposure to O_3 significantly influenced the transition to recovery, with those living in areas with higher levels of O_3 having a lower chance of recovery. Exposure to O_3 increased the risks of death after recovery and discharge from the hospital. This outcome may have occurred if patients living in more polluted areas were more likely to experience cardiopulmonary effects of long COVID, making them more susceptible to the effects of air pollution.

Unexpectedly, there was a negative association between $PM_{2.5}$ and NO_2 exposures and the risk of transitioning from hospitalization to death; however, O_3 exposure was positively associated with a large increased risk of this outcome. Only a small number of patients (n = 62) in the analysis cohort transitioned from hospitalization to death, potentially leading to instabilities in the statistical inferences, making these results potentially unreliable and difficult to interpret. The unexpected finding regarding NO_2 and $PM_{2.5}$, therefore, could have occurred because of unstable statistical inference resulting from insufficient sample size. Moreover, we conducted detailed investigations, including chart reviews, for these 62 patients. (Data on patient characteristics for the group of those who experienced this transition, compared to other transition groups, as well as additional discussion, are presented in Appendix Table D10.) This additional analysis suggested that the unexpected findings may have been due to misclassification of COVID-19 deaths in older adult patients with other strong risk factors for death who, by chance, lived in areas with lower exposure to $PM_{2.5}$ and NO_2.

The consistency in the results from the multistate and Cox models further supports the conclusion that air pollution exposure contributes to the progression from hospitalization to deterioration and from deterioration to death in patients with COVID-19. Additionally, exposure

to air pollution reduces the chances of sustained recovery, with positive associations between recovery being defined as discharge from the hospital for 90 days and death. Our analyses were based on the Markov assumption that time spent in a previous health state did not influence subsequent transition states. Thus, we would expect similar results from the Cox model and the multistate survival model, provided that the statistical power was not substantially lowered in the Cox model. When this phase of the study was being conducted, COVID-19 remained a novel virus, and we lacked sufficient prior knowledge to determine how time spent in one COVID-19–related health state may influence future transitions to other states of health. It is plausible that patients who spent a much longer time in the ICU had a higher probability of dying; however, it is also possible that the opposite is true if patients who were severely ill were admitted to the ICU and died very soon thereafter. At the time of the study, we were unable to predict how the amount of time a patient spent in one health state would influence their subsequent transitions to other states of health; thus, we made the simplifying Markov assumption, which was prudent under the circumstances. Given the novelty of both COVID-19 and our analysis, we are unable to conjecture how changing this assumption to account for patients' time spent in previous states may have influenced our results.

A weakness in our analysis is the fact that we did not allow for a state representing readmission to the hospital after discharge. In examining the data, we realized that several patients were readmitted multiple times after discharge, with 22.6% of the 2,830 readmitted patients having multiple readmissions. The heterogeneity in this group led us to conclude that classifying all readmitted patients in the same group would have potentially resulted in ascertainment bias for this health state. We did, however, allow for the readmitted patients to follow all six transition states after readmission to the hospital, where about 22% of the readmitted patients eventually died.

Other limitations of the study stemmed from the use of EHRs. Specifically, we defined deaths as all-cause mortality. Data from EHRs do not include information on deaths that occur outside of a healthcare facility (e.g., hospital). Mortality data are available from state death records. The cause of death-specific details in death records, however, are only published with multiyear delays, and the coding of cause of death is complex and subject to significant ascertainment bias. In the setting of infectious diseases, such as COVID-19, diverse pathways may lead directly to death or exacerbate existing diseases, resulting in premature death. Thus, COVID-19–related mortality has routinely been identified via EHRs by identifying patients with COVID-19–related diagnoses and then identifying those patients whose death can be ascertained via all-cause death records within a predetermined time frame after the diagnosis.[130–134] We did not exclude suicides and accidents, as both could have been affected by neurological and physical effects of COVID-19.[5] Nonetheless, some deaths may have occurred without the patient having COVID-19. For example, among the 62 patients who transitioned directly from hospital admission to death, detailed chart reviews of approximately 14% of these patients revealed that several of them had serious chronic diseases, such as stage IV breast cancer or recent coronary events. As we were unable to ascertain whether COVID-19 played an aggravating role in these deaths, we included all deaths in the analysis and did not evaluate the risk of infection related to disease or progression. Any discussion of the links between infection to subsequent severity would only be speculative on our part, precluding our ability to offer further discussion.

Overloading of the ICU, with resulting degradation of care, was a potential concern. To address this, we consulted with both hospital administrators and clinicians attending to patients with COVID-19. We also queried an internal KPSC system that tracked ICU utilization. We determined that KPSC did not run out of ventilators or physical space for admitting seriously ill patients with COVID-19. An overflow facility that could have accepted KPSC patients was never used. For some patients, however, intensive-level care was provided outside of the physical ICU.

In accordance with the study design, we excluded patients who received care outside the KPSC health system; these patients composed about 25% of the total number of patients admitted to the hospital (Appendix Table D5). Compared with patients who received care at a KPSC facility, patients treated outside the KPSC system were older, were more likely to be White and less likely to be Hispanic, included a higher proportion of smokers, and had slightly lower air pollution exposures. We are unable to conjecture about how these differences may have affected our results, although the composition of the study population may limit the generalizability of the findings to patients treated within the KPSC health system. Nonetheless, the internal validity of the findings would be maintained.

Another potential weakness of this study is the use of exposure fields for 2016 in relation to outcomes that occurred in 2020–2021. The overall pattern of air pollutant exposures in Southern California, however, is generally consistent over time, given the major meteorological, topographical, and transportation influences throughout the region. Inland areas around San Bernardino and Riverside have consistently higher levels of pollution than do areas in the west of the region, because of the prevailing westerly winds from the Pacific Ocean, temperature inversions that form inland and keep the pollution close to ground level, and physical blocking from the mountain ranges that are present in the north, east, and south of the region.[135] Earlier studies demonstrated that the spatial pattern for $PM_{2.5}$ exposure has been maintained over 10 years.[136] Thus, in the context of our assessment of chronic exposure to

air pollution, it is unlikely that the spatial patterns would have changed dramatically over the 4–5 years between the estimation of exposures and the assessment of COVID-19 severity.

An exception to the likelihood of relatively sustained spatial patterns of air pollutants may be the COVID-19 lockdown period in 2020, when traffic levels were substantially reduced. Recent studies have shown that near-source NO_2 declined by approximately 20% to 25% during this period.[114] Near-source traffic pollution estimated during normal conditions in 2016 may have overestimated exposures during the lockdown. Although such overestimation could possibly affect the accuracy of exposure estimations, this relatively short-term event is unlikely to affect the longer-term chronic exposures that we hypothesized would lead to more severe adverse outcomes of COVID-19. The 1-km scale of our model outputs may have imparted relatively more error in the estimated NO_2 exposures, which often vary sharply near emission sources, such as major roads and highways, potentially attenuating the reported effects of NO_2.

Because of the waves of COVID-19 that occurred in the region, including one major wave occurring from November 2020 to January 2021 and a smaller wave in June and July 2020, we were unable to evaluate the relative contribution of acute exposures to air pollution, as these periods had fairly similar short-term exposures. Therefore, we cannot rule out the possibility that short-term pollutant exposures during the lockdown period may also have influenced the sequelae of COVID-19. The strong consistency of the spatial patterns over time, combined with the short period of the lockdown, however, likely mitigated this potential source of error in the estimation of exposures.

Despite these limitations, our findings strengthen the body of evidence that air pollution contributes to most aspects of the sequelae experienced by patients with COVID-19. The reported results have several possible implications for medical practice, public health policies, and individual behavior. First, physicians treating patients with COVID-19 could benefit from knowing the likely air pollution exposures of these patients, as this information may help clinicians specifically target the most efficacious treatments to patients at high risk for severe outcomes. Second, public health decision-makers would benefit from having this information to inform their decisions about future controls on air pollution. Third, many areas that have experienced or are experiencing severe COVID-19 outbreaks and the associated demands on the healthcare system and increased mortality (e.g., Southern California, Northern Italy, India, China) continue to experience air pollution levels that exceed both World Health Organization guidelines and local air quality regulations. Fourth, if the information is properly communicated, people living in high-exposure environments could be less hesitant to receive the COVID-19 vaccination if they are aware that they have an elevated risk of severe COVID-19 outcomes because of their exposure to air pollution. In summary, reducing air pollution could provide an important means of reducing the severity of both COVID-19 and possibly other novel viruses that may emerge in the future. Such reductions may thus protect vast populations from the most severe outcomes of various viruses.

CHAPTER 7: ASSOCIATION BETWEEN AIR POLLUTION AND POST-ACUTE SEQUELAE OF SARS-COV-2

INTRODUCTION

Post-acute sequelae of SARS-CoV-2 (PASC, also known as long COVID) can be a debilitating illness that occurs after SARS-CoV-2 infection.[5] It is estimated that PASC has affected more than 7.3% of the US population, nearly 18.8 million people, in the first 3 years after the pandemic.[1,2] Recent studies show that approximately 17.8 million people in the United States continue to experience PASC symptoms, with higher rates of PASC among women than men.[1] In the United States, the economic costs of PASC, resulting from reduced quality of life, lost earnings, and increased medical expenses, likely exceed $3 trillion in the United States.[137]

PASC represents a multisystem syndrome that leads to an array of outcomes. Although approximately 60% to 70% of the specific etiologies are still being investigated, biologically plausible mechanisms have been identified.[138] Studies using individual-level data have demonstrated a relationship between air pollution and both COVID-19 incidence and severity.[139] Many of the same mechanisms that influence disease severity in COVID-19 could contribute to PASC, including oxidative stress in the lung, inflammation, and suppression of the immune system.

Three recent studies have reported an association between air pollution and risk of PASC.[140–142] One such study focused on a cohort of young adults in Stockholm, Sweden.[140] Of the 753 individuals surveyed, 116 (15%) displayed symptoms of PASC, which persisted for at least 2 months after infection. Air pollution exposures were estimated with a dispersion model and appeared to be very low overall, with a $PM_{2.5}$ annual mean of 6.39 mg/m^3. For each incremental increase in $PM_{2.5}$ concentration that was equivalent to the IQR, the authors reported adjusted odds ratios (ORs) of 1.28 (95% CI, 1.02–1.60) for long COVID, 1.65 (95% CI, 1.09–2.50) for dyspnea, and 1.29 (95% CI, 0.97–1.70) for altered smell or taste. Other modeled pollutant exposures were also associated with elevated risks of outcomes related to PASC

The second study enrolled 500 adults in the Makkah region of Saudi Arabia, with a final sample of 410 individuals included in the analysis.[141] Exposures to PM_{10} and $PM_{2.5}$ were assessed with ground-based monitoring stations assigned to subregions of the study area. Levels of air pollutants were very high, with $PM_{2.5}$ seasonal means ranging from 67.0 mg/m^3 to 233.5 mg/m^3. Of the 410 individuals in the study cohort, 140 (34%) reported having at least one symptom of long COVID. For each increase in $PM_{2.5}$ exposure equivalent to the IQR, the authors reported a rate ratio of 1.28 (95% CI, 1.06–1.54), which is remarkably similar to the comparable result reported in the Swedish study. Exposure to PM_{10} was also associated with elevated risks of a similar magnitude. All study participants had received two doses of vaccine, indicating that elevated risks of PASC associated with air pollution exposure exist even after vaccination.

A third study utilized an exploratory exposomic approach and EHR data from Florida and New York City to evaluate nearly 200 risk factors for long COVID.[142] The study used several publicly available exposure estimates assigned to the ZIP code of residence for each patient. Investigators reported positive associations between long COVID-19 and exposure to air pollutants, including several air toxics and speciated particles (e.g., ammonium). The relatively coarse resolution of the exposure assignments at the ZIP code level, however, could have introduced measurement error that may have biased some results toward the null hypothesis.

These three studies collectively suggest that exposure to common air pollutants may increase the risk of PASC symptoms; however, two of the studies had relatively small sample sizes, and the other study used low-resolution exposure assignments. Moreover, the Swedish study reported remarkably low levels of air pollution, whereas the Saudi Arabian study involved extremely high levels of pollution. Given the substantial consequences of PASC and the apparent inability of vaccines to completely prevent PASC symptoms after infection,[143] a need exists to investigate whether air pollution increases the risk of PASC in larger study populations, with well-characterized exposures assigned at high resolution to the home address of participants.

In this study, we hypothesized that exposure to air pollutants would be associated with elevated risk of PASC in a cohort of patients hospitalized with COVID-19 in Southern California. Our previous research indicated that air pollution exposure increased the risk of death after hospitalization in this cohort and that air pollution was associated with progression to more severe states of illness, such as admission to the ICU.[139,144] The present study extended the analysis of this cohort to investigate the risk of developing PASC in relation to air pollution exposure.

KPSC COHORT AND HEALTH DATA

We identified 12,634 patients who were 18 years of age or older at the time of their COVID-19 diagnosis or positive COVID-19 test; hospitalized with COVID-19 from June 1, 2020, to January 31, 2021; and alive at the time of discharge. The Delta variant of SARS-CoV-2 was dominant during most of this period, and nearly all enrolled patients were unvaccinated.[144] A COVID-19–related hospitalization was defined as a hospitalization occurring within 21 days

of a positive COVID-19 test. To enable assessment of comorbidities, only patients who were members of the KPSC health system for 12 months before and after being diagnosed with or testing positive for COVID-19 were included in the study. A flowchart summarizing the construction of the cohort used for analysis is presented in **Figure 17**.

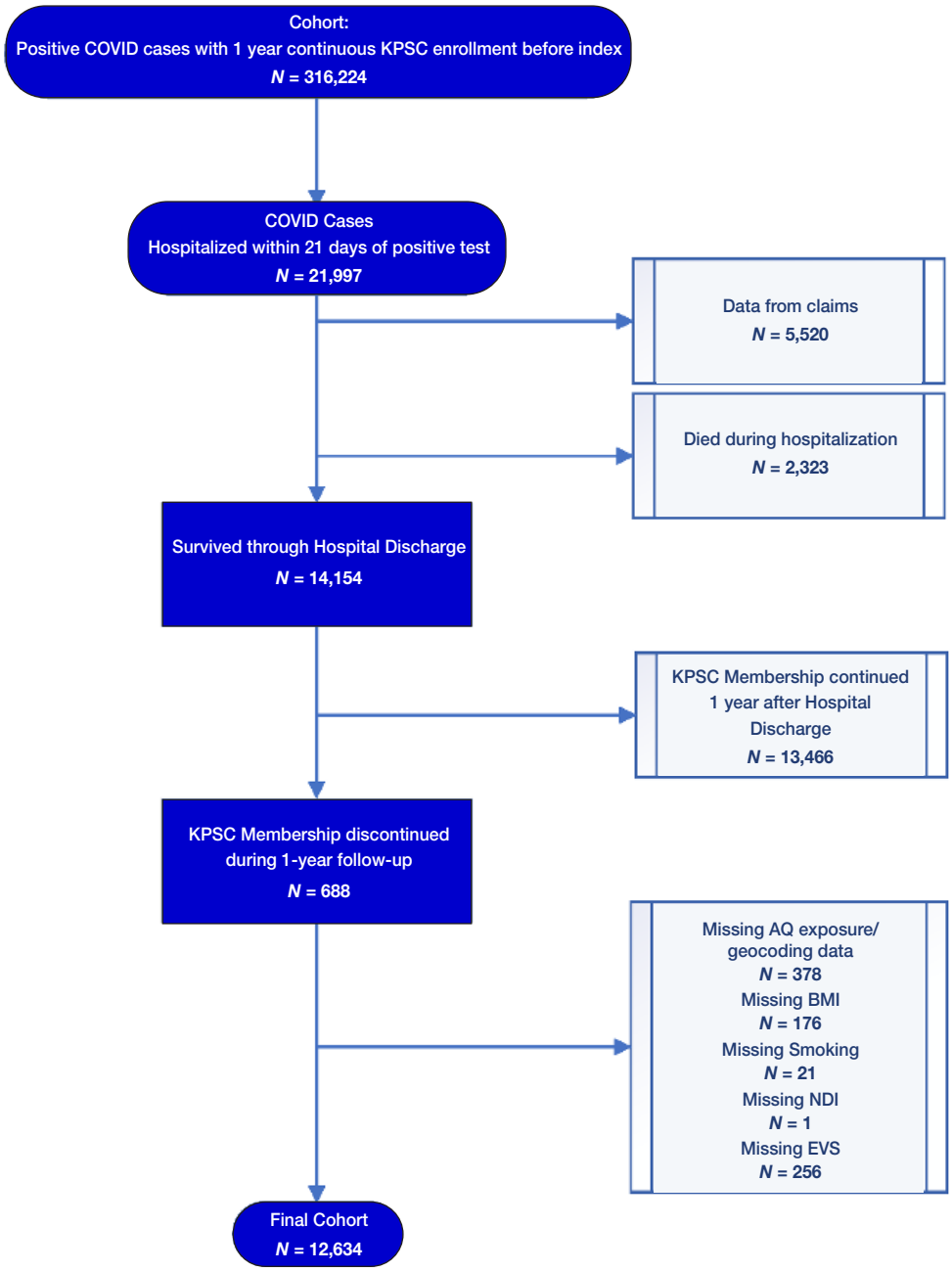


Figure 17. Flow chart depicting selection of the study cohort for an analysis of air pollutant exposures and risk of long COVID in Southern California.

DEFINITION OF PASC

PASC conditions were defined as a set of 45 diagnoses described in detail elsewhere.[43] We collaborated with a KPSC hospitalist to create clinically meaningful categories grouping these 45 diagnostic codes by organ system; these categories included pulmonary, cardiac, dermatologic, cardiometabolic, endocrine, gastroenterological, hematological, renal, neurological, constitutional (e.g., fatigue, malaise), and psychiatric diseases. We then selected a subgroup of these categories, which represented specific biological systems that we expected would be most affected by air pollution; this subgroup included cardiac, cardiometabolic, pulmonary, and neurological conditions.[145–149] We used a conservative definition of PASC, such that those patients presenting with a new disease or condition (e.g., atrial fibrillation) during their hospital stay would not be counted as having a PASC condition if they were subsequently diagnosed with the same condition after discharge. To avoid identification bias involving pre-existing conditions, patients diagnosed with any of the PASC conditions during the 12 months prior to hospitalization or during hospitalization were excluded from being a candidate for that PASC condition in the context of this study. Patients were considered to have a PASC condition in the cardiac, cardiometabolic, pulmonary, or neurological categories if they had at least one diagnosis in that category during a healthcare encounter within 3 months or 12 months after discharge from their first COVID-19–related hospitalization.

For a sensitivity analysis, we further separated the subgroup of pulmonary diseases into PASC diagnoses related to (Group 1) bronchitis, cough, or cold-related symptoms; (Group 2) oxygen- and breathing-related illnesses (e.g., dyspnea, hypoxemia); or (Group 3) serious respiratory or cardiorespiratory disease (e.g., pulmonary edema, interstitial lung disease). Of the 12,634 patients in the analysis cohort of this study, 7,753 (61.4%) developed one or more PASC conditions within 12 months of hospital discharge.

EXPOSURE MODEL

Exposures to NO_2, O_3, $PM_{2.5}$ mass, $PM_{0.1}$, $PM_{2.5}$ EC, $PM_{2.5}$ nitrate, and $PM_{2.5}$ biomass combustion were specified using a CTM as described in Appendix E.[139,144] The CTM predictions were combined with available ground-based and satellite measurements, using an RFR model to remove bias in predictions. All exposures were assigned on the basis of the home address of each study participant as 30-day and 365-day averages before their COVID-19–related hospital admission.

STATISTICAL ANALYSIS

We used conditional logistic regression to evaluate the association between air pollution exposure and a PASC diagnosis. All models were stratified to control for age, sex, and race/ethnicity. We included several confounding variables a priori, including smoking status, exercise, BMI, and poverty as indicated by enrollment in MediCal (a government assistance program for persons in poverty). Neighborhood-level confounding variables included a deprivation index, proportion of workers aged 16 or older taking public transit (another marker of deprivation), temperature, and humidity in the month of the initial COVID-19 diagnosis, and the NDVI (a measure of green cover locally, extracted from the Terra MODIS Vegetation Indices [MOD13Q1.006] 16-day global dataset with a resolution of 250 m).

For those pollutants found to be significantly associated with PASC outcomes in single-pollutant models, we ran deviation from the mean models; these models included the annual mean, calculated as the average exposure 1 year before hospital admission, and the deviation from the annual mean for the 30-day exposure used in the main analysis. Including both the 365-day average and the deviation terms in the same model allowed us to investigate whether associations were likely driven by relatively acute exposures 30 days before hospitalization, longer-term annual average exposures before admission, or both. We also ran the 365-day exposure as a separate model to further investigate which exposure window appeared to influence the observed associations.

We conducted sensitivity analyses, including two- and three-pollutant models for $PM_{2.5}$, $PM_{0.1}$, O_3, and NO_2. We also performed separate analyses for wildfires, but found that the majority of COVID-19 hospitalizations in the study occurred nearly 90 days after the wildfire activity in 2020. The temporal misalignment between the timing of wildfire-related exposures and the dates of hospital admission likely biased findings toward the null hypothesis or even negative associations (Appendix Figure E2). Therefore, we conducted sensitivity analyses with the wildfire tracer removed from the $PM_{2.5}$ mass variable to assess whether the temporal misalignment had biased the $PM_{2.5}$ results toward either the null hypothesis or negative relationships.

RESULTS

A descriptive summary of the study cohort is presented in **Table 9**. Women were more likely than men to experience the PASC condition. Patients with higher rates of exercise were less likely to experience PASC, compared to patients who exercised less. Patients with lower BMIs were less likely than those with higher BMIs to experience PASC. Otherwise, there were no notable differences in the incidence of PASC by demographic characteristics.

The number of patients diagnosed with each PASC diagnosis group is displayed in **Table 10**. For all diagnosis groups, the ascertainment of PASC within the 12-month follow-up identified a larger proportion of patients than did ascertainment within the 3-month follow-up. Pulmonary diagnoses were the most commonly identified PASC diagnosis group within both the 3-month and 12-month follow-ups, with neurological diagnoses being the next most prevalent at both ascertainment points.

Average pollutant exposures in the 30-day and 365-day exposure windows before hospitalization are summarized in **Table 11**. Additionally, the correlations between pollutant exposures of the study participants over the 30 days before their hospitalization with COVID-19 are presented in **Table 12**. Exposures to $PM_{2.5}$ mass and $PM_{2.5}$ from wildfires ($PM_{2.5}$ biomass combustion) were moderately highly correlated, reflecting the substantial influence of very high wildfire-related pollutant concentrations on a limited number of study participants. The correlation between $PM_{2.5}$ mass and $PM_{2.5}$ mass not associated with wildfires ($PM_{2.5}$ mass without $PM_{2.5}$ biomass combustion) better represented the exposures experienced by the majority of study participants. All other correlations between air pollutant exposures, summarized in Table 12, had *r* values of less than 0.6. Correlations between NO_2 and O_3 exposures were negative, likely reflecting the titration of O_3 in zones with fresh NO_x emissions.

Appendix Figure E2 shows the time history of wildfire-related exposures during the study period. Exposure concentrations were highest during the wildfire season, beginning in late August 2020 and lasting through early November 2020. By coincidence, the surge in COVID-19

Table 9. Descriptive Characteristics of the Study Cohort Used to Investigate Associations Between Air Pollution Exposures and PASC Outcomes

	PASCs at 12 Months			
	No PASCs (*N* = 4,881)	**PASCs (*N* = 7,753)**	**Total (*N* = 12,634)**	***P* value**
Age at index, mean (SD)	60.9 (17.18)	62.5 (15.58)	61.9 (16.23)	<0.000a
Race/ethnicity, n (%)				0.48012
Asian/Pacific Islander	587 (12.0%)	857 (11.1%)	1,444 (11.4%)	
Black	439 (9.0%)	678 (8.7%)	1,117 (8.8%)	
Hispanic	2,813 (57.6%)	4,561 (58.8%)	7,374 (58.4%)	
Other/multiple/unknown	42 (0.9%)	70 (0.9%)	112 (0.9%)	
White	1,000 (20.5%)	1,587 (20.5%)	2,587 (20.5%)	
Sex, n (%)				<0.000b
Female	1,938 (39.7%)	3,654 (47.1%)	5,592 (44.3%)	
Male	2,943 (60.3%)	4,099 (52.9%)	7,042 (55.7%)	
Smoking, n (%)				0.04282
Ever-smoker	1,616 (33.1%)	2,703 (34.9%)	4,319 (34.2%)	
Never-smoker	3,265 (66.9%)	5,050 (65.1%)	8,315 (65.8%)	
BMI (kg/m2), mean (SD)	31.8 (7.91)	32.6 (7.74)	32.3 (7.81)	<0.0001a
Medicaid, n (%)				0.00132
No	4,309 (88.3%)	6,692 (86.3%)	11,001 (87.1%)	
Yes	572 (11.7%)	1,061 (13.7%)	1,633 (12.9%)	
Exercise Vital Sign_ Mean (SD)	68.1 (103.97)	61.2 (95.11)	63.9 (98.68)	0.00741
NDI, Mean (SD)	0.6 (1.04)	0.5 (1.01)	0.6 (1.02)	0.44381

[a]Kruskal-Wallis *P* value.
[b]Chi-square *P* value.

hospitalizations occurred in midsummer and early winter, temporally opposite the peak of the wildfire cycle.

SINGLE-POLLUTANT MODELS AND SENSITIVITY ANALYSES

All significant associations between 30-day single-pollutant exposures and the PASC outcomes ascertained within 3 months and 12 months are summarized in **Table 13**. For each exposure increment equivalent to the IQR, exposure to $PM_{0.1}$ was significantly associated with several PASC outcomes at 3 months, including cardiac outcomes (OR, 1.115; 95% CI, 1.006–1.235), cardiometabolic outcomes (OR, 1.130; 95% CI, 1.038–1.230), and pulmonary outcomes (OR, 1.062; 95% CI, 1.009–1.118). O_3 exposure was associated with pulmonary outcomes at 3 months (OR, 1.097; 95% CI, 1.019–1.180), and $PM_{2.5}$ nitrate exposure was associated with cardiometabolic outcomes at 3 months (OR, 1.181; 95% CI, 1.013–1.377). Exposures to NO_2 and $PM_{2.5}$ EC were not significantly associated with any PASC outcome, although several risk estimates for each pollutant were elevated. Exposure to $PM_{2.5}$ mass (OR, 0.935; 95% CI, 0.876–0.998) was negatively associated with pulmonary outcomes at 3 months. Similarly, exposure to $PM_{2.5}$ OC, a major component of wildfire smoke, had a borderline significant negative association with pulmonary outcomes (OR, 0.959; 95% CI, 0.914–1.006) at 3 months, with a nearly identical result for the corresponding 12-month outcome.

We found fewer significant associations with the 12-month PASC outcomes compared to the PASC outcomes at 3 months. In many cases, the directions of the effects at 3 months and 12 months were consistent (Table 13 and **Figure 18**). For $PM_{0.1}$ exposure, the associations with PASC outcomes that were significant at 3 months were not statistically significant and of much smaller magnitude at 12 months, with point estimates being at least 50% less than those at 3 months. By contrast, associations between O_3 exposure and pulmonary outcomes and associations

Table 10. PASC Diagnosis Groups

Diagnosis Group	Diagnoses	Incidence at 3 Months	Incidence at 12 Months
Cardiac	Arrhythmias, myocarditis/pericarditis, stress cardiomyopathy	524 (4.3%)	778 (6.5%)
Cardiometabolic	Diabetes, renal disease, arrhythmias	757 (6.4%)	1,203 (10.4%)
Pulmonary	Bronchitis, chest/throat, cough, dyspnea, hypoxemia, ILD, PE/DVT, pulmonary edema	2,859 (23.1%)	4,130 (34.0%)
Neurologic	Ataxia/trouble walking, autonomic dysfunction, delirium or encephalopathy, dementia, encephalitis, headache, myoneural disorders, ophthalmologic conditions following stroke, Parkinsonism and other extrapyramidal syndromes, peripheral nerve disorders, seizures, stroke, stroke (intracranial hemorrhage), stroke (ischemic), vertigo	1,550 (12.6%)	2,817 (23.2%)
Pulmonary (group 1 only)	Bronchitis, chest/throat, cough	1,213 (10.3%)	2,197 (19.1%)
Pulmonary (group 2 only)	Dyspnea, hypoxemia	1,821 (15.3%)	2,497 (21.5%)
Pulmonary (group 3 only)	ILD, PE/DVT, pulmonary edema	406 (3.4%)	626 (5.4%)

DVT = deep vein thrombosis; ILD = interstitial lung disease; PE = pulmonary embolism.

Table 11. Average Pollutant Exposures 30 Days and 365 Days Prior to COVID-19–Related Hospitalization

	30 Days			365 Days		
Characteristic	**Median (IQR)**	**Mean (SD)**	**Range**	**Median (IQR)**	**Mean (SD)**	**Range**
Temperature (°C)	15.1 (13.84,16.23)	15.22 (1.52)	12.84, 20.14	NA		
Relative humidity (%)	12.36 (11.53, 14.59)	13.00 (1.85)	9.74, 19.97			
NDVI	164 (149, 178)	163 (24)	73, 212			
NO_2 (ppb)	14 (9, 21)	15 (7)	1, 41	13.4 (9.4, 16.9)	13.2 (5.0)	1.0, 31.2
O_3 (ppb)	48 (43, 56)	52 (12)	33, 108	57 (52, 63)	58 (7)	36, 85
$PM_{0.1}$(μg/m^3)	0.83 (0.66, 1.01)	0.87 (0.34)	0.14, 4.30	0.99 (0.85, 1.08)	0.96 (0.17)	0.18, 4.00
$PM_{2.5}$ elemental carbon (μg/m^3)	0.59 (0.40, 0.82)	0.62 (0.28)	0.02, 3.87	0.58 (0.43, 0.68)	0.56 (0.18)	0.06, 1.35
$PM_{2.5}$ mass (μg/m^3)	12.9 (10.2, 15.6)	13.1 (4.6)	2.0, 94.0	13.14 (11.56, 14.35)	12.85 (2.17)	4.14, 28.58
$PM_{2.5}$ nitrate (μg/m^3)	1.91 (0.89, 3.10)	2.07 (1.31)	0.00, 9.42	1.63 (1.26, 1.89)	1.57 (0.44)	0.14, 5.15
$PM_{2.5}$ organic compounds (μg/m^3)	2.13 (1.39, 2.89)	2.37 (1.60)	0.08, 37.25	2.53 (1.99, 2.91)	2.48 (0.70)	0.23, 8.86
$PM_{2.5}$ biomass combustion (μg/m^3)	0.39 (0.12, 0.83)	1.07 (2.58)	0.01, 81.21	1.71 (1.14, 1.91)	1.60 (0.84)	0.05, 15.85
LUR NO_2 (ppb)	17.0 (12.6, 21.7)	17.2 (6.1)	0.0, 42.4	14.6 (10.9, 17.2)	14.3 (4.1)	0.0, 37.5
LUR $PM_{2.5}$ (μg/m^3)	10.28 (8.90, 11.74)	10.53 (2.74)	0.00, 25.45	10.08 (9.01, 11.11)	10.02 (1.82)	0.00, 17.87
$PM_{2.5}$ without biomass combustion (μg/m^3)	12.2 (9.6, 14.6)	12.0 (3.6)	1.9, 25.7	11.68 (10.29, 12.64)	11.25 (1.83)	3.27, 19.81

NA = not available.

Table 12. Pearson Correlations Between Pollutant Exposures for Study Participants 30 Days Before COVID-19–Related Hospitalization.

	NO_2	O_3	$Pm_{2.5}$ Mass	$Pm_{2.5}$ Biomass Combustion	$PM_{2.5}$ (without biomass combustion)	$PM_{0.1}$	NO_2 (LUR)
NO_2	1.00	−0.53	0.33	−0.07	0.47	0.06	0.79
O_3	−0.53	1.00	0.13	0.29	−0.05	0.49	−0.62
$PM_{2.5}$ mass	0.33	0.13	1.00	0.62	0.83	0.42	0.27
$PM_{2.5}$ biomass combustion	−0.07	0.29	0.62	1.00	0.08	0.03	−0.05
$PM_{2.5}$ (without biomass combustion)	0.47	−0.05	0.83	0.08	1.00	0.52	0.38
$PM_{0.1}$	0.06	0.49	0.42	0.03	0.52	1.00	−0.16
NO_2 (LUR)	0.79	−0.62	0.27	−0.05	0.38	−0.16	1.00

Table 13. Significant Associations Between Air Pollutant Exposures and PASC Diagnosis Groups at 3 Months and 12 Months After Hospital Discharge: Results of Single-Pollutant Models

PASC Group	Pollutant	Outcome Time (Months)	Estimate (95% CI)
Cardiac	$PM_{0.1}$	3	1.115[a] (1.006, 1.235)
Cardiac	$PM_{2.5}$ nitrate	12	1.204 [a] (1.032, 1.405)
Cardiac	$PM_{2.5}$ biomass combustion	3	0.956 [a] (0.915, 0.999)
Cardiometabolic/ diabetes	$PM_{2.5}$ nitrate	3	1.181[a] (1.013, 1.377)
Cardiometabolic/ diabetes	$PM_{0.1}$	3	1.130[b] (1.038, 1.230)
Cardiometabolic/ diabetes	$PM_{2.5}$ nitrate	12	1.160 [a] (1.023, 1.314)
Pulmonary	$PM_{0.1}$	3	1.062[a] (1.009, 1.118)
Pulmonary	O_3	3	1.097[a] (1.019, 1.180)
Pulmonary	$PM_{2.5}$	3	0.935[a] (0.876, 0.998)
Pulmonary	O_3	12	1.082[a] (1.012, 1.156)
Pulmonary	$PM_{2.5}$ (without biomass combustion)	12	0.926[a] (0.871, 0.985)
Pulmonary	$PM_{2.5}$ mass	12	0.924[b] (0.872, 0.980)

[a] $P \leq 0.05$.
[b] $P \leq 0.01$.

between $PM_{2.5}$ nitrate exposure and cardiometabolic outcomes were similarly elevated at 3 months and 12 months. Exposure to $PM_{2.5}$ mass was negatively associated with pulmonary outcomes in both analysis windows. Negative effects of wildfire-related exposures on cardiac outcomes became nonsignificant in the 12-month models, possibly reflecting even more severe temporal misalignment between COVID-19 incidence and the wildfires. Several other outcomes at 12 months were significantly associated with pollutant exposures, including the relationship between $PM_{2.5}$ nitrate exposure and cardiac outcomes (OR, 1.204; 95% CI, 1.032–1.405).

We further investigated the negative effect of $PM_{2.5}$ mass exposure on pulmonary outcomes in sensitivity analyses. Specifically, we removed the wildfire component of $PM_{2.5}$ mass and controlled for co-pollutants (**Table 14**). In all instances, the negative effects of $PM_{2.5}$ mass exposure became nonsignificant in the 3-month analysis. Removing the temporally misaligned wildfire component of $PM_{2.5}$ mass did not eliminate the negative associations, but the results were no longer statistically significant. Controlling for O_3 further reduced the effect sizes of $PM_{2.5}$ mass and rendered them nonsignificant.

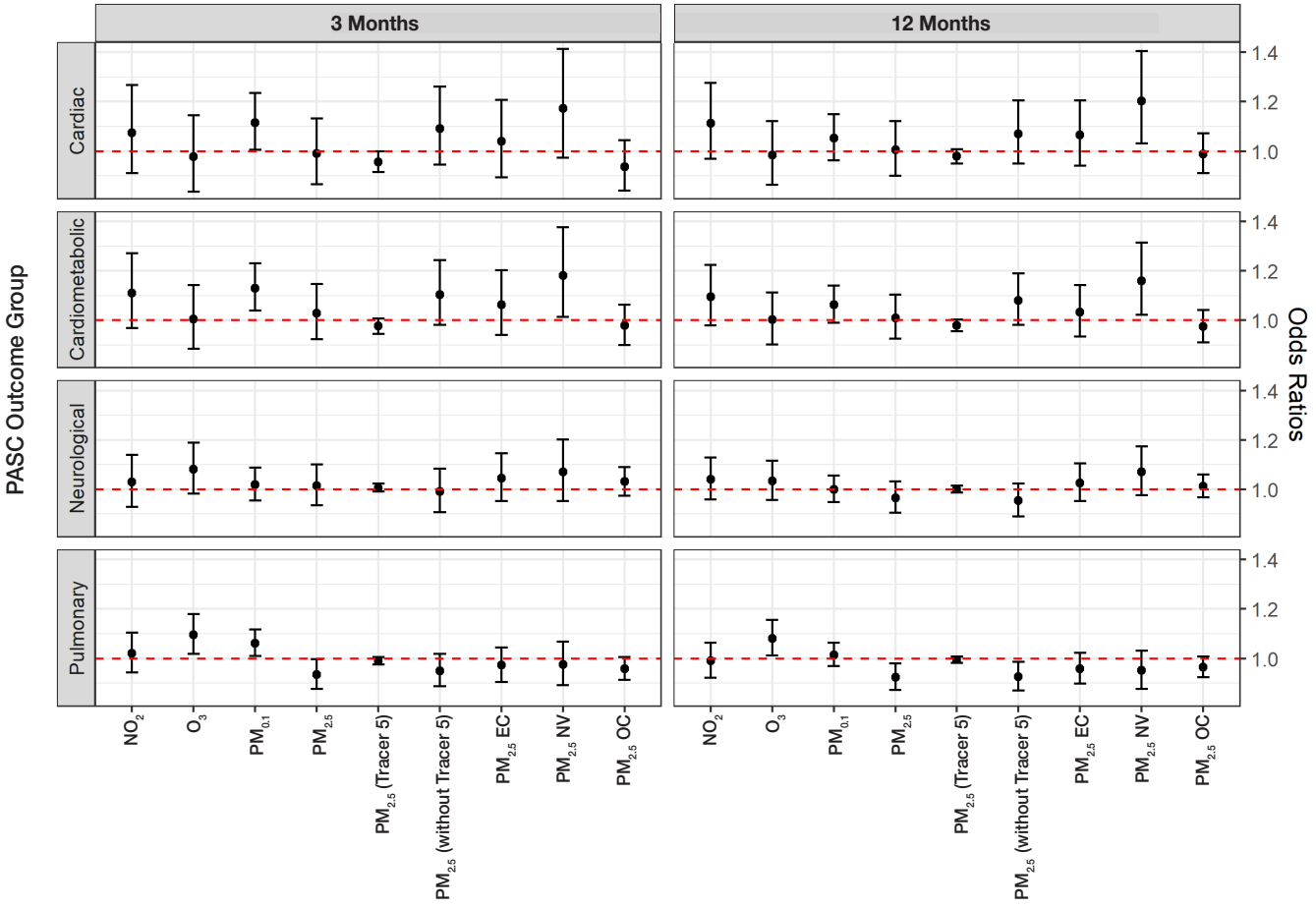


Figure 18. Odds ratios for pollutant exposures significantly associated with specific groups of PASC outcomes at 3 months and 12 months among patients hospitalized for COVID-19 in Southern California. Data are based on results from single-pollutant models.

We investigated different exposure models for findings that were statistically significant in single-pollutant models. Specifically, we investigated whether the 30-day exposure, the 365-day exposure, or the deviation of the 30-day mean from the 365-day mean was driving the observed associations (**Table 15**). All ORs resulting from these alternative exposure models were positive, suggesting that both the 30-day and 365-day exposures may have influenced the development of PASC symptoms.

We also ran analyses using the 365-day mean in single-pollutant models. These models using the 365-day means generally demonstrated pollutant exposure effects, some of which were significantly elevated. Most of the effects, however, were smaller than those seen in the models using the 30-day mean, except for the effect of O_3 exposure on pulmonary outcomes at 12 months, which was slightly larger.

We extracted the Akaike information criterion (AIC) for all models (Appendix Table E6). In six out of eight models, the 30-day exposure window had the lowest AIC. In two models, the AIC was lower for the 365-day exposure window (i.e., the effect of $PM_{2.5}$ nitrate exposure on cardiometabolic outcomes at 3 months and the effect of O_3 exposure on pulmonary outcomes at 12 months). We used the log likelihood ratio test to separately compare the deviation models with two terms to the 356-day mean models, which demonstrated that there was no improvement in the model fit. Thus, the deviation models yielded inconclusive results, as including both terms simultaneously did not show improvement over the use of the single 365-day exposure window.

We replicated all results in Appendix Table E4 with a sandwich estimator, which provided a robust variance to account for the nonindependence of patients within the same census tracts. The results of this analysis are presented in Appendix Table E7. Most ORs were either unchanged or slightly elevated. The overall conclusions remained constant, with the same pollutant exposures demonstrating statistically significant effects quantified by elevated ORs of similar magnitude.

Table 14. $PM_{2.5}$ Sensitivity Analyses for Pulmonary PASC Outcomes at 3 Months and 12 Months After Hospital Discharge

	Estimate (95% CI)	
Pollutant	**3-Month PASC Outcome**	**12-Month PASC Outcome**
$PM_{2.5}$ (CTM)	0.935[a] (0.876–0.998)	0.924[b] (0.872–0.980)
$PM_{2.5}$ minus wildfire (CTM)	0.951 (0.888–1.018)	0.926[a] (0.871–0.985)
$PM_{2.5}$ (CTM), controlled for O_3	0.958 (0.894–1.026)	0.940 (0.883–1.001)
$PM_{2.5}$ minus wildfire (CTM), controlled for O_3	0.982 (0.911–1.059)	0.946 (0.884–1.012)

[a]$P \leq 0.05$.
[b]$P \leq 0.01$.

Table 15. Results Comparing Various Exposure Time Windows with Different Model Specifications

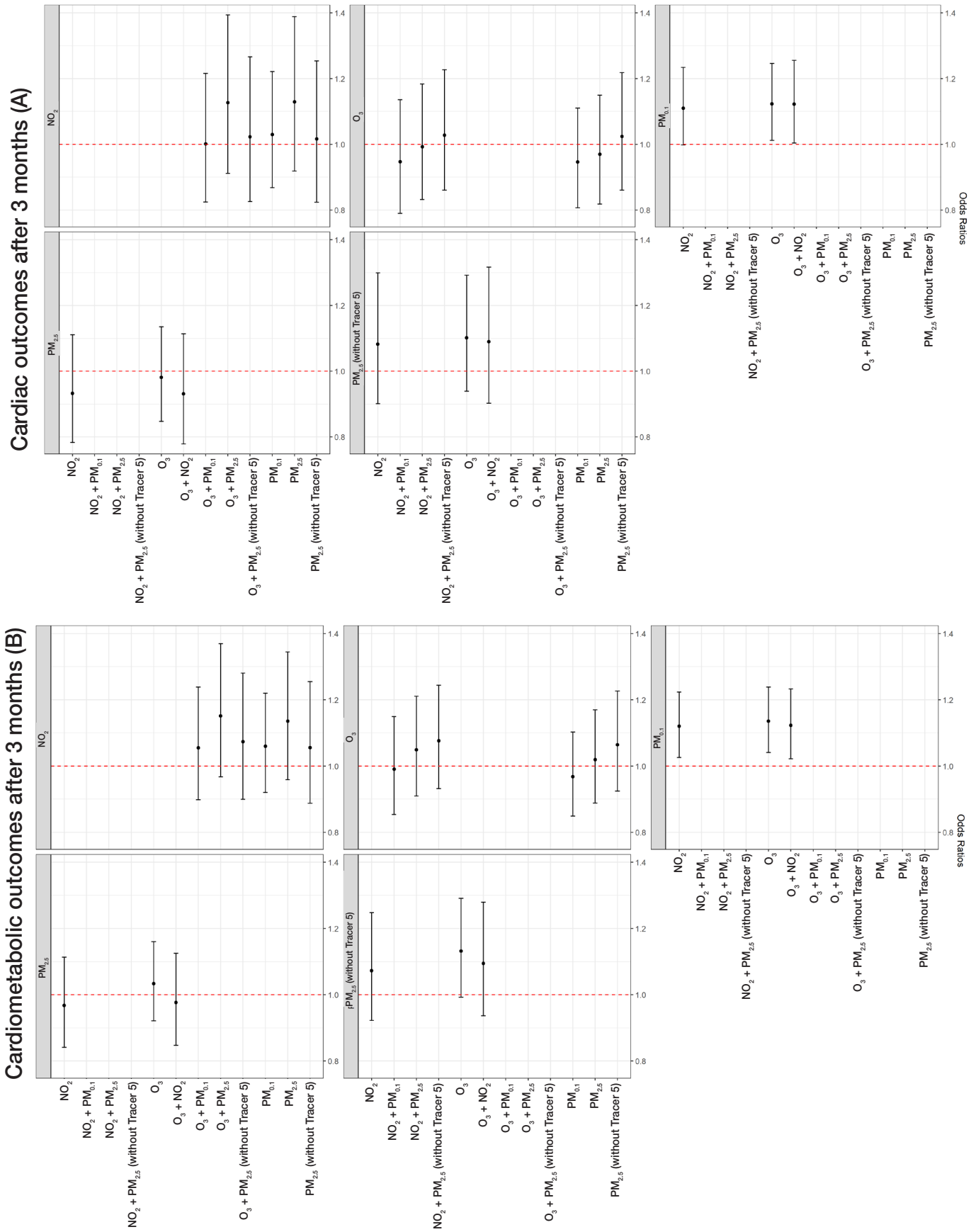
PASC Group	Pollutant	Outcome Time (Months)	Estimate (95% CI) 30-Day	Estimate (95%CI) 365-Day	Estimate (95% CI) 30-Day Deviation from 365-Day	Estimate (95% CI) 365-Day from Deviation Model
Cardiac	$PM_{0.1}$	3	1.115[a] (1.006, 1.235)	1.078 (0.954, 1.218)	1.110 (0.985, 1.252)	1.095 (0.971, 1.236)
Cardiac	$PM_{2.5}$ nitrate	12	1.204[a] (1.032, 1.405)	1.115 (0.997, 1.246)	1.114 (0.959, 1.293)	1.078 (0.955, 1.216)
Cardiometabolic/ diabetes	$PM_{2.5}$ nitrate	3	1.181[a] (1.013, 1.377)	1.147[b] (1.026, 1.283)	1.046 (0.903, 1.213)	1.131[a] (1.001, 1.277)
Cardiometabolic/ diabetes	$PM_{0.1}$	3	1.130[b] (1.038, 1.230)	1.046 (0.944, 1.158)	1.146[b] (1.038, 1.266)	1.069 (0.966, 1.183)
Cardiometabolic/ diabetes	$PM_{2.5}$ nitrate	12	1.160[a] (1.023, 1.314)	1.103[a] (1.008, 1.207)	1.073 (0.952, 1.210)	1.079 (0.979, 1.190)
Pulmonary	$PM_{0.1}$	3	1.062[a] (1.009, 1.118)	1.040 (0.980, 1.104)	1.061[a] (1.000, 1.125)	1.052 (0.990, 1.117)
Pulmonary	O_3	3	1.097[a] (1.019, 1.180)	1.082[a] (1.012, 1.156)	1.101 (0.958, 1.264)	1.106[b] (1.022, 1.196)
Pulmonary	O_3	12	1.082[a] (1.012, 1.156)	1.111[a] (1.040, 1.186)	1.026 (0.905, 1.164)	1.113[b] (1.037, 1.195)

[a]$P \leq 0.05$.
[b]$P \leq 0.01$.

MULTIPOLLUTANT MODELS

We ran multipollutant models for $PM_{0.1}$, $PM_{2.5}$, O_3, and NO_2 (30-day exposures) for any outcome that demonstrated a significant association in the single-pollutant models. The multipollutant models were constructed as either two- or three-pollutant models, with the three-pollutant models including either $PM_{2.5}$ mass or $PM_{0.1}$. The results of the multipollutant models are depicted in **Figures 19 and 20**. In the multipollutant models, all effects of exposures to $PM_{2.5}$ and $PM_{2.5}$ minus wildfire smoke on cardiac PASC outcomes became nonsignificant. We observed positive associations between NO_2 and cardiac outcomes in two- and three-pollutant models; the ORs from three-pollutant models were similar for the 12-month outcome (OR, 1.179; 95% CI, 0.987–1.407) and the 3-month outcome.

For the pulmonary PASC outcomes, several pollutant exposures continued to display significant ORs, especially in the three-pollutant models for both the 3-month and 12-month follow-up periods. In both models (i.e., 3 and 12 months), NO_2 and O_3 exposures had positive and statistically significant or borderline effects, whereas $PM_{2.5}$ exposure continued to be negatively associated with the pulmonary outcomes, although in two-pollutant models with O_3, the effects were confounded.



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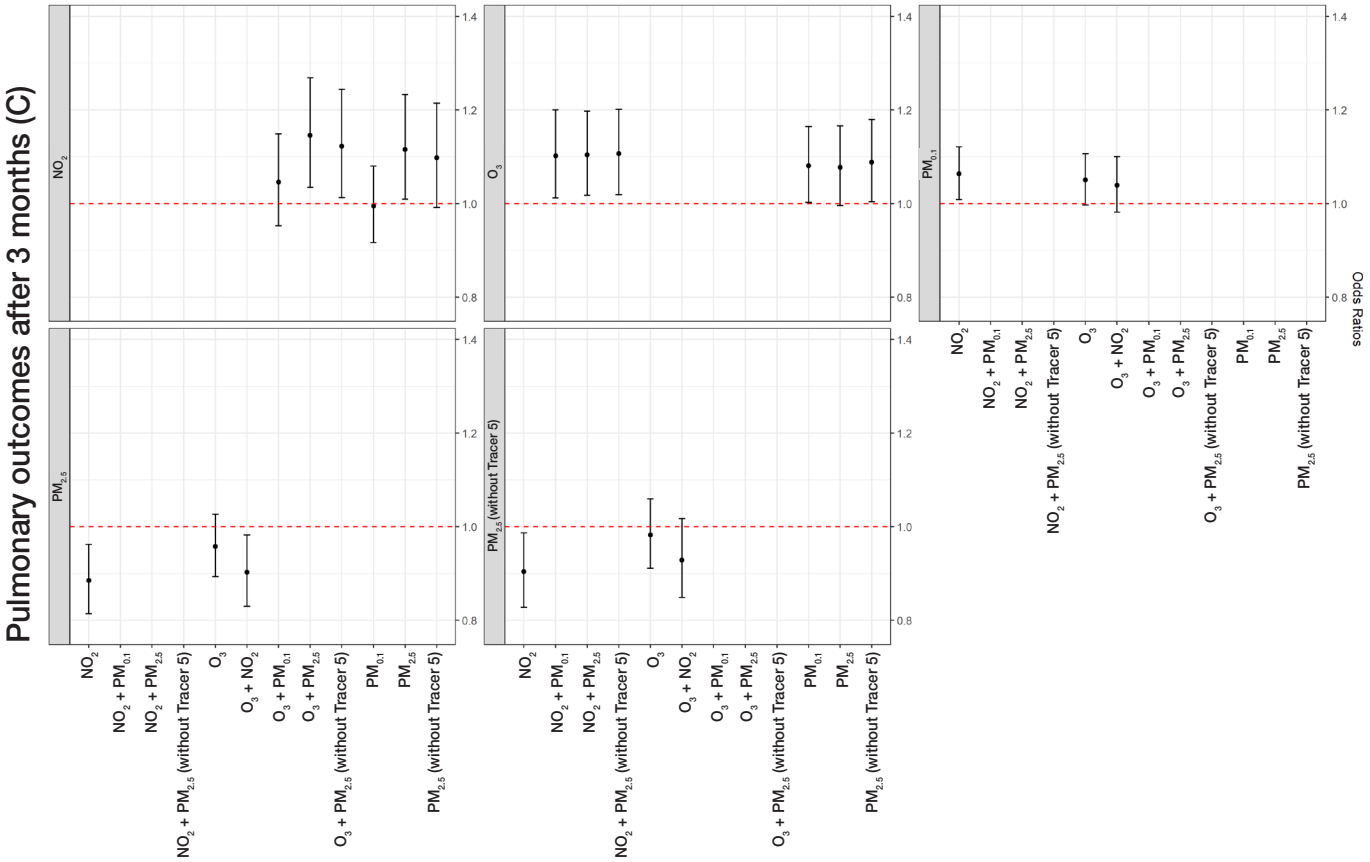
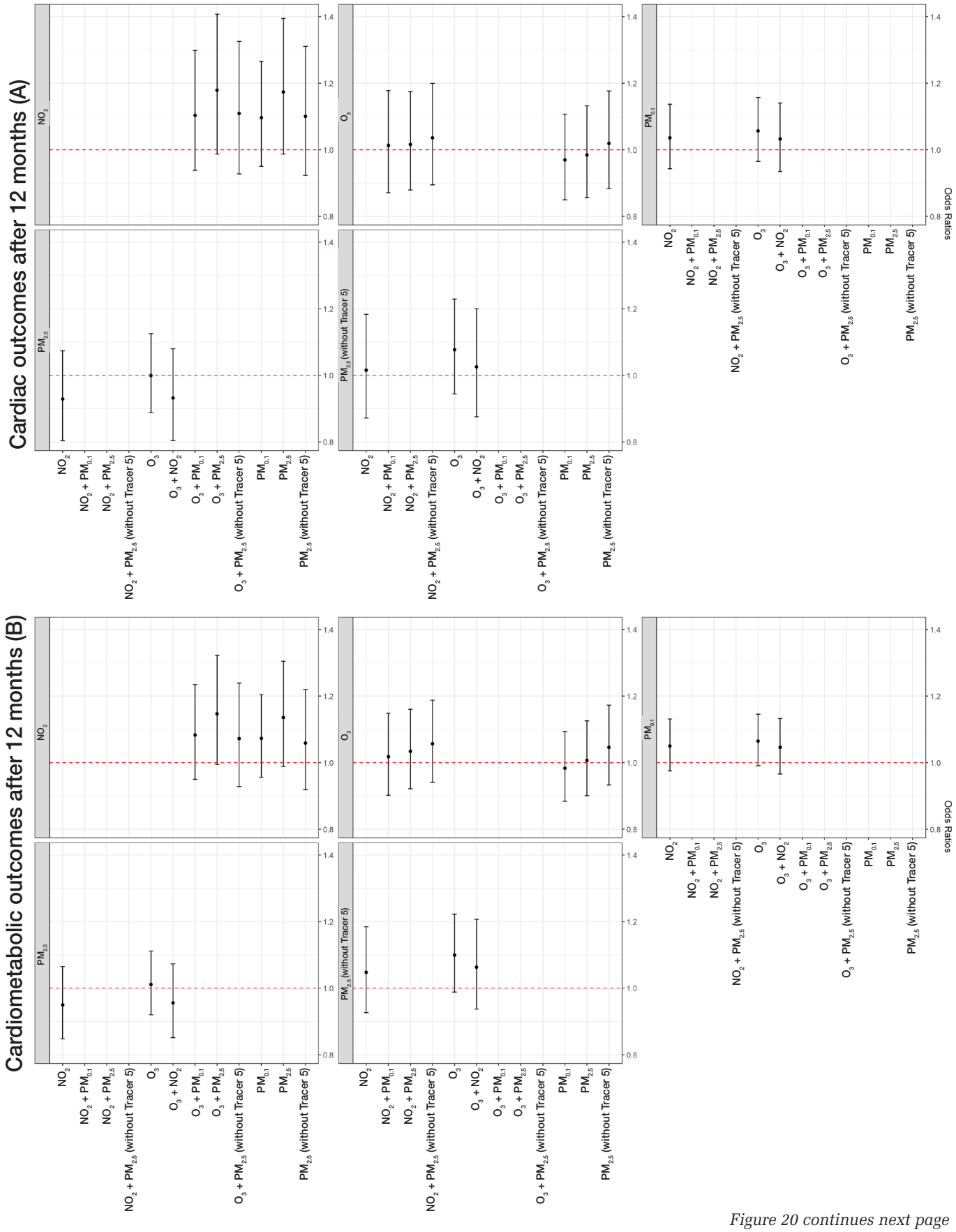


Figure 19. Odds ratios for 30-day exposure effects on cardiac (A), cardiometabolic (B), and pulmonary (C) PASC outcomes at 3 months among patients hospitalized for COVID-19 in Southern California. Data are based on results from multipollutant models.



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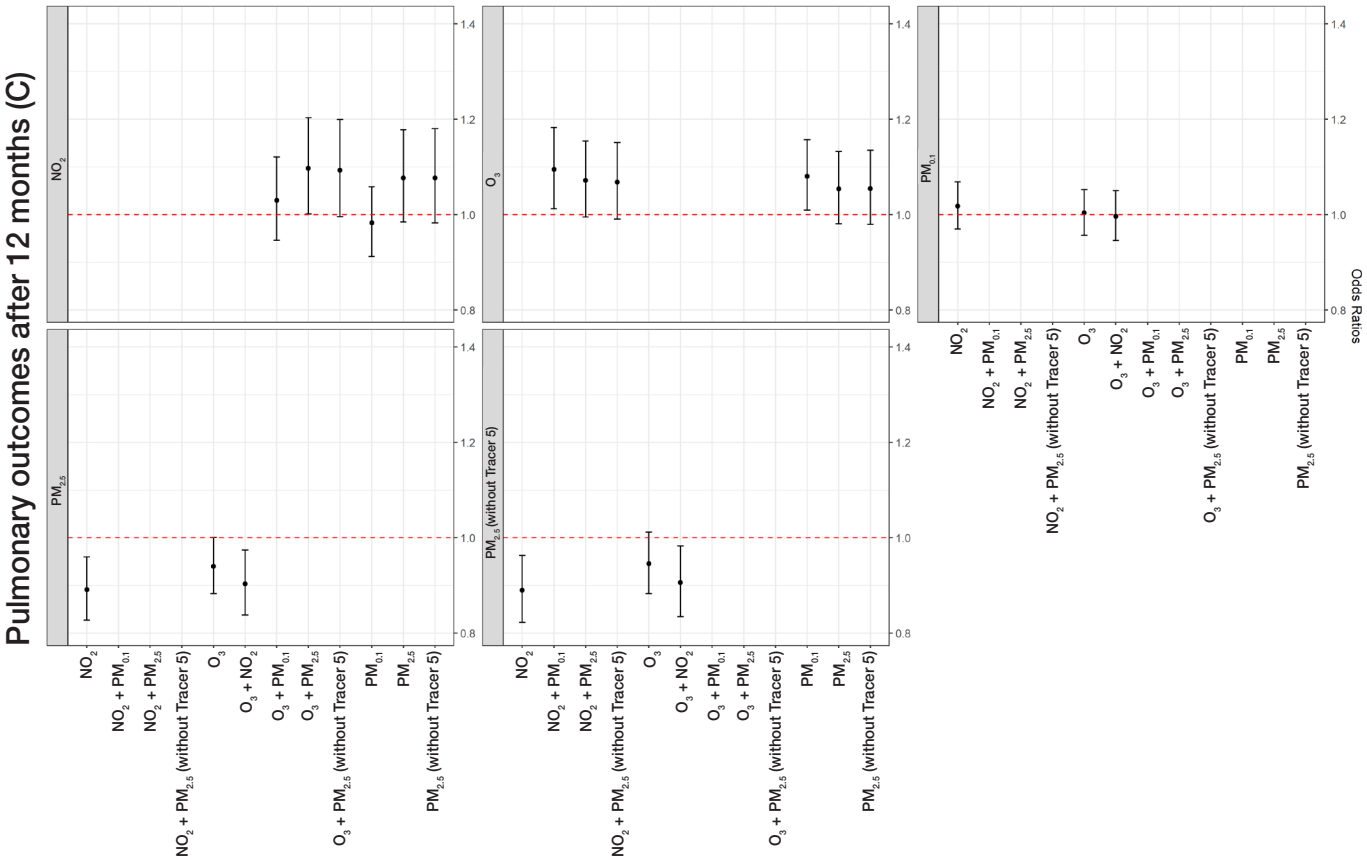

Figure 20. Odds ratios for 30-day exposure effects on cardiac (A), cardiometabolic (B), and pulmonary (C) PASC outcomes at 12 months among patients hospitalized for COVID-19 in Southern California. Data are based on results from multipollutant models.

In multipollutant models that included $PM_{0.1}$ rather than $PM_{2.5}$ as a potential confounding predictor of pulmonary outcomes, the effect of O_3 exposure remained significantly elevated in every model, with effect sizes generally similar to those in single-pollutant models. In three-pollutant models, the effects of NO_2 and $PM_{0.1}$ exposures were diminished by confounding; whereas, in two-pollutant models, the effect of NO_2 exposure was affected by confounding, but the effect of $PM_{0.1}$ exposure remained elevated and, in some instances, significantly so.

Multipollutant models of the effect of $PM_{0.1}$ exposure on cardiac outcomes at 3 months were largely unaffected by confounding due to NO_2 alone, O_3 alone, or NO_2 and O_3 together. The smaller associations identified in the single-pollutant models for 12-month outcomes persisted in the multipollutant models.

For the cardiometabolic outcomes, the effects of NO_2 exposure were slightly amplified when other pollutants were included in the model. Specifically, the effects of NO_2 on the 12-month outcome became slightly larger in models including either $PM_{2.5}$ alone or $PM_{2.5}$ and O_3 together; the point estimates for the 3-month outcome were similar. None of the effects of $PM_{2.5}$ exposure approached statistical significance for either the 3-month or 12-month cardiometabolic outcomes. The effects of $PM_{0.1}$ exposure on the 3-month cardiometabolic outcomes remained significant when either NO_2, O_3, or both were included in the model. As with the single-pollutant models, the effects of $PM_{0.1}$ exposure were smaller in size and generally nonsignificant for the 12-month cardiometabolic outcomes. The effect of O_3 exposure on cardiometabolic outcomes was not statistically significant in single-pollutant models and remained nonsignificant when other pollutants were included in the model.

DISCUSSION AND CONCLUSION

Our findings from the single- and multipollutant models examining associations between air pollution exposures and PASC are summarized in Figures 18–20.

Many of the potential risks associated with pollutant exposures appeared elevated but did not reach statistical significance, likely indicating a lack of statistical power to detect effects on several of the outcomes. We also observed some negative associations between PASC and exposures to $PM_{2.5}$ wildfire tracer, $PM_{2.5}$ mass, and, in some models, $PM_{2.5}$ OC and $PM_{2.5}$ EC, both of which are associated with wildfire events. As described above, when we further controlled for co-pollutants, removed the wildfire tracer from $PM_{2.5}$ mass, or did some combination of both, all negative associations became statistically nonsignificant. (A summary of the sensitivity analyses of the effects of $PM_{2.5}$ biomass combustion is presented in Table 14.) Given the results of these analyses, we concluded that these unexpected protective effects resulted from the temporal misalignment of wildfire smoke exposures and the surge in COVID-19 cases that occurred in late 2020.

The strongest negative associations with $PM_{2.5}$ exposures were observed for the groups of PASC pulmonary outcomes that included the most serious conditions and diseases (Group 3; data not shown). This finding suggests a survival effect, whereby patients with severe pulmonary disease were more likely to die before they could be ascertained in the study as having a PASC outcome. Patients who died before PASC ascertainment were excluded from the analysis, which may have biased the effect estimates downward for the more serious pulmonary outcomes. In our earlier studies, $PM_{2.5}$ exposure was the strongest predictor of mortality.[70,123] This finding suggests that deaths that occurred before PASC ascertainment may likely have been due to conditions included in the pulmonary group of PASC outcomes, which would have spuriously contributed to the negative findings.

Among the positive findings, O_3 exposure was strongly and robustly associated with pulmonary outcomes, suggesting that patients living in areas with higher levels of O_3 either 30 days or 365 days before their hospitalization were more likely to experience PASC, compared to those living in areas with less exposure to O_3. These associations were present at both the 3-month and 12-month analysis windows after hospital discharge. Including co-pollutants in the models revealed minimal effects of confounding in the association between O_3 exposure and pulmonary outcomes.

Exposure to $PM_{2.5}$ nitrate was strongly associated with cardiac and cardiometabolic PASC outcomes. These associations were significant at either the 3-month or 12-month follow-up times for different outcomes; the magnitudes of effects were similar for both follow-up times, suggesting stable results that may have reached statistical significance with a larger sample size. For cardiometabolic outcomes at 3 months and 12 months, the 365-day exposure window for $PM_{2.5}$ nitrate also displayed significant effects, suggesting that both the acute and longer-term exposures may have contributed to this association.

At the 3-month follow-up, $PM_{0.1}$ exposure was significantly associated with cardiac, cardiometabolic, and pulmonary outcomes; however, these effects, while remaining positive, became considerably smaller and did not reach statistical significance at the 12-month follow-up. It is unclear why these effects became smaller and nonsignificant in the ensuing 9 months after completion of the 3-month follow-up. It is possible, however, that the relatively short exposure window of 30 days before hospitalization could have failed to capture important aspects of exposure that occurred after discharge from the hospital; with the longer follow-up, this deficiency in fully assessing exposure could have been exacerbated. Generally, we would expect that the closer temporality between the 30-day exposure window and the 3-month follow-up would result in more accurate exposure estimates, compared to the 12-month follow-up, at which time the exposures could have occurred up to 1 year before the ascertainment of PASC conditions. This could have heightened exposure measurement error, which may have biased the 12-month follow-up analyses toward the null hypothesis. Future research could usefully investigate other exposure windows.

Taken together, our results suggest that exposure to air pollution — particularly O_3, $PM_{2.5}$ nitrate, and $PM_{0.1}$ — could increase patients' risk of experiencing PASC. These results broadly concur with the findings of prior studies conducted in Sweden, Saudi Arabia, and the United States,[142] which reported positive associations between exposure to air pollutants and the development of PASC outcomes.[140,141] The present study, however, strengthens the evidence base, given the larger cohort size sampled from a region with pollutant exposures that are somewhat higher than the US average but probably more representative of general population exposures than those in either the Swedish study, with very low exposure levels, or the Saudi Arabian study, with extremely high levels of exposure. Additionally, our study used high-resolution exposure modeling combined with the home address of patients, improving the exposure assessments compared to those in the prior US study that used ZIP codes for residential addresses.

Approximately 17.8 million people in the United States continue to experience long COVID. Thus, the findings presented here suggest that mitigating air pollution could be a means of reducing the incidence of PASC. Although vaccines and other preventive measures, such as social distancing, remain the primary line of defense against SARS-CoV-2, variable uptake of COVID-19 vaccines and difficulty in maintaining the social measures over long periods underscore the importance of preventive measures that target ubiquitous and modifiable exposures, such as air pollution, and require no individual decision-making or actions. Moreover, PASC can occur in vaccinated patients,[141] which further highlights the importance of pursuing all available risk-reduction strategies.

CHAPTER 8: SYNTHESIS, INTERPRETATION, AND IMPLICATIONS OF FINDINGS

In this study, we investigated relationships between ambient air pollution and aspects of COVID-19 incidence, severity, and mortality, as well as conditions consistent with long COVID (also known as PASC). We used advanced CTMs and LUR models to estimate pollutant exposures. Our ability to assess exposure to numerous air pollutants, particle species, and other pollutant sources, such as wildfire smoke, represents a primary strength of the study. We used administrative public health surveillance data on COVID-19 and several distinct cohorts of hospitalized patients with COVID-19, each drawn from the patient membership of the KPSC health system, to evaluate different hypotheses. Broadly, we demonstrated that exposures to several common air pollutants are associated with COVID-19 incidence and mortality, progression from hospitalization to more severe health states, and long COVID conditions, or PASC. Although the public health emergency surrounding COVID-19 has passed, the disease continues to pose substantial risks to individual and population health. As of December 2023, COVID-19 continued to result in nearly 35,000 persons being hospitalized and 900–1,400 deaths per week in the United States.[150]

Approximately 10% to 30% of individuals with COVID-19 will experience some form of long COVID, which can have lifelong and debilitating effects. Thus, the importance of addressing modifiable environmental risk factors, such as air pollution, cannot be underestimated. As noted in a recent *Lancet* editorial, the societal investment in gaining an understanding of both the pathogenesis of long COVID and potential measures to prevent its development has lagged well behind the actual levels needed to effectively treat and mitigate the clinical features and effects of this complex disease.[6]

The results of our study broadly support the hypotheses that air pollution increases an individual's risk of COVID-19, although our study investigating this outcome relied solely on administrative data from the state of California. Nonetheless, that study suggested that several air pollutants contributed to increased incidence of COVID-19, a finding that is consistent with earlier ecological studies from Los Angeles[42] and the broader literature. Our study, however, could not control for many potentially important determinants of COVID-19 transmission, such as occupational exposure or residential crowding; this limitation must be taken into account in considering our results regarding associations with COVID-19 incidence.

We investigated COVID-19 mortality by using administrative data as well as individual patient data. Both analyses suggested that mortality due to COVID-19 is significantly associated with common air pollution exposures. Our analyses based on individual patient data indicated that meteorological factors, specifically temperature and humidity, also influence COVID-19 mortality. These meteorological variables also modified the relationship between air pollution and mortality, with cooler and less humid conditions (typical of winter weather in the study area) accentuating the effects of air pollution on COVID-19 mortality.

We extended our patient-level analyses with the use of multistate models to investigate the progression of COVID-19 in hospitalized patients. These results demonstrated that exposure to air pollution was significantly associated with progression toward more extreme states of illness, such as admission to the ICU and, ultimately, death. The multistate models also showed that O_3 exposure was significantly related to death after recovery from COVID-19. These results corroborate our previous findings on mortality but also highlight the concept that air pollution may also affect both the severity of COVID-19 and the likelihood of recovery among patients discharged after hospitalization for COVID-19.

Finally, our in-depth investigation of air pollution and long COVID revealed significant associations between PASC conditions and several air pollutants, namely O_3, $PM_{0.1}$, and $PM_{2.5}$ nitrate. We also identified unexpected protective effects associated with exposure to $PM_{2.5}$ and various species related to wildfires. After conducting extensive sensitivity analyses, however, we concluded that these seemingly protective effects likely resulted from temporal misalignment between wildfire smoke and COVID-19 incidence as well as a lack of control for other co-pollutants, such as O_3, which was also a significant positive predictor of pulmonary PASC outcomes.

Our findings on long COVID are perhaps the most novel and important findings of our investigations, given that long COVID continues to affect nearly 18 million people in the United States, many who experience severe debilitation and loss of work,[151] and can even occur in vaccinated individuals, although vaccination reduces the risk of developing PASC conditions.[141] All of these factors point to the ongoing, sizeable impact of COVID-19 on public health, which may not be completely mitigated with pharmaceutical and nonpharmaceutical control measures. Additionally, research suggests that symptoms of long COVID partly depend on the severity of the initial infection and the number of times a person is infected, both of which appear to be influenced by exposure to air pollutants.[152]

STRENGTHS AND LIMITATIONS

We encountered several challenges in conducting the data analyses for this study. First, the various exclusions

required for the mortality, multistate, and long COVID analyses necessitated the use of different analysis cohorts for each substudy. Consequently, direct comparisons of results across substudies are somewhat problematic, as we cannot determine whether observed differences resulted from underlying differences in the composition of the cohorts. Nevertheless, we did note corroborative findings among the analyses overall. Second, the majority of the study cohort was composed of patients diagnosed with COVID-19 during a large surge in cases that occurred from November 2020 to January 2021. This characteristic of the study population limited our ability to thoroughly investigate the influence of highly temporally variable exposures, such as wildfire smoke or pollution reductions resulting from prior COVID-19 lockdown periods. The temporal distribution of the study population likely also introduced a negative bias in some of our findings, given that only a small number of COVID-19 hospitalizations occurred during the period when exposure to wildfire smoke was high. Third, with regard to the transmission question, we did not use formal infectious disease models that rely on factors like social interaction data; instead, our findings based on administrative data for the study cohort were associative and subject to possible confounding.

Despite these challenges, the investigations described in this report had many strengths. First, we estimated exposures by using two advanced exposure models, and we investigated several different pollutant exposures that had high temporal and spatial resolution. Second, for most of the studies, we used well-characterized clinical cohorts from the membership of the KPSC health system, which is largely representative of the overall population of Southern California. As previously noted, however, the analytical requirements of each substudy necessitated the use of different subsets of the overall cohort. For the investigation regarding long COVID, we worked closely with clinicians and epidemiologists from the KPSC system to define outcomes likely indicative of long COVID, recognizing that the science underlying these definitions continues to evolve. The long COVID-19–related outcomes that we investigated have prior evidence of being associated with air pollution; given our reliance on prior evidence, however, we may have missed some relevant novel findings.

On balance, our research demonstrates that exposure to air pollution likely contributes to heightened risks of developing COVID-19, experiencing more severe health states during hospitalization for COVID-19, dying from COVID-19, and experiencing long COVID. Recent studies have shown that the risk of long COVID increases each time an individual is infected with SARS-CoV-2, such that those who have had three SARS-CoV-2 infections are 2.6 times more likely to experience long COVID than those who have had only one such infection.[9] Thus, if air pollution increases the risk of SARS-CoV-2 infection, as our findings suggest, this presents another pathway from air pollution exposure to long COVID conditions. Thus, both preventing SARS-CoV-2 infection and reducing the severity of COVID-19 disease could reduce risks for developing long COVID. Furthermore and more specifically, reduced air pollution might also lead to decreased risks of long COVID, via biological pathways such as reduced oxidative stress, systemic inflammation, and immunological dysregulation. Future research is needed to examine these common biological mechanisms underlying the health effects of air pollution on long COVID, investigate these relationships in other populations with different pollutant exposure profiles, and examine wider exposure windows that would facilitate the assessment of longer-term and/or ongoing air pollution exposures.

CONFOUNDING

In observational epidemiology, residual confounding due to missing or mis-specified variables that can simultaneously influence both the exposure and outcome is a chief concern regarding the validity of the results of statistical analyses. Our approach to addressing confounding evolved as parts of our work underwent independent peer review by academic journals and as knowledge about potential risk factors for COVID-19 emerged. During peer review of the multistate model (Chapter 6), one reviewer asked us to include all potential confounders in the model a priori. We adopted this suggestion and compared the results of the updated model to those of the models chosen by the 10% selection rule that we had used in Chapter 5 and in the initial analyses of EHR data in Chapter 6. In the multistate analysis, the inclusion of additional confounders had minimal effect on the estimated associations between air pollutant exposures and the severity of health states experienced by hospitalized patients with COVID-19. In the multistate analyses and all subsequent analyses of PASC outcomes, we then included all confounders a priori to avoid similar criticisms in future work.

We used several strategies to address spatial confounding. First, for the models based on EHR data from the HPSC health system, we used well-specified individual-level data, which would presumably have reduced residual spatial confounding. In examining the various risks investigated in this study for positive or negative confounding, we were unable to draw firm conclusions. In some instances, a model including the confounders demonstrated larger effects than did a minimally adjusted model; in other instances, however, models including confounders revealed negative confounding that reduced the magnitude of effect of the pollution exposure. We were unable to draw generalized conclusions from this comparison of the fully versus minimally adjusted models, apart from noting that several confounders substantially affected the final associations reported as our main results; this observation suggests that the inclusion of confounders likely reduced residual spatial variation.

Second, we included contextual neighborhood variables, intended to further reduce residual confounding. Several of these variables were selected using our initial 10% criterion, demonstrating potential confounding that was controlled in the models. Based on emerging evidence of a potential protective effect of green space on COVID-19 severity,[126] we also included the NDVI as a confounder. Additionally, although we did not initially include the meteorological variables as confounders in the mortality analyses, we decided to test the sensitivity of the results by including the temperature and humidity variables as confounders, given the evolving knowledge base on COVID-19 severity and the potential role of meteorology, which can also influence air pollutant concentrations. Unlike many of the other confounders that minimally influenced the estimated pollution coefficients, inclusion of temperature and humidity substantially affected pollutant coefficients, particularly for $PM_{2.5}$ and O_3, with $PM_{2.5}$ having larger effects and O_3 having smaller effects with the meteorological variables in the model. Both meteorological variables also demonstrated significant interactions with the pollutant effects, revealing potentially important multiplicative risks that had not been explored in other studies of COVID-19 mortality. In all of our studies using the KPSC cohorts, we also used a sandwich estimator to account for possible nonindependence in the census tracts where patients lived, thereby providing a robust variance estimate that accounts for clustering.

Along with the administrative data in Los Angeles County, which contained only minimal information on individual characteristics, we also included data on variables such as smoking and obesity (obtained from PLACES, a Centers for Disease Control and Prevention online tool that provides access to US health-related data) to compensate for missing individual confounders. In this analysis (Chapter 4), which involved large sample sizes due to the complete population coverage, we formally assessed residual autocorrelation using a Global Moran's *I* test, which was significant. We then refit the models with a Bayesian CAR model that used the nearest neighbors for the spatial weight matrix. Results changed only slightly for most pollutants when we explicitly accounted for spatial autocorrelation in the model specification; for $PM_{2.5}$ nitrate, however, the combination of a CAR model and controlling for O_3 as a co-pollutant changed the demonstrated effect from a negative association to a positive association.

For the Cox (Chapter 5), multistate (Chapter 6), and logistic regression (Chapter 7) analyses, we did not attempt to formally evaluate residual spatial variation, as the relatively limited sample size was likely too small to support estimation of stable spatial random effects that could be discerned from background variability. If such analyses had been possible, they may have revealed residual spatial confounding. Our decision in this setting was informed by prior modeling using even larger cohorts,[153] with which we attempted to fit random effects that could be used to probe (and potentially adjust for) residual spatial confounding by including new contextual variables or spatially autoregressive error terms. The sample size and number of events, although larger than in most existing studies, limited our ability to formally evaluate residual spatial confounding in the same way that we addressed this concern in the larger cohort involving administrative data from Los Angeles County. We recommend that any future studies use larger samples, which would provide sufficient power for formal analyses of residual spatial confounding.

GENERALIZABILITY

As mentioned in several chapters of this report, our results are not likely to be generalizable to the entire population of the study area. Given that all patients in these studies were hospitalized with COVID-19, generalizability is probably restricted to hospitalized patients, who would be among the more severely ill patients with this disease. In some instances, patients who rapidly died outside the hospital setting may have been more ill, but we lacked data to address this question. Earlier analyses cited in Chapter 5 have shown that the population of patients in the KPSC membership approximates the characteristics of the general population of Southern California. Consequently, the generalizability of our findings likely extends to other hospitalized patients in Southern California, but we cannot assert generalizability beyond this region.

As this study occurred during a period when the population was largely unvaccinated, it is difficult to predict how vaccination and natural immunity acquired through infection would influence the results or whether the results are generalizable to current populations. Existing evidence suggests that vaccinations reduce the severity of both COVID-19 and long COVID, or PASC conditions. To date, only one study has investigated whether vaccination minimizes the risk of COVID-19 severity.[156] That study reported that air pollution continued to exacerbate the risks of COVID-19, although vaccination appeared to lower the elevated risks associated with $PM_{2.5}$ exposure. Another study from Spain suggested that air pollution can affect antibody response to vaccination, potentially reducing the efficacy of vaccines.[157] This topic merits further research, especially if vaccination partly blunts the adverse effects of air pollution exposure on COVID-19 and, conversely, if air pollution reduces vaccine efficacy. Given this complex interplay, we cannot predict whether our findings would be generalizable to a vaccinated population.

EFFECTS OF PARTICLE SPECIES AND TRACERS

One of the biggest strengths of this study is the use of the CTM, which allowed us to investigate specific chemical species of $PM_{2.5}$ and source tracers, such as wildfires and traffic-related air pollution. Some of the tracers and $PM_{2.5}$ species contribute very little to mass concentrations; however, they were still highly predictive of all the COVID-19 outcomes that

we investigated. These effects may indicate that the specific constituents or the mixture of pollutants associated with them are more toxic. Alternatively, this finding could indicate that the potentially more toxic pollutants concentrate in areas with more susceptible populations, which would suggest that the observed associations could be the combined result of heightened toxicity and higher susceptibility, as observed in recent studies in Los Angeles.[158] In the analyses using EHR data, we identified significant associations between COVID-19 mortality and traffic-related pollution represented by either specific tracers for on-road diesel or gasoline exhaust or chemical species known to be associated with traffic, such as EC and $PM_{0.1}$

Notably, $PM_{2.5}$ nitrate, which represents a secondary pollutant with more spatially smooth patterns, displayed larger effects in the mortality analysis than any of the traffic-related species or tracers.

In the long COVID analysis, we also observed $PM_{2.5}$ nitrate having some of the strongest associations with cardiac and cardiometabolic PASC outcomes. Exposure to $PM_{0.1}$ also displayed significant associations with cardiac, cardiometabolic, and pulmonary PASC outcomes, although these effects were of smaller magnitude than those with $PM_{2.5}$ nitrate. Thus, the results of the speciated analysis suggest that pollutants showing fine-scale variations as well as those with large-area variations are associated with long COVID outcomes, although the regional-scale constituent is related to the larger effect sizes when evaluated across the IQR exposure increment. As previously stated, the PM mass attributable to these species or markers, particularly the traffic-related markers, is quite small. The results of our analyses do not clarify whether these effects are due to heightened toxicity per unit mass, the mixtures associated with these PM species or tracers, or elevated susceptibility among populations in areas with higher concentrations of these species or tracers. Notably, however, research in other health outcomes has demonstrated similar associations with pollutants that account for small proportions of the total mass, such as the relationship between barium exposure and birth outcomes, as recently reported from studies in Los Angeles.[159] As the science of pollutant exposures advances toward more refined analyses of species and tracers, there is a need for further research into how and why exposures assessed as having relatively small mass concentrations appear to be associated with several quite different COVID-19–related health outcomes.

METEOROLOGY VERSUS SEASONALITY

The observed confounding and effect modification due to temperature and humidity in the mortality study (Chapter 5) provided novel contributions to the literature on air pollution and COVID-19 severity. Although we highlighted the biological plausibility of this finding, given the impacts of cooler and drier conditions on mucociliary dysfunction and respiratory barrier impairment, it is possible that seasonality more generally affected our results. Like other viral respiratory diseases, COVID-19 has demonstrated increased incidence and mortality in the late fall and early winter period, when humidity and temperature tend to be lower. Although respiratory viruses are more frequently transmitted during the winter months, partly due to the heightened probability of transmission associated with increased human activity indoors, this pattern does not necessarily result in more severe outcomes of infection, which would support the role of meteorological factors in exacerbating severity. We investigated whether the KPSC health system was overwhelmed by cases during the fall-winter surge that occurred during the period of our study and found that at no time was the ICU or ICU-level care unavailable to patients, which rules out this factor as a confounder of the results pertaining to the meteorological variables. Another hypothesis is that individuals have worse immune responses during the winter as a result of depleted vitamin D levels, which are associated with lower sunlight exposure, as discussed in Chapter 6. We attempted to obtain vitamin D data on patients in the study cohort but found that the EHRs likely provided incomplete information on vitamin D deficiency. The lack of these data on vitamin D status tempers the meteorology findings, as lower vitamin D levels also could have coincided with the fall-winter period, leading to increased mortality among patients with COVID-19 who may have had reduced immune response to the virus in those seasons.

IMPLICATIONS FOR FUTURE PANDEMICS

As previously discussed, the generalizability of our findings to current populations with some immunity due to natural infection or vaccination cannot be directly determined from our findings, because our results were based on an unvaccinated population. Nevertheless, future novel respiratory viruses with the potential to generate pandemics could emerge, and our findings suggest that reducing ambient exposure to air pollution could lead to a lower incidence of infection, fewer severe outcomes, and, if applicable, reduced development of post-acute symptoms and conditions. Although some of the pollutants that were significantly associated with COVID-19–related outcomes in our studies, such as $PM_{2.5}$ and O_3, are already regulated, our findings also point to novel exposures, such as $PM_{0.1}$ and $PM_{2.5}$ nitrate, neither of which is currently regulated. Given the wide range of health benefits that can accrue from reducing air pollution, such as preventing chronic diseases and lowering rates of hospital admissions and mortality, the additional possibility of reducing the risks of infection and severe outcomes associated with future novel viruses further incentivizes efforts to achieve continued reductions in ambient air pollution.

DATA AVAILABILITY STATEMENT

The 2020 air pollution exposure fields generated in the current project can be accessed at *https://doi.org/10.5281/zenodo.12674134* in comma-separated value files or GIS raster files for easy interpretation by other researchers. Software is provided to calculate exposures for participant locations described by latitude and longitude. The source code for the CTM is available from the principal investigator upon request from qualified investigators; please contact *mjkleeman@ucdavis.edu* to request this information.

The statistical analysis programs (written in R) used to process the data can be accessed at *https://doi.org/10.5281/zenodo.12674134*. The patient data used in the analyses are subject to privacy restrictions and cannot be distributed to researchers outside the Kaiser Permanente Southern California health system.

The CDPH data are available by request and only directly from the CDPH. A summary of the data is available at *https://data.chhs.ca.gov/dataset/covid-19-time-series-metrics-by-county-and-state*.

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The analysis described in this report was partially conducted by graduate students, postdoctoral scholars, and research scientists, with guidance from the principal investigators. In some instances, these individuals were coauthors of individual chapters that have been submitted for publication in peer-reviewed journals. The student, postdoctoral scholar, and research scientist team consisted of the following individuals: Lee Barton, KPSC Research Scientist; Jia Jiang, University of California, Davis, postdoctoral scholar; and Yusheng Zhao, University of California, Davis, graduate student.

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HEI QUALITY ASSURANCE STATEMENT

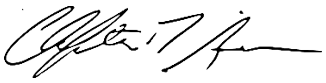
Eastern Research Group, Inc. (ERG) independently provided quality assurance (QA) oversight for this study. ERG staff members Dr. Clifton Dassuncao, John Wilhelmi, and Dr. Rebecca Devries conducted a remote audit of the final report. The audit team has expertise in QA oversight and subject areas relevant to this study, including epidemiological and statistical methods, exposure assessment, air quality modeling, and health outcomes research. Dr. Dassuncao, an environmental epidemiologist, served as the lead auditor and coordinated interactions with the principal investigators, reviewed R code, and evaluated all aspects of the final report. Mr. Wilhelmi, an air quality specialist, and Dr. Devries, an epidemiologist, provided additional independent reviews of the final report.

The remote audit was conducted between October and December 2024. Its objectives were to assess whether study methods were clearly documented, results were accurately reported, findings and limitations were appropriately highlighted, and documented study protocols were followed. To meet these objectives, ERG reviewed the final report text, tables, and figures for accuracy and clarity, and evaluated study and QA protocols for consistency with reported methods. ERG also reviewed R codes and executable Fortran files documenting data processing and analyses, and compared

these materials to the methods and findings described in the report. A subset of exposure data was provided to ERG; however, COVID-19 incidence and mortality data were not shared due to confidentiality restrictions. ERG was nonetheless able to review data-processing code to verify that key calculations were implemented as described.

The audit identified opportunities to improve clarity and accuracy in portions of the report text. Minor discrepancies were noted but were addressed and did not affect the study's findings or conclusions. Because ERG did not have access to all the underlying data, auditors were unable to independently reproduce all numerical results; however, exposure values were reproduced when feasible, numerical values were checked for internal consistency, and reported analyses were consistent with the code. Audit findings were documented in an ERG audit report and an HEI follow-up memorandum.

Overall, the audit did not identify issues that materially affected the study's results, and the audit team concluded that the final report accurately represents the research conducted, with primary analyses clearly documented, and the study followed valid, documented procedures.



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SUPPLEMENTARY APPENDICES ON THE HEI WEBSITE

Appendices A through E contain material not included in the main report. They are available on the *HEI website.*

Appendix A. Supplemental Information for Chapter 3: Development of Chronic and Subchronic Exposure Fields

Appendix B. Supplemental Information for Chapter 4: Risks of Species-Specific Air Pollution for COVID-19 Incidence and Mortality in Los Angeles

Appendix C. Supplemental Information for Chapter 5: Air Pollution and Meteorology as Risk Factors for COVID-19 Mortality in Southern California

Appendix D. Supplemental Information for Chapter 6: Air Pollution and Sequelae of COVID-19: A Multistate Analysis

Appendix E. Supplemental Information for Chapter 7: Association Between Air Pollution and Post-Acute Sequelae of SARS-CoV-2

ABOUT THE AUTHORS

Michael Kleeman earned his BASc in mechanical engineering from the University of Waterloo and his MS and PhD in environmental engineering science from the California Institute of Technology. He is a professor of civil and environmental engineering at the University of California, Davis, where he researches urban and regional air pollution. He served as the principal investigator on the current project, and his research group produced the CTM fields used in the exposure analysis.

Claudia Nau is a research scientist in the Division of Behavioral Research of the Department of Research and Evaluation at KPSC. She led the KPSC research team and provided scientific oversight of data extraction and quality control, and also led the analyses conducted at KPSC. Claudia monitored adherence to policies for the protection of human subjects and collaborated on presentations and manuscripts that have resulted from the study.

Jason Su, PhD, is a researcher at the School of Public Health at the University of California, Berkeley. He specializes in analyzing the impact of environmental exposures on human populations, particularly underserved communities. His expertise encompasses environmental exposure modeling, statistics, epidemiology, and environmental health research. Jason utilizes advanced LUR modeling techniques to examine small-area variations in air pollutant concentrations and employs the Stochastic Time-Inverted Lagrangian Transport dispersion modeling framework to trace sources and simulate pollutant concentrations. In this project, he contributed to the air pollution exposure modeling.

Deborah Young is the director of the Behavioral Research Division in the Department of Research and Evaluation at KPSC. She has a PhD in health education and postdoctoral fellowships in cardiovascular epidemiology and prevention. Before joining KPSC in 2011, Deborah was a professor and chair of the Department of Epidemiology and Biostatistics at the University of Maryland School of Public Health. Before that, she was an associate professor at the Johns Hopkins School of Medicine. She is an expert on research in the areas of physical activity, epidemiology of obesity, and obesity prevention interventions, and she has received funding from the National Institute of Health for multiple projects throughout her career. For this project, Deborah was a co-investigator supporting the KPSC team that prepared the dataset composed of the appropriate variables for the study cohort.

Rebecca Butler is a biostatistician in the Biostatistics Division at the KPSC Department of Research and Evaluation. She joined KPSC in 2017, after receiving her ScM in epidemiology from the Harvard T.H. Chan School of Public Health. For this project, she helped oversee the preparation of KPSC data and performed the epidemiological analyses.

Lin-Syuan Yang was a graduate student researcher and assisted the project team with data management, statistical modeling, and spatial analysis, while pursuing a master's degree in environmental health sciences at the University of California, Los Angeles. After graduation, she began work as an air quality scientist with INTERA in Austin, Texas.

Christina Batteate is a research program manager in the Environmental Health Sciences Department at the University of California, Los Angeles. She obtained a PhD in environmental health sciences and an MPH in community health sciences from the University of California, Los Angeles. Her work primarily centers on health geography, geospatial statistics, and environmental epidemiology in the United States. She served as project manager, assisting with all aspects of the study, including working with institutional review boards, interpreting results, and co-authoring resultant publications.

Sarah Eng, MPH, was a biostatistician in the Health Services Research Division of the KPSC Department of Research and Evaluation, providing analytic and statistical support to KPSC studies, including this study. She is currently a research analyst at Truveta, providing similar analytic and statistical support to studies using real-world EHR data.

Richard T. Burnett has a PhD in mathematical statistics from Queen's University, Canada, and is a senior research scientist in the Healthy Environments and Consumer Safety Branch at Health Canada in Ottawa.

Michael Jerrett has a PhD in geography and is a professor in the Department of Environmental Health Sciences at the University of California, Los Angeles. He has expertise in the science of air pollution exposure, assessment of the health effects of air pollution, health impacts of climate change and meteorology, and spatial modeling and geographic information science. His roles in this project included contributing to the epidemiological analysis and quality assurance, as well as serving as the lead writer.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Jerrett M, Nau CL, Young DR, Butler RK, Batteate CM, Padilla A, et al. 2023. Air pollution and the sequelae of COVID-19 patients: a multistate analysis. Environ Res 236:116814, *https://doi.org/10.1016/j.envres.2023.116814.*

Jerrett M, Nau CL, Young DR, Butler RK, Batteate CM, Su J, et al. 2022. Air pollution and meteorology as risk factors for COVID-19 death in a cohort from Southern California. Environ Int 171:107675, *https://doi.org/10.1016/j.envint.2022.107675.*

Yang L, Kleeman MJ, Cushing L, Lipsitt J, Su J, Burnett R, et al. 2024. Risks of source and species-specific air pollution for COVID-19 incidence and mortality in Los Angeles. Environ Res Health 2:041001, *http://dx.doi.org/10.1088/2752-5309/ad67fb.*

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 $PM_{2.5}$.

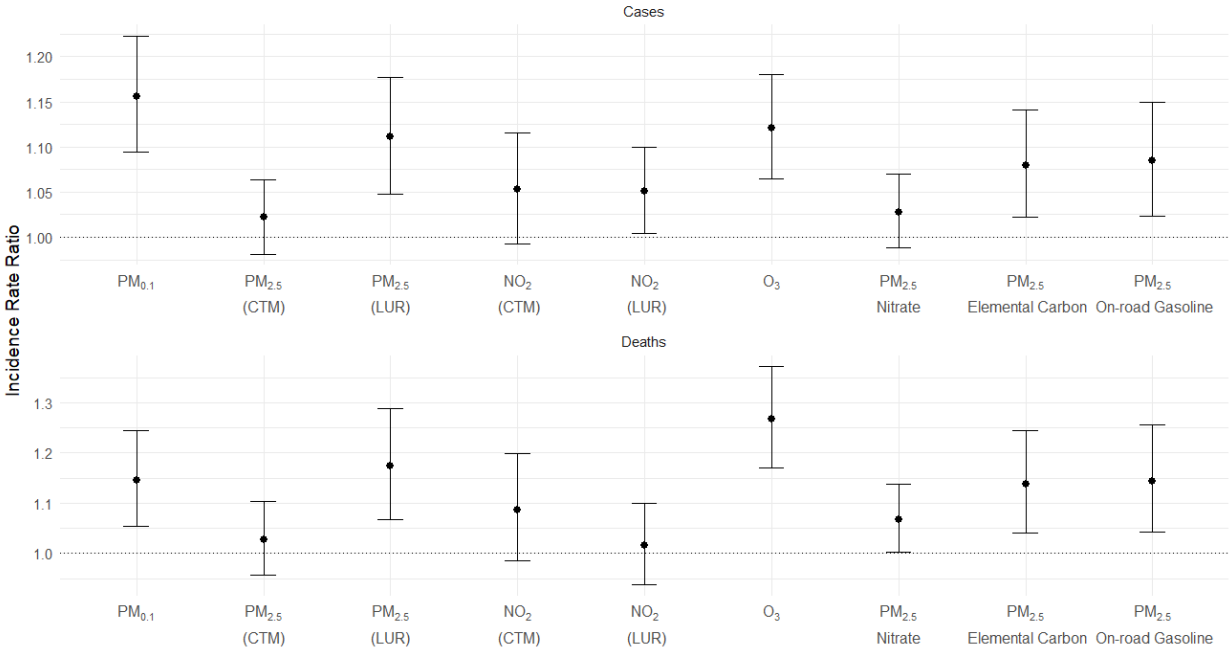
In analyses of the progression to more severe COVID-19 states, Kleeman and colleagues reported elevated HRs in single-pollutant models of the associations between $PM_{2.5}$, NO_2, and O_3 exposures (comparing the highest versus lowest quartiles of exposure) and several COVID-19–related transitional 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.

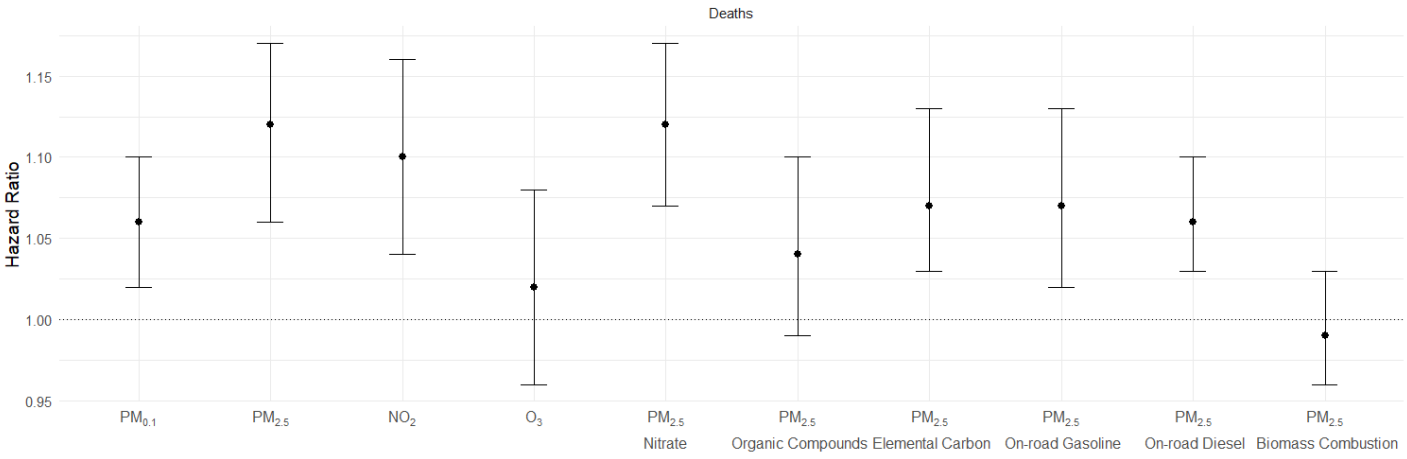
Associations Between Estimated Air Pollutant Exposures and Long COVID-19 (Aim 4)

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)

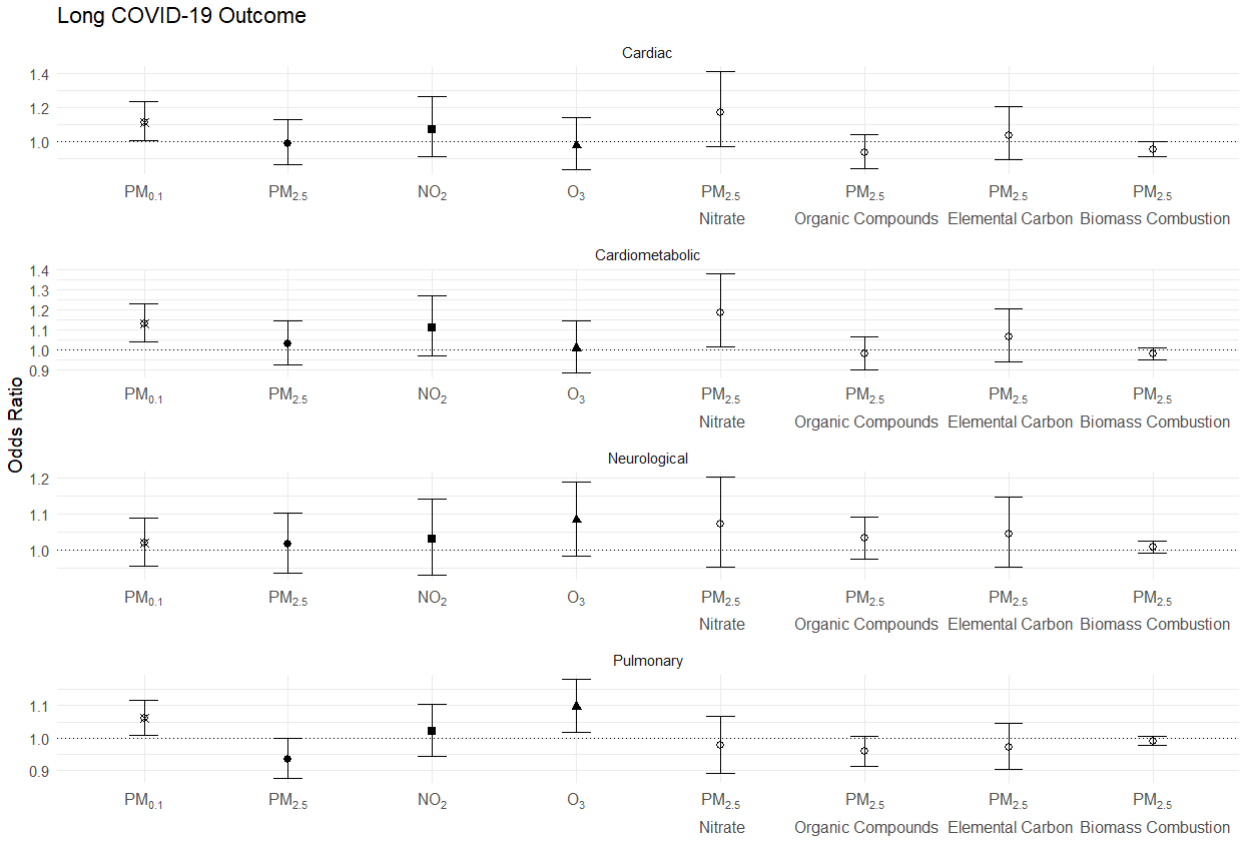
[a]Results shown are hazard ratios and 95% confidence intervals. Source: Investigators' Report Table 8.

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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ABBREVIATIONS AND OTHER TERMS

AIC	Akaike information criterion
BMI	body mass index
CALINE	California Line Source Dispersion Model
CAR	conditional autoregressive
CARB	California Air Resources Board
CDPH	California Department of Public Health
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CTM	chemical transport model
CVD	cardiovascular disease
DVT	deep vein thrombosis
EC	elemental carbon
EHR	electronic health record
EVS	Exercise Vital Sign
HR	hazard ratio
ICU	intensive care unit
ILD	interstitial lung disease
IQR	interquartile range
IRR	incidence rate ratio
KPSC	Kaiser Permanente Southern California
LUR	land use regression
Max	maximum
MCMC	Markov Chain Monte Carlo
Min	minimum
MLR	multiple linear regression
MODIS	Moderate Resolution Imaging Spectroradiometer
NA	not available
NDVI	Normalized Difference Vegetation Index
NDI	Neighborhood Deprivation Index
NO_x	nitrogen oxides
NO_2	nitrogen dioxide
O_3	ozone
OC	organic compounds
OR	odds ratio
PASC	post-acute sequelae of SARS-CoV-2
PE	pulmonary embolism
PM	particulate matter
$PM_{0.1}$	particulate matter ≤0.1 µm in aerodynamic diameter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
ppb	parts per billion
ppm	parts per million
RFR	random forest regression
SD	standard deviation
SES	socioeconomic status
Tracer 1	primary particulate matter from on-road gasoline vehicles
Tracer 2	primary particulate matter from off-road gasoline vehicles
Tracer 3	primary particulate matter from on-road diesel vehicles
Tracer 4	primary particulate matter from off-road diesel vehicles
Tracer 5	primary particulate matter from biomass combustion, including wood burning and wildfires
Tracer 6	primary particulate matter from food cooking
Tracer 7	primary particulate matter from aircraft
Tracer 8	primary particulate matter from natural gas combustion
Tracer 9	primary particulate matter from other sources
UCD/CIT	University of California, Davis/California Institute of Technology
US EPA	United States Environmental Protection Agency
UVB	ultraviolet B
VOC	volatile organic compound

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