

ORIGINAL ARTICLE

Ambient Air Pollutant Exposures and COVID-19 Severity and Mortality in a Cohort of Patients with COVID-19 in Southern California

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Abstract

Rationale: Ecological studies have shown air pollution associations with coronavirus disease (COVID-19) outcomes. However, few cohort studies have been conducted.

Objectives: To conduct a cohort study investigating the association between air pollution and COVID-19 severity using individual-level data from the electronic medical record.

Methods: This cohort included all individuals who received diagnoses of COVID-19 from Kaiser Permanente Southern California between March 1 and August 31, 2020. One-year and 1-month averaged ambient air pollutant (particulate matter $\leq 2.5 \mu\text{m}$ in aerodynamic diameter [$\text{PM}_{2.5}$], NO_2 , and O_3) exposures before COVID-19 diagnosis were estimated on the basis of residential address history. Outcomes included COVID-19–related hospitalizations, intensive respiratory support (IRS), and ICU admissions within 30 days and mortality within 60 days after COVID-19 diagnosis. Covariates included socioeconomic characteristics and comorbidities.

Measurements and Main Results: Among 74,915 individuals (mean age, 42.5 years; 54% women; 66% Hispanic), rates of

hospitalization, IRS, ICU admission, and mortality were 6.3%, 2.4%, 1.5%, and 1.5%, respectively. Using multipollutant models adjusted for covariates, 1-year $\text{PM}_{2.5}$ and 1-month NO_2 average exposures were associated with COVID-19 severity. The odds ratios associated with a 1-SD increase in 1-year $\text{PM}_{2.5}$ (SD, $1.5 \mu\text{g}/\text{m}^3$) were 1.24 (95% confidence interval [CI], 1.16–1.32) for COVID-19–related hospitalization, 1.33 (95% CI, 1.20–1.47) for IRS, and 1.32 (95% CI, 1.16–1.51) for ICU admission; the corresponding odds ratios associated with 1-month NO_2 (SD, 3.3 ppb) were 1.12 (95% CI, 1.06–1.17) for hospitalization, 1.18 (95% CI, 1.10–1.27) for IRS, and 1.21 (95% CI, 1.11–1.33) for ICU admission. The hazard ratios for mortality were 1.14 (95% CI, 1.02–1.27) for 1-year $\text{PM}_{2.5}$ and 1.07 (95% CI, 0.98–1.16) for 1-month NO_2 . No significant interactions with age, sex or ethnicity were observed.

Conclusions: Ambient $\text{PM}_{2.5}$ and NO_2 exposures may affect COVID-19 severity and mortality.

Keywords: air pollution; coronavirus disease; particulate matter $\leq 2.5 \mu\text{m}$ in aerodynamic diameter; NO_2

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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At a Glance Commentary

Scientific Knowledge on the

Subject: Ecological studies have shown that long-term air pollution exposure, particularly particulate matter ≤ 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) and NO_2 , was associated with increased risk of coronavirus disease (COVID-19) incidence and mortality. To date, only four cohort studies have been conducted to investigate associations between individual-level air pollution exposure and COVID-19 outcomes. These cohort studies assessed long-term exposure in older and mostly non-Hispanic White populations and revealed that long-term $\text{PM}_{2.5}$ and NO_2 exposures were associated with increased risk of COVID-19 hospitalization, ICU admission, and mortality. No studies have been conducted to assess the impact of short-term air pollution exposure on COVID-19 outcomes.

What This Study Adds to the

Field: We assessed 1-year and 1-month individual-level exposure to air pollution ($\text{PM}_{2.5}$, NO_2 , and O_3) before COVID-19 diagnosis on a spectrum of COVID-19 outcomes in a multiethnic cohort of approximately 75,000 patients with COVID-19 diagnosed between March 1 and August 31, 2020, in southern California. Results showed that 1-month NO_2 and 1-year $\text{PM}_{2.5}$ exposures were independently associated with increased risk of COVID-19 hospitalization, ICU admission, need for intensive respiratory support, and mortality, with little heterogeneity across age, sex, and race/ethnicity.

The coronavirus disease (COVID-19) pandemic has continued to be a major health crisis and is very likely to become endemic in the future. Beyond virus transmission, the severity and mortality of COVID-19 are top public health concerns. Evidence from prior ecological studies has suggested that chronic exposure to outdoor air pollution may be

associated with COVID-19 incidence and mortality (1–10). Air pollution is the fourth leading risk factor for all-cause mortality worldwide (11–13), and long-term air pollution exposure has been shown to increase the risk of comorbidities linked to severe COVID-19, such as hypertension, cardiovascular disease, and diabetes (14–16). Beyond the effect on comorbidities, air pollution may also perturb the immune response, increase susceptibility to respiratory infection (17), and promote oxidative stress and procoagulation (18, 19), further increasing the risk of severe COVID-19. Rodent models have demonstrated that exposure to particulate matter ≤ 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) and nitrogen dioxide (NO_2) may upregulate pulmonary expression of angiotensin-converting enzyme 2, a binding site for coronaviruses, and has been implicated in mediating COVID-19 severity (12, 20–22). Therefore, air pollution may directly or indirectly affect COVID-19 severity and mortality.

The previous ecological studies on air pollution had several important limitations, such as aggregated exposure and outcome data from large geographic areas and heterogeneous populations, lack of adjustment for important confounders (i.e., comorbidities and social characteristics), and potential misclassification of COVID-19 diagnosis and associated severity and mortality. Also, most ecological studies have focused on associations between long-term air pollution exposure and COVID-19 mortality (1, 2, 5–9, 23), whereas the effect of short-term air pollution exposure has been less studied (4, 24, 25). Prior literature has suggested that short-term air pollution exposure may also increase the risk of severe COVID-19 through immunotoxicity and inflammation (26, 27). To our knowledge, three studies have investigated associations between individual-level $\text{PM}_{2.5}$ and particulate matter ≤ 10 μm in aerodynamic diameter exposures and COVID-19 hospitalizations (28–30). One population-based cohort study in Spain revealed associations of historical exposures to NO_2 and $\text{PM}_{2.5}$ with increased risk of COVID-19, and the associations were larger for the risk of severe cases including hospitalizations and ICU admissions (31). One study in New York using hospital-based patient data showed that long-term $\text{PM}_{2.5}$ exposure was associated with increased risk of COVID-19 mortality and ICU admissions from March to August 2020, when the mortality rate was

extremely high and 31% of the cohort died (32). No association was found for long-term NO_2 and black carbon exposures. Studies of exposures to other air pollutants, such as NO_2 and ozone (O_3), in both long- and short-term time windows, as well as other severe COVID-19 outcomes including the risk of requiring intensive respiratory support (IRS), ICU admissions, and deaths, are needed. In addition, as previous studies were focused on either older or mainly non-Hispanic White populations, more studies with diverse age and race/ethnicity groups are warranted.

To address the limitations of previous studies, we investigated the association between exposures to ambient air pollutants ($\text{PM}_{2.5}$, NO_2 , and O_3) and COVID-19 severity and mortality using individual-level data from a large and ethnically diverse population from an integrated healthcare system in southern California. Ambient air pollutant exposures were estimated using individual residential address history, while severity and mortality outcomes after COVID-19 diagnosis and a spectrum of comorbidities and socioeconomic characteristics were extracted from the electronic medical record (EMR). Our analysis included patients with COVID-19 between March 1 and August 31, 2020, and accounted for important individual-level confounders. Findings from this study will help clarify the role and magnitude of the effect of air pollution exposure on COVID-19 severity during the early pandemic period, when the confounding effects of virus variants and vaccination were minimal compared with the later pandemic period. Some of the results of this study have been previously reported in the form of an abstract (33).

Methods

Details of the cohort and ascertainment of outcome data are described in the online supplement. Briefly, this is a retrospective cohort study with data collected from the EMR at Kaiser Permanente Southern California (KPSC), a large integrated healthcare system with more than 4.5 million members across southern California. This analysis included 74,915 patients who received diagnoses of COVID-19 between March 1 and August 31, 2020, with follow-up to October 31, 2020. Positive COVID-19 diagnosis was defined as a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR laboratory test result or

a diagnosis code (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, and internal KPSC codes) for COVID-19 (see Table E1 in the online supplement). The study was approved by the KPSC Institutional Review Board with a waiver of the requirement to obtain informed consent.

The outcomes included COVID-19 severity, defined as COVID-19–related hospitalizations, IRS, and ICU admissions within 30 days after COVID-19 diagnosis, and mortality within 60 days.

Details of ambient air pollution exposure assessment are described in the online supplement. Twenty-four-hour averages of PM_{2.5} and NO₂ concentrations, as well as 8-hour daily maximum O₃ exposure at participants' residential addresses during 1 year before COVID-19 diagnosis, were estimated using inverse distance squared weighting on the basis of air quality data from ambient monitoring stations (34). Daily residential air quality data were further averaged to assign exposure degrees during 1 month and 1 year before the diagnosis date to represent shorter and longer term exposures, respectively.

Demographics (age, sex, and race/ethnicity), Medicaid insurance status, body mass index categories, smoking history (current, former, or never), and categories of Charlson comorbidity index (0, 1, or ≤ 2) at the time of COVID-19 diagnosis were obtained from the KPSC EMR. Neighborhood-level education and income information were estimated using Nielsen demographic data for the census tract (35). Census tract-level population density was obtained from 2019 Environmental Systems Research Institute data (36) and census tract neighborhood deprivation index was derived on the basis of the 2019 U.S. Census Bureau American Community Survey (37). More details of covariates are described in the online supplement.

Statistical Analysis

To assess the association between each air pollutant exposure and COVID-19 severity, we first used single-pollutant models to analyze associations between the average of each air pollutant exposure during the 1-year or 1-month period and each outcome, adjusting for covariates. Because exposure degrees of multiple air pollutants could be correlated, multipollutant models were further used to analyze the independent effect of each air pollutant exposure,

adjusting for exposure to other copollutants; for this, two or three pollutants were included together in one model. Potential nonlinear relationships were assessed using generalized additive models with a penalized smoothing spline. As no evidence of nonlinear relationships was found, all air pollutants were modeled as continuous variables with linear effects (see Figure E1). For severity, COVID-19–related hospitalization, IRS, and ICU admission within 30 days were modeled as separate binary variables (yes vs. no) using mixed-effects logistic regression models to estimate the odds ratios (ORs) associated with air pollution exposures, with medical center included as a random effect to account for potential within-center correlations and unknown spatial confounders. For mortality within 60 days, shared frailty survival models with medical center as the clustering variable were used to estimate the hazard ratios (HRs) of prior 1-month or 1-year air pollution exposure associated with time to death since COVID-19 diagnosis. Individuals were followed from COVID-19 diagnosis up to 60 days after the index date, date of death, end of membership, or end of study (October 31, 2020), whichever occurred first. All models were adjusted for age (<35, 35–64, or ≥ 65 yr), race/ethnicity (White, Black, Asian, Hispanic, or other), sex, body mass index (underweight/normal, overweight, obese [class 1 and 2], or obese [class 3]), smoking status (current, former, or never), Charlson comorbidity index (0, 1, or ≤ 2), Medicaid insurance status, median neighborhood income (<\$40,000, \$40,000–\$79,999, or $\geq$ \$80,000), college education (on the basis of neighborhood proportion of highest education), population density, and neighborhood deprivation index. Participants with missing data for covariates were coded as “missing” as a category in the covariates and were included in all data analyses. To adjust for temporal variations of the COVID-19 pandemic, indicators for month of COVID-19 diagnosis were included.

Potential effect modifications by age, sex, and race/ethnicity were assessed using global multiplicative interactions across categories between these covariates and exposures, each at a time, using $P < 0.05$ to indicate significance and stratified analyses by each of the covariates. All ORs and HRs together with 95% confidence intervals (CIs) are scaled to a 1-SD increase in exposure. Analyses were

conducted using SAS version 9.4 (SAS Institute) or R version 3.6.0 (RStudio).

Results

Among the 74,915 individuals, the mean (SD) age was 42.5 (16.5) years, with 28,788 (38.4%) <35 years, 38,942 (52%) 35–64 years, and 7,185 (9.6%) ≥ 65 years (Table 1). There were 53.7% women, 65.9% of Hispanic race/ethnicity, 76% overweight or obese, 16.1% former and 5.2% current smokers, and 28.8% with histories of comorbidities (Table 1). After COVID-19 diagnosis, 4,752 (6.3%) had COVID-19–related hospitalization within 30 days, 1,764 (2.4%) had COVID-19–related IRS, 1,125 (1.5%) had COVID-19–related ICU admission within 30 days, and 1,107 (1.5%) died within 60 days.

The 1-month mean (SD) PM_{2.5}, NO₂, and O₃ measures were 11.8 (3.4) $\mu\text{g}/\text{m}^3$, 8.7 (3.3) ppb, and 54.2 (12.0) ppb, respectively, and the 1-year mean (SD) values were 11.0 (1.5) $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 13.9 (3.7) ppb for NO₂, and 47.3 (5.6) ppb for O₃ (Table 1). Correlations between 1-month and 1-year NO₂ and O₃ had Pearson's r values > 0.7 , while 1-month PM_{2.5} was less correlated with 1-year PM_{2.5} ($r = 0.4$) (see Table E2). Across multiple pollutants, 1-month PM_{2.5} and NO₂ were correlated at $r = 0.21$, while 1-year PM_{2.5} and NO₂ were correlated at $r = 0.64$.

Figure 1 depicts the ORs and HRs from the single-pollutant models adjusting for confounders. For 1-year exposures, a 1-SD (1.5 $\mu\text{g}/\text{m}^3$) increase in PM_{2.5} exposure before COVID-19 diagnosis was associated with 23% higher odds of COVID-19–related hospitalization (OR, 1.23; 95% CI, 1.17–1.30), 34% higher odds of IRS (OR, 1.34; 95% CI, 1.24–1.46), 35% higher odds of ICU admission (OR, 1.35; 95% CI, 1.21–1.50), and an 11% higher risk of mortality within 60 days (HR, 1.11; 95% CI, 1.02–1.21). Single-pollutant models also showed that 1-year NO₂ exposure had statistically significant associations with increased odds for COVID-19–related hospitalization (OR, 1.13; 95% CI, 1.07–1.18), IRS (OR, 1.20; 95% CI, 1.11–1.29), and ICU admission (OR, 1.20; 95% CI, 1.09–1.32). However, the association between 1-year NO₂ exposure and mortality was not statistically significant (HR, 1.04; 95% CI, 0.95–1.13). The associations of prior

Table 1. Characteristics of Study Cohort and Pollution Exposure Distribution (*N* = 74,915)

Total COVID-19 Cases (<i>N</i> = 74,915)	
Age	
Mean (SD), yr	42.5 (16.47)
By age group, <i>n</i> (%)	
<35 yr	28,788 (38.4)
35–64 yr	38,942 (52)
≥65 yr	7,185 (9.6)
Sex, <i>n</i> (%)	
Female	40,237 (53.7)
Male	34,678 (46.3)
Race/ethnicity, <i>n</i> (%)	
Asian/Pacific Islander	4,795 (6.4)
Black	4,373 (5.8)
Hispanic	49,338 (65.9)
Other	5,026 (6.7)
White	11,383 (15.2)
BMI category, <i>n</i> (%)	
Underweight/normal	14,106 (18.8)
Overweight	22,341 (29.8)
Obese (classes 1 and 2)	27,681 (36.9)
Obese (class 3)	6,979 (9.3)
Missing	3,808 (5.1)
Tobacco use, <i>n</i> (%)	
Current	3,930 (5.2)
Former	12,091 (16.1)
Never	54,494 (72.7)
Unknown	4,400 (5.9)
Median household income, <i>n</i> (%)	
<\$40,000	8,274 (11)
\$40,000–\$79,999	41,939 (56)
≥\$80,000	21,484 (28.7)
Missing	3,218 (4.3)
College education, <i>n</i> (%)	
No	44,336 (59.2)
Yes	27,361 (36.5)
Missing	3,218 (4.3)
Medicaid status, <i>n</i> (%)	242 (0.3)
Charlson comorbidity index, <i>n</i> (%)	
0	53,319 (71.2)
1	14,697 (19.6)
2+	6,899 (9.2)
Diagnosis month (2020), <i>n</i> (%)	
March	1,841 (2.5)
April	5,674 (7.6)
May	5,497 (7.3)
June	18,686 (24.9)
July	31,371 (41.9)
August	11,846 (15.8)
Neighborhood deprivation index	
1 (lowest level of deprivation)	3,417 (4.6)
2	10,992 (14.7)
3	18,447 (24.6)
4	22,785 (30.4)
5 (highest level of deprivation)	19,274 (25.7)
Population density, mean (SD)	10,032.7 (8,095.10)
Pollution exposure variables, mean (SD)	
PM _{2.5} , µg/m ³	
1 mo	11.8 (3.36)
1 yr	11.0 (1.51)
NO ₂ , ppb	
1 mo	8.7 (3.27))
1 yr	13.9 (3.67)

(Continued)

1-year O₃ exposures with COVID-19 severity and mortality were not statistically significant. Results of univariate and fully adjusted models are presented in Table E3.

For 1-month exposures (Figure 1), a 1-SD (3.3 ppb) increase in NO₂ exposure was associated with 12% higher odds of hospitalization (OR, 1.12; 95% CI, 1.07–1.18), 20% higher odds of IRS (OR, 1.20; 95% CI, 1.11–1.29), 23% higher odds of ICU admission (OR, 1.23; 95% CI, 1.13–1.35), and a 9% higher risk of mortality (HR, 1.09; 95% CI, 1.00–1.19). One-month PM_{2.5} exposure was statistically significantly associated with higher odds of IRS (OR, 1.12; 95% CI, 1.03–1.23) and ICU admission (OR, 1.16; 95% CI, 1.03–1.31) and a higher risk of mortality (HR, 1.14; 95% CI, 1.04–1.26) (Figure 1). The only statistically significant association observed for 1-month O₃ exposure was with COVID-19 mortality (HR, 1.12; 95% CI, 1.00–1.24).

Table 2 presents the multipollutant models including PM_{2.5} and NO₂ exposures over the same time periods in the same model. For 1-year exposures, associations between PM_{2.5} and all four COVID-19 outcomes remained statistically significant, whereas associations between NO₂ and COVID-19 outcomes were attenuated and not statistically significant after adjusting for 1-year PM_{2.5} exposure. In contrast, for 1-month exposures, NO₂ exposures remained statistically significantly associated with COVID-19 severity besides COVID-19 mortality, whereas associations between 1-month PM_{2.5} exposure and COVID-19 outcomes were attenuated and not statistically significant after adjusting for 1-month NO₂ exposures for most COVID-19 severity outcomes. The association between 1-month PM_{2.5} exposure and COVID-19 mortality remained statistically significant after adjusting for 1-month NO₂ exposure. Three-pollutant models were explored, including PM_{2.5}, NO₂, and O₃ in one model (see Table E4), and similar effect sizes were found as for two-pollutant models for 1-year and 1-month PM_{2.5} and NO₂ exposures. Associations between 1-month PM_{2.5} and IRS and ICU admission were also statistically significant after adjusting for 1-month NO₂ and O₃ exposures. The only statistically significant result found for O₃ was the inverse

Table 1. (Continued)

Total COVID-19 Cases (N = 74,915)	
O ₃ , ppb	
1 mo	54.2 (11.96)
1 yr	47.3 (5.64)
Outcomes, n (%)	
COVID-19–related hospitalization within 30 d	4,752 (6.3)
COVID-19–related IRS within 30 d	1,764 (2.4)
COVID-19–related ICU admission within 30 d	1,125 (1.5)
Mortality within 60 d	1,107 (1.5)

Definition of abbreviations: BMI = body mass index; COVID-19 = coronavirus disease; IRS = intensive respiratory support; PM_{2.5} = particulate matter ≤ 2.5 μm in aerodynamic diameter.

association of 1-month O₃ exposure with hospitalization and IRS, which could be caused by its negative association with the NO₂ exposure because

of photochemical reactions in the atmosphere. Therefore, the results for 1-month O₃ need to be interpreted with caution.

Finally, no statistically significant interactions with age (see Table E5) and sex (see Table E6) were observed for the associations with 1-month NO₂ and 1-year PM_{2.5} exposures. A statistically significant interaction was observed for 1-year PM_{2.5} exposure and race/ethnicity for the association with COVID-19–related IRS (interaction $P = 0.05$) (see Table E7). Generally, 1-year PM_{2.5} exposure was associated with higher risk in all race/ethnicity groups, whereas effect sizes of associations were larger among White subjects compared with other race/ethnicity groups. A statistically significant interaction was also found for 1-year NO₂ exposure with race/ethnicity for the association

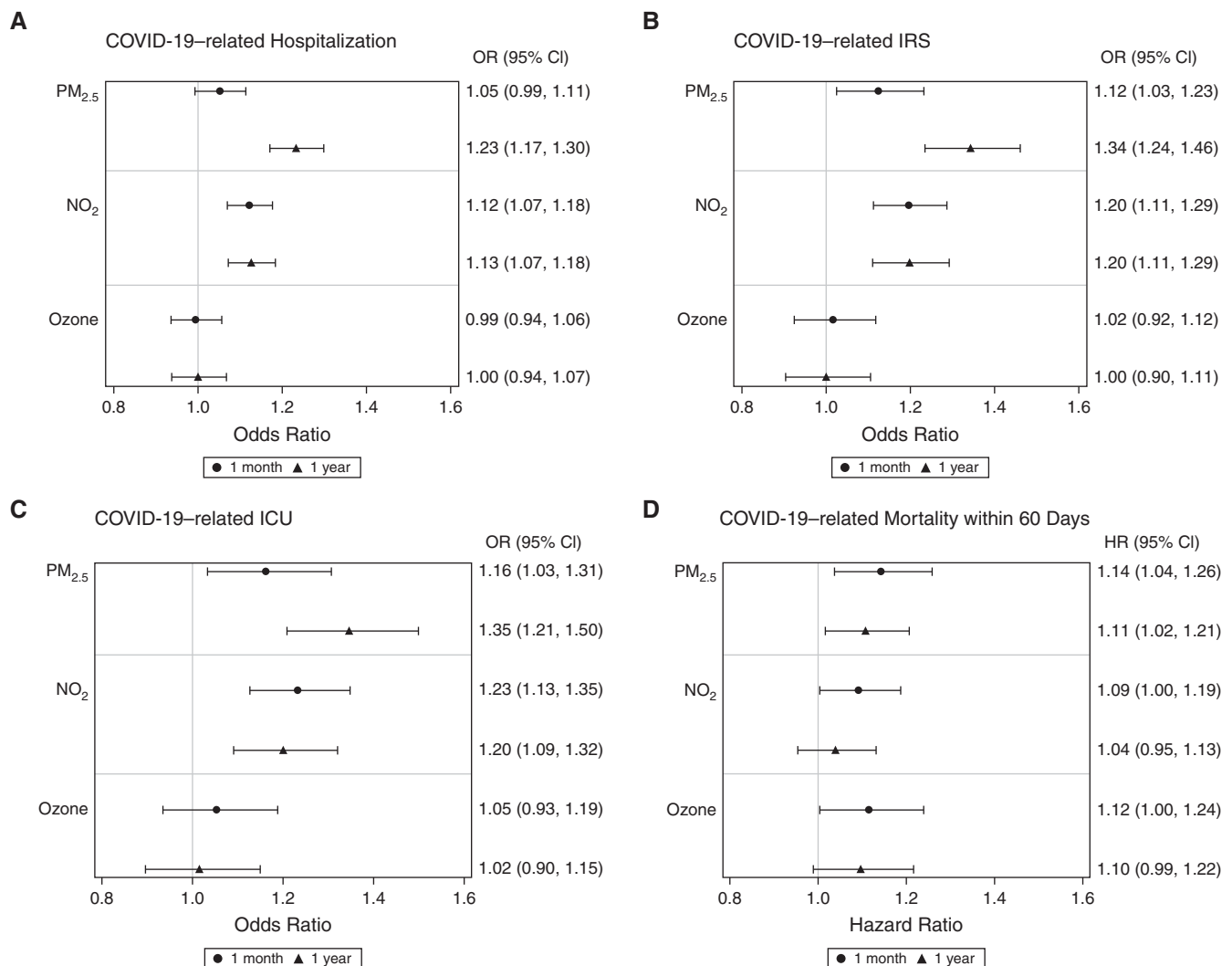


Figure 1. Associations of 1-month and 1-year averaged air pollution (PM_{2.5}, NO₂, and O₃) exposures before COVID-19 diagnosis with COVID-19 severity on the basis of single-pollutant models among 74,915 patients with COVID-19 identified at Kaiser Permanente Southern California from March 1 to August 31, 2020. (A) COVID-19–related hospitalization within 30 days after diagnosis. (B) COVID-19–related IRS. (C) COVID-19–related ICU admission. (D) Mortality within 60 days after COVID-19 diagnosis. CI = confidence interval; COVID-19 = coronavirus disease; HR = hazard ratio; IRS = intensive respiratory support; OR = odds ratio; PM_{2.5} = particulate matter ≤ 2.5 μm in aerodynamic diameter.

Table 2. Odds Ratios or Hazard Ratios and 95% Confidence Intervals for Multipollutant Models That Include 1-Month Particulate Matter ≤ 2.5 μm in Aerodynamic Diameter and NO_2 or 1-Year Averaged Particulate Matter ≤ 2.5 μm in Aerodynamic Diameter and NO_2 Exposures in the Same Models ($N = 74,915$)

		COVID-19–Related Hospitalization within 30 d OR (95% CI)	COVID-19–Related IRS within 30 d OR (95% CI)	COVID-19–Related ICU Admission within 30 d OR (95% CI)	Death within 60 d HR (95% CI)
1 mo	$\text{PM}_{2.5}$	1.02 (0.97–1.09)	1.08 (0.98–1.19)	1.11 (0.98–1.25)	1.12 (1.02–1.24)
	NO_2	1.12 (1.06–1.17)	1.18 (1.10–1.27)	1.21 (1.11–1.33)	1.07 (0.98–1.16)
1 yr	$\text{PM}_{2.5}$	1.24 (1.16–1.32)	1.33 (1.20–1.47)	1.32 (1.16–1.51)	1.14 (1.02–1.27)
	NO_2	0.99 (0.93–1.06)	1.02 (0.93–1.12)	1.03 (0.91–1.16)	0.96 (0.86–1.07)

Definition of abbreviations: CI = confidence interval; COVID-19 = coronavirus disease; HR = hazard ratio; IRS = intensive respiratory support; OR = odds ratio; $\text{PM}_{2.5}$ = particulate matter ≤ 2.5 μm in aerodynamic diameter.

Adjusted for age, gender, race/ethnicity, body mass index, smoking, income, education, Medicaid, Charlson comorbidity index, study month, population density, neighborhood deprivation index, and random effect of medical centers. ORs and HRs and 95% CIs are expressed as increase in risk associated with a 1-SD increase in air pollution exposure.

with COVID-19–related hospitalization (interaction $P = 0.03$). The associations of 1-month $\text{PM}_{2.5}$ and O_3 with COVID-19–related hospitalization, IRS, and ICU admission significantly differed by age (interaction $P \leq 0.01$) (see Table E4). The associations between 1-month $\text{PM}_{2.5}$ and O_3 exposures and COVID-19 were statistically significant and stronger among individuals ≤ 65 years of age compared with the associations observed in individuals < 35 or 35–64 years of age.

Discussion

Data from this cohort of 74,915 patients with COVID-19 showed that 1-year and 1-month exposures to $\text{PM}_{2.5}$ and NO_2 before the COVID-19 diagnosis date were associated with increased risks of COVID-19–related hospitalization, IRS, ICU admission, and mortality using single-pollutant models. In multipollutant models including both $\text{PM}_{2.5}$ and NO_2 , only 1-year $\text{PM}_{2.5}$ exposure had statistically significant associations with all four outcomes. One-month NO_2 exposure had statistically significant associations with COVID-19–related hospitalization, IRS, and ICU admission, and 1-month $\text{PM}_{2.5}$ exposure was associated with COVID-19–related mortality. The only statistically significant association found for O_3 was for 1-month O_3 exposure association with a lower risk of COVID-19–related hospitalization and IRS after adjusting for 1-month $\text{PM}_{2.5}$ and NO_2 exposures. This negative association with O_3 might be caused by the negative correlations between O_3 and NO_2 and therefore should be interpreted with caution. There was little evidence for

heterogeneity of the associations across age groups, sex, and ethnicity. One-month $\text{PM}_{2.5}$ and O_3 exposures had larger associations with COVID-19 severity in older populations. The COVID-19 cohort included in this analysis was more than 65% Hispanic and more than 90% aged 65 years or younger, which is different from two previous cohort studies of air pollution and COVID-19 hospitalization conducted in an older veteran population or a primarily non-Hispanic White population (28, 29). Compared with previous ecological and cohort studies, this study is also unique in investigating associations of both shorter term (1 mo) and longer term (1 yr) exposures to multiple air pollutants ($\text{PM}_{2.5}$, NO_2 , and O_3) with a spectrum of COVID-19–related severity outcomes. Our results suggest that longer term $\text{PM}_{2.5}$ and shorter term NO_2 exposures may affect COVID-19 severity and mortality beyond history of comorbidities.

Many ecological studies were focused on longer term $\text{PM}_{2.5}$ and NO_2 exposure on COVID-19 incidence and mortality rates (1, 2, 5–9, 23). Two ecological studies in the United States assessed longer term air pollution exposures in association with COVID-19 mortality (1, 3). Among them, one investigated long-term average $\text{PM}_{2.5}$ exposure from 2000 to 2016 (1), while the other investigated averaged exposures to both $\text{PM}_{2.5}$ and NO_2 from 2010 to 2016. The second study showed that both $\text{PM}_{2.5}$ and NO_2 exposures were associated with increased COVID-19 mortality rates in the single-pollutant model; however, in the multipollutant model including both $\text{PM}_{2.5}$ and NO_2 , only the association with NO_2 was

significant (3). Fewer cohort studies have been conducted to evaluate the association between individual-level air pollution exposure and COVID-19 outcome data. To our knowledge, only two cohort studies focusing on COVID-19 hospitalization revealed that long-term exposure to $\text{PM}_{2.5}$ was associated with an increased risk of hospitalization after adjusting for individual and community-level covariates (28, 29). One cohort study in Spain also showed that long-term $\text{PM}_{2.5}$ and NO_2 exposures were associated with increased risk of COVID-19, especially for severe cases represented by COVID-19–related hospitalization and ICU admission and higher concentrations of IgG among patients (31). One recent study based on patient data from seven hospitals in New York showed that 1-year exposure to $\text{PM}_{2.5}$ was associated with increased risk of ICU admissions and mortality during the early pandemic period in 2020, when the COVID-19 mortality rate was high ($> 30\%$ deaths among a total of 6,542 patients with COVID-19, and half of the cohort was older than 65 years) (32). However, researchers did not find any association between 1-year NO_2 exposure and COVID-19 mortality. No other cohort study has investigated the impact of gaseous air pollutants on COVID-19 severity and outcomes beyond hospitalization, such as IRS, ICU admission, and mortality. In this study, we found that 1-year averaged exposures to both $\text{PM}_{2.5}$ and NO_2 were associated with COVID-19–related hospitalization, IRS, and ICU admission for patients with COVID-19 from single-pollutant models. However, our data revealed that the 1-year $\text{PM}_{2.5}$ exposure appeared to play a greater role than 1-year

NO₂ exposure on COVID-19 severity and mortality. Of note, 1-year PM_{2.5} and NO₂ were modestly correlated in our sample ($r = 0.64$). In addition, our effect size of a 13% higher risk of mortality per 1-SD (1.5 µg/m³) increase in 1-year PM_{2.5} exposure is comparable to that observed in a previous U.S. ecological study that showed an 11% higher county-level COVID-19 mortality rate per 1 µg/m³ increase in the averaged county-level PM_{2.5} from 2000 to 2016 (1).

For the shorter term exposures, we found that 1-month NO₂ appeared to play a greater role than 1-month PM_{2.5} on COVID-19 severity, whereas 1-month PM_{2.5} had a statistically significant association with COVID-19 mortality only after adjusting for 1-month NO₂. To our knowledge, few and limited previous studies have assessed shorter term air pollution exposures. A cohort study in Italy only assessed the association between 1-month prior particulate matter ≤10 µm in aerodynamic diameter exposure and the risk of developing pneumonia after COVID-19 (30). A study in Queens, New York, in March and April 2020 revealed that 21-day moving average exposure to O₃ was associated with an increased number of new COVID-19 cases, but there was no association with new COVID-19 deaths (25). PM_{2.5} was not observed to be associated with COVID-19 incidence or mortality in this study, and NO₂ was not investigated. An ecological study in Italy and Spain revealed that 78% of COVID-19 deaths by March 19, 2020, were from five regions with high 2-month averaged NO₂ concentrations in January and February 2020 (4). More studies are needed to assess the effect of shorter term air pollution exposure on COVID-19 severity and mortality.

Air pollution may influence COVID-19 severity through various pathways. Longer term air pollution exposure may increase the susceptibility of severe COVID-19 through the adverse effect on comorbidities such as chronic respiratory and cardiometabolic diseases (14–17, 38, 39). Air pollution induces oxidative stress and systemic inflammation, which may perturb the immune response to SARS-CoV-2 infection and increase the risk of severe COVID-19 (40, 41). At the same time, short-term air pollution exposure may increase the risk of COVID-19 severity through the air pollution-induced immunotoxicity and inflammation (26, 27). Short-term exposure to NO₂ and PM_{2.5} has been shown to

increase the expression of the SARS-CoV-2 cell surface receptor angiotensin-converting enzyme 2 in the lungs and heart (12, 20–22), which may further increase binding of the virus and the severity of COVID-19. Future studies are needed to clarify biological mechanisms linking long- and short-term air pollution exposure and severe COVID-19.

Strengths of this study include the large and multiethnic cohort of patients with COVID-19 with individual-level air pollution exposure, severity and mortality outcomes, and covariate data. Our study design was based on patients with COVID-19 from the KPSC membership system, which has the advantage of minimizing the bias of testing and treatment accessibility, as all KPSC medical centers follow uniform guidelines, and all members have equal access to testing and treatment options. Also, we aimed to minimize potential bias due to the dynamic nature of the pandemic by including time as a fixed covariate in our data analysis. We assessed a spectrum of COVID-19 severity outcomes, including hospitalization, IRS, and ICU admission and mortality with adjustment for important risk factors, including social demographics, smoking, obesity, and history of comorbidities. All data were obtained from the comprehensive EMR at KPSC. Air pollutant concentrations were estimated using residential address histories of each individual, and we assessed both shorter and longer term of air pollution exposure using single- and multipollutant analyses. Because temporal variation is much larger than geospatial variation within each medical center area, the inverse distance squared weighted approach to estimate individual residential exposure is an efficient method to capture exposure variations across different time windows in the large population. This exposure assessment method has been used in many large epidemiological studies in southern California (42–44). We explored potential effect modification by social demographics, which to our knowledge has not been studied in previous research.

We acknowledge several important limitations of our study. First, we included patients infected with COVID-19 only during the early pandemic period before September 2020. It is noted that accessibility to testing and treatment, as well as intervention policy, varied over this time period, which may influence the observed

association of air pollution and COVID-19 outcomes. Healthcare capacity, such as the number of hospitals and ICU beds, can influence COVID-19 severity outcomes. However, this was not accounted for in the study analysis, because the number of patients hospitalized with COVID-19 in KPSC never reached the maximum capacity. Also, more transmissible SARS-CoV-2 variants were found after our study period (45), and it is unknown whether ambient air pollution will also influence the severity of infections from new variants. Future studies are needed to incorporate more recent data to compare the air pollution effect across various SARS-CoV-2 variants and across earlier versus later pandemic periods.

Second, we did not assess indoor exposures and the built environment, which needs time activity and personal monitoring data and is not feasible in this large population study. Future studies are warranted to investigate the effects of both outdoor and indoor environment on COVID-19 severity.

Third, occupations, household crowding, and public health interventions are important factors contributing to infection, but it is unclear whether these factors could influence COVID-19 severity outcomes. To fill this gap, mobile data collection tools could be used in future research to monitor mobility patterns, social contacts, and geolocations such that individual-level covariate dynamic data can be collected (46).

Fourth, we could not include meteorological factors in the covariate adjustment, because temperature and relative humidity were highly correlated with air pollutant concentrations in the KPSC cohort because of the geographic clustering across seaside and inland areas. Adjustment for medical center was used to account for geographic clustering instead.

Fifth, no multiple testing was adjusted for in the analyses, as the focus was on assessing specific hypotheses and estimation of effect sizes and precision of those estimates. Last, because of the nature of the observational and retrospective cohort design, we cannot prove causality between air pollution exposure and COVID-19 outcomes; longitudinal and natural experimental studies are needed to investigate the pathophysiological mechanisms of air pollution exposures in longer and shorter time windows.

Conclusions

Results from this large, multiethnic, population-based cohort study showed that 1-year PM_{2.5} exposure and 1-month NO₂ exposure before COVID-19 diagnosis were significantly associated with COVID-19 severity, including hospitalizations, need for IRS, ICU admission, and mortality. Given

that ambient air pollutants are modifiable through public health regulations and individual interventions, our results support public health and individual efforts to reduce air pollution exposure. ■

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References

- Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. Air pollution and COVID-19 mortality in the United States: strengths and limitations of an ecological regression analysis. *Sci Adv* 2020;6:eabd4049.
- Bianconi V, Bronzo P, Banach M, Sahebkar A, Mannarino MR, Pirro M. Particulate matter pollution and the COVID-19 outbreak: results from Italian regions and provinces. *Arch Med Sci* 2020;16:985–992.
- Liang D, Shi L, Zhao J, Liu P, Samat JA, Gao S, et al. Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. *Innovation (N Y)* 2020;1:100047.
- Ogen Y. Assessing nitrogen dioxide (NO₂) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci Total Environ* 2020;726:138605.
- Andrée BPJ. Incidence of COVID-19 and connections with air pollution exposure: evidence from the Netherlands [preprint]. medRxiv; 2020 [accessed 2021 July 1]. Available from: <https://www.medrxiv.org/content/10.1101/2020.04.27.20081562v1>.
- Yao Y, Pan J, Wang W, Liu Z, Kan H, Qiu Y, et al. Association of particulate matter pollution and case fatality rate of COVID-19 in 49 Chinese cities. *Sci Total Environ* 2020;741:140396.
- Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. Links between air pollution and COVID-19 in England. *Environ Pollut* 2021;268:115859.
- Pozzer A, Dominici F, Haines A, Witt C, Münzel T, Lelieveld J. Regional and global contributions of air pollution to risk of death from COVID-19. *Cardiovasc Res* 2020;116:2247–2253.
- Hutter HP, Poteser M, Moshhammer H, Lemmerer K, Mayer M, Weitensfelder L, et al. Air pollution is associated with COVID-19 incidence and mortality in Vienna, Austria. *Int J Environ Res Public Health* 2020;17:9275.
- Frontera A, Cianfanelli L, Vlachos K, Landoni G, Cremona G. Severe air pollution links to higher mortality in COVID-19 patients: the “double-hit” hypothesis. *J Infect* 2020;81:255–259.
- Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature* 2015;525:367–371.
- Aztatzi-Aguilar OG, Uribe-Ramírez M, Arias-Montaña JA, Barbier O, De Vizcaya-Ruiz A. Acute and subchronic exposure to air particulate matter induces expression of angiotensin and bradykinin-related genes in the lungs and heart: angiotensin-II type-I receptor as a molecular target of particulate matter exposure. *Part Fibre Toxicol* 2015;12:17.
- GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1659–1724.
- Langrish JP, Bosson J, Unosson J, Muala A, Newby DE, Mills NL, et al. Cardiovascular effects of particulate air pollution exposure: time course and underlying mechanisms. *J Intern Med* 2012;272:224–239.
- An Z, Jin Y, Li J, Li W, Wu W. Impact of particulate air pollution on cardiovascular health. *Curr Allergy Asthma Rep* 2018;18:15.
- Lawal AO. Air particulate matter induced oxidative stress and inflammation in cardiovascular disease and atherosclerosis: the role of Nrf2 and AhR-mediated pathways. *Toxicol Lett* 2017;270:88–95.
- Lin CI, Tsai CH, Sun YL, Hsieh WY, Lin YC, Chen CY, et al. Instillation of particulate matter 2.5 induced acute lung injury and attenuated the injury recovery in ACE2 knockout mice. *Int J Biol Sci* 2018;14:253–265.
- Chen R, Li H, Cai J, Wang C, Lin Z, Liu C, et al. Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction. *Environ Health Perspect* 2018;126:017007.
- Robertson S, Miller MR. Ambient air pollution and thrombosis. *Part Fibre Toxicol* 2018;15:1.
- Sagawa T, Tsujikawa T, Honda A, Miyasaka N, Tanaka M, Kida T, et al. Exposure to particulate matter upregulates ACE2 and TMPRSS2 expression in the murine lung. *Environ Res* 2021;195:110722.
- Meulenbelt J, van Bree L, Dormans JA, Boink AB, Sangster B. Biochemical and histological alterations in rats after acute nitrogen dioxide intoxication. *Hum Exp Toxicol* 1992;11:189–200.
- Patel JM, Sekharam KM, Block ER. Oxidant injury increases cell surface receptor binding of angiotensin II to pulmonary artery endothelial cells. *J Biochem Toxicol* 1990;5:253–258.
- Cole MA, Ozgen C, Strobl E. Air pollution exposure and COVID-19 in Dutch municipalities. *Environ Resour Econ (Dordr)* [online ahead of print] 4 Aug 2020; DOI: 10.1007/s10640-020-00491-4.
- Yao Y, Pan J, Liu Z, Meng X, Wang W, Kan H, et al. Temporal association between particulate matter pollution and case fatality rate of COVID-19 in Wuhan. *Environ Res* 2020;189:109941.
- Adhikari A, Yin J. Short-term effects of ambient ozone, PM_{2.5}, and meteorological factors on COVID-19 confirmed cases and deaths in Queens, New York. *Int J Environ Res Public Health* 2020;17:4047.
- Calderón-Garcidueñas L, Macías-Parra M, Hoffmann HJ, Valencia-Salazar G, Henríquez-Roldán C, Osuna N, et al. Immunotoxicity and environment: immunodysregulation and systemic inflammation in children. *Toxicol Pathol* 2009;37:161–169.
- Stanek LW, Brown JS, Stanek J, Gift J, Costa DL. Air pollution toxicology—a brief review of the role of the science in shaping the current understanding of air pollution health risks. *Toxicol Sci* 2011; 120:S8–S27.
- Bowe B, Xie Y, Gibson AK, Cai M, van Donkelaar A, Martin RV, et al. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: cohort study. *Environ Int* 2021;154:106564.
- Mendy A, Wu X, Keller JL, Fassler CS, Apewokin S, Mersha TB, et al. Air pollution and the pandemic: Long-term PM_{2.5} exposure and disease severity in COVID-19 patients. *Respirology* 2021;26: 1181–1187.
- Pegoraro V, Heiman F, Levante A, Urbinati D, Peduto I. An Italian individual-level data study investigating on the association between air pollution exposure and COVID-19 severity in primary-care setting. *BMC Public Health* 2021;21:902.
- Kogevinas M, Castaño-Vinyals G, Karachaliou M, Espinosa A, de Cid R, García-Aymerich J, et al. Ambient air pollution in relation to SARS-CoV-2 infection, antibody response, and COVID-19 disease: a cohort study in Catalonia, Spain (COVICAT study). *Environ Health Perspect* 2021; 129:117003.
- Bozack A, Pierre S, DeFelice N, Colicino E, Jack D, Chillrud SN, et al. Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York City. *Am J Respir Crit Care Med* 2022; 205:651–662.
- Chen Z, Sidell MA, Huang BZ, Chow T, Eckel SP, Martinez MP, et al. Longer- and shorter-term air pollution exposure associated with COVID-19 severity and mortality: a large cohort study in southern California [accessed 2022 Feb 8]. Presented at the 33rd Annual Conference of the International Society for Environmental Epidemiology. August 23–26, 2021, New York. Available from: <https://ehp.niehs.nih.gov/doi/abs/10.1289/isee.2021.O-TO-179>.

34. Eckel SP, Cockburn M, Shu YH, Deng H, Lurmann FW, Liu L, *et al.* Air pollution affects lung cancer survival. *Thorax* 2016;71: 891–898.
35. Claritas. Nielsen demographic data. Cincinnati, OH: Claritas; 2021 [accessed 2021 Mar 9]. Available from: <https://claritas.com/data/>.
36. Environmental Systems Research Institute. 2021 USA population density. Redlands, CA: Environmental Systems Research Institute; 2021 [accessed 2022 Feb 9]. Available from: <https://www.arcgis.com/home/item.html?id=a8407298de7e48078a2bc9cdd76c79af>.
37. Messer LC, Laraia BA, Kaufman JS, Eyser J, Holzman C, Culhane J, *et al.* The development of a standardized neighborhood deprivation index. *J Urban Health* 2006;83:1041–1062.
38. Chen Z, Salam MT, Eckel SP, Breton CV, Gilliland FD. Chronic effects of air pollution on respiratory health in Southern California children: findings from the Southern California Children's Health Study. *J Thorac Dis* 2015;7:46–58.
39. Chen Z, Salam MT, Toledo-Corral C, Watanabe RM, Xiang AH, Buchanan TA, *et al.* Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. *Diabetes Care* 2016;39:547–554.
40. Gangwar RS, Bevan GH, Palanivel R, Das L, Rajagopalan S. Oxidative stress pathways of air pollution mediated toxicity: Recent insights. *Redox Biol* 2020;34:101545.
41. Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. *J Toxicol* 2011;2011:487074.
42. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057–1067.
43. Berhane K, Zhang Y, Linn WS, Rappaport EB, Bastain TM, Salam MT, *et al.* The effect of ambient air pollution on exhaled nitric oxide in the Children's Health Study. *Eur Respir J* 2011;37:1029–1036.
44. Gilliland FD. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. *Pediatrics* 2009;123:S168–S173.
45. Hadfield J, Megill C, Bell SM, Huddleston J, Potter B, Callender C, *et al.* Nextstrain: real-time tracking of pathogen evolution. *Bioinformatics* 2018;34:4121–4123.
46. Grantz KH, Meredith HR, Cummings DAT, Metcalf CJE, Grenfell BT, Giles JR, *et al.* The use of mobile phone data to inform analysis of COVID-19 pandemic epidemiology. *Nat Commun* 2020;11:4961.