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The Independent Effect of COVID-19 Vaccinations and Air Pollution Exposure on Risk of COVID-19 Hospitalizations in Southern California

To the Editor:

Studies including ours showed that air pollution exposure was associated with increased risks of coronavirus disease (COVID-19) incidence and severity, including COVID-19–related hospitalizations (1–4). Most studies were conducted during the early pandemic when COVID-19 vaccination was not administered widely. Few studies have been conducted after the vaccination campaign (5, 6). It is unknown how COVID-19 vaccination affects the adverse effects of air pollution exposure. This research letter reports findings assessing associations of long- and short-term exposures to three ambient air pollutants: nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$), and ozone (O_3) with COVID-19–related hospitalizations during July and August of 2021 when the Delta variant was the dominant strain, COVID-19 vaccines had been distributed over 7 months, and booster vaccines had not yet started (7); and effect modification with COVID-19 vaccination.

Methods

This study cohort included 50,010 KPSC (Kaiser Permanente Southern California) health plan members aged 12 years or older diagnosed with COVID-19 from July 1, 2021 to August 31, 2021. KPSC is an integrated healthcare system in which members with medical procedures or with COVID-19 symptoms require COVID-19 testing. COVID-19 tests were also administered for patients by request. Self-reported positive tests were captured in the KPSC electronic medical records (EMR). The outcome was hospitalization within 30 days after COVID-19 diagnosis date with COVID-19–related reason for hospitalization. The study was approved by the KPSC Institutional Review Board with an informed consent waiver.

Daily averages of $PM_{2.5}$, NO_2 concentrations, and 8-hour daily maximum O_3 exposure at patients' residential addresses 1 year before COVID-19 diagnosis were estimated using inverse distance squared weighting on the basis of air quality data from central air monitors (8). Daily air pollution data was further averaged 1 month and 1 year before the diagnosis date to represent shorter- and longer-term exposures. COVID-19 vaccination status was retrieved from the EMR. Vaccines obtained outside of KPSC were entered by KPSC from the California Immunization Registry. Vaccination status before COVID-19 diagnosis was categorized into none, partially vaccinated (one dose of Pfizer–BioNTech or Moderna), or fully vaccinated (one dose of Johnson and Johnson or two doses of Pfizer–BioNTech or Moderna) on the basis of the Centers for Disease Control and Prevention definitions at that time. No restriction of time lag between vaccination and COVID-19 diagnosis was applied.

Covariates including age, sex, race and/or ethnicity, Medicaid insurance status, body mass index categories, smoking history, and Charlson comorbidity index were obtained from the EMR. Census tract neighborhood-level education and income were estimated using Nielsen demographic data (9). The neighborhood-level population density was obtained from 2019 Environmental Systems Research Institute data, and the neighborhood deprivation index was derived on the basis of the 2019 U.S. Census American Community Survey data (10).

Mixed effects logistic regression models were used to assess associations between air pollution exposure and COVID-19 vaccination status (none, partially, or fully vaccinated) on COVID-19–related hospitalizations, adjusting for covariates and testing for the multiplicative interaction between air pollution and vaccination status. We also presented the air pollution associations stratified by vaccination status. Because most patients were either unvaccinated or fully vaccinated, the stratified analyses were only

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Author Contributions: Z.C., M.A.S., F.D.G., and A.H.X. were responsible for the study concept and design. A.H.X. and Z.C. obtained funding. A.H.X., Z.C., M.A.S., B.Z.H., T.C., M.P.M., F.L., and F.D.G. conducted the study. M.A.S., B.Z.H., T.C., M.P.M., and A.H.X. acquired data. M.A.S., B.Z.H., T.C., and A.H.X. analyzed data. Z.C., M.A.S., and A.H.X. drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final version to be published.

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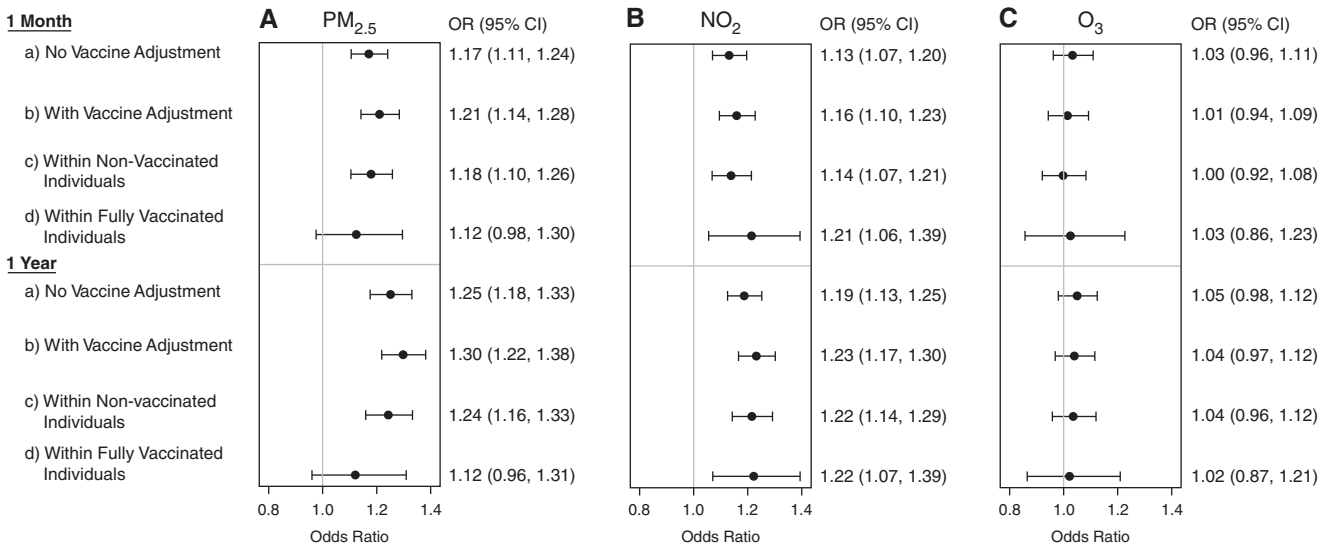

Figure 1. OR and 95% CIs for an increase of one SD in (*A*) $PM_{2.5}$, (*B*) NO_2, and (*C*) O_3 associated with coronavirus disease (COVID-19)–related hospitalization within 30 days after COVID-19 diagnosis for the full cohort ($N = 50{,}010$), adjusting for age, sex, race and/or ethnicity, body mass index, smoking status, income, college, Medicaid, Charlson comorbidity, population density, neighborhood deprivation index, month, and random effect of medical centers with a) no vaccine adjustment, b) with vaccine adjustment, c) within nonvaccinated individuals ($n = 30{,}912$), and d) within fully vaccinated individuals ($n = 17{,}019$). CI = confidence interval; NO_2 = nitrogen dioxide; O_3 = ozone; OR = odds ratio; $PM_{2.5}$ = fine particulate matter.

Table 1. Characteristics of Study Cohort and Pollution Exposure Distribution ($N = 50{,}010$)

	Total (*N = 50,010*)
Age (yr), mean (SD)	40.9 (16.9)
By age group, *n* (%)	
12–34	20,623 (41.2)
35–64	24,689 (49.4)
65+	4,698 (9.4)
Sex, *n* (%)	
Female	27,214 (54.4)
Male	22,796 (45.6)
Race and/or ethnicity, *n* (%)	
Asian and Pacific Islander	2,805 (5.6)
Black	5,519 (11)
Hispanic	22,243 (44.5)
Other	3,768 (7.5)
White	15,675 (31.3)
BMI, *n* (%)	
Underweight and normal	13,433 (26.9)
Overweight	14,950 (29.9)
Obese (class 1 and 2)	16,045 (32.1)
Obese (class 3)	3,914 (7.8)
Missing	1,668 (3.3)
Smoking status, *n* (%)	
Current	3,458 (6.9)
Former	8,613 (17.2)
Never	36,046 (72.1)
Unknown	1,893 (3.8)
Median household income ($), *n* (%)	
<40,000	2,566 (5.1)
40,000–79,999	22,856 (45.7)
⩾80,000	23,577 (47.1)
Missing	1,011 (2)
College education, *n* (%)	
No	22,369 (44.7)
Yes	26,630 (53.2)
Missing	1,011 (2)

Table 1. (*Continued*).

	Total (*N = 50,010*)
Medicaid status, *n* (%)	237 (0.5)
Charlson comorbidity score, *n* (%)	
0	38,426 (76.8)
1	7,898 (15.8)
2+	3,686 (7.4)
Diagnosis month (2021), *n* (%)	
July	16,967 (33.9)
August	33,043 (66.1)
Neighborhood deprivation index, *n* (%)	
1 (lowest degree of deprivation)	4,846 (9.7)
2	11,553 (23.1)
3	13,886 (27.8)
4	11,539 (23.1)
5 (highest degree of deprivation)	8,186 (16.4)
Population density, mean (SD)	8,201.1 (6,948.08)
Vaccine status, *n* (%)	
None	30,912 (61.8)
Partially vaccinated	2,079 (4.2)
Fully vaccinated	17,019 (34.0)
Pollution exposure variables, mean (SD)	
$PM_{2.5}$, μg/m^3	
1 mo	12.1 (2.7)
1 yr	13.0 (2.7)
NO_2, ppb	
1 mo	10.0 (4.3)
1 yr	13.5 (4.4)
O_3, ppb	
1 mo	55.4 (13.0)
1 yr	49.4 (6.1)
Outcome, *n* (%)	
COVID-19–related hospitalization within 30 d	3,073 (6.1)

Definition of abbreviations: BMI = body mass index; COVID-19 = coronavirus disease; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = fine particulate matter.

done for these two groups. KPSC medical centers were adjusted as a random effect to account for potential within-center correlations and unknown spatial confounders. Missing data for covariates were coded as missing as a category; thus, all patients were included in the analyses.

Results were reported as odds ratios and 95% confidence intervals, scaled to one SD increase in air pollution exposure. Analyses were conducted using SAS version 9.4 or R version 3.6.0.

Results

Among the 50,010 patients with COVID-19, the mean (SD) age was 40.9 (16.9) years, with 41.2% younger than 35 years, 49.4% 35–64 years, and 9.4% 65 years or older (Table 1). Before COVID-19 diagnosis, 17,019 (34.0%) patients were fully vaccinated and 2,079 (4.2%) were partially vaccinated. The rates of fully vaccinated were 22.6% for ages younger than 35 years, 38.0% for ages 35–64 years, and 63.5% for ages 65 years or older. After COVID-19 diagnosis, 3,073 (6.1%) had COVID-19–related hospitalization within 30 days, with 17.1% for age 65 years or older and 2.3% and 7.3% for ages younger than 35 years and 35–64 years, respectively. The 1-month mean (SD) $PM_{2.5}$, NO_2, and O_3 were 12.1 (2.7) $\mu g/m^3$, 10.0 (4.3) ppb, and 55.4 (13.0) ppb, respectively; the corresponding 1-year mean (SD) were 13.0 (2.7) $\mu g/m^3$, 13.5 (4.4) ppb, and 49.4 (6.1) ppb, respectively.

Vaccination significantly reduced the risk of hospitalization: 7.9%, 4.9%, and 3.1% for unvaccinated, partial, and fully vaccinated, respectively; and the adjusted odds ratio (95% confidence interval) were 0.46 (0.37–0.57) and 0.16 (0.15–0.18) for partially and fully vaccinated compared with unvaccinated with adjustment for air pollutants and covariates. Exposures to $PM_{2.5}$ and NO_2 were significantly associated with an increased risk of COVID-19–related hospitalizations without or with adjusting for vaccination status (Figure 1); the adjusted odds ratio (95% confidence interval) per one SD increase were 1.17 (1.11–1.24) and 1.13 (1.07–1.20) for 1-month $PM_{2.5}$ and NO_2, and 1.25 (1.18–1.33) and 1.19 (1.13–1.25) for 1-year $PM_{2.5}$ and NO_2, respectively, when vaccination status was not adjusted; adjusting for vaccination status slightly increased the odds ratio of hospitalizations associated with $PM_{2.5}$ and NO_2 (Figure 1). O_3 was not associated with the risk of COVID-19–related hospitalizations. There were no statistically significant interactions between air pollutants and vaccination status (all interactions $P > 0.09$); however, stratified analyses by vaccination showed that the associations with 1-year and 1-month $PM_{2.5}$ were smaller, and 1-month NO_2 was larger in the fully vaccinated group than in the unvaccinated group (Figure 1).

Discussion

In this large cohort of patients with COVID-19 in Southern California, 1-month and 1-year exposures to $PM_{2.5}$ and NO_2 were associated with increased risk, and COVID-19 vaccination was associated with reduced risk of COVID-19–related hospitalizations. The two appeared independent of each other, affecting the risk of hospitalization. COVID-19 vaccination did not significantly mitigate the risk associated with air pollution; however, the reduced associations with $PM_{2.5}$ for the fully vaccinated suggest that the COVID-19 vaccine may slightly attenuate the effect of $PM_{2.5}$. Our findings are consistent with previous reports (1–6) that both short- and long-term exposures to $PM_{2.5}$ and NO_2 were associated with an increased risk of COVID-19 severity. We extended the findings to the Delta variant and showed that the adverse effect of air pollution exposure on a higher risk of COVID-19 remained, although vaccination reduced COVID-19 severity. ■

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Impact of Adherence to Continuous Positive Airway Pressure on Outcomes in Obstructive Sleep Apnea Chronic Obstructive Pulmonary Disease Overlap Syndrome

To the Editor:

Sterling and colleagues analyzed the impact of adherence to positive airway pressure (PAP) treatment in obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) overlap syndrome and concluded that adherence to PAP treatment was associated with reduced all-cause hospitalizations and emergency room visits, severe acute exacerbations, and healthcare costs (1). This study has a significant impact owing to its compelling strengths: this is a large real-life study, easy to measure and generalize to the population and the individual patient, and its results are compatible with the currently available data (2).

Nevertheless, this study has some limitations that make the results challenging to interpret.

First, a selection bias might have led to more hospitalizations and ER visits in the nonadherent group. This group included far more patients with psychotic disorders than the adherent group (98 vs. 57 patients, respectively, out of 712). This correlates not only with low adherence to PAP therapy but also to general medical nonadherence, less control of comorbidities, and increased risk of subsequent medical consequences (3). Moreover, the nonadherent group was less obese than the adherent group (34.7% vs. 40% morbidly obese and 34% vs. 30.2% nonobese, respectively). It is now known that a higher proportion of nonobese patients have a low respiratory arousal threshold, suggesting that nonanatomical causes may be particularly important for the pathogenesis of OSA in the absence of obesity (4). These patients are less likely to adhere to PAP therapy (4); in fact, the preferable treatment and the prognosis in these patients are still to be studied. Furthermore, 51.8% of the nonadherents were tobacco users, compared with 44.4% in the adherent group. Thus, the former group might be at a higher risk for adverse health events regardless of PAP therapy.

Second, previous COPD exacerbation, the single most important predictor of future exacerbations, which is among the leading causes of emergency room visits and hospitalizations (5), was not reported in the study. Although the overall emergency room visits and hospitalizations in the year before PAP therapy were reported, excluding previous COPD exacerbations in patients with COPD as inclusion criteria, may affect the reliability of the model.

Finally, the study does not distinguish between patients who are hypercapnic and nonhypercapnic, nor between continuous PAP and bilevel PAP. As noninvasive positive pressure ventilation reduces mortality in patients who are hypercapnic with COPD regardless of OSA status (6), the unpublished data regarding hypercapnia status makes results interpretation challenging.

Despite what preceded, we believe that OSA COPD overlap syndrome should be treated on the basis of the current guidelines for OSA and COPD, including PAP as a cornerstone of OSA treatment. We also believe that overlap syndrome has more health impact than either OSA or COPD on the basis of the cumulative data. However, the exact impact of PAP treatment and the causality for health improvement should be further studied. ■

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