



# Air pollution and the pandemic: Long-term PM<sub>2.5</sub> exposure and disease severity in COVID-19 patients

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## Funding information

National Institute of Environmental Health Sciences, Grant/Award Numbers: P30 ES006096, T32ES010957; National Center for Advancing Translational Sciences of the National Institute of Health (NIH), Grant/Award Number: 5UL1TR001425-03; US NIH, Grant/Award Numbers: R01 HL132344, K08CA237735

**Associate Editor:** Alexander Larcombe and

**Senior Editor:** Paul King

## Abstract

**Background and objective:** Ecological studies have suggested an association between exposure to particulate matter  $\leq 2.5$   $\mu\text{m}$  (PM<sub>2.5</sub>) and coronavirus disease 2019 (COVID-19) severity. However, these findings are yet to be validated in individual-level studies. We aimed to determine the association of long-term PM<sub>2.5</sub> exposure with hospitalization among individual patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

**Methods:** We estimated the 10-year (2009–2018) PM<sub>2.5</sub> exposure at the residential zip code of COVID-19 patients diagnosed at the University of Cincinnati healthcare system between 13 March 2020 and 30 September 2020. Logistic regression was used to determine the odds ratio (OR) and 95% CI for COVID-19 hospitalizations associated with PM<sub>2.5</sub>, adjusting for socioeconomic characteristics and comorbidities.

**Results:** Among the 14,783 COVID-19 patients included in our study, 13.6% were hospitalized; the geometric mean (SD) PM<sub>2.5</sub> was 10.48 (1.12)  $\mu\text{g}/\text{m}^3$ . In adjusted analysis, 1  $\mu\text{g}/\text{m}^3$  increase in 10-year annual average PM<sub>2.5</sub> was associated with 18% higher hospitalization (OR: 1.18, 95% CI: 1.11–1.26). Likewise, 1  $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> estimated for the year 2018 was associated with 14% higher hospitalization (OR: 1.14, 95% CI: 1.08–1.21).

**Conclusion:** Long-term PM<sub>2.5</sub> exposure is associated with increased hospitalization in COVID-19. Therefore, more stringent COVID-19 prevention measures may be needed in areas with higher PM<sub>2.5</sub> exposure to reduce the disease morbidity and healthcare burden.

## KEYWORDS

air pollution, coronavirus disease, COVID-19 hospitalization, PM<sub>2.5</sub> exposure, SARS-CoV-2

## INTRODUCTION

The recently identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes the coronavirus disease 2019 (COVID-19) appeared in China in December 2019 and spread into a pandemic and global public health crisis by March 2020.<sup>1</sup> SARS-CoV-2 is transmitted through

direct contact, droplets or airborne, especially in closed environments.<sup>2,3</sup> The infection may be asymptomatic or cause symptoms ranging from cough and dyspnoea to severe disease with respiratory failure resulting in hospitalization and admission to intensive care unit and, occasionally, death.<sup>3</sup> Known risk factors for severe COVID-19 include older age and pre-existing comorbidities such as cardiovascular,

endocrine, digestive and respiratory diseases.<sup>3</sup> Hospitalized COVID-19 patients may also develop complications that may be respiratory, cardiovascular, haematological, neurological and/or renal.<sup>4</sup>

Mounting evidence suggests that exposure to ambient air pollution could affect susceptibility to SARS-CoV-2 infection as well as COVID-19 severity.<sup>5,6</sup> Air pollution is a mixture of particles and gases that ubiquitously affects all individuals; it includes particulate matter  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ) that are inhalable particles particularly detrimental to human health because of their small size.<sup>7</sup> These particles could potentially increase the risk of COVID-19 by acting as carriers for viruses such as SARS-CoV-2, by damaging airways epithelium and/or by impairing the lung's ability to clear pathogens.<sup>6,8</sup>  $\text{PM}_{2.5}$  may also increase the severity of existing COVID-19 by exacerbating respiratory and cardiovascular diseases through airway inflammation and free radicals' release from alveolar macrophages activated by the phagocytosis of particles.<sup>7,9</sup> The pathogenic effects of  $\text{PM}_{2.5}$  can be aggravated by their content in substances such as polycyclic aromatic hydrocarbons and heavy metals.<sup>7</sup>

To date, studies on exposure to  $\text{PM}_{2.5}$  and COVID-19 outcomes have been ecological and have correlated geographic rates of COVID-19 outcomes with geographic levels of  $\text{PM}_{2.5}$  exposure. These ecological studies suffer from ecological fallacy and require individual-level data for validation.<sup>10</sup> Therefore, we proposed to investigate the association between long-term exposure to  $\text{PM}_{2.5}$  and COVID-19 outcomes in a large sample of SARS-CoV-2-infected individuals.

## METHODS

### Data source

We included all COVID-19 patients residing in Ohio who were diagnosed at the University of Cincinnati (UC) healthcare system from 13 March 2020 to 30 September 2020 using the electronic medical record system. COVID-19 was diagnosed using the nasopharyngeal reverse transcriptase PCR test for SARS-CoV-2.<sup>3</sup> A total of 14,834 patients were diagnosed with COVID-19 and, after exclusion of patients with missing data, 14,783 participants were included in our study.

### Exposure and outcome assessment

$\text{PM}_{2.5}$  exposure was estimated on a  $0.01^\circ \times 0.01^\circ$  grid using a validated exposure prediction model merging satellite, modelled and monitored  $\text{PM}_{2.5}$  data.<sup>11</sup> As we were not able to obtain the exact address from the UC health system, zonal statistics were used to aggregate annual  $\text{PM}_{2.5}$  exposure estimates at the zip code of the patients' residential address over the 10-year period from 2009 to 2018.<sup>5</sup>

### SUMMARY AT A GLANCE

We examined the association between long-term exposure to particulate matter  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ) and coronavirus disease 2019 (COVID-19) outcomes in 14,783 COVID-19 patients diagnosed at the University of Cincinnati Health System. Our results suggested that a  $1\text{-}\mu\text{g}/\text{m}^3$  increase in annual average  $\text{PM}_{2.5}$  between 2009 and 2018 was associated with 14%–18% higher odds of hospitalization for COVID-19.

COVID-19 hospitalization was defined as admission to hospital following COVID-19 diagnosis for at least 24 consecutive hours.<sup>3</sup>

### Covariates

Age at the time of COVID-19 diagnosis was calculated using patients' date of birth. Sex and race/ethnicity were self-reported. Comorbidities were defined using the 10th revision of the International Classification of Diseases (ICD10) codes. They included conditions previously reported to be associated with COVID-19 outcomes, such as obesity (E66), diabetes (E10), hypertension (I10), asthma (J45), chronic obstructive pulmonary disease (COPD) (J44), chronic kidney disease (CKD) (N18), neoplasm or a history of neoplasm (C00-D49). To account for socioeconomic status, social deprivation index (SDI) was estimated at the zip code of participants' residential address. SDI is a composite metric of seven sociodemographic characteristics assessed by the American Community Survey (ACS), which includes the percent living in poverty, percent with less than 12 years of education, percent of single-parent households, percent living in a rented housing unit, percent living in overcrowded housing unit, percent of households without a car and percent of non-employed adults under 65 years of age. Details on the SDI metric and methodology have been described elsewhere.<sup>12</sup>

### Statistical analysis

Descriptive analyses were performed to summarize the central tendency and variability of 10-year annual average  $\text{PM}_{2.5}$  concentrations overall and participants' characteristics and differences. *p*-Values across the characteristics were estimated. The association of  $\text{PM}_{2.5}$  with COVID-19 outcomes was assessed using logistic regression to estimate the ORs and corresponding 95% CIs for  $1 \mu\text{g}/\text{m}^3$  increase in exposure. The models were adjusted for age; sex; race/ethnicity; comorbidities such as obesity, diabetes, hypertension, asthma, COPD, CKD and neoplasm or history of neoplasm;

as well as for population size and SDI to rigorously account for socioeconomic and demographic characteristics. Additionally, we performed sensitivity analyses in which we examined the association of PM<sub>2.5</sub> with COVID-19 outcomes in participants without each of the studied comorbidities. The dose–response relationship between PM<sub>2.5</sub> and the COVID-19 outcomes that were significant was assessed using restricted cubic splines of ORs as a function of exposure levels, with three PM<sub>2.5</sub> knots and reference value set to 10 µg/m<sup>3</sup>.<sup>13</sup> The analyses were performed in SAS Version 9.4 (SAS Institute, Cary, NC) and STATA Version 15 (STATA Corp, College Station, TX), and two-sided *p*-values of <0.05 were considered statistically significant.

## RESULTS

### Descriptive results

Among the 14,783 COVID-19 participants included our study, 21.3% were older adults aged 65 or older, 70.7% were women and 61.7% were non-Hispanic Whites. The comorbidities found in study participants included obesity (12.9%), diabetes (11.2%), asthma (8.5%), COPD (4.8%), hypertension (23.2%), CKD (5.8%) and neoplasm or a history of neoplasm (15.1%). About 13.6% of the patients diagnosed with COVID-19 during the study period were hospitalized (Table 1).

The 10-year annual geometric mean (SD) PM<sub>2.5</sub> was 10.48 (1.12) µg/m<sup>3</sup> and ranged from 7.02 to 12.32 µg/m<sup>3</sup>. Older adults, men, non-Hispanic Blacks and patients with comorbidities tended to live in areas with higher PM<sub>2.5</sub> exposure levels. Likewise, areas with a higher deprivation index had higher ambient PM<sub>2.5</sub> levels (Table 1). Over the 10-year study period, annual PM<sub>2.5</sub> increased from 10.90 µg/m<sup>3</sup> in 2009 to 12.90 µg/m<sup>3</sup> in 2010, and then decreased significantly to 8.64 µg/m<sup>3</sup> in 2018 (trend *p*-value <0.001) (Figure 1).

### Association of PM<sub>2.5</sub> with COVID-19 hospitalization

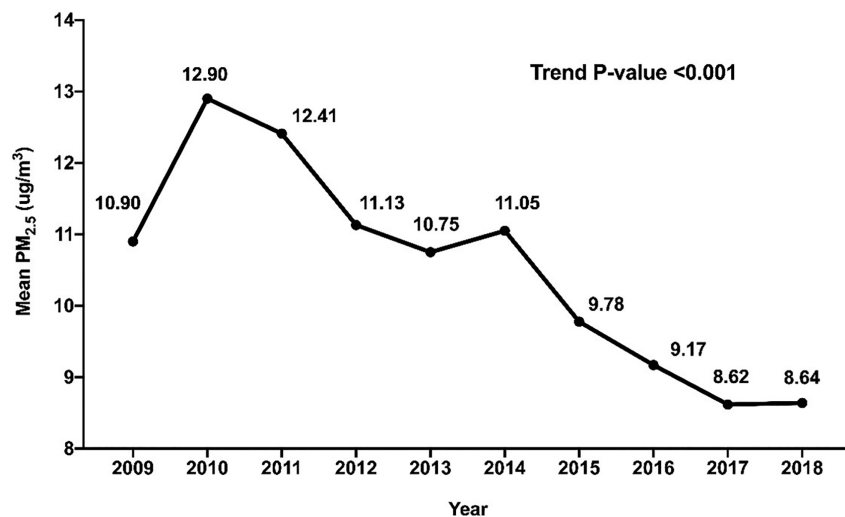
In logistic regression analysis adjusted for the covariates, a 1-µg/m<sup>3</sup> increment in the 10-year annual average PM<sub>2.5</sub> was associated with an 18% increase in admission to hospital (OR: 1.18, 95% CI: 1.11–1.26) in all participants. The association between 10-year annual average PM<sub>2.5</sub> and hospitalization remained significant after excluding patients with obesity (OR: 1.22, 95% CI: 1.14–1.32), diabetes (OR: 1.26, 95% CI: 1.17–1.36), hypertension (OR: 1.32, 95% CI: 1.21–1.45), asthma (OR: 1.19, 95% CI: 1.11–1.27), COPD (OR: 1.22, 95% CI: 1.14–1.30), neoplasm or history of neoplasm (OR: 1.28, 95% CI: 1.19–1.38) or CKD (OR: 1.21, 95% CI: 1.13–1.30) (Table 2). Likewise, considering only 2018 estimates of PM<sub>2.5</sub>, a 1-µg/m<sup>3</sup> increment was associated with a 14% increase in hospitalization (OR: 1.14, 95% CI: 1.08–1.21). The associations between PM<sub>2.5</sub> exposure and

**TABLE 1** The 10-year annual average PM<sub>2.5</sub> concentrations overall and characteristics of the study participants

Characteristics	N (%)	Average PM <sub>2.5</sub> (µg/m <sup>3</sup> )	
		GM (SD)	<i>p</i> -Value
All participants	14,783 (100.0)	10.48 (1.12)	
Age groups (years)			<0.001
<65	11,639 (78.7)	<b>10.46 (1.12)</b>	
≥65	3144 (21.3)	<b>10.54 (1.12)</b>	
Sex			<0.001
Men	4335 (29.3)	<b>10.65 (1.07)</b>	
Women	10,448 (70.7)	<b>10.40 (1.12)</b>	
Race/ethnicity			
Non-Hispanic Whites	9123 (61.7)	<b>10.18 (1.16)</b>	<0.001
Non-Hispanic Blacks	3947 (26.7)	<b>11.11 (0.67)</b>	<b>Ref</b>
Hispanics	503 (3.4)	<b>10.89 (0.73)</b>	<0.001
Other	1210 (8.2)	<b>10.53 (1.11)</b>	<0.001
SDI			<0.001
<50	7000 (47.4)	<b>10.41 (0.84)</b>	
≥50	7783 (52.6)	<b>10.54 (1.34)</b>	
Obesity			<0.001
No	12,869 (87.1)	<b>10.41 (1.13)</b>	
Yes	1914 (12.9)	<b>10.94 (0.80)</b>	
Diabetes			<0.001
No	13,130 (88.8)	<b>10.42 (1.12)</b>	
Yes	1653 (11.2)	<b>10.93 (0.88)</b>	
Asthma			<0.001
No	13,530 (91.5)	<b>10.43 (1.12)</b>	
Yes	1253 (8.5)	<b>11.02 (0.76)</b>	
COPD			<0.001
No	14,067 (95.2)	<b>10.45 (1.11)</b>	
Yes	716 (4.8)	<b>10.95 (0.95)</b>	
Hypertension			<0.001
No	11,358 (76.8)	<b>10.34 (1.12)</b>	
Yes	3425 (23.2)	<b>10.93 (0.94)</b>	
CKD			<0.001
No	13,929 (94.2)	<b>10.45 (1.12)</b>	
Yes	854 (5.8)	<b>10.97 (0.92)</b>	
Neoplasm or history of neoplasm			<0.001
No	12,551 (84.9)	<b>10.40 (1.15)</b>	
Yes	2232 (15.1)	<b>10.89 (0.85)</b>	
Hospitalization			<0.001
No	12,768 (86.4)	<b>10.42 (1.13)</b>	
Yes	2015 (13.6)	<b>10.86 (0.92)</b>	

Note: *p*-values were estimated using t-test and, for race/ethnicity, analysis of variance. Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GM, Geometric mean; N, number of participants; PM<sub>2.5</sub>, particulate matter ≤2.5 µm; SDI, Social deprivation index.

hospitalization for COVID-19 were not influenced by additional adjustment for period of COVID-19 diagnosis (OR: 1.18, 95% CI: 1.11–1.26) or the exclusion of participants



**FIGURE 1** Mean annual PM<sub>2.5</sub> (particulate matter ≤2.5 µm) concentration (µg/m<sup>3</sup>) from 2009 to 2018

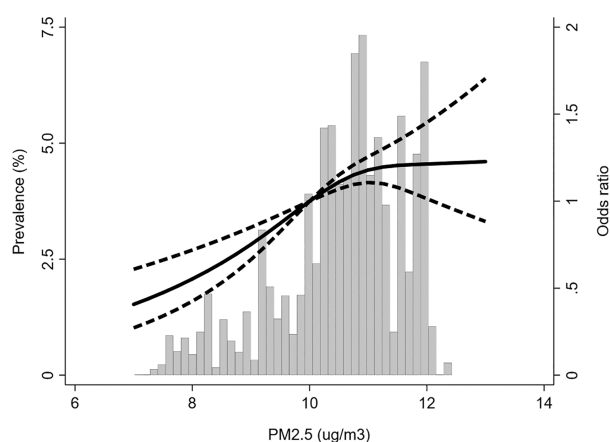
**TABLE 2** OR (95% CI) for association of 10-year PM<sub>2.5</sub> and COVID-19 hospitalization

Population	Hospitalization
In all patients	<b>1.18 (1.11–1.26)*</b>
After excluding patients with obesity	<b>1.22 (1.14–1.32)*</b>
After excluding patients with diabetes	<b>1.26 (1.17–1.36)*</b>
After excluding patients with hypertension	<b>1.32 (1.21–1.45)*</b>
After excluding patients with asthma	<b>1.19 (1.11–1.27)*</b>
After excluding patients with COPD	<b>1.22 (1.14–1.30)*</b>
After excluding patients with cancer history	<b>1.28 (1.19–1.38)*</b>
After excluding patients with CKD	<b>1.21 (1.13–1.30)*</b>

Note: ORs (95% CI) were calculated using logistic regression. The models were adjusted for age, sex, race/ethnicity, obesity, diabetes, hypertension, asthma, COPD, CKD, neoplasm or history of neoplasm, population size and SDI. Values in bold indicate significant ORs and 95% CIs.

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; PM<sub>2.5</sub>, particulate matter ≤2.5 µm; SDI, social deprivation index.

\**p* < 0.001.



**FIGURE 2** Distribution of 10-year annual average particulate matter ≤2.5 µm (PM<sub>2.5</sub>) (µg/m<sup>3</sup>) and restricted cubic splines of ORs of admission to hospital. The graph shows an increase in OR for hospitalization with higher PM<sub>2.5</sub> levels. Solid lines show the ORs and dashed lines indicate the 95% CIs

diagnosed during the initial peak of the pandemic between March and June 2020 (OR: 1.17, 95% CI: 1.09–1.24).

We next characterized the dose–response relationship between the 10-year annual average PM<sub>2.5</sub> levels and hospitalization for COVID-19 using restricted cubic splines. As illustrated in Figure 2, there was a positive exposure–response relationship between PM<sub>2.5</sub> and hospitalization for COVID-19 without any evidence of a threshold effect.

## DISCUSSION

This large study of 14,834 COVID-19 patients demonstrates that long-term exposure to PM<sub>2.5</sub> was associated with increased admission to hospitalization due to COVID-19 independent of sociodemographic and socioeconomic characteristics as well as comorbidities.

Few previous individual-level studies on PM<sub>2.5</sub> and COVID-19 outcomes have been published and current literature on ambient air pollution and COVID-19 has mainly been limited to ecological studies that have produced conflicting results. In the United States, Wu et al. examined the relationship between PM<sub>2.5</sub> exposure over a 17-year period from 2000 to 2016 and COVID-19 mortality in 3089 counties across the country and observed that a 1-µg/m<sup>3</sup> increment in PM<sub>2.5</sub> was associated with an 11% increase in the COVID-19 death rate.<sup>5</sup> Another US nationwide study found a significant association between long-term exposure to PM<sub>2.5</sub> and COVID-19 mortality in single pollutant analysis and a marginally significant association when adjusting for the other ambient air pollutants such as nitrogen dioxide and ozone.<sup>14</sup> The study estimated PM<sub>2.5</sub> exposure from 2010 to 2016 in 3122 US counties, at the spatial resolution of 1 km × 1 km using machine learning modelling.<sup>14</sup> However, another US national study that linked 2014–2019 air



pollution data from the US Environmental Protection Agency (EPA) Environmental Justice Screen (EJSCREEN) with COVID-19 cumulative prevalence and fatality rates up to 31 May 2020 failed to find a correlation after adjusting for covariates.<sup>15</sup> On a smaller urban scale, Adhikari and Yin monitored air pollution and COVID-19 infection as well as mortality in Queens, New York, and found no relationship between daily PM<sub>2.5</sub> and COVID-19 infection or mortality.<sup>16</sup> Studies conducted outside of the United States have also produced inconsistent results. PM<sub>2.5</sub> was reported to be associated with COVID-19 mortality and/or hospital admission in nine Asian cities (four from India, three from China, two from Pakistan and one from Indonesia), in 355 Dutch municipalities and in Italian regions and provinces.<sup>17–19</sup> While, in 32,844 small areas of England, PM<sub>2.5</sub> levels estimated during 2014–2018 had no relationship with COVID-19 mortality.<sup>20</sup> However, all these reports were ecological studies that only allow for inferences at the geographic level which may not apply to individual patients.<sup>10</sup> They preclude controlling for each patient's characteristics and risk factors and, therefore, these studies require individual-level data for validation.<sup>10</sup> We previously performed the first individual-level study on PM<sub>2.5</sub> and COVID-19 outcomes.<sup>21</sup> We analysed data on 1128 COVID-19 patients diagnosed at the UC health system and found that PM<sub>2.5</sub> was associated with higher odds of hospitalization only in patients with asthma or COPD, but not in those without respiratory conditions.<sup>21</sup>

Consistent with our results, individual-level studies have demonstrated an association of PM<sub>2.5</sub> exposure with respiratory infections and related outcomes. In children, both long- and short-term exposure to PM<sub>2.5</sub> have been reported to be associated with hospitalization and healthcare use for respiratory syncytial virus bronchiolitis, especially during infancy.<sup>22,23</sup> Similar findings have been reported in older adults for influenza in relation to short-term PM<sub>2.5</sub> exposure.<sup>23</sup> In support of our findings, there are several mechanisms through which long-term exposure to PM<sub>2.5</sub> might be associated with COVID-19 hospitalization. PM<sub>2.5</sub> suspended in the air may play a role in SARS-CoV-2 transmission and infection by carrying the virus, but also by impairing bronchial immunity and epithelial cell integrity to enhance the bronchial attachment and replication of SARS-CoV-2.<sup>8</sup> Moreover, PM<sub>2.5</sub> particles can penetrate the respiratory tract and reach the alveoli to deliver the virus to its target type II alveolar cells.<sup>8</sup> Inside the lungs, PM<sub>2.5</sub> can cause injury through inflammation and free radical peroxidation which could aggravate COVID-19.<sup>24</sup> The particles have been reported to stimulate the release of proinflammatory cytokines from activated alveolar macrophages and cytokine-producing genes.<sup>24</sup> They also prompt the production of free radicals that may oxidize alveolar cells due to the presence of metal and other transition elements, as well as polycyclic aromatic hydrocarbons and LPS on PM<sub>2.5</sub> surface.<sup>24</sup> Excessive free radicals' production reduces cellular antioxidant capacity and leads to lipid peroxidation as well as increase in intracellular calcium concentrations which can further induce cellular damage.<sup>24</sup>

Our sample consisted predominantly of women (70.7%). Inconsistent with the distribution of our study population, it has been hypothesized that males may be at higher risk for SARS-CoV-2 infection as they have higher activity of angiotensin-converting enzyme 2 (ACE2), which serve as entry point to the virus in alveolar epithelial cells.<sup>25</sup> Moreover, the transmembrane protease serine 2 (TMPRSS2) gene that facilitates the fusion of the viral and cellular membranes is influenced by male sex hormones.<sup>26</sup> Sex differences in immune response profiles during COVID-19 have also been described; males may tend to have more innate immune cytokines, while females may have more robust T-cell activation.<sup>27</sup> Although epidemiological studies have reported no clear evidence of sex difference in COVID-19 prevalence, men have been observed to be more at risk for worse COVID-19 outcomes.<sup>28</sup> Yet, the reason for the high prevalence of women in our study population is unclear. It is possible that women are more likely to perceive the pandemic as with more seriousness and to seek care more often than man.

Our study had limitations. PM<sub>2.5</sub> exposure was estimated at the residential zip code level from 2009 to 2018; PM<sub>2.5</sub> estimates for the year 2019 and exposure data for more precise locations were not available. We adjusted for socioeconomic status at the zip code level and not at the individual level. We also used the address at the time of hospital encounter for the PM<sub>2.5</sub> and did not account for other addresses over the 10-year period. However, potential exposure misclassification using zip codes instead of better resolution of PM<sub>2.5</sub> estimates that may exist is expected to be non-differential and to diminish the strength of the reported associations.<sup>29</sup> Comorbidities were defined using electronic health records and variables such as smoking were not included in our analysis due to a large proportion of patients with missing data. Behaviours and preventive measures that could reduce viral load may vary with geographic location and may have introduced residual confounding in our analysis. Our study included patients from a single health system in the Midwest of the United States and may not be generalizable to the overall US population. Nevertheless, our study had major strengths. It included a large sample of 14,834 COVID-19 patients of various races and ethnicities and adjusted for sociodemographic characteristics and comorbidities. Our analysis rigorously adjusted for socioeconomic status, an important confounder in air pollution studies, using the deprivation index.<sup>30</sup> In addition to adjusting for comorbidities, we performed sensitivity analyses by excluding patients with each of the comorbidities and our results remained consistent.

In conclusion, long-term exposure to PM<sub>2.5</sub> is associated with increased admission to hospital for COVID-19. Future studies should include study samples that are nationally representative and a better resolution of PM<sub>2.5</sub> exposure at patients' residential address to confirm these findings. If the associations observed in this study are indeed causal, appropriate measures to prevent SARS-CoV-2 infection among patients residing in high PM<sub>2.5</sub> exposure areas or public health efforts to decrease PM<sub>2.5</sub> levels could lessen COVID-19 morbidity as well as its burden on the healthcare system.

## ACKNOWLEDGEMENTS

The authors acknowledge Matthew Benjamin Sabath for his assistance in PM<sub>2.5</sub> data collection.

*Research funding:* Contributions of Angelico Mendy, Changchun Xie and Susan M. Pinney were partly funded by grant P30 ES006096 from the US NIH. Cecily S. Fassler's contribution was funded by grant T32ES010957 from NIH. Senu Apewokin's contribution was partly funded by K08CA237735 from the US NIH. Tesfaye B. Mersha's contribution was partly funded by R01 HL132344 from the US NIH. The COVID-19 data collection was supported by the National Center for Advancing Translational Sciences of the NIH, grant 5UL1TR001425-03.

## AUTHOR CONTRIBUTIONS

**Angelico Mendy:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing & original draft (equal); writing & review and editing (equal). **Xiao Wu:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); resources (equal); writing & original draft (equal). **Jason Keller:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing & original draft (equal). **Cecily Fassler:** Formal analysis (equal); methodology (equal); writing & original draft (equal); writing & review and editing (equal). **Senu Apewokin:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); validation (equal); writing & original draft (equal); writing & review and editing (equal). **Tesfaye Mersha:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing & original draft (equal); writing & review and editing (equal). **Changchun Xie:** Conceptualization (equal); formal analysis (equal); methodology (equal); writing & original draft (equal); writing & review and editing (equal). **Susan Pinney:** Funding acquisition (equal); methodology (equal); resources (equal); writing & original draft (equal); writing & review and editing (equal).

## CONFLICT OF INTEREST

None declared.

## HUMAN ETHICS APPROVAL DECLARATION

The UC Institutional Review Board (IRB) exempted the study from IRB ethics approval and informed consent as it used a de-identified data set of the electronic medical record system of the UC healthcare system stripped of all Health Insurance Portability and Accountability Act (HIPAA) identifiers.

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### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Mendy A, Wu X, Keller JL, Fassler CS, Apewokin S, Mersha TB, et al. Air pollution and the pandemic: Long-term PM<sub>2.5</sub> exposure and disease severity in COVID-19 patients. *Respirology.* 2021;26:1181–7. <https://doi.org/10.1111/resp.14140>