Association Between Outdoor Air Pollution Levels and Inpatient Outcomes in Pediatric Pneumonia Hospitalizations, 2007 to 2008

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Received for publication February 9, 2018; accepted December 9, 2018.

ABSTRACT

OBJECTIVE: Pneumonia is a leading cause of pediatric admissions. Although air pollutants are associated with poor outcomes, few national studies have examined associations between pollutant levels and inpatient pediatric pneumonia outcomes. We examined the relationship between ozone (O_3) and fine particulate matter with a diameter ≤2.5 μm ($PM_{2.5}$) and outcomes related to disease severity.

METHODS: In this cross-sectional study, we obtained discharge data from the 2007 to 2008 Nationwide Inpatient Sample and pollution data from the Air Quality System. Patients ≤18 years with a principal diagnosis of pneumonia were included. Discharge data were linked to O_3 and $PM_{2.5}$ levels (predictors) from the patient's ZIP Code (not publicly available) from day of admission. Outcomes were mortality, intubation, length of stay (LOS), and total costs. We calculated weighted national estimates and performed multivariable analyses adjusting for sociodemographic and hospital factors.

RESULTS: There were a total of 57,972 (278,871 weighted) subjects. Median $PM_{2.5}$ level was 9.5 (interquartile range [IQR] 6.8−13.4) $\mu g/m^3$. Median O_3 level was 35.6 (IQR 28.2−45.2) parts per billion. Mortality was 0.1%; 0.75% of patients were intubated. Median LOS was 2 (IQR 2−4) days. Median costs were $3089 (IQR $2023−$5177). Greater levels of $PM_{2.5}$ and O_3 were associated with mortality, longer LOS, and greater costs. Greater O_3 levels were associated with increased odds of intubation.

CONCLUSIONS: Greater levels of O_3 and $PM_{2.5}$ were associated with more severe presentations of pneumonia. Future work should examine these relationships in more recent years and over a longer time period.

KEYWORDS: air pollution; children; disease severity; hospitalizations; mortality; pneumonia

ACADEMIC PEDIATRICS 2019;19:414−420

WHAT'S NEW

Greater levels of ozone and fine particulate matter with a diameter ≤2.5 μm are associated with more severe disease in children admitted with pneumonia. More severe disease was seen at pollution levels above standards set by the Environmental Protection Agency.

PNEUMONIA IS ONE of the most common illnesses of childhood in the United States. There are approximately 2 million pediatric ambulatory visits for pneumonia in the United States annually.[1] In addition, pneumonia is the most common reason for children <18 years old to be hospitalized in the United States, with hospitalization rates of nearly 170 per 100,000 annually.[2] Annual hospitalization rates for pneumonia are even greater (over 700 per 100,000) for children <2 years old.[3] It is the second most expensive reason for pediatric admissions in the United States.[4]

Several studies have documented the role of outdoor air pollutants as risk factors for pneumonia and other respiratory illnesses and subsequent poor outcomes.[5,6] Several of these pollutants, including particulate matter and ozone (O_3), are tracked by the Environmental Protection Agency (EPA) as part of the Air Quality Index.[7] Exposures to these pollutants cause lung dysfunction and harmful effects on the respiratory tract.[8,9] Fine particulate matter with a diameter ≤2.5 μm ($PM_{2.5}$) and O_3 have been linked to mortality[10,11] and increased hospitalizations due to respiratory causes in studies mostly focusing on adults.[11,12]

Some pediatric studies have linked $PM_{2.5}$ and O_3 to poor outcomes. Greater levels of these and other air pollutants are associated with pediatric emergency department visits,[13,14] as well as increased rates of hospitalization due to respiratory diagnoses.[15,16] Few studies have examined the association between outdoor air pollutant exposures and subsequent inpatient outcomes for children admitted with pneumonia. In addition, most studies linking these pollutants to poor outcomes have focused on urban populations.[6,11,12] Nationally representative studies have linked long-term air pollution exposure to increased costs in children admitted for bronchiolitis[17] and increased costs and length of stay (LOS) with pediatric asthma hospitalizations.[18] Acute exposure to air pollution also can be harmful; 1 study showed that young adults subjected to O_3 for 6.6 hours had increased neutrophilic airway inflammation and decreased forced expiratory volume over 1 second.[9] Exposure to greater levels of $PM_{2.5}$ and O_3 over a short time frame is associated with increased mortality in adults.[19] Few studies have examined the acute effects of air pollution exposure on mortality, intubation, LOS, and costs for pediatric inpatients with pneumonia on a national level. In addition, few studies have examined the effects of specific recommended air pollutant levels[7] on these outcomes.

The purpose of this hypothesis-generating pilot study was to determine whether acute exposure to levels of O_3 and $PM_{2.5}$ in a patient's ZIP Code is associated with inpatient outcomes of mortality, intubation, LOS, and costs in children admitted for pneumonia between 2007 and 2008. This is the first time these relationships are being studied in this way while linking 2 nationally representative data sets on US hospitalizations and air quality; we aimed to gather preliminary data over this 2-year period to inform the design of larger future studies.

METHODS

STUDY DESIGN/DATA SOURCE

In this cross-sectional study, discharge level data were abstracted from the 2007 to 2008 Nationwide Inpatient Sample (NIS), the largest all-payer publicly available inpatient data set; the data set is part of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Quality and Research. The NIS contains a stratified sample of approximately 20% of US hospitals; national estimates can be calculated given the complex sampling design.[20] A special discharge data analysis file was created for this study that included patient ZIP Code, a variable not publicly available but that allowed linkage to pollution data.

Air pollution data were taken from the EPA's Aerometric Information Retrieval System, now known as the Air Quality System. The data set contains estimated air pollution data collected at national, state, and local levels.[21] Levels are monitored at ~4000 sites nationwide (43% of US population within 10 km of a site, while some are >300 km from a site) and are collected over a time frame ranging from hourly to every 3 days; Bayesian modeling is used to estimate air pollution levels within a ZIP Code.[22] Estimated O_3 and $PM_{2.5}$ levels for each day from 2007 to 2008 and ZIP Code in the United States were then matched to ZIP Code (of the subject's residence)-day combination from the NIS by HCUP (similar linkages performed in other studies[19]) so the estimated admission date outdoor air pollution levels were known for each hospitalization. Given that the NIS and Air Quality System are deidentified and all matching was performed by HCUP, this study was exempt from full review by the New York University School of Medicine Institutional Review Board, as it did not meet the definition for human subjects research.

SUBJECTS

Subjects records were included if they had a principal diagnosis of pneumonia by Clinical Classification Software Code 122 (codes developed by HCUP for *International Classification of Diseases Ninth Revision, Clinical Modification*),[23] were ≤18 years old, and were able to be linked to air pollution data via patient ZIP Code. There were no additional exclusion criteria.

MEASURES

The primary predictor variables were $PM_{2.5}$ and O_3. Effect of $PM_{2.5}$ was assessed at a threshold of 12 $\mu g/m^3$ (the EPA's National Ambient Air Quality Standards [NAAQS] primary standard for $PM_{2.5}$ averaged over 1 year).[24] O_3 cutoffs were set at 60 parts per billion (ppb; suggested as a possible O_3 standard by the Clean Air Scientific Advisory Committee[25]) and 70 ppb (current primary and secondary standard averaged over 8 hours per the NAAQS[24]). We dichotomized pollutant levels at the listed cut points. As part of a sensitivity analysis and to determine whether mortality and other outcomes associated with more severe disease were more likely above pollutant standards established by the EPA or were simply a function of increasing pollutant levels in general, we ran separate models in which we assessed each pollutant 1) as a log-transformed continuous variable (given a non-normal distribution) and 2) grouped as quartiles.

Outcome variables included mortality, intubation (*International Classification of Diseases Ninth Revision, Clinical Modification* procedural codes: 96.04, 96.70, 96.71, 96.72), LOS, and total costs. Estimated total hospitalization costs were calculated by using NIS charge data and converting them to costs using NIS group-weighted Cost-to-Charge data files.[26]

Additional covariates, both patient-related and hospital-level, were included a priori in the analyses due to their association with outcomes for respiratory conditions[27,28] and availability in the NIS.[20] Added patient-related variables were as follows: asthma as a secondary diagnosis (the only other respiratory-related diagnosis coded for in an adequate number of subjects in the data set to allow for analysis); race/ethnicity, combined into a single variable in the NIS; insurance type; median household income quartile by patient ZIP code; sex; and age, grouped as ages 0 to 1, 2 to 5, 6 to 12, and 13 to 18 years. Hospital-level variables were region; rural/urban setting; teaching status; bed size; and hospital admission timing

by year, discharge quarter, and weekend versus weekday admission. A hospital's "bed size" is categorized as small, medium, or large and varies, per HCUP definitions, based on hospital location and teaching status.[20]

ANALYSIS

Descriptive statistics were used to assess demographic variables. Unadjusted regression analyses were performed including one pollutant (O_3 or $PM_{2.5}$ as categorized by EPA standards[24]) as a predictor in models for the outcomes of mortality and intubation (logistic regression), LOS (Poisson regression), and costs (linear regression). Multivariable regression analyses were then performed, now adjusting for other covariates described previously. The same method was used with pollutants levels grouped into quartiles or as log-transformed continuous variables as predictors in the model. To evaluate whether O_3 and $PM_{2.5}$ were independently associated with outcomes, we first evaluated the relationship between these pollutants using the Spearman correlation. We then included both pollutants as predictors for the aforementioned outcomes (along with the other covariates) in a 2-pollutant model, using pollutant thresholds set by the EPA; we evaluated for possible effect modification between O_3 and $PM_{2.5}$ by including the product of these variables dichotomized by levels set by the EPA as an interaction term in the analysis. Missing data for covariates were reassigned to a separate missing data category. Cost data were log-transformed as distributions were skewed. After performing the linear regressions for costs, we applied Duan's method to retransform linear regression results from the log to the original scale.[29] A P value less than .05 was considered significant. All analyses respected the complex survey design using sample weighting in Stata SE 12.1 (StataCorp, College Station, Tex). Unweighted analyses also were performed, given potential bias associated with sample weighting; unweighted regression analyses mirrored results from weighted regressions and are presented in Appendix 1.

RESULTS

DESCRIPTIVE RESULTS

Of the 60,137 discharges representing children ≤18 years old with a primary diagnosis of asthma, 57,972 (96.4%) could be linked to pollution data; this represents a weighted statistical sample of 278,871 discharges. Data related to patient demographics, hospital and hospitalization-level factors, patient outcomes, and air pollution levels are presented in Table 1. Most patients were <6 years old. Slightly more than one half were male and had public

Table 1. Patient/Hospital Characteristics (n = 57,972)

Variable	N (%)	Variable	N (%)
Particle pollution <2.5 μm, $\mu g/m^3$		Sex	
<12	39,300 (67.8)	Female	25,746 (44.4)
≥12	18,672 (32.2)	Male	31,947 (54.9)
Ozone, ppb		Missing	379 (0.7)
<60	54,602 (94.2)	Region	
60 to <70	2514 (4.3)	Northeast	7539 (13.0)
≥70	856 (1.5)	Midwest	13,104 (22.6)
Race/ethnicity		South	27,569 (47.6)
White	21,773 (37.6)	West	9760 (16.8)
Black	7603 (13.1)	Location/teaching status	
Hispanic	10,096 (17.4)	Rural	12,337 (21.3)
Asian/Pacific Islander	1009 (1.7)	Urban/non-teaching	21,278 (36.7)
Native American	729 (1.3)	Urban/teaching	24,357 (42.0)
Other	2559 (4.4)	Bed size*	
Missing	14,203 (24.5)	Small	9237 (15.9)
Insurance		Medium	13,963 (24.1)
Public	30,198 (52.1)	Large	34,772 (60.0)
Private	23,524 (40.6)	Weekend admission	13,416 (22.1)
Other	4116 (7.1)	Year	
Missing	134 (0.2)	2007	29,375 (50.7)
Median income by ZIP Code		2008	28,597 (49.3)
$1–$38,999	21,471 (37.0)	Quarter	
$39,999–$47,999	15,372 (26.5)	January to March	19,862 (34.3)
$48,000–$62,999	11,247 (19.4)	April to June	10,106 (17.4)
$63,000+	8778 (15.1)	July to September	6727 (11.6)
Missing	1104 (1.9)	October to December	15,188 (26.2)
Age, y		Missing	6089 (10.5)
0–1	23,585 (40.7)	Outcomes	
2–5	19,269 (33.2)	Mortality	82 (0.1)
6–12	10,792 (18.6)	Intubated	433 (0.75)
13–18	4326 (7.5)	Median LOS (IQR), days	2 (2 to 4)
Asthma diagnosis	18,402 (31.7)	Median Total Costs (IQR)	$3089 ($2023–$5177)

IQR indicates interquartile range; and LOS, length of stay.
*Definition differs depending on hospital location and teaching status.[18]

Table 2. Association of $PM_{2.5}$ With Inpatient Mortality, Intubation, LOS, and Costs*

$PM_{2.5}$ Level, $\mu g/m^3$	Mortality aOR (95% CI)	Intubation aOR (95% CI)	LOS Increment, d (95% CI)	Costs Increment (95% CI)
>12 (reference ≤12)	1.92 (1.25–2.94)†	1.15 (0.96–1.37)	+0.05 (+0.01 to +0.10)†	+$278 (+$49 to +$588)‡

$PM_{2.5}$ indicates fine particulate with a diameter ≤2.5μm; LOS, length of stay; aOR, adjusted odds ratio; and CI, confidence interval.

*Models were adjusted for the following variables (chosen a priori based on review of the literature[27,28] and availability in the NIS[20]): diagnosis of asthma, race/ethnicity, median income by ZIP Code, age group, sex, region, hospital bed size, and timing of admission (by quarter of year, weekend vs weekday, and year).

†$P < .01$.

‡$P < .05$.

insurance. A total of 0.1% of patients died; 0.75% were intubated. Median LOS was 2 (interquartile range [IQR] 2–4) days. Median total costs (2008 dollars) were $3089 (IQR $2023–$5177).

Median $PM_{2.5}$ level was 9.5 (IQR 6.8–13.4, range 0.4–86.8) $\mu g/m^3$. Median O_3 level was 35.6 (IQR 28.2–45.2, range 0.7–115.3) ppb. Spearman correlation between the 2 pollutants was 0.055 ($P < .001$). Results of unadjusted analyses are presented in Appendix 2.

Multivariable Analyses

$PM_{2.5}$

Table 2 represents results of regression models assessing the associations between $PM_{2.5}$ level (>12 $\mu g/m^3$) and mortality, intubation, LOS, and costs. Results of sensitivity analyses are presented in Appendix 3.

Mortality. There was an increased odds of mortality when $PM_{2.5}$ levels were >12 $\mu g/m^3$ (adjusted odds ratio [aOR] = 1.92, 95% confidence interval [CI], 1.25–2.94, $P = .003$). Associations were also found when $PM_{2.5}$ level was assessed as a log-transformed continuous variable and as an ordinal variable.

Intubation. $PM_{2.5}$ was not associated with intubation in adjusted analyses.

LOS. LOS was +0.05 (95% CI, +0.01 to +0.10) days longer when $PM_{2.5}$ was >12 $\mu g/m^3$. Similar results were seen when $PM_{2.5}$ was assessed as a log-transformed continuous variable and at levels >14.2 $\mu g/m^3$.

Costs. Cost of admission was significantly greater at $PM_{2.5}$ levels >12 $\mu g/m^3$ (increment +$278; 95% CI, +$49 to +$588, $P = .01$).

O_3

Associations between O_3 levels as a dichotomous variable and study outcomes are presented in Table 3. Sensitivity analyses are presented in Appendix 4.

Mortality. When O_3 levels were dichotomized, increased odds of mortality were observed with levels >60 ppb (aOR = 2.33; 95% CI, 1.14–4.78, $P = .02$) and >70 ppb (aOR = 3.11; 1.24–7.79, $P = .02$).

Intubation. Significantly greater odds of intubation were seen for patients subjected to O_3 >60 ppb (aOR = 1.61; 95% CI, 1.19–2.17, $P = .002$). Similar results were seen when O_3 was assessed as a log-transformed continuous variable.

Length of Stay. Patients exposed to >70 ppb O_3 had a +0.19 (95% CI, +0.05 to +0.33, $P = .008$) day longer LOS.

Costs. Costs of admission were $820 greater at exposures >70 ppb O_3 (95% CI, +$35 to +$1935, $P = .04$).

Two-Pollutant Models

Table 4 presents results for a 2-pollutant model, using a cutoff of $PM_{2.5}$ >12 $\mu g/m^3$ and O_3 >70 ppb. Greater $PM_{2.5}$ levels were associated with increased odds of mortality, greater costs, and longer LOS. O_3 levels of >70 ppb were associated with longer LOS. The interaction term between O_3 and $PM_{2.5}$ was not significant for any of the 4 outcomes.

Discussion

In this national pilot study of pediatric admissions for pneumonia, significant associations were observed between pollutants ($PM_{2.5}$ and O_3) and outcomes of mortality, intubation, LOS, and costs over the 2-year study

Table 3. Association of O_3 With Inpatient Mortality, Intubation, LOS, and Costs*

O_3 Level, ppb	Mortality aOR (95% CI)	Intubation aOR (95% CI)	LOS Increment, d (95% CI)	Costs Increment (95% CI)
>60 (reference ≤60)	2.33 (1.14–4.78)‡	1.61 (1.19–2.17)†	+0.04 (−0.02 to +0.10)	−$98 (−$421 to $363)
>70 (reference ≤70)	3.11 (1.24–7.79)‡	1.50 (0.94–2.38)	+0.19 (+0.05 to +0.33)†	+$820 (+$35 to +$1935)‡

O_3 indicates ozone; LOS, length of stay; aOR, adjusted odds ratio; and CI, confidence interval.

*Models were adjusted for the following variables (chosen a priori based on review of the literature[27,28] and availability in the NIS[20]): diagnosis of asthma, race/ethnicity, median income by ZIP code, age group, sex, region, hospital bed size, and timing of admission (by quarter of year, weekend vs weekday, and year).

†$P < .01$.

‡$P < .05$.

Table 4. Two-Pollutant Model Assessing Pollutant Associations With Inpatient Mortality, Intubation, LOS, and Costs*

Pollutant	Mortality aOR (95% CI)	Intubation aOR (95% CI)	LOS Increment, d (95% CI)	Costs Increment (95% CI)
$PM_{2.5}$ >12 $\mu g/m^3$ (reference ≤12)	1.81 (1.18–2.80)†	1.13 (0.94–1.36)	+0.05 (+0.01 to +0.09)‡	+$252 (+$31 to +$551)‡
O_3 >70 ppb (reference ≤70 ppb)	2.36 (0.97–5.77)	1.41 (0.87–2.29)	+0.16 (+0.03 to +0.30)‡	+$662 (−$72 to +$1716)

LOS indicates length of stay; aOR, adjusted odds ratio; CI, confidence interval; $PM_{2.5}$, fine particulate with a diameter ≤2.5 μm; and O_3, ozone.

*Model was adjusted for the following variables (chosen a priori based on review of the literature[27,28] and availability in the NIS[20]): diagnosis of asthma, race/ethnicity, median income by ZIP Code, age group, sex, region, hospital bed size, and timing of admission (by quarter of year, weekend vs. weekday, and year).

†$P < .01$.

‡$P < .05$.

period. To our knowledge, this is the first time that associations between acute exposures to these air pollutants and adverse inpatient outcomes in children admitted with pneumonia has been studied using nationally representative data sets

Mortality was more likely in patients exposed to greater levels of either pollutant. Mortality was almost twice as likely when $PM_{2.5}$ level was >12 $\mu g/m^3$ (the NAAQS primary yearly average standard).[24] Odds of mortality were more than double for exposures to O_3 levels > 60 ppb and more than triple when >70 ppb. Only $PM_{2.5}$ was associated with mortality in a 2-pollutant model. The serious health effects of exposure to $PM_{2.5}$ and O_3 have been well documented; elevated levels have been linked to mortality in patients with pneumonia.[10,30] Much of this work has been performed in adult patients, in the outpatient setting, and subchronic or chronic exposure to these pollutants.[10,30]

Intubation was more likely at greater O_3 levels. After adjusting for other variables, odds of intubation were 60% greater when O_3 levels were >60 ppb, a clinically meaningful result. Intubation was not statistically more likely for O_3 levels >70 ppb (the current standard), although our study may not be powered to detect a difference, as only 1.5% of cases were exposed to levels >70 ppb. Intubation was not independently related to $PM_{2.5}$ levels; intubation was not associated with elevated O_3 levels when adjusting for $PM_{2.5}$ in 2-pollutant models. Interestingly, elevated $PM_{2.5}$ levels have been associated with intensive care unit admissions,[6] another indicator of severe illness. Few studies have specifically examined the impact of air pollution on intubation, although intubation is more likely in urban areas compared with rural areas[28]; this may be a function of there being more air pollution in urban areas or that rural hospitals may be less well equipped to treat the sickest patients who might require intubation. As our definition of intubation is dependent on accuracy and completeness of coding by the physicians who saw these patients initially, future prospective work is needed to confirm these findings.

O_3 and $PM_{2.5}$ also were associated with increased LOS and costs. LOS was 0.19 days longer for children exposed to O_3 >70 ppb on their day of admission, which translates to 1 day added onto the LOS for every 5 children with this exposure. Although $PM_{2.5}$ was significantly associated with LOS, these results are likely less clinically meaningful (increment of only 0.05 days) compared with the impact of O_3. In single-pollutant models, costs were greater in the setting of elevated levels of either pollutant, supporting associations found in other studies.[18,31] Hospitalization costs were notably $820 greater for O_3 levels >70 ppb; this translates into an additional $700,000 in total hospitalization costs for the 856 children (unweighted) exposed to O_3 >70 ppb (and an estimated $3.5 million when accounting for sample weighting). In our 2-pollutant model, only $PM_{2.5}$ levels >12 $\mu g/m^3$ were predictive of greater costs, with an additional increment of more than $250 per hospitalization.

It is also important to examine the results of this study in the context of pollutant standards set by the EPA as part of the NAAQS. The largest impact of $PM_{2.5}$ was found using a cutoff of 12 $\mu g/m^3$ (primary standard for $PM_{2.5}$ averaged over 1 year).[24] Mortality was greater, LOS was longer, and costs were greater when $PM_{2.5}$ levels were above this threshold. This supports the results of other studies that have shown the benefits of an annual average threshold of 12 $\mu g/m^3$ in terms of preventing premature deaths.[32] Our study has shown the potential harm of short-term exposure to $PM_{2.5}$ >12 $\mu g/m^3$ (the current annual average threshold).[24] The current EPA short-term $PM_{2.5}$ standard (8-hour average) is 35 $\mu g/m^3$, nearly triple the level associated with poor outcomes in our study. Future work should explore whether short-term $PM_{2.5}$ exposure above a lower threshold such as 12 $\mu g/m^3$ is associated with mortality and other adverse outcomes for other diagnoses (eg, asthma, bronchiolitis) as well as if setting lower short-term thresholds would be cost effective. Analysis of $PM_{2.5}$ levels as a continuous variable also showed effects on mortality and costs, indicating overall that greater levels of this pollutant can incrementally lead to more severe illness, although few significant effects were observed when $PM_{2.5}$ levels were broken up into quartiles, and the largest associations were observed >12 $\mu g/m^3$, indicating that using a threshold lower than 12 $\mu g/m^3$ would likely not be beneficial.

Analysis of O_3 according to recommended thresholds provided support for use of 70 ppb as the NAAQS standard.[24] We found greater mortality, LOS, and cost outcomes at this level, providing evidence for continuing this standard, which may be a difficult standard to achieve

consistently.[33] Other work has established the benefits of using 70 ppb and a stricter standard of 60 ppb in decreasing the likelihood of premature deaths.[34] We found that intubation was more likely at a threshold of 60 ppb (and not at 70 ppb, although our study may not have been powered to detect a difference). There appeared to be a dose response for the association of O_3 with mortality, which was twice as high above an O_3 threshold of 60 ppb but 3 times as high above 70 ppb. Although the benefits of using a cut point of 70 ppb are clear, our results support clinically meaningful outcomes for mortality and intubation using the lower threshold of 60 ppb. Future work could focus on what additional benefits could come from a lower O_3 standard.

We also examined associations between the 2 pollutants in the same model with our study outcomes. Although exposure to O_3 above 70 ppb was associated with mortality and increased costs in single-pollutant models, these associations were no longer present after we added $PM_{2.5}$ to the model. The associations between $PM_{2.5}$ and study outcomes were largely unchanged after we added O_3 to the model. The more severe outcomes observed, therefore, are more likely a function of elevated $PM_{2.5}$ rather than O_3 levels. In addition, in the 2-pollutant models for all 4 outcomes, an interaction term was not statistically significant, so the impact of these pollutants on the study outcomes are likely independent of each other. Future work should further explore the interrelationships between air pollutants and their impact on child health outcomes.

This study has limitations. These data are from 2007 to 2008, which were the most recent data available to be linked during our initial data matching and analysis. Future work should examine whether the preliminary associations identified in 2007 to 2008 are found in more recent years and over a longer time period, especially for uncommon outcomes such as mortality and intubation. We also recognize that using $P < .05$ as a cutoff for significance may lead to an increased chance of a type I error. This was a hypothesis-generating study meant to lay the groundwork for larger future studies covering a larger number of years. Our selection of cases of pneumonia, as well as the ability to account for other relevant diagnoses in our analyses, was dependent on accurate physician diagnosis and documentation in the medical record. Missing data can be a problem in any large retrospective study using administrative data. Only 3.6% of otherwise-eligible cases in the NIS were missing pollution data and were therefore excluded. In addition, nearly 25% of cases were missing data for race/ethnicity. Many states did not report race/ethnicity data to the NIS in 2007 to 2008.[20] Although missing race/ethnicity data was not associated with any of the outcome studied (data not shown), it is possible that the presence of any missing data may have implications on the conclusions drawn. It is possible that the sample may not be fully nationally representative despite the large national sample frame. In addition to air pollution, several other factors in our analyses were associated with adverse outcomes (data not shown); for example, mortality was more likely in children who were older, lacked a diagnosis of asthma, and those at larger teaching hospitals. These variables, as well as other factors not controlled for in our study, including presence of other (outdoor or indoor) pollutants, medical history, or vaccination status, should be examined in future studies. We also appreciate the potential for ecological fallacy in our analysis. Our study examined the effect of O_3 and $PM_{2.5}$ on outcomes for children sick enough to be admitted to the hospital for pneumonia and does not reflect pollutants' effect on admission rates, emergency department visit rates, or other preadmission outcomes, nor does it assess associations with outcomes for other diagnoses. Finally, although pollution data are linked to patient home ZIP Code, we cannot guarantee that patients were necessarily present in their ZIP Code on the day of admission.

In conclusion, our large, nationally representative study found that among children admitted to the hospital with pneumonia, greater levels of outdoor air pollutants ($PM_{2.5}$ and O_3) were associated with inpatient mortality and other indicators of more severe inpatient disease. Worse outcomes were seen with short-term (1-day) estimated $PM_{2.5}$ level exposures >12 $\mu g/m^3$, the current long-term (annual) average NAAQS standard; a lower short-term standard (currently 35 $\mu g/m^3$) would likely be beneficial. Future work also should further explore the value of using a lower O_3 standard (eg, 60 ppb compared with the current standard of 70 ppb), given our study's likely clinically meaningful results at the lower threshold; potential harm associated with loosening of O_3 standards (a topic of recent discussion[35]) also should be evaluated. The deleterious effects of the air pollutants studied may be even worse in certain subgroups of patients, such as younger children and asthmatics; future studies with a larger data set should explore these interrelationships. Future work should examine whether the effects of air pollution observed in our preliminary analysis from 2007 to 2008 are applicable in more recent years and over a longer time period (especially with improving air pollution levels in recent years[21]) and should explore whether additional factors not available in this data set affect mortality and measures of more severe disease.

ACKNOWLEDGMENTS

We acknowledge the following states that participate in the HCUP Nationwide Inpatient Sample: Alaska, Arizona, Arkansas, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming (https://www.hcup-us.ahrq.gov/db/hcupdatapartners.jsp).

Financial disclosure: This study was funded by Health Resources and Services Administration (HRSA) 1 T32HP22238 Department of Health and Human Services, HRSA, Primary Care (NRSA T32: Postdoctoral Primary Care Research Training Program) and the NYU CTSA grant UL1 TR001445 from the National Center for Advancing Translational Sciences, National Institutes of Health. The sponsor had no role in the

study design, collection/analysis/interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.acap.2018.12.001.

REFERENCES

1. Kronman MP, Hersh AL, Feng R, et al. Ambulatory visit rates and antibiotic prescribing for children with pneumonia, 1994–2007. *Pediatrics*. 2011;127:411–418.
2. Witt WP, Weiss AJ, Elixhauser A. Overview of hospital stays for children in the United States, 2012: Statistical brief #187. Rockville, MD: Agency for Healthcare Research and Quality; December 2014. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb187-Hospital-Stays-Children-2012.pdf. Accessed November 19, 2017.
3. Griffin MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369:155–163.
4. Keren R. Prioritization of comparative effectiveness research topics in hospital pediatrics. *Arch Pediatr Adolesc Med*. 2012;166:1155–1164.
5. Malley CS, Henze DK, Kuylenstierna JCI, et al. Updated global estimates of respiratory mortality in adults ≥30 years of age attributable to long-term ozone exposure. *Environ Health Perspect*. 2017;125:087021.
6. Zhang Z, Hong Y, Liu N. Association of ambient particulate matter 2.5 with intensive care unit admission due to pneumonia: a distributed lag non-linear model. *Sci Rep*. 2017;7:8679.
7. Environmental Protection Agency. AirNow. Published 2017. Available at: https://www.airnow.gov/. Accessed October 29, 2017.
8. Chen S, Gu Y, Qiao L, et al. Fine particulate constituents and lung dysfunction: a time-series panel study. *Environ Sci Technol*. 2017;51:1687–1694.
9. Kim CS, Alexis NE, Rappold AG, et al. Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours.. *Am J Respir Crit Care Med*. 2011;183:1215–1221.
10. Pun VC, Kazemiparkouhi F, Manjourides J, et al. Long-Term PM2.5 exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol*. 2017;186:1–9.
11. Atkinson RW, Kang S, Anderson HR, et al. Epidemiological time series studies of PM 2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax*. 2014;69:660–665.
12. Medina-Ramón M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol*. 2006;163:579–588.
13. Xiao Q, Liu Y, Mulholland JA, et al. Pediatric emergency department visits and ambient air pollution in the U.S. state of Georgia: a case-crossover study. *Environ Health*. 2016;15:115.
14. Darrow LA, Klein M, Dana Flanders W, et al. Air pollution and acute respiratory infections among children 0–4 years of age: an 18-year time-series study. *Am J Epidemiol*. 2014;180:968–977.
15. Nhung NTT, Amini H, Schindler C, et al. Short-term association between ambient air pollution and pneumonia in children: a systematic review and meta-analysis of time-series and case-crossover studies. *Environ Pollut*. 2017;230:1000–1008.
16. Patto NV, Nascimento LFC, Mantovani KCC, et al. Exposure to fine particulate matter and hospital admissions due to pneumonia: effects on the number of hospital admissions and its costs. *Rev Assoc Med Bras (1992)*. 2016;62:342–346.
17. Sheffield P, Roy A, Wong K, et al. Fine particulate matter pollution linked to respiratory illness in infants and increased hospital costs. *Health Aff*. 2011;30:871–878.
18. Roy A, Sheffield P, Wong K, et al. The effects of outdoor air pollutants on the costs of pediatric asthma hospitalizations in the United States, 1999 to 2007. *Med Care*. 2011;49:810–817.
19. Di Q, Dai L, Wang Y, et al. Association of short-term exposure to air pollution with mortality in older adults. *JAMA*. 2017;318:2446.
20. Agency for Healthcare Research and Quality. Overview of the National (Nationwide) Inpatient Sample (NIS). Published 2017. Available at: https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed November 19, 2017.
21. Environmental Protection Agency. Air Quality System (AQS). Published 2016. Available at: https://www.epa.gov/aqs. Accessed November 15, 2017.
22. United States Environmental Protection Agency. Bayesian space-time downscaling fusion model (downscaler) - derived estimates of air quality for 2009. 2009. doi:EPA-454/S-15-001. Available at: https://nepis.epa.gov/Exe/ZyPDF.cgi/P100OOP7.PDF?Dockey=-P100OOP7.PDF. Accessed November 19, 2017.
23. Agency for Healthcare Research and Quality. Clinical Classifications Software (CCS) for ICD-9-CM. Published 2017. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed November 29, 2017.
24. US Environmental Protection Agency. NAAQS Table. Published 2017. Available at: https://www.epa.gov/criteria-air-pollutants/naaqs-table. Accessed November 15, 2017.
25. Mccarthy JE, Lattanzio RK. EPA's 2015 Ozone Air Quality Standards. Published 2017. Available at: https://fas.org/sgp/crs/misc/R43092.pdf. Accessed November 19, 2017.
26. HCUP Cost-to-Charge Ratio Files (CCR). Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; 2007–2011. Available at: https://www.hcup-us.ahrq.gov/db/state/costtocharge.jsp. Accessed March 2, 2015.
27. Sonego M, Pellegrin MC, Becker G, et al. Risk factors for mortality from acute lower respiratory infections (ALRI) in children under five years of age in low and middle-income countries: a systematic review and meta-analysis of observational studies. *PLoS One*. 2015;10:1–18.
28. Glick AF, Tomopoulos S, Fierman AH, et al. Disparities in mortality and morbidity in pediatric asthma hospitalizations, 2007 to 2011. *Acad Pediatr*. 2016;16:430–437.
29. Duan N. Smearing estimate: a nonparametric retransformation method.. *J Am Stat Assoc*. 1983;78:605–610.
30. Hoek G, Brunekreef B, Verhoeff A, et al. Daily mortality and air pollution in the Netherlands. *J Air Waste Manage Assoc*. 2000;50:1380–1389.
31. Carpenter BH, Chromy JR, Bach WD, et al. Health costs of air pollution: a study of hospitalization costs. *Am J Public Health*. 1979;69:1232–1241.
32. Davidson K, Hallberg A, McCubbin D, et al. Analysis of PM2.5 using the environmental benefits mapping and analysis program (BenMAP). *J Toxicol Environ Health A*. 2007;70:332–346.
33. Sather ME, Cavender K. Trends analysis of ambient 8 hour ozone and precursor monitoring data in the south central U.S. *J Environ Monit*. 2007;9:143–150.
34. Berman JD, Fann N, Hollingsworth JW, et al. Health benefits from large-scale ozone reduction in the United States. *Environ Health Perspect*. 2012;120:1404–1410.
35. Associated Press. EPA moving forward with review of standard for ozone. The Tribune. Published 2018. Available at: http://www.tribtown.com/2018/06/25/us-epa-ozone/. Accessed July 15, 2018.