

Short-Term Elevation of Fine Particulate Matter Air Pollution and Acute Lower Respiratory Infection

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Abstract

Rationale: Nearly 60% of U.S. children live in counties with particulate matter less than or equal to 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) concentrations above air quality standards. Understanding the relationship between ambient air pollution exposure and health outcomes informs actions to reduce exposure and disease risk.

Objectives: To evaluate the association between ambient $\text{PM}_{2.5}$ levels and healthcare encounters for acute lower respiratory infection (ALRI).

Methods: Using an observational case-crossover design, subjects ($n = 146,397$) were studied if they had an ALRI diagnosis and resided on Utah's Wasatch Front. $\text{PM}_{2.5}$ air pollution concentrations were measured using community-based air quality monitors between 1999 and 2016. Odds ratios for ALRI healthcare encounters were calculated after stratification by ages 0–2, 3–17, and 18 or more years.

Measurements and Main Results: Approximately 77% ($n = 112,467$) of subjects were 0–2 years of age. The odds of ALRI encounter for these young children increased within 1 week of elevated $\text{PM}_{2.5}$ and peaked after 3 weeks with a cumulative 28-day odds ratio of 1.15 per $+10 \mu\text{g}/\text{m}^3$ (95% confidence interval, 1.12–1.19). ALRI encounters with diagnosed and laboratory-confirmed respiratory syncytial virus and influenza increased following elevated ambient $\text{PM}_{2.5}$ levels. Similar elevated odds for ALRI were also observed for older children, although the number of events and precision of estimates were much lower.

Conclusions: In this large sample of urban/suburban patients, short-term exposure to elevated $\text{PM}_{2.5}$ air pollution was associated with greater healthcare use for ALRI in young children, older children, and adults. Further exploration is needed of causal interactions between $\text{PM}_{2.5}$ and ALRI.

Keywords: respiratory syncytial virus; influenza virus; bronchiolitis; bronchitis; $\text{PM}_{2.5}$

Acute lower respiratory infections (ALRI), including infections of the lungs and alveoli (pneumonia) and the airways (bronchitis and bronchiolitis), are a leading cause of

morbidity and mortality in children and adults worldwide (1). Viruses responsible for ALRI include respiratory syncytial virus (RSV), influenza, parainfluenza,

adenovirus, and human metapneumovirus. Bronchiolitis is the most common ALRI in children and 50–90% of cases are caused by RSV, with RSV being the most common

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At a Glance Commentary

Scientific Knowledge on the Subject

Subject: Acute lower respiratory infections (ALRI) are a major source of morbidity and mortality often caused by viruses, such as respiratory syncytial virus and influenza virus. ALRI occur more often in the winter months and may be associated with greater exposure to elevated ambient air pollution, including particulate matter less than or equal to 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) and other air pollutants. Evidence linking short-term elevation in $\text{PM}_{2.5}$ with ALRI is weak and contradictory.

What This Study Adds to the Field

Field: Among a very large sample of patients from a single healthcare system, each short-term 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was associated with 15–32% higher odds of an ALRI encounter. Thus, a short-term exposure to elevated $\text{PM}_{2.5}$ air pollution may be associated with greater healthcare use for the diagnosis of ALRI among children and adults. The higher number of healthcare encounters for ALRI followed the elevated $\text{PM}_{2.5}$ exposure by between 1 and 4 weeks, and differed depending on respiratory pathogen and age of subjects.

cause of hospitalization in the first 2 years of life in the United States (2). Bronchiolitis is generally characterized by mild inflammation and congestion in the bronchioles; however, it can occasionally lead to wheezing and breathing problems that require hospitalization. Although RSV infection is also possible among older children and adults (2, 3), in the United States, RSV as a cause of ALRI is far less common in these older age groups where pneumonia and bronchitis predominate. ALRI primarily occur during winter months, suggesting weather may have an effect (4, 5), but also potentially connecting ALRI with short-term increases in ambient particulate matter (PM) air pollution.

Over the last several decades, a growing body of evidence has linked short- and long-term exposures to ambient air pollution with respiratory and cardiovascular diseases

and mortality (6, 7). Short-term elevations in PM less than or equal to 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$; quantity measured in $\mu\text{g}/\text{m}^3$) have been associated with acute pulmonary and cardiovascular events, including asthma and chronic obstructive pulmonary disease exacerbations (8–10), thrombosis (11), triggering of myocardial infarction (12), exacerbation of heart failure (13), and mortality (14). Evidence also exists that long-term exposures to air pollution contributes to the prevalence of respiratory illness in children (15). Long- and short-term $\text{PM}_{2.5}$ exposure may also be associated with hospitalization of newborns and infants within the first year of life for ALRI (16). Effect estimates for lifetime $\text{PM}_{2.5}$ exposure in these young children were greater when analyses were restricted to RSV-caused bronchiolitis (adjusted odds ratio, 1.14 per +10 $\mu\text{g}/\text{m}^3$), but no association was statistically significant (16). Other $\text{PM}_{2.5}$ studies of short-term exposure using 3- to 8-day lags showed no association with ALRI in 0- to 1-year-old infants and 0- to 4-year-old children (17, 18), and studies of short-term exposure to carbon monoxide or nitrogen oxide in infants (age ≤ 1 yr) showed little association with RSV infection (17, 19). A few studies of children ages less than 2 or less than 3 years and of children and adults reported significant associations of short-term exposure to PM less than or equal to 1.0 μm in aerodynamic diameter with ALRI (20–22).

Because of the inconclusive results of those studies, the effects of short-term exposure to air pollution on all ALRI and specifically among the youngest children (ages 0–2 yr) require further investigation. The goal of this study was to evaluate associations of short-term exposure to ambient $\text{PM}_{2.5}$ air pollution with ALRI in a very large population with rich clinical data from an integrated healthcare system in Utah. None of the results in this study were previously reported in abstract form.

Methods

Study Aims

The primary aim of this study was to evaluate the association of short-term increases in $\text{PM}_{2.5}$ air pollution with healthcare encounters for ALRI diagnoses among young patients ages 0–2 years seen at Intermountain Healthcare facilities.

Secondary aims were to examine ALRI outcomes in subgroups defined by older ages (3–17 and ≥ 18 yr), sex, or encounter type (i.e., inpatient, emergency department [ED], outpatient, or ED transferred to another setting), and by specific pathogenic agents (RSV, influenza). This study was approved by an Intermountain Healthcare institutional review board with a waiver of consent.

Study Area and Participants

The study area included the Wasatch Front region of Utah, a relatively narrow landmass (about 80 miles long from north to south and 10–20 miles wide) in north central Utah bordered on the east by the Wasatch Mountain Range and on the west by the Great Salt Lake, Utah Lake, and smaller mountain ranges. The area includes the city of Ogden and surrounding communities to the north, Salt Lake City and surrounding communities in the center, and Provo/Orem and surrounding communities to the south. The Wasatch Front experiences substantial variability in ambient air pollution because of its dense population; the surrounding mountain topography; and, especially in the winter, frequent temperature inversions that result in stagnant atmospheric conditions and elevated concentrations of air pollution. Although there is large variation over time in $\text{PM}_{2.5}$ concentrations, the mean and the median $\text{PM}_{2.5}$ are lower than in other more populated regions, such as Los Angeles, California (17); Seattle, Washington (16); and Atlanta, Georgia (18).

Study subjects were Wasatch Front residents who received care at Intermountain Healthcare hospitals or clinics and were diagnosed with ALRI from 1999 to 2016. Male and female patients of unrestricted age were studied. Subject information included residential zip code, date of encounter, age on that encounter date, sex, and encounter type (inpatient hospitalizations, ED admissions, or outpatient visits). Data were queried from the Intermountain electronic data warehouse. The ED disposition was further stratified to identify patients who were discharged versus transferred to another setting.

Pollution and Weather Data

Daily weather data, including minimum temperature (Fahrenheit), dew point temperature (Fahrenheit), and barometric pressure (inches, adjusted to pressure at sea level), were collected from the U.S. National Weather Service using the Salt Lake City

International Airport Station from January 1, 1999, through December 31, 2016. PM_{2.5} data for the same time period were gathered from the U.S. Environmental Protection Agency Air Quality System Data Mart (23). Monitoring was conducted in accordance with the Environmental Protection Agency federal reference method (24). Specific PM_{2.5} exposure estimates were based primarily on PM_{2.5} data from three monitoring stations along the Wasatch Front where approximately 80% of the Utah population resides: 1) the Ogden site in Ogden, 2) the Hawthorne site in Salt Lake City, and 3) the Lindon site in the Provo/Orem area. PM_{2.5} data were also obtained from five secondary sites on the Wasatch Front: 1) Bountiful, 2) Magna, 3) Salt Lake City-Rose Park, 4) North Provo, and 5) Spanish Fork. Daily PM_{2.5} values from the three primary sites were regressed on nearby secondary sites, producing highly correlated results (R^2 values 0.73–0.94).

Missing PM_{2.5} measurements at the primary sites were imputed using the regression results for PM_{2.5} concentrations from the most highly correlated secondary monitor with available data. Overall, 84% of the measurements were measured at the primary sites, 15% were imputed from secondary sites, and 1% was missing. PM_{2.5} exposure estimates were assigned to event periods and referent periods according to the metropolitan area in which the subject resided.

Study Health Outcomes

Each subject's clinical diagnoses and clinical laboratory test results (if tested) were also obtained from the Intermountain electronic data warehouse, including the primary diagnosis of ALRI (see online supplement for diagnostic codes) or the primary diagnosis of respiratory failure (International Classification of Diseases 9th edition [ICD-9] 518.81 or 10th edition [ICD-10] J96.00) that also had a secondary diagnosis listed for ALRI. Infections with RSV and influenza were clinically diagnosed and data were defined based on ICD-9 and ICD-10 codes. Laboratory testing for RSV, influenza, parainfluenza, and human metapneumovirus was performed using the rapid RSV test, various influenza assays, the Respiratory FilmArray by PCR, or a viral respiratory panel by direct fluorescent antibody. All-cause mortality was also examined, descriptively, for the three age-based cohorts, with mortality information obtained from

hospital records, Utah death certificates, and the Social Security death master file.

Statistical Analysis

Data analysis used a time-stratified case-crossover design (25, 26). In this approach, the day of a healthcare encounter (the event day) was matched with several control or referent days. For each event day, referent days are the 3 or 4 other days in the same month and year that share the same day of the week. Odds ratios and 95% confidence intervals were estimated by conditional logistic regression, matching the event day with the referent days using SAS (SAS Institute Inc.). Choosing matching referent days close in time and on the same day of the week allows for the control of time-dependent

risk factors (including day of the week, seasonality, and long-term time trends) by design. In addition, near-perfect close-in-time matching for subject-specific characteristics (i.e., age, health history, smoking status) by using subjects as their own controls, results in control of these characteristics by design. The time-stratified approach to referent-day selection was used in this analysis because it has been shown to provide unbiased conditional logistic regression estimates even when there may be time trends in exposures (26).

Because the incubation period of RSV and other viral infections may be as long as a week or more (27–29), mean values for PM_{2.5} exposure, barometric pressure, minimum temperature, and dew point

Table 1. Baseline Characteristics of Subjects from Intermountain Healthcare on Utah's Wasatch Front

Variable	Ages 0–2 yr	Ages 3–17 yr	Ages ≥18 yr
Events	112,567 (77)	17,828 (12)	16,002 (11)
Sex			
Male	65,424 (58.12)	9,702 (54.42)	6,970 (43.56)
Female	47,143 (41.88)	8,126 (45.58)	9,032 (56.44)
Age, yr	0.45 (0–2)	6.36 (3–17)	43.42 (18–100)
Healthcare encounter type			
Outpatient	57,499 (51.08)	6,452 (36.19)	5,823 (36.39)
Inpatient	22,941 (20.38)	2,631 (14.76)	2,567 (16.04)
Emergency	32,127 (28.54)	8,745 (49.05)	7,612 (47.57)
Admit from ED*	16,097 (14.30)	2,013 (11.29)	2,167 (13.54)
Clinical discharge diagnosis			
ALRI	112,139 (99.62)	17,757 (99.60)	15,780 (98.61)
Respiratory failure	428 (0.38)	71 (0.40)	222 (1.39)
Etiologic infectious diseases			
RSV diagnosed [†]	35,774 (31.78)	2,236 (12.54)	274 (1.71)
RSV tested [‡]	22,243 (19.76)	2,605 (14.61)	2,264 (14.15)
RSV positive [§]	11,797 (10.48)	779 (4.37)	189 (1.18)
Influenza diagnosed	8,116 (7.21)	8,561 (48.02)	12,603 (78.76)
Influenza tested [¶]	16,772 (14.90)	3,731 (20.93)	5,522 (34.51)
Influenza positive ^{**}	2,150 (1.91)	1,899 (10.65)	3,901 (24.38)
Metapneumovirus tested ^{††}	11,279 (10.02)	1,915 (10.74)	1,987 (12.42)
Metapneumovirus positive ^{‡‡}	946 (0.84)	168 (0.94)	171 (1.07)
Parainfluenza tested ^{§§}	15,084 (13.40)	2,384 (13.37)	2,015 (12.59)
Parainfluenza positive ^{¶¶}	867 (0.77)	130 (0.73)	114 (0.71)

Definition of abbreviations: ALRI = acute lower respiratory infections; ED = emergency department; RSV = respiratory syncytial virus.

Data are *n* (%) or mean (range).

*Subjects admitted to hospital inpatient or observation from the ED were a subset of the other encounter types.

[†]Clinical diagnosis of RSV.

[‡]Laboratory tested for RSV.

[§]Positive for RSV by laboratory testing.

^{||}Clinical diagnosis of influenza.

[¶]Laboratory tested for the influenza virus.

^{**}Positive for influenza virus by laboratory testing.

^{††}Laboratory tested for human metapneumovirus.

^{‡‡}Positive for human metapneumovirus by laboratory testing.

^{§§}Laboratory tested for the parainfluenza virus.

^{¶¶}Positive for the parainfluenza virus by laboratory testing.

temperature were calculated for each of the 4 weeks before the day of the event or referent days (0–6 days prior, 7–13 days prior, 14–20 days prior, and 21–27 days prior). Squared terms for each of these lagged weather variables were also calculated. Means were calculated using all nonmissing values, and a 28-day mean (the event or referent day with the preceding 27 d) was also constructed for PM_{2.5}.

The baseline model was a conditional logistic regression model that included the 7-day means for PM_{2.5} (using both data from the central sites and imputed data) and the weather controls (minimum temperature, dew point temperature, barometric pressure, and squared terms for each) for each of the previous 4 weeks—with all 4 weeks included in the model together. Odds ratios associated with 10 µg/m³ incremental increases in PM_{2.5} concentration were estimated. A model using the same weather controls but with a single 28-day lagged mean PM_{2.5} exposure variable was also estimated.

To explore the sensitivity of the results, odds ratios were estimated and compared from models that included and excluded weather variables and excluded the use of imputed PM_{2.5} data. Analyses were conducted, stratifying by age (0–2, 3–17, and ≥18 yr), sex, healthcare encounter type, RSV or influenza diagnosis, and test results. Stratifications by parainfluenza, human metapneumovirus, and adenovirus were not performed because of the limited numbers of cases of these individual pathogens. The primary hypothesis among

subjects ages 0–2 years was tested at P less than or equal to 0.05, whereas secondary hypotheses and subgroup analyses were evaluated at P less than or equal to 0.05 with the understanding that these are exploratory and require further validation in additional populations.

Results

Daily measurements of PM_{2.5} concentrations at the three primary Wasatch Front air pollution monitoring stations are summarized in Table E1 in the online supplement. Median daily concentration was 7 µg/m³, with a mean daily value of 10 ± 10 µg/m³. Table 1 provides the baseline characteristics of the subjects with ALRI ($n = 146,397$) who were evaluated in this study, of whom $n = 112,567$ (76.9%) were 0–2 years of age. Overall, 12.0% of subjects ($n = 17,558$) were ages 3–17 years, whereas 11.1% ($n = 16,272$) were adults (aged ≥18 yr). ALRI was the discharge diagnosis for 99.51% of subjects, whereas 0.49% had respiratory failure with ALRI as a secondary diagnosis. Table 2 provides the distribution of subjects by age group and ICD-9/10 code for the eight diagnostic codes used among more than 1% of all study subjects. Overall, 64.0% of subjects received a bronchiolitis diagnosis, including 76.5% of subjects ages 0–2 years (1.4% of subjects ages 0–2 yr had infrequent codes not listed on Table 2) compared with 32.4% of ages 3–17 years and 11.7% of ages greater than or equal to 18 years.

Other RSV codes were found in 12.1% of ages 0–2 years. Table E2 provides the sensitivity and specificity of RSV and influenza laboratory tests in relation to the actual diagnoses assigned. Figure E1 demonstrates the timing of air pollution elevations and how short-term these tend to be and provides a few examples of event versus referent days.

Figure 1 provides the adjusted odds ratios with 95% confidence intervals for the association of a 10 µg/m³ increase in PM_{2.5} with ALRI. For young children ages 0–2 years, the baseline model shows a peak in association for the third week after the pollution elevation, although the association was statistically significant in the first week and throughout each of the 4 weeks of the study. Higher PM_{2.5} exposures were also associated with elevated ALRI encounters in older children; however, the lag structure was much flatter for older children. Figure 1 also illustrates sensitivity analysis results for associations of PM_{2.5} with ALRI when weather variables and imputed pollution data were excluded, indicating that the results are not highly sensitive to control for weather variables or the inclusion (or exclusion) of imputed PM_{2.5} data. Table 3 provides the actual odds ratios and confidence intervals by age group, and it further includes the results of analyses using a lag structure of the combined 4 weeks.

Secondary analyses examined the association of PM_{2.5} with RSV and influenza infection-related encounters, or the lack of these diagnoses (Figure 2), for all

Table 2. Distribution of Study Subjects by Age Category for ICD-9 and ICD-10 Codes Used among >1% of the Study Population

	Description of ICD-9/10 Code	Ages 0–2 yr	Ages 3–17 yr	Ages ≥18 yr
Number of events, n (% of total)				
ICD-9 code, n (% of age category)				
079.6	Respiratory syncytial virus	112,567 (77)	17,558 (12)	16,272 (11)
466.11	Acute bronchiolitis caused by respiratory syncytial virus	13,310 (11.8)	1,021 (5.8)	110 (0.7)
466.19	Acute bronchiolitis caused by other infectious organisms	20,131 (17.9)	670 (3.8)	30 (0.2)
480.1	Pneumonia caused by respiratory syncytial virus	59,741 (53.1)	4,736 (27.0)	1,757 (10.8)
480.9	Viral pneumonia, unspecified	1,330 (1.2)	449 (2.6)	110 (0.7)
487.0	Influenza with pneumonia	2,156 (1.9)	1,269 (7.2)	446 (2.7)
487.1	Influenza with other respiratory manifestations/acute bronchitis	321 (0.3)	282 (1.6)	911 (5.6)
ICD-10 code, n (% of age category)				
J21.9	Acute bronchiolitis, unspecified	8,052 (7.2)	7,986 (45.5)	11,308 (69.5)
Sum, n (% of age category)	—	4,642 (4.1)	145 (0.8)	42 (0.3)
		109,683 (97.4)	16,558 (94.3)	14,714 (90.4)

Definition of abbreviation: ICD = International Classification of Diseases.

Subjects with diagnosis codes not represented here were assigned other less frequently used ICD-9/10 codes (see METHODS).

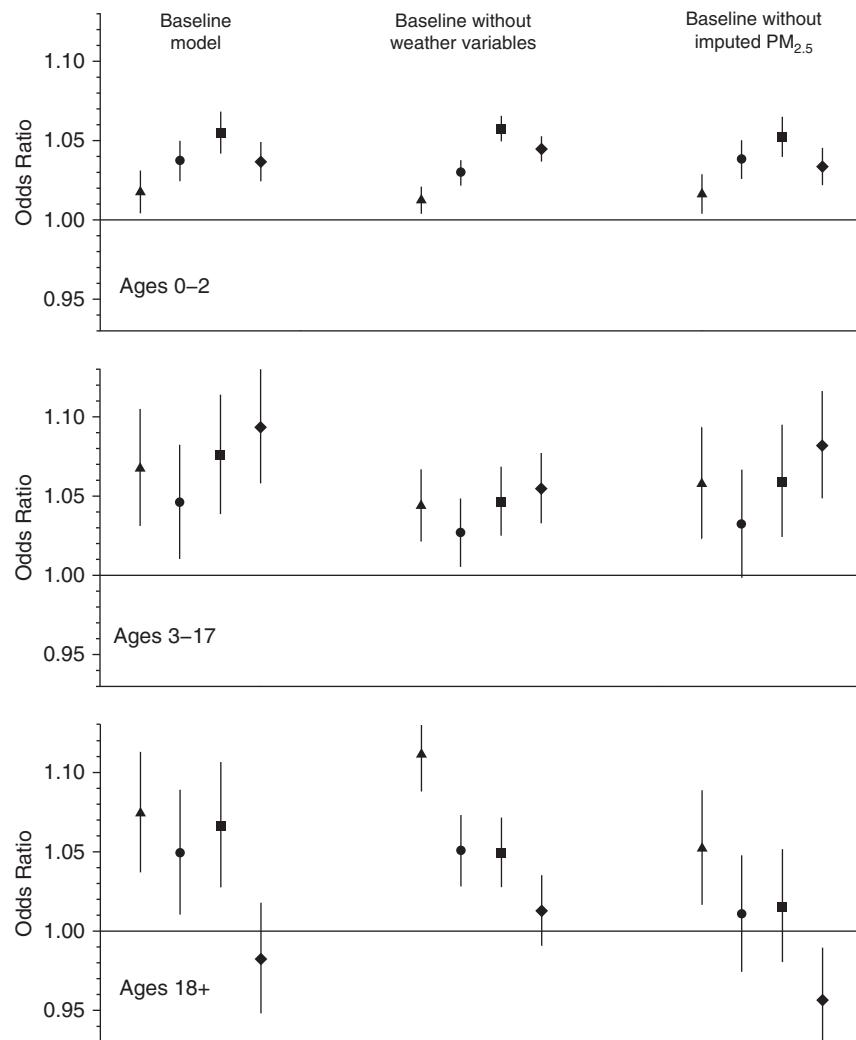


Figure 1. Odds ratios (and 95% confidence intervals) for the association of a $10 \mu\text{g}/\text{m}^3$ increase in particulate matter less than or equal to $2.5 \mu\text{m}$ in aerodynamic diameter ($\text{PM}_{2.5}$) exposure with acute lower respiratory infections for ages 0–2, 3–17, and 18 or more years. Triangles, circles, squares, and diamonds represent odds ratios for mean $\text{PM}_{2.5}$ concentrations 0–6, 7–13, 14–20, and 21–27 days before the day of event, respectively. The baseline model included all four lagged mean exposure periods in the model together and included all weather variables.

age groups. Because RSV and influenza had both clinical diagnosis and laboratory-based test results as indicators of their presence, two analyses were performed for

each of these pathogens. $\text{PM}_{2.5}$ -associated odds of RSV-related encounters in young children (ages 0–2 yr) peaked at a lag of 3 weeks for RSV diagnosis with a lag of

2 weeks almost as high, but the odds were slightly higher for the 2-week lag among those with laboratory-positive RSV tests. For a diagnosis of influenza, $\text{PM}_{2.5}$ was associated with elevated odds of healthcare use but the lag structure was not as well defined. $\text{PM}_{2.5}$ was also associated with elevated odds of ALRI encounters in older children, although the number of encounters and precision of estimates were much lower. Reassuringly, only limited differences across seasons existed in the diagnoses made and the laboratory testing ordered for each infection (data not shown). Further substratified results were based on sex and encounter type (see Figure E2). There were no substantive sex differences in the $\text{PM}_{2.5}$ -associated odds. There were not large differences in the $\text{PM}_{2.5}$ -associated odds across inpatient, ED, and admit from ED encounter types, but for older children and adults the $\text{PM}_{2.5}$ -associated odds were not significant for outpatient encounters. Importantly, analysis of mortality found that 17 subjects (0.015%) ages 0–2 years, nine subjects (0.051%) ages 3–17 years, and 81 subjects (0.498%) ages greater than or equal to 18 years experienced all-cause mortality within 30 days of their ALRI event.

Discussion

Summary of Findings

Short-term increases in $\text{PM}_{2.5}$ air pollution were associated with elevated odds of receiving medical care for ALRI in a large patient population, with a 15–32% increase in the odds over the course of 1 month for each additional $10 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ concentration. This effect was found among very young children where 76.5% of subjects were diagnosed with bronchiolitis, but also existed for all ALRI among older children and adults. The odds of ALRI

Table 3. Adjusted Odds Ratios (and 95% Confidence Intervals) from the Baseline Model for the Association of a $10 \mu\text{g}/\text{m}^3$ Increase in $\text{PM}_{2.5}$ Exposure with Acute Lower Respiratory Infection

Cohort	Days* 0–6	Days 7–13	Days 14–20	Days 21–27	Days 0–27
Ages 0–2 yr	1.02 (1.00–1.03)	1.04 (1.02–1.05)	1.06 (1.04–1.07)	1.04 (1.02–1.05)	1.15 (1.11–1.19)
Ages 3–17 yr	1.07 (1.03–1.10)	1.05 (1.01–1.08)	1.08 (1.04–1.11)	1.09 (1.06–1.13)	1.32 (1.20–1.44)
Ages ≥ 18 yr	1.07 (1.04–1.11)	1.05 (1.01–1.09)	1.07 (1.03–1.11)	0.98 (0.95–1.02)	1.19 (1.09–1.31)

Definition of abbreviation: $\text{PM}_{2.5}$ = particulate matter less than or equal to $2.5 \mu\text{m}$ in aerodynamic diameter.

These analyses include all events in the specified age group, and the models control for weather.

*Effect estimates used mean pollution values from the specified days before the event with all four lagged means included in the model together. A 28-day mean exposure (Days 0–27) was analyzed in a separate model that included only 28-day mean exposure.

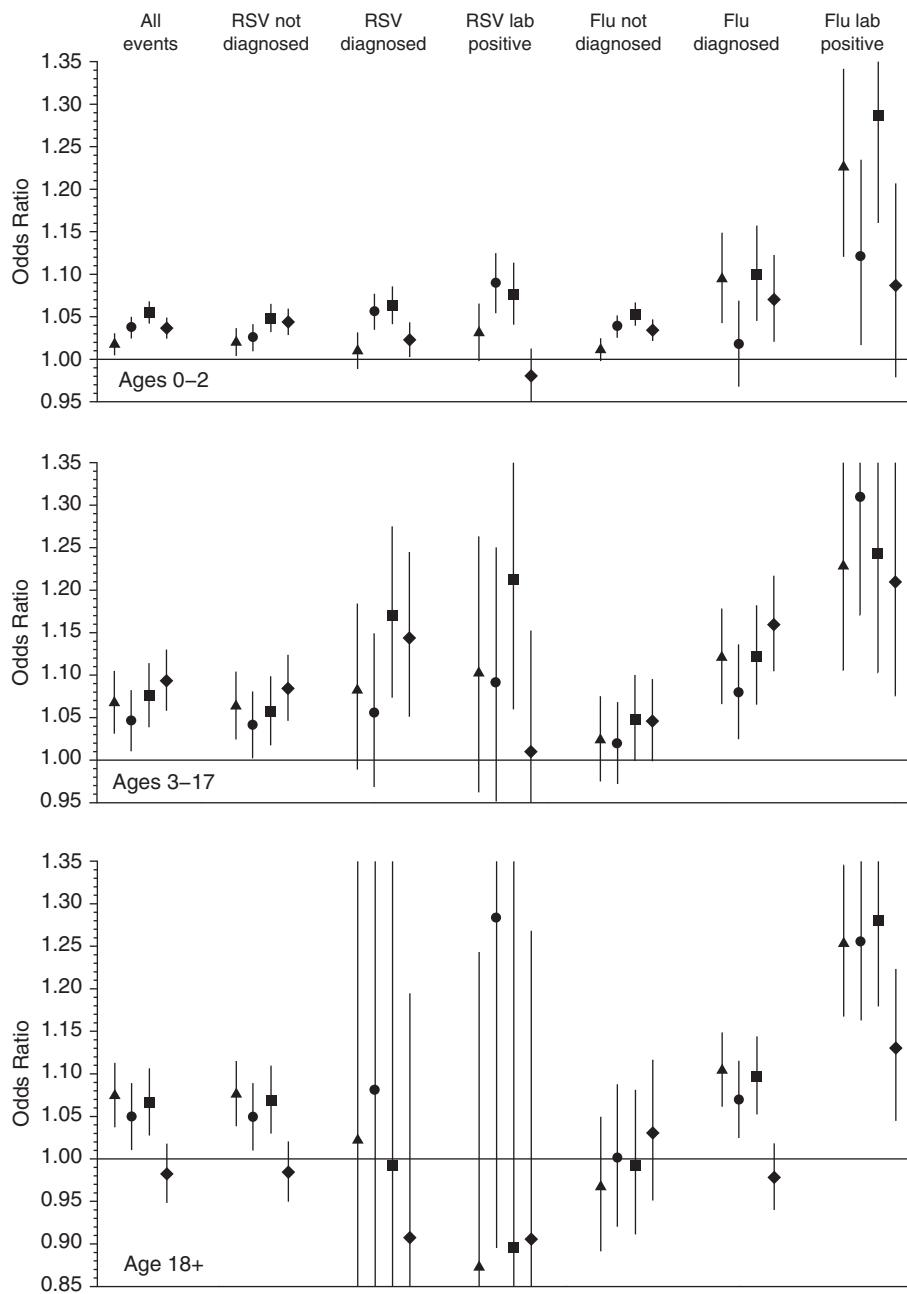


Figure 2. Odds ratios (and 95% confidence intervals with some extending beyond the scale of the figure) for the association of a $10 \mu\text{g}/\text{m}^3$ increase in particulate matter less than or equal to $2.5 \mu\text{m}$ in aerodynamic diameter exposure with infection categories, stratifying by respiratory syncytial virus and influenza diagnosis for the baseline model. Triangles, circles, squares, and diamonds represent odds ratios for mean particulate matter less than or equal to $2.5 \mu\text{m}$ in aerodynamic diameter concentrations 0–6, 7–13, 14–20, and 21–27 days before the day of event, respectively. The model included all four lagged mean exposure periods in the model together and included all weather variables. RSV = respiratory syncytial virus.

peaked about 3 weeks after the elevation in ambient air pollution occurred but was statistically significantly elevated within a lag time of as little as 1 week afterward. Odds of RSV diagnosis were higher following a PM_{2.5} increase, especially

among the very young, beginning after a lag of 2 weeks and peaking at 3 weeks. Odds of influenza diagnosis were also greater following a PM_{2.5} increase, especially among older children and adults, and the odds tended to peak earlier.

Previous Evidence

Prior reports regarding PM_{2.5} exposure and associations with ALRI or RSV infection have provided a mixed message, with hints at potential associations, but no statistically significant results (16–18). In part, the lack of association may be attributable to the lag structure and sample sizes in those studies (e.g., only $n = 2,604$ ALRI cases in one study) (16). Furthermore, outcomes were only evaluated for a lag of up to 8 days after exposure to elevated air pollution (17, 18); given that the average RSV incubation period is about 5 days (27, 29), it may be that many of the infections occurred before the time of elevated pollution.

Context of the Present Findings

The current study provides improved estimates of the risks of acute ALRI and related infections associated with short-term PM_{2.5} exposure through the use of high-quality data from an integrated healthcare system that serves approximately two-thirds of the population in a tightly defined geographic region and where a wide range of PM_{2.5} concentrations provide a natural experiment of the effects of short-term changes in PM_{2.5}. Previous studies in this study area have observed that PM air pollution was associated with acute respiratory illness (30, 31).

In the present study, the large sample size ($>100,000$ cases) combined with clinical phenotyping and a 4-week evaluation phase allowed the discernment of outcome patterns not previously seen and provided sufficient sample size to detect statistical significance. These data confirm the various trends that previous studies had provided regarding the association of PM_{2.5} with ALRI. They also clarify the results of studies that may not have followed patients long enough after the pollution exposure to find an effect (e.g., the association with RSV was not significant herein during the first 7 d, but was for the second, third, and fourth weeks).

These findings, coupled with prior results (17), may indicate that PM_{2.5} exposure contributes in part to susceptibility to RSV and influenza, to exposure to these pathogens, to infection *per se*, and to severity of infection (Figure 3). This epidemiologic study does

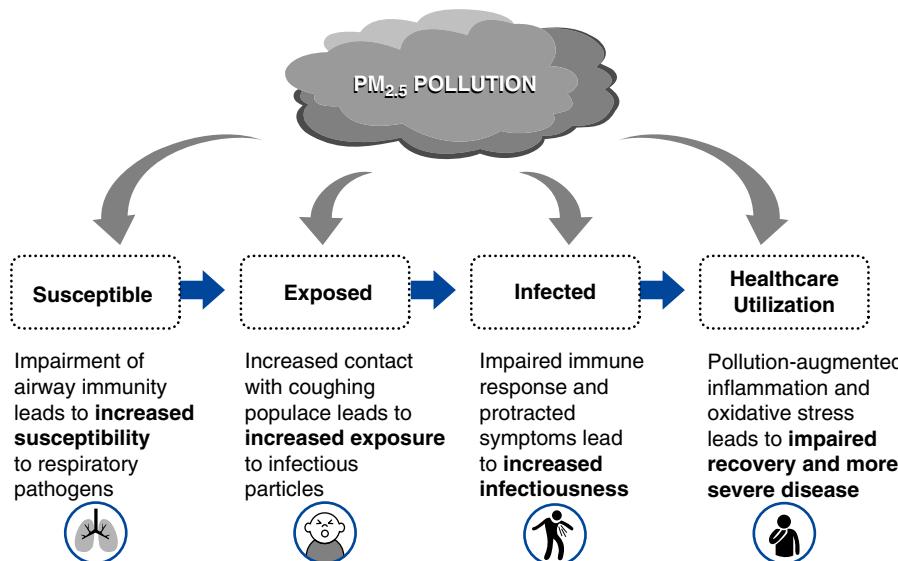


Figure 3. Putative mechanisms of particulate matter less than or equal to $2.5 \mu\text{m}$ in aerodynamic diameter pollution on acute lower respiratory infections risk in a population simultaneously experiencing exposure to pollution and respiratory pathogen activity. $\text{PM}_{2.5}$ = particulate matter less than or equal to $2.5 \mu\text{m}$ in aerodynamic diameter.

not reveal the mechanisms related to air pollution that may be active in these processes, although further investigations are needed. More than the 5-day RSV incubation period had passed before RSV-related effects became significant herein, thus the susceptibility to infection may be enhanced by $\text{PM}_{2.5}$ exposure and biologic mechanisms, such as suppression of the immune response, may be involved (32). Air pollution and winter weather conditions may contribute to the likelihood of infectious exposure, in part by driving people indoors or otherwise into closer proximity. This study suggests that $\text{PM}_{2.5}$ levels may affect severity of ALRI. For example, the effects of $\text{PM}_{2.5}$ were not only statistically significant for outpatient, emergency, and inpatient settings, but the associated risk was greater for subjects seen in an emergency setting than for outpatient visits and was especially high for those with inpatient hospital admission. Further exploration of potential mechanisms of the effect of $\text{PM}_{2.5}$ on ALRI is provided in the online supplement DISCUSSION section.

As expected, RSV infection and bronchiolitis were primarily problems for the very young ages 0–2 years. Bronchiolitis deserves special attention given the disproportionate magnitude of the effect on healthcare use, where 77% of subjects in

this study belonged to that very young age group. However, the findings that elevated $\text{PM}_{2.5}$ concentrations were associated with more diagnosed and laboratory-confirmed influenza, even in older children and adults, may also be important given that previous studies of adults have observed higher risk of mortality caused by influenza/pneumonia associated with long-term exposures to $\text{PM}_{2.5}$ (33, 34). These findings further suggest that $\text{PM}_{2.5}$ exposures contribute to susceptibility and/or severity of infection.

Study Limitations

This study may be limited by its observational design, including that a potential exists for uncontrolled confounding to remain in the statistical models because of unmeasured covariates. This may include confounding caused by individual behaviors that were unmeasured and which behaviors may have been modified by changes in pollution or the weather, or by comorbidities that may have influenced the health of adults more than young children who typically have not developed comorbidities. Furthermore, the community-level measurement of the $\text{PM}_{2.5}$ levels at centralized sampling stations may have resulted in inaccurate assignment of subject exposures that would be corrected by expensive but more

accurate individual-level measurement of $\text{PM}_{2.5}$ concentrations. Notably, weather variables were measured and controlled for in the study analyses, and the case-crossover design explicitly controlled for subject-specific factors that do not appreciably vary over the short term. Also, Intermountain Healthcare provides healthcare services to about two-thirds of the residents of Utah and operates the only children's hospital in a multistate region, thus these results should represent the outcomes of the general population and be generalizable to other populations. It may be that diagnostic coding errors existed in records used by this study, but through the quality controls on clinical documentation and coding at Intermountain such errors were found to be minimal in previous manual data checking (35). Events observed in this study were healthcare encounters and not infections *per se*, thus individuals in the population who were exposed to $\text{PM}_{2.5}$ and infected but who did not seek healthcare services were not included in study analyses. Finally, no information about the onset of symptoms is available from before the start of each subject's healthcare encounter, thus varying times from infection to the time that medical care was sought and differences in severity of symptoms at the time of entry were likely between study subjects. This includes that some of those differences may be systematic because of physiologic and psychosocial differences between age groups and may have played a part in the different age-dependent patterns of association of $\text{PM}_{2.5}$ with ALRI observed at each lag time.

Conclusions

Associations of $\text{PM}_{2.5}$ air pollution levels with ALRI were found in a large patient population over a period of days and weeks after short-term $\text{PM}_{2.5}$ elevations. Not surprisingly, a disproportionate concentration of the ALRI cases was found among the very young (ages of 0–2 yr); bronchiolitis was the diagnosis in 76.5% of these, and RSV was the primary etiologic agent. Among older individuals, the ALRI were primarily caused by influenza. Additional research regarding the causal connections of ambient air pollution and ALRI is needed, as well as the consideration

of RSV immunization for the public health. Community and health system approaches, such as predicting hospital staffing needs, coordinating timely medical supplies delivery, and community alerting

to expected times of higher infectious susceptibility, may be possible and useful for ameliorating the effect of higher ambient PM_{2.5} levels on adverse health outcomes, improving health

and healthcare quality, and reducing costs (36). ■

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