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

Benjamin D. Horne, PhD, MStat, MPH[1,2]; Elizabeth A. Joy, MD, MPH[3,4]; Michelle G. Hofmann, MD, MPH[5,6]; Per H. Gesteland, MD, MS[2,5,6]; John B. Cannon, BS[7]; Jacob S. Lefler[7]; Denitza P. Blagev, MD[8]; E. Kent Korgenski, MS, MT[5]; Natalie Torosyan, BS[9]; Grant I. Hansen, MS[10]; David Kartchner, BS[9,11]; C. Arden Pope III, PhD[7]

[1]Intermountain Medical Center Heart Institute, Salt Lake City, UT; [2]Department of Biomedical Informatics, University of Utah, Salt Lake City, UT; [3]Community Health & Food and Nutrition, Intermountain Healthcare, Salt Lake City, UT; [4]Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT; [5]Primary Children's Hospital, Salt Lake City, UT; [6]Department of Pediatrics, University of Utah, Salt Lake City, UT; [7]Department of Economics, Brigham Young University, Provo, UT; [8]Pulmonary and Critical Care Medicine Division, Department of Internal Medicine, Intermountain Healthcare, Salt Lake City, UT; [9]Population Health, Intermountain Healthcare, Salt Lake City, UT; [10]Business Intelligence, Intermountain Healthcare, Salt Lake City, UT; [11]Department of Mathematics, Brigham Young University, Provo, UT.

Author Contributions: BDH had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. Study concept and design: BDH, EAJ, MGH, PHG, and CAP. Acquisition, analysis, or interpretation of data: BDH, EAJ, MGH, PHG, JBC, JSL, DPB, KK, NT, GIH, DK, and CAP. Drafting of the manuscript: BDH, EAJ, JBC, JSL, and CAP. Critical revision of the manuscript for important

intellectual content: all authors. Statistical analysis: BDH, JBC, JSL, and CAP. Study Supervision: BDH, EAJ, and CAP.

Corresponding Author

Benjamin D. Horne

Intermountain Heart Institute

5121 S. Cottonwood St.

Salt Lake City, UT 84107

Tel: 801-507-4708; Fax: 801-507-4792

e-mail: benjamin.horne@imail.org

Running Title: Air Pollution as Predecessor of ALRI Encounters

Funding: No external funding was utilized.

Subject Codes: 6.01, 10.11

Word Count: 236 words in abstract, 3462 words of text

Scientific Knowledge on the 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 fine particulate matter ($PM_{2.5}$) and other air pollutants. Evidence linking short-term elevation in $PM_{2.5}$ with ALRI is weak and contradictory.

What This Study Adds to the Field: Among a very large sample of patients from a single healthcare system, each short-term 10 μg/m^3 increase in $PM_{2.5}$ was associated with 15%-23% higher odds of an ALRI encounter. Thus, a short-term exposure to elevated $PM_{2.5}$ air pollution may be associated with greater healthcare utilization for the diagnosis of ALRI among both children and adults. The higher number of healthcare encounters for ALRI followed the elevated $PM_{2.5}$ exposure by between 1 to 4 weeks, and differed depending on respiratory pathogen and age of subjects.

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

Abstract

Rationale: Nearly 60% of U.S. children live in counties with $PM_{2.5}$ 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 $PM_{2.5}$ 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. $PM_{2.5}$ air pollution concentrations were measured using community-based air quality monitors between 1999 and 2016. Odds ratios (OR) for ALRI healthcare encounters were calculated after stratification by ages 0-2, 3-17, and 18+ 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 $PM_{2.5}$ and peaked after 3 weeks with a cumulative 28-day OR= 1.15 per +10 $\mu g/m^3$ (95% CI= 1.12, 1.19). ALRI encounters with diagnosed and laboratory-confirmed RSV and influenza increased following elevated ambient $PM_{2.5}$ 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 $PM_{2.5}$ air pollution was associated with greater healthcare utilization for ALRI in both young children, older children, and adults. Further exploration is needed of causal interactions between $PM_{2.5}$ and ALRI.

Keywords: Respiratory Syncytial Virus, RSV, Influenza Virus, Bronchiolitis, Bronchitis, Pneumonia, $PM_{2.5}$

Introduction

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 cause of hospitalization in the first two years of life in the US.(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. While RSV infection is also possible among older children and adults,(2,3) in the US, 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-term and long-term exposures to ambient air pollution with respiratory and cardiovascular diseases and mortality.(6,7) Short-term elevations in fine PM air pollution of particle diameter ≤2.5 μm ($PM_{2.5}$, quantity measured in $\mu g/m^3$) 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-term and short-term $PM_{2.5}$ exposure may also be associated with hospitalization of newborns and infants

within the first year of life for ALRI.(16) Effect estimates for lifetime $PM_{2.5}$ exposure in these young children were greater when analyses were restricted to RSV-caused bronchiolitis (adjusted odds ratio [OR]=1.14 per +10 $\mu g/m^3$), but no association was statistically significant.(16) Other $PM_{2.5}$ studies of short-term exposure using 3-8 day lags showed no association with ALRI in 0-1 year old infants and 0-4 year old children,(17,18) and studies of short-term exposure to carbon monoxide (CO) or nitrogen oxide (NO) in infants (age ≤1 year) showed little association with RSV infection.(17,19) A few studies of children ages <2 or <3 years and of children and adults reported significant associations of short-term exposure to particulate matter diameter ≤10 μm (PM_{10}) with ALRI.(20-22)

Due to 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 years) require further investigation. The goal of this study was to evaluate associations of short-term exposure to ambient $PM_{2.5}$ 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 fine particulate matter ($PM_{2.5}$) 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 years), 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 due to 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 $PM_{2.5}$ concentrations, the mean and the median $PM_{2.5}$ are lower than in other more populated regions such as Los Angeles, CA,(17) Seattle, WA,(16) and Atlanta, GA.(18)

Study subjects were Wasatch Front residents who received care at Intermountain Healthcare hospitals or clinics and were diagnosed with ALRI from 1999-2016. 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 sub-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 US 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 US 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: the Ogden site in Ogden, the Hawthorne site in Salt Lake City, and the Lindon site in the Provo/Orem area. $PM_{2.5}$ data were also obtained from five secondary sites on the Wasatch Front: Bountiful, Magna, Salt Lake City-Rose Park, North Provo, and 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 data supplement for diagnostic codes) or the primary diagnosis of respiratory failure (ICD-9 518.81 or 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 three or four other days in the same month and year that share the same day of the week. ORs and 95% confidence intervals (CI) were estimated by conditional logistic regression, matching the event day with the referent days using SAS (SAS Institute Inc., Cary, NC). 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, etc.) 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 temperature were calculated for each of the 4 weeks prior to 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 non-missing values, and a 28-day mean (the event or referent day with the preceding 27 days) 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 four weeks—with all four weeks included in the model together. Odds ratios associated with 10 $\mu g/m^3$ 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+ years), sex, healthcare encounter type, RSV or influenza diagnosis, and test results. Stratifications by parainfluenza, human metapneumovirus, and adenovirus were not performed due to the limited numbers of cases of these individual pathogens. The primary hypothesis among subjects ages 0-2 years was tested at $p \leq 0.05$, while secondary hypotheses and subgroup analyses were evaluated at $p \leq 0.05$ 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. Median daily concentration was 7 $\mu g/m^3$, with a mean daily value of 10 ± 10 $\mu g/m^3$. 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, while 11.1% (n=16,272) were adults (aged ≥18 years). ALRI was the discharge diagnosis for 99.51% of subjects, while 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 utilized among >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 years had infrequent codes not listed on Table 2) compared to 32.4% of ages 3-17 years and 11.7% of ages ≥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 vs. 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 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. $PM_{2.5}$-associated odds of RSV-related encounters in young children (ages 0-2 years) 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, $PM_{2.5}$ was associated with elevated odds of healthcare utilization but the lag structure was not as well defined. $PM_{2.5}$ 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 sub-stratified results were based on sex and encounter type (Figure E2). There were no substantive sex differences in the $PM_{2.5}$-associated odds. There were not large differences in the $PM_{2.5}$-associated odds across inpatient, ED, and admit from ED encounter types, but for older children and adults the PM2.5-associated odds were not significant for outpatient encounters. Importantly, analysis of mortality found that 17 subjects (0.015%) ages 0-2 years, 9 subjects (0.051%) ages 3-17 years, and 81 subjects (0.498%) ages ≥18 years experienced all-cause mortality within 30 days of their ALRI event.

Discussion

Summary of Findings. Short-term increases in $PM_{2.5}$ air pollution were associated with elevated odds of receiving medical care for ALRI in a large patient population, with a 15%-23% increase in the odds over the course of one month for each additional 10 $\mu g/m^3$ of $PM_{2.5}$

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 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 afterwards. 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 prior to 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 particulate matter 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 days, 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 not reveal the mechanisms related to air pollution that may be active in these processes, though, thus 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 $PM_{2.5}$ exposure and biological 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 $PM_{2.5}$ levels may affect severity of ALRI. For example, the effects of $PM_{2.5}$ 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 $PM_{2.5}$ on ALRI is provided in the online data 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 utilization, where 77% of subjects in this study belonged to that very young age group. However, the findings that elevated $PM_{2.5}$ 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 due to influenza/pneumonia associated with long-term exposures to $PM_{2.5}$.(33,34) These findings further suggest that $PM_{2.5}$ exposures contribute to susceptibility and/or severity of infection.

Limitations. This study may be limited by its observational design, including that a potential exists for uncontrolled confounding to remain in the statistical models due to unmeasured covariables. This may include confounding due to individual behaviors that were unmeasured and which behaviors may have been modified by changes in pollution or the weather, or due to comorbidities that may have influenced the health of adults more than young children who typically have not developed comorbidities. Further, the community-level measurement of the $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 prior to 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 due to physiologic and psychosocial differences between age groups and may have played a part in the different age-dependent patterns of association of $PM_{2.5}$ with ALRI observed at each lag time.

Conclusions. Associations of ambient fine particulate matter ($PM_{2.5}$) air pollution levels with ALRI were found in a large patient population over a period of days and weeks after short-term $PM_{2.5}$ elevations. Not surprisingly, a disproportionate concentration of the ALRI cases was found among the very young (ages of 0-2 years); bronchiolitis was the diagnosis in 76.5% of these, and RSV was the primary etiologic agent. Among older individuals, the ALRI were primarily due to 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)

Acknowledgments

None.

References

1. Michaud CM, Murray CJL, Bloom BR. Burden of disease—implications for future research. *JAMA* 2001;285:535-539.
2. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med* 2001;344:1917-1928.
3. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005;352:1749-1759.
4. Passos SD, Gazeta RE, Felgueiras AP, Beneli PC, Chelho MDSZS. Do pollution and climate influence respiratory tract infections in children? *Rev Assoc Med Bras* 2014;60:276-283.
5. Leecaster M, Gesteland P, Greene T, Walton N, Gundlapalli A, Rolfs R, Byington C, Samore M. Modeling the variations in pediatric respiratory syncytial virus seasonal epidemics. *BMC Infect Dis* 2011;11:105.
6. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 1995;151:669-674.
7. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities Study. *Am J Respir Crit Care Med* 2006;173:667-672.
8. Lindgren A, Stroh E, Montnemery P, Nihlen U, Jakobsson K, Axmon A. Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden. *Int J Health Geogr* 2009;8:25.

9. Song Q, Christiani DC, XiaorongWang, Ren J. The global contribution of outdoor air pollution to the incidence, prevalence, mortality and hospital admission for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2014;11:11822-11832.
10. Berhane K, Change CC, McConnell R, Gauderman J, Avol E, Rapapport E, Urman R, Lurmann F, Gilliland F. Association of changes in air quality with bronchitic symptoms in children in California, 1993-2012. *JAMA* 2016;315:1491-1501.
11. Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, Ohman-Strickland P, Hu M, Philipp C, Diehl SR, Lu SE, Tong J, Gong J, Thomas D, Zhu T, Zhang J. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. *JAMA* 2012;307:2068-2078.
12. Pope CA III, Muhlestein JB, Anderson JL, Cannon JB, Hales NM, Meredith KG, Le V, Horne BD. Short-term exposure to fine particulate matter air pollution is preferentially associated with the risk of ST-segment elevation acute coronary events. *J Am Heart Assoc* 2015;4:e002506.
13. Pope CA III, Renlund DG, Kfoury AG, May HT, Horne BD. Relation of heart failure hospitalization to exposure to fine particulate air pollution. *Am J Cardiol* 2008;102:1230-1234.
14. Pope CA III, Burnett R, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132-1141.

15. Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H, Thomas DC. *Am J Respir Crit Care Med* 1999;159:760-767.

16. Karr CJ, Rudra CB, Miller KA, Gould TR, Larson T, Sathyanarayana S, Koenig JQ. Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. *Environ Res* 2009;109:321-327.

17. Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, Kaufman J. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. *Environ Health Perspect* 2006;114:277-281.

18. Darrow LA, Klein M, Flanders WD, Mulholland JA, Tolbert PE, Strickland MJ. 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.

19. Mohammed NI, Everard ML, Ayres JG, Barker NJ, Litchfield IJ. A preliminary assessment of the role of ambient nitric oxide exposure in hospitalization with respiratory syncytial virus bronchiolitis. *Int J Environ Res Public Health* 2016;13:578.

20. Ségala C, Poizeau D, Mesbah M, Willems S, Maidenberg M. Winter air pollution and infant bronchiolitis in Paris. *Environ Res* 2008;106:96-100.

21. Fukuda K, Hider PN, Epton MJ, Jennings LC, Kingham SP. Including viral infection data supports an association between particulate pollution and respiratory admissions. *Aust N Z J Public Health* 2011;35:163-169.

22. Vandini S, Corvaglia L, Alessandroni R, Aquilano G, Marsico C, Spinelli M, Lanari M, Faldella G. Respiratory syncytial virus infection in infants and correlation with meteorological factors and air pollutants. *Ital J Ped* 2013;39:1.

23. US Environmental Protection Agency. Air Quality System Data Mart [internet database] available via https://www.epa.gov/airdata. Accessed March 21, 2017.

24. Ambient air monitoring reference and equivalent methods, 40 CFR Part 53. (2012).

25. Janes H, Sheppard L, Lumley T. Overlap bias in the case-crossover design, with application to air pollution exposures. *Stat Med* 2005;24:285-300.

26. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology* 2005;16:717-726.

27. American Academy of Pediatrics. Respiratory syncytial virus. In: Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Elk Grove Village, IL 2015. P.667.

28. Centers for Disease Control and Prevention. Outbreaks of human metapneumovirus in two skilled nursing facilities –West Virginia and Idaho, 2011-2012. *MMWR Morb Mortal Wkly Rep* 2013;62:909-913.

29. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DAT. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis* 2009;9:291-300.

30. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am J Public Health* 1989;79:623-628.

31. Pope CA III, Dockery DW. Acute health effects of PM10 pollution on symptomatic and asymptomatic children. *Am Rev Respir Dis* 1992;145:1123-1128.

32. Becker S, Soukup JM. Exposure to urban air particulates alters the macrophage-mediated inflammatory response to respiratory viral infection. *J Toxicol Environ Health A* 1999;57:445-457.

33. Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71-77.

34. Pope CA III, Ezzati M, Cannon JB, Allen RT, Jerrett M, Burnett RT. Mortality risk and $PM_{2.5}$ air pollution in the USA: an analysis of a national prospective cohort. *Air Qual Atmos Health 2017*;(In press): doi.org/10.1007/s11869-017-0535-3.

35. Knight S, Klaskala W, Woller SC, Horne BD, Bunch TJ, Le V, Mills RM, Muhlestein JB. Anticoagulation therapy in patients with acute coronary syndrome in the Intermountain Heart Collaborative Study. *Cardiol Res Pract* 2015;Article ID 270508.

36. Sheffield P, Roy A, Wong K, Trasande L. Fine particulate matter pollution linked to respiratory illness in infants and increased hospital costs. *Health Aff (Millwood)* 2011;30:871-878.

Figure Legends

Figure 1. Odds ratios (and 95% confidence intervals) for the association of a 10 μg/m³ increase in $PM_{2.5}$ exposure with ALRI for ages 0-2, 3-17, and 18+ years. Triangles, circles, squares, and diamonds represent odds ratios for mean $PM_{2.5}$ concentrations 0-6, 7-13, 14-20, and 21-27 days prior to the day of event, respectively. The baseline model included all four lagged mean exposure periods in the model together and included all weather variables.

Figure 2. Odds ratios (and 95% confidence intervals with some extending beyond the scale of the figure) for the association of a 10 μg/m³ increase in $PM_{2.5}$ exposure with infection categories, stratifying by RSV and influenza diagnosis for the baseline model. Triangles, circles, squares, and diamonds represent odds ratios for mean $PM_{2.5}$ concentrations 0-6, 7-13, 14-20, and 21-27 days prior to the day of event, respectively. The model included all four lagged mean exposure periods in the model together and included all weather variables.

Figure 3. Putative mechanisms of PM2.5 pollution on ALRI risk in a population simultaneously experiencing exposure to pollution and respiratory pathogen activity.

Table 1. Baseline characteristics of subjects from Intermountain Healthcare on Utah's Wasatch Front. Data are n (percent) or mean (range).

Variable	Ages 0-2	Ages 3-17	Ages ≥18
Events	112,567 (77%)	17,828 (12%)	16,002 (11%)
Gender			
Male	65,424 (58.12%)	9,702 (54.42%)	6,970 (43.56%)
Female	47,143 (41.88%)	8,126 (45.46%)	9,032 (56.44%)
Age (years)	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%)

*Subjects admitted to hospital inpatient or observation from the emergency department (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.

Table 2. Distribution of study subjects by age category for ICD-9 and ICD-10 codes utilized among >1% of the study population. Subjects with diagnosis codes not represented here were assigned other less frequently used ICD-9/10 code (see Methods).

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

Table 3. Adjusted odds ratios (and 95% CIs) from the baseline model for the association of a 10 μg/m^3 increase in $PM_{2.5}$ exposure with acute lower respiratory infection (these analyses include all events in the specified age group and the models control for weather).

Cohort	Days[a] 0-6	Days 7-13	Days 14-20	Days 21-27	Days 0-27
Ages 0-2	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	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	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)

[a] Effect estimates used mean pollution values from the specified days prior to 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 1.

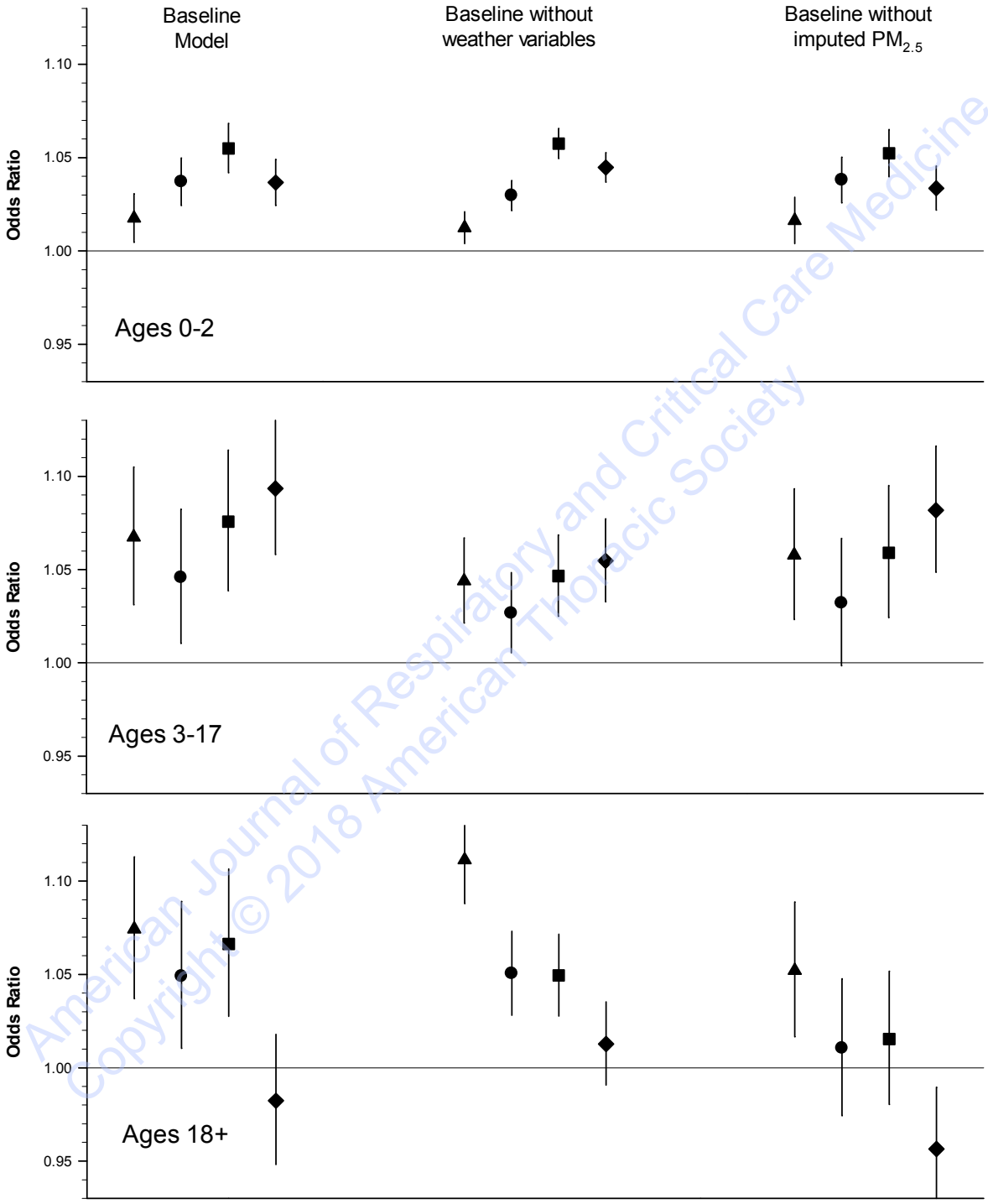


Figure 2.

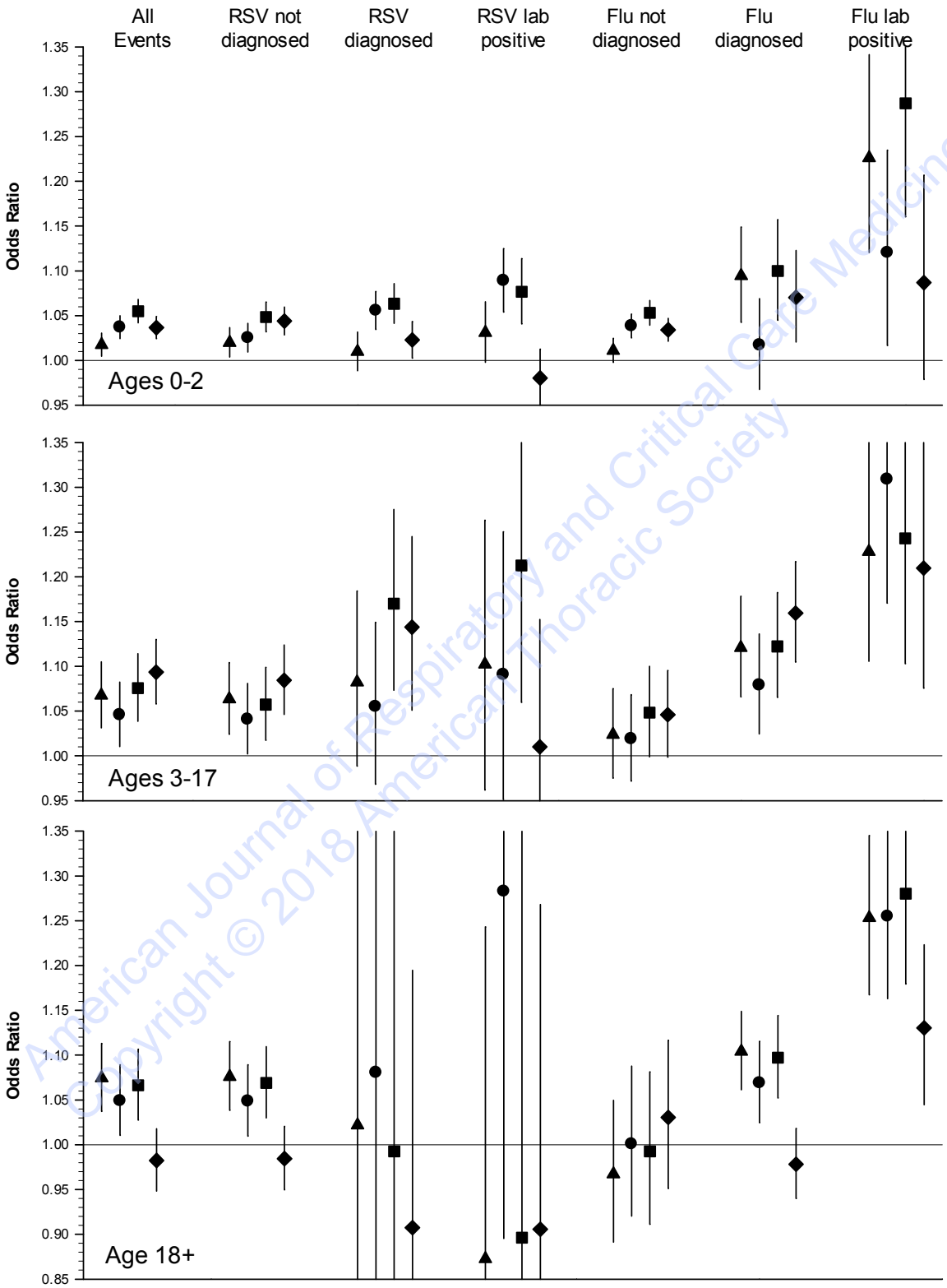
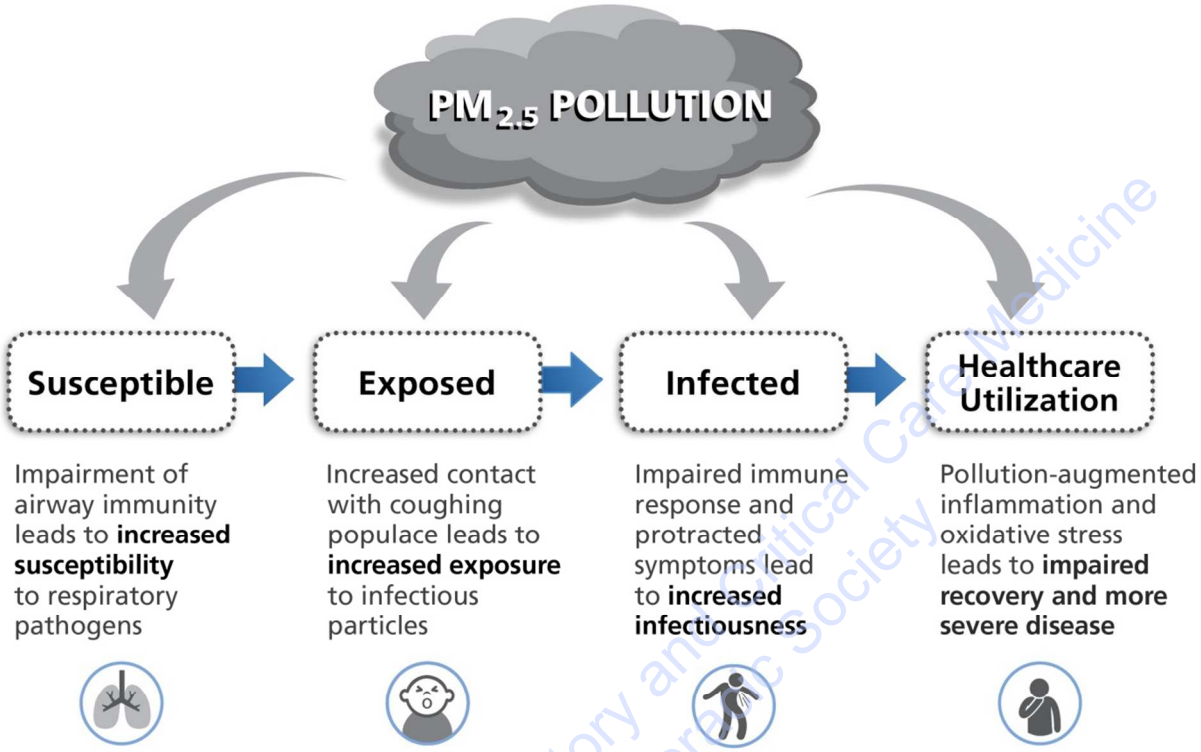


Figure 3.



Online Data Supplement for the manuscript:

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

Benjamin D. Horne, PhD, MStat, MPH; Elizabeth A. Joy, MD, MPH; Michelle G. Hofmann, MD, MPH; Per H. Gesteland, MD, MS; John B. Cannon, BS; Jacob S. Lefler; Denitza P. Blagev, MD; E. Kent Korgenski, MS, MT; Natalie Torosyan, BS; Grant I. Hansen, MS; David Kartchner, BS; C. Arden Pope III, PhD

Supplemental Methods

ALRI Codes. The ICD-9 and ICD-10 codes for ALRI were: ICD-9 codes: 079.3, 079.6, 079.89, 466.11, 466.19, 480.0, 480.1, 480.2, 480.8, 480.9, 483.0, 486, 487.0, 487.1, 488.11, 488.12, 488.81, 488.82; ICD-10 codes: B97.4, J09.X1, J09.X2, J10.00, J10.01, J10.08, J10.1, J11.00, J11.08, J11.1, J12.0, J12.1, J12.2, J12.3, J12.89, J12.9, J21.0, J21.1, J21.8, J21.9. Specific codes for infection by RSV and influenza were as follows, RSV: 079.6, 466.11, 480.1; B97.4, J12.1, J21.0; influenza: 487.0, 487.1, 488.11, 488.12, 488.81, 488.82; J09.X1, J09.X2, J10.00, J10.01, J10.08, J10.1, J11.00, J11.08, J11.1.

Supplemental Discussion

Tobacco Smoke and ALRI. Several studies examining the association between environmental tobacco smoke (ETS) exposure and ALRI in children may offer some insight into the mechanisms whereby risk modification seen between ambient air pollution and ALRI. In infants aged 2-18 months, serum cotinine was higher among cases with RSV bronchiolitis than the non-respiratory-symptom controls.(E1) Interestingly, cotinine levels (a biomarker for ETS exposure) measured in the blood were higher among cases at the time of their ALRI admission than one month later at a follow-up visit.(E1) In another study among children aged <2 years who were hospitalized for ALRI in Italy, exposure to ETS was associated with more severe RSV-related effects.(E2) A third study examined infants (ages <12 months) with a severe RSV infection and bronchiolitis diagnosis in which the clinical severity was greater for those exposed to ETS.(E3) Two additional studies examined ETS exposure in the home and found that it was a risk factor for RSV-related hospitalization among infants <1 year of age (odds ratio=5.06),(E4) and among late-preterm infants (odds ratio=2.35).(E5) These results suggest that ETS exposure

results in greater severity of ALRI, and while of lower magnitude, a similar impact is plausible for other combustion sources of fine particulates.

Biological Plausibility. Further evidence exists regarding the biological effects of ambient air pollutants on ALRI and the subsequent inflammatory response. In a basic laboratory study, the alveolar macrophage response to RSV infection was blunted in the presence of PM_{10} compared to pollution-free environment.(32) PM_{10} resulted in lower RSV-induced monocyte chemotactic protein 1, lower levels of macrophage inflammatory protein 1 and interleukin 8, and 50% lower viral antigen.(32) RSV-induced production of RANTES by epithelial cells was not changed by PM_{10} exposure but was reduced by exposure to alveolar macrophages.(32) In another study, common pollutants of indoor air, including bacterial lipopolysaccharides and proteolytically active house dust mite allergens, were found to modify the level of cellular infection with RSV.(E6) These studies provide fundamental evidence regarding the potential mechanisms and the biological plausibility of risk modification by air pollutants on viral-mediated ALRI risk and severity.

Supplemental References

E1. Gürkan F, Kiral A, Dağli E, Karakoç F. The effect of passive smoking on the development of respiratory syncytial virus bronchiolitis. *Eur J Epidemiol* 2000;16:465-468.

E2. Lanari M, Giovannini M, Giuffré L, Marini A, Rondini G, Rossi GA, Merolla R, Zuccotti GV, Salvioli GP. Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity. *Pediatr Pulmonol* 2002;33:458-465.

E3. Bradley JP, Bacharier LB, Bonfiglio J, Schechtman KB, Strunk R, Storch G, Castro M. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics* 2005;115:e7-e14.

E4. Von Linstow ML, Høgh M, Nordbø SA, Eugen-Olsen J, Koch A, Høgh B. A community study of clinical traits and risk factors for human metapneumovirus and respiratory syncytial virus infection during the first year of life. *Eur J Pediatr* 2008;167:1125-1133.

E5. Carbonell-Estrany X, Fullarton JR, Gooch KL, Vo PG, Figueras-Aloy J, Lanari M, Gouyon JB, Liese JG. Effects of parental and household smoking on the risk of respiratory syncytial virus (RSV) hospitalization in late-preterm infants and the potential impact of RSV prophylaxis. *J Matern Fetal Neonatal Med* 2013;26:926-931.

E6. Foster S, Bedford KJ, Gould ML, Coward WR, Hewitt CA. Respiratory syncytial virus infection and virus-induced inflammation are modified by contaminants of indoor air. *Immunology* 2003;108:109-115.

Table E1. Summary of daily $PM_{2.5}$ concentrations ($\mu g/m^3$) at the three primary monitoring sites (January, 1999-December, 2016).

Monitoring Sites		n	Mean	SD	Max.	Median	IQR	Events
Ogden	$PM_{2.5}$ monitored	4,016	10.0	9.1	108.3	7.4	5.1-10.7	44,331
Ogden	+ imputed	6,442	10.4	8.9	108.3	7.7	5.8-11.0	-
Salt Lake City, Hawthorne	$PM_{2.5}$ monitored	6,279	10.3	10.7	94.2	6.7	4.7-10.7	70,117
Salt Lake City, Hawthorne	+ imputed	6,450	10.2	10.7	94.2	6.7	4.8-10.7	-
Provo/Orem, Lindon	$PM_{2.5}$ monitored	6,197	9.7	9.8	123.3	6.8	4.8-10.5	31,949
Provo/Orem, Lindon	+ imputed	6,564	9.7	9.7	123.3	6.9	4.8-10.6	-

Table E2. Sensitivity and specificity of the laboratory testing for RSV and influenza compared to the clinical diagnoses of RSV and influenza.

	RSV		Influenza	
Age Group	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
0-2 years	93.2%	82.7%	80.0%	96.8%
3-17 years	91.7%	93.9%	84.0%	93.3%
≥18 years	93.1%	98.1%	81.7%	74.8%

Figure E1. Daily fine particulate matter concentrations at Salt Lake City (Hawthorne Monitor, plus imputed) plotted over time from January 1999 through December 2016 (Panel A), demonstrating short-term elevations in $PM_{2.5}$. For a more detailed illustration, a shorter period of time of September 2003 through April 2004 is provided (Panel B). The blue line illustrates 7-day mean concentrations for a lagged period of 0-6 days. The red, green, and black triangles illustrate three examples of ALRI event days (filled) with referent days (unfilled) which are the other days in the same month that share the same day of the week.

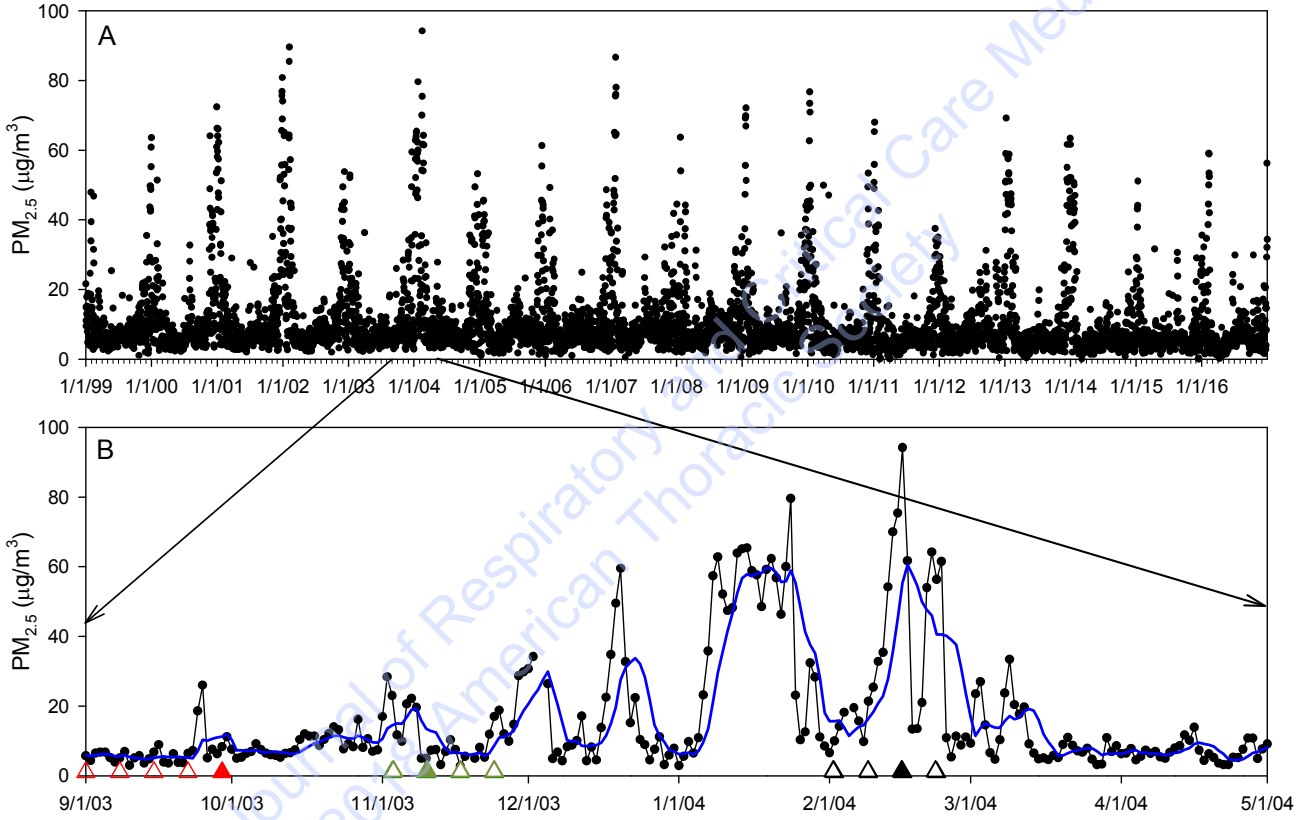


Figure E2. Odds ratios (and 95% confidence intervals) for the association of a 10 μg/m³ increase in $PM_{2.5}$ exposure with acute lower respiratory infection, stratifying by gender and patient-hospital encounter type using the baseline model. Triangles, circles, squares, and diamonds represent odds ratios for mean $PM_{2.5}$ concentrations 0-6, 7-13, 14-20, and 21-27 days prior to the day of event, respectively. The model included all four lagged mean exposure periods in the model together and included all weather variables.