Exposure to Acute Air Pollution and Risk of Bronchiolitis and Otitis Media for Preterm and Term Infants

Mariam S. Girguis, PhD\textsuperscript{a}, Matthew J. Strickland, PhD\textsuperscript{b}, Xuefei Hu, PhD\textsuperscript{c}, Yang Liu, PhD\textsuperscript{c}, Howard H. Chang, PhD\textsuperscript{c}, Itai Kloog, PhD\textsuperscript{d}, Candice Belanoff, PhD\textsuperscript{e}, Scott M. Bartell, PhD\textsuperscript{a,f,g}, and Verónica M. Vieira, DSc\textsuperscript{a}

\textsuperscript{a}Program in Public Health, University of California, Irvine, Irvine, CA, USA
\textsuperscript{b}School of Community Health Sciences, University of Nevada, Reno, NV, USA
\textsuperscript{c}Department of Environmental Health, Emory University Rollins School of Public Health, Atlanta, GA, USA
\textsuperscript{d}The Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel
\textsuperscript{e}Department of Community Health Sciences, Boston University School of Public Health, Boston, MA, USA
\textsuperscript{f}Department of Statistics, Donald Bren School of Information and Computer Sciences, University of California, Irvine, CA, USA
\textsuperscript{g}Department of Epidemiology, School of Medicine, University of California, Irvine, Irvine, CA, USA

Abstract

Our aim is to estimate associations between acute increases in particulate matter with diameter of 2.5 μm or less (PM\textsubscript{2.5}) concentrations and risk of infant bronchiolitis and otitis media among Massachusetts births born 2001 through 2008. Our case-crossover study included 20017 infant bronchiolitis and 42336 otitis media clinical encounter visits. PM\textsubscript{2.5} was modeled using satellite, remote sensing, meteorological and land use data. We applied conditional logistic regression to estimate odds ratios (ORs) and confidence intervals (CIs) per 10-μg/m\textsuperscript{3} increase in PM\textsubscript{2.5}. We assessed effect modification to determine the most susceptible subgroups. Infant bronchiolitis risk was elevated for PM\textsubscript{2.5} exposure 1 day (OR = 1.07, 95% CI = 1.03–1.11) and 4 days (OR = 1.04, 95% CI = 0.99–1.08) prior to clinical encounter, but not 7 days. Non-significant associations with otitis media varied depending on lag. Preterm infants were at substantially increased risk of bronchiolitis 1 day prior to clinical encounter (OR = 1.17, 95% CI = 1.08–1.28) and otitis media 4 and 7 days prior to clinical encounter (OR = 1.09, 95% CI = 1.02–1.16 and OR = 1.08, 95% CI =
1.02–1.15, respectively). In conclusion, preterm infants are most susceptible to infant bronchiolitis and otitis media associated with acute PM$_{2.5}$ exposures.

**Keywords**

child exposure/health; epidemiology; particulate matter

---

**INTRODUCTION**

Particulate matter with an aerodynamic diameter of 2.5 microns or less (PM$_{2.5}$) is a widespread air pollutant suspected to be harmful to infants and adults.$^{1,2,3}$ Infants may be more susceptible to adverse effects of PM$_{2.5}$ because they are more likely to be active, breathe more air per pound of body mass, and are still physiologically developing.$^{4}$ It is suspected that PM$_{2.5}$ also plays a role in infant mortality and adverse developmental outcomes, such as low birth weight.$^{1,4,5,6}$ In this paper, we investigate the role of acute PM$_{2.5}$ exposure on the risk of infant bronchiolitis, the leading cause of hospitalizations among children during their first year of life$^{7}$ and otitis media, the most frequent childhood infection among children less than 3 years of age$^{8}$. We also aim to identify infant subgroups most vulnerable to the effects of acute PM$_{2.5}$ exposure. This study is the first environmental epidemiologic analysis of the population-based Pregnancy to Early Life Longitudinal cohort, which includes all 619250 births in Massachusetts from 2001–2008.

Bronchiolitis is a lower respiratory tract infection with variability in symptoms and severity. Some infants experience no symptoms while others are hospitalized with risk of mortality.$^{9}$ Exposures such as indoor wood burning and environmental tobacco smoke have been associated with risk of hospitalization for bronchiolitis.$^{10,11}$ Although the literature on infant bronchiolitis and PM$_{2.5}$ is limited, it is suggestive of a possible association.$^{12,13,14}$ Analysis in geographic areas with relatively high PM$_{2.5}$ background levels, such as Los Angeles, have found positive associations with risk of bronchiolitis and increased chronic PM$_{2.5}$ exposure.$^{14}$ Acute PM$_{2.5}$ exposure has been positively correlated with infant bronchiolitis in Italy$^{15}$ and associated with risk of infant bronchiolitis among low birthweight infants.$^{13}$

Otitis media, or inflammation of the middle ear, is the most common cause for medical care besides a healthy child visit and a major cause for antibiotic use within the first few years of life.$^{16,17}$ Sixty percent of infants experience at least one episode of otitis media by one year of life.$^{18}$ Much like bronchiolitis, otitis media is typically caused by a viral infection and environmental exposures such as tobacco smoke and indoor wood burning also appear to be involved in the etiology of disease.$^{19,20,21,22}$ Currently, there is little literature on the association between otitis media and PM$_{2.5}$. One study found that there was an association between lifetime PM$_{2.5}$ exposure and otitis media.$^{23}$ Even in geographic locations of relatively low PM$_{2.5}$ levels (mean levels between 3.9–5.5 μg/m$^3$), increased PM$_{2.5}$ exposure two months prior to the clinical encounter was associated with risk of otitis media.$^{24}$ Studies investigating the association between other traffic related air pollutants, such as nitrogen oxide and benzene, have found positive associations.$^{25}$
We conducted a case-crossover study of infant bronchiolitis and otitis media that utilizes satellite-based PM$_{2.5}$ estimates covering the entire geographic region of Massachusetts at a 4 kilometer (km) gridded spatial resolution. Many previous studies have relied on exposure measurements from the nearest stationary air monitoring station, limiting their study populations (particularly to the urban core) and raising concerns regarding exposure measurement error.

**METHODS**

**Study Population**

Cases were obtained from the Pregnancy to Early Life Longitudinal study, a Massachusetts data linkage system which links all births to hospital encounter records. Cases of infant bronchiolitis were selected among infants born between 2001–2008 in Massachusetts and were defined as the first clinical encounter (hospitalizations, observational stays, or emergency department visit) with a primary or secondary diagnosis of infant bronchiolitis (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 466.0-466.1). Cases of otitis media were selected among infants born between 2001–2006 and were defined as the first clinical encounter with a primary or secondary diagnosis (ICD-9-CM 381-382). Infants aged 3 weeks to 12 months and 36 months were included in the analysis for bronchiolitis and otitis media, respectively, as these are the ages that infants are most susceptible to these illnesses and therefore outcome misclassification due to misdiagnosis will be minimized. We excluded cases less than 3 weeks of age to increase the likelihood that infants in our analyses left the hospital and were exposed to PM$_{2.5}$. We also excluded infants born with birth defects (4%) or whose maternal birth address could not be successfully geocoded (1.3%). The Institutional Review Boards of the University of California at Irvine, Boston University, and the Massachusetts Department of Public Health approved the research.

**Exposure Assessment**

PM$_{2.5}$ exposures were modeled using satellite remote sensing, meteorological and land use data. The exposure model is described in detail by Girguis et al. Briefly, aerosol optical depth measured by satellite instrument was used to estimate PM$_{2.5}$ exposure. Aerosol optical depth is the integral of particle light extinction from the surface to the top of the atmosphere; it is related to the loadings of fine particles in the atmosphere and is a strong predictor of ground-level PM$_{2.5}$ concentrations as most fine particles are emitted and confined in the boundary layer. In this study, aerosol optical depth measurements (available from 9 am to 3 pm local time) were averaged to generate daily mean aerosol optical depth estimates.

We developed a linear mixed effects model with 24-hour average PM$_{2.5}$ measurements from 2001 to 2009 as the dependent variable and aerosol optical depth, meteorological fields and land use variables as predictors. Model parameters included temperature, wind speed, elevation, near major roadway length, land use, and forest cover, primary point PM$_{2.5}$ emissions (obtained from the Environmental Protection Agency National Emission Inventory facility emissions reports), and 24-hour average Environmental Protection Agency PM$_{2.5}$ measurements (as the dependent variable). The model structure can be expressed as

\[ \text{Girguis et al. Page 3} \]

\[ \text{J Expo Sci Environ Epidemiol. Author manuscript; available in PMC 2018 June 22.} \]
where $PM_{2.5,st}$ is the measured ground level PM$_{2.5}$ concentration ($\mu$g/m$^3$) at site $s$ in day $t$, $\beta_0$ and $\beta_{0,t}$ (day-specific) are the fixed and random intercept, respectively; $AOD_{st}$ is the aerosol optical depth value (unitless) at site $s$ in day $t$; $\beta_1$ and $\beta_{1,t}$ (day-specific) are the fixed and random slopes for aerosol optical depth, respectively; $Temperature_{st}$ is the air temperature (K) at site $s$ in day $t$; $\beta_2$ and $\beta_{2,t}$ (day-specific) are the fixed and random slopes for temperature, respectively; $Wind\,Speed_{st}$ is the 2-m wind speed (m/sec) at site $s$ in day $t$; $\beta_3$ and $\beta_{3,t}$ (day-specific) are the fixed and random slopes for wind speed, respectively; $Elevation_s$ is elevation values (m) at site $s$; $Major\,Roads_s$ is road length (m) at site $s$; $Forest\,Cover_s$ is percentage of forest cover (unitless) at site $s$; $Point\,Emissions_s$ is point emissions (tons per year) at site $s$ and $\Psi$ is an unstructured variance-covariance matrix for the random effects. The model incorporates day-specific random intercepts and slopes for aerosol optical depth, temperature, and wind speed to account for the temporally varying relationship between PM$_{2.5}$ (based on fixed ground monitors) and aerosol optical depth. This model was run annually for a 4 km modeling grid covering the spatial extent of Massachusetts to estimate daily PM$_{2.5}$ concentrations from 2001 to 2009. Birth addresses of cases were geocoded to the street level and assigned to a 4km grid. To increase the likelihood that exposures were obtained for the correct residential address, we excluded infants who had a different zip code at birth and clinical encounter (20%) (zip code at time of clinical encounter was different than zip code address at time of birth). Daily PM$_{2.5}$ estimates were assigned to 98% of Massachusetts births included in our study according to their birth grid and dates of exposure.

**Covariates**

For the case-crossover study design, each case serves as his/her own control. Therefore, exposures such as tobacco smoke, wood burning, or other pollutants are automatically controlled for with this design and only variables that changed over the short time periods were controlled for in the analysis: temperature, humidity, barometric pressure and whether the event (index) or referent date falls on a holiday. Temperature was obtained at 1 km resolution using methods described by Kloog et al. Humidity and barometric pressure were obtained for each 14km grid of the geographic study location. The following national holidays were considered: New Year’s Day, Independence Day, Thanksgiving Day, Christmas Day, Memorial Day, and Labor Day.

**Statistical Analysis**

Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for bronchiolitis and otitis media medical encounters per 10-$\mu$g/m$^3$ increase in PM$_{2.5}$. Hospitalizations, emergency department visits, and observational stays were combined into a single analysis for infant bronchiolitis, as these cases are similar in etiology and symptoms. Due to the differing etiology between of otitis media and bronchiolitis, otitis media clinical encounter analyses were run separately for emergency
department and observational stays versus hospitalizations, since a primary or secondary hospitalization diagnosis of otitis media might represent more severe cases, which may have different etiologies from those taken to the emergency department or admitted for observational stays.

We used a semi-symmetric bidirectional referent design\textsuperscript{33,34} with narrow referent windows to minimize bias due to seasonal and longer-term confounding. Because PM\textsubscript{2.5} emissions differ by day of the week, referent days were selected to be the same day of the week as the index period, allowing for the referent day to be selected 7 days before or after the clinical event. The semi-symmetric bidirectional referent design randomly assigns an eligible referent day either before or after the clinical encounter. An offset term of log 2 was assigned to referent observations for which one of the potential referent days fell outside the start and end date of our study when PM\textsubscript{2.5} estimates were not available.\textsuperscript{35} The offset for all other referent and index days was 0. In order to investigate both the viral incubation and replication periods, we examined the influence of PM\textsubscript{2.5} on (1) symptom exacerbation using very short exposure lags of 0 and 1 day (for index and referent days), which fall during the viral replication period and (2) susceptibility to infection using longer exposure lags of 4 and 7 days, which span across the viral incubation period. The estimated timeline for respiratory syncytial virus, a common cause of infant bronchiolitis and otitis media, suggests that after infection, viral incubation occurs for 5 days and subsequently viral replication occurs for two more days. It is suspected that 8 days after infection, symptoms peak and this is the time of a probable clinical encounter.\textsuperscript{36}

We assessed effect modification by gestational age, birth weight, season of diagnosis, subsequent clinical encounter, insurance payer codes, median income by census block group, infant sex, breastfeeding initiation in hospital at birth, age of infant at time of clinical encounter and maternal race to determine susceptible subgroups. We did this by stratifying our analyses according to each susceptibility variable of interest and obtaining the p-value for the interaction term of the variable of interest and PM\textsubscript{2.5} by testing product-interaction terms to determine if differences exist between strata. Information on potential effect modifiers was obtained from birth and hospital records as well as census information matched by birth address (median income by census block group).

RESULTS

Of the 20,017 first time primary or secondary bronchiolitis cases and 42,336 otitis media cases, respectively, 59.9% and 55.7% were male, 75.8% and 76.5% were born to mothers who received adequate prenatal care, and 72.4% and 71.3 had mothers who initiated breastfeeding in the hospital during birth (Table 1).

Due to the presence of cloud or snow, the satellite based exposure models did not produce estimates for all days and locations. Day specific PM\textsubscript{2.5} values were missing from the analyses for approximately 10% and 15% of index or referent days for bronchiolitis and otitis media, respectively. Individuals with missing index or referent days were dropped from the analysis. Mean PM\textsubscript{2.5} values ranged between 9.56–19.76 \textmu g/m\textsuperscript{3} for each lag. With the exception of 1 day lag among the otitis media cases, mean and median PM\textsubscript{2.5} levels were
slightly elevated during index versus referent day. Distributions of PM$_{2.5}$ levels during index and referent days are presented in Table 2 as the difference between the index and referent measures (referent value subtracted from the index value) for each lag. The mean difference between index and referent PM$_{2.5}$ was between 0.01 and 0.17 μg/m$^3$ for bronchiolitis and −0.08 and 0.06 μg/m$^3$ for otitis media. The interquartile range of the difference was between 8.03–18.23 μg/m$^3$ and standard deviation of the difference was between 7.21–17.64 μg/m$^3$.

Increased PM$_{2.5}$ exposure 1 day prior to clinical encounter (lag 1) is associated with increased risk of bronchiolitis hospitalization (OR = 1.07, 95% CI = 1.03–1.11) (Table 3). For bronchiolitis, the adjusted odds ratio was slightly elevated for acute PM$_{2.5}$ exposure 0 and 4 days prior to hospitalization (lag 0 OR =1.03, 95% CI = 0.98–1.07; lag 4 OR = 1.04, 95% CI = 0.99–1.08). The association between bronchiolitis hospitalization and PM$_{2.5}$ exposure 7 days prior to hospitalization (lag 7) was null (OR = 1.00, 95% CI = 0.96–1.05). The adjusted OR for otitis media clinical encounter 4 days prior to hospitalization (OR = 1.02, 95% CI = 0.99–1.05) and 7 days prior to clinical encounter (OR = 1.01, 95% CI = 0.99–1.04) were slightly elevated. Odds ratios for the day of clinical encounter (OR = 1.00, 95% CI = 0.97–1.02) and 1 day prior to clinical encounter (OR = 0.97, 95% CI = 0.95–1.00) for otitis media were null and inverted with narrow confidence intervals.

Overall, we found elevated odds ratios for lags 0, 1 and 4 days for infant bronchiolitis and lags 4 and 7 days for otitis media. Results were similar when using only otitis media emergency room visits and observational stays clinical encounters. As such, we report stratified results from all clinical encounters for these specific lags to identify potentially susceptible subgroups. Stratified analyses suggest preterm infants are at increased risk (OR = 1.17, 95% CI = 1.08–1.28) for bronchiolitis hospitalization due to increases in PM$_{2.5}$ 1 day prior to clinical encounter compared to full term infants (OR = 1.04, 95% CI = 0.99–1.09; p-value for interaction, 0.018), but not 4 days prior to hospitalization (Table 4). For otitis media, we also found evidence that preterm infants were at increased risk of otitis media both 4 days (OR = 1.09, 95% CI = 1.02–1.16) and 7 days (OR = 1.08, 95% CI = 1.02–1.15) prior to clinical encounter due to increases in PM$_{2.5}$ compared to full term infants (lag4 OR = 1.01, 95% CI = 0.98–1.04; lag7 OR = 1.00, 95% CI = 0.97–1.03; p-interaction: 0.026 and 0.019 for lag 4 and 7, respectively; Table 5). Young infants (<6 months) displayed significantly higher risk of infant bronchiolitis clinical encounter due to elevated PM$_{2.5}$ exposure 4 days prior to clinical encounter (lag4 OR = 1.09, 95% CI = 1.02–1.15) compared to older infants (p-value for interaction= 0.027). A similar pattern was observed for otitis media risk four and seven days prior to clinical encounter, but this was not statistically significant.

There were no statistical differences in risk for infant bronchiolitis or otitis media according to season, birthweight, breastfeeding initiation in the hospital, subsequent clinical encounter, infant sex, delivery payment source (insurance), median income of residential block group, or maternal race (Tables 4 and 5). We found that odds ratios for cold months were elevated compared to warm months across all lags for infant bronchiolitis (this difference was not statistically significant, Table 4), while odds ratios for cold months were similar to warm months across all lags for otitis media (Table 5). Further.
we found an elevated infant bronchiolitis odds ratio for low birthweight infants, infants who did not breastfeed in the hospital and infants who had multiple clinical encounters 1 day prior to clinical encounter (lag 1), but this was not different from the odds ratio of greater than normal weight infants (p= 0.052), infants who did initiate breastfeeding in the hospital (p= 0.101) or infants with a single clinical encounter for bronchiolitis (p= 0.459). Infant bronchiolitis elevated odds ratios were also consistently observed for males and infants living in census block groups with higher median income.

For otitis media, we found elevated odds ratios for cases who initiated breastfeeding in the hospital and cases with no subsequent record of otitis media clinical encounter. Although these associations were consistent across lags, they were not statistically significant.

**DISCUSSION**

Using a self-matched case crossover epidemiological design, which controls for measured and unmeasured factors which do not vary over a short time period, we found that clinical encounters for infant bronchiolitis and otitis media were positively associated with increases in PM$_{2.5}$. Increased PM$_{2.5}$ exposure 1 day prior to hospitalization was associated with risk of infant bronchiolitis, and infants who are preterm are at significantly greater risk compared to full term infants. We observed an increased risk of otitis media only for preterm infants exposed to PM$_{2.5}$ at lag 4 or lag 7 days.

We are aware of only one other study that has examined risk of infant bronchiolitis with acute PM$_{2.5}$ exposure. This investigation, using a southern California cohort, also found a positive association between PM$_{2.5}$ and infant bronchiolitis among very preterm infants (<29 weeks) using a 3–5 day average lag (OR = 1.26, 95% CI = 1.01–1.57) and a 6–8 day average lag (OR = 1.41, 95% CI = 1.11–1.79). Unlike our findings, all other lags investigated in the Karr et al. study yielded negative results (OR = 0.96, 95% CI = 0.94–0.99) across all time periods investigated. This may be due to differing exposure assessment methodologies, differences in PM$_{2.5}$ composition in California and Massachusetts, and/or random error.

The effects of increased acute PM$_{2.5}$ exposure on preterm infants have widespread implications as currently more than 1 in 10 babies are born preterm and preterm birth rates are increasing internationally. This finding is even more meaningful given that PM$_{2.5}$ levels in Massachusetts are relatively low compared to international levels. Future studies are needed to better assess the effects of higher levels of acute PM$_{2.5}$ exposure and risk of infant bronchiolitis or otitis media clinical encounter on infants, with emphasis on preterm infants. To explain the increased risk observed among preterm infants, we further hypothesize that lungs and ears of preterm infants are not fully developed with decreased mucosal clearing capacity leaving preterm infants with an increased PM$_{2.5}$ related risk of infant bronchiolitis compared to their full term counterparts. Since surfactant has been shown to improve ciliary transport and surfactant metabolism is slower in younger infants, we also expect to observe elevated risk among younger infants. Although not consistent across lags, we did find that risk of bronchiolitis was elevated for infants diagnosed before 6 months compared to those diagnosed after six months for lag 4 and the
same pattern was observed among otitis media diagnosis before 1 year of age compared to 2 and 3 years across both lag 4 and 7.

Increased risk of otitis media among preterm infants was associated with increased PM$_{2.5}$ exposures 4 or 7 days prior to clinical encounter corresponding to the viral replication period, indicating that PM$_{2.5}$ exposure may increase susceptibility to otitis media infection. There is evidence that PM$_{2.5}$ exposure may further decrease mucus clearance by the cilia$^{41}$, causing inflammation leading to increased susceptibility to otitis media. For infant bronchiolitis, elevated risk was observed 1 or 4 days prior to clinical encounter, corresponding to the estimated viral incubation period, indicating possible influence of exposure on bronchiolitis susceptibility.

We used satellite data to obtain fine spatial distribution estimates of PM$_{2.5}$ for all of Massachusetts. The use of such exposure assessment methods allows inclusion of all eligible infants and decreases risk of exposure misclassification. Although benefits are high, such exposure measures are limited by spatial heterogeneity of PM$_{2.5}$ within a 4km cell. We believe that such limitations are non-differential between index and referent periods and if result in exposure misclassification would underestimate the true effect.

Our study only included infants who were born in Massachusetts and subsequently had a clinical encounter for infant bronchiolitis or otitis media. However, we do not have reason to believe our findings could not be generalized to children born in other geographic regions with similar PM$_{2.5}$ levels, especially since similar results were seen in California$^{13}$, Italy$^{15}$, and Canada$^{42}$. This analysis only included the most severe of clinical encounters (hospitalizations, observational stays and emergency department visits) and did not include primary care physician visits. Individuals seeking care in the emergency department may represent a group of individuals with limited access to alternative health care$^{43}$, therefore generalizability may be limited by clinical encounter type.

Using a time focused case-crossover design, we were able to evaluate the influence of temporally and spatially resolved individual level air pollution on risk of infant bronchiolitis and otitis media clinical encounters. The case crossover design allows for control of individual time invariant level risk factors and integrates analysis of potential effect modifiers. Given the short incubation period of pathogens associated with bronchiolitis and otitis media$^{44}$, such acute outcomes are applicable for analysis utilizing a case-crossover design. As there is a difference between disease onset time and clinical encounter time, apriori, we have carefully determined critical windows of exposure for testing based on the biologically relevant timelines of pathogens. We suspect that clinical encounter for bronchiolitis or otitis media would occur anywhere between 0–7 days after disease onset and therefore, we have investigated various lags within that time period. The use of various lags addresses the discrepancies between time of disease onset and clinical encounter. We also believe that because the clinical encounters in this analysis are hospitalizations, observational stays, or emergency department visits, there is likely to be slight delay between symptoms and clinical encounter. We do acknowledge that not all cases of bronchiolitis and otitis media are caused by respiratory syncytial virus or similar agents.
Therefore, the windows of exposure may not be accurate for these cases, leading to possible exposure misclassification.

Overall, we observed an increased risk of infant bronchiolitis diagnosis with increased acute PM$_{2.5}$ exposure 1 and 4 days prior to clinical encounter. This suggests that PM$_{2.5}$ exposure may play a role in bronchiolitis susceptibility and severity. We also found that preterm infants are at increased risk of infant bronchiolitis with increasing PM$_{2.5}$ levels. We did not find strong evidence to support an association between PM$_{2.5}$ exposures and otitis media diagnosis except among preterm infants. Such findings indicate that when investigating the influence of PM$_{2.5}$ exposure on other infant health outcomes, preterm births should be examined closely as they may be most affected.

**Acknowledgments**

**Funding Source:** This work was supported by grant number 5R01ES019897 from the National Institute of Environmental Health (NIEHS). Its contents are solely the responsibility of the authors and do not necessarily represent the views of NIH. This work was partially supported by NASA Applied Sciences Program (grant no. NNX11AI53G to Y.L and X.H).

**References**

1. Krzyzanowski M, Cohen A, Anderson R. Quantification of health effects of exposure to air pollution. Occup Environ Med. 2002; 59:791–93. [PubMed: 12468743]
2. Pope CA III, Burnett RT, Thun MJ. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002; 287:1132–41. [PubMed: 11879110]
3. Silva R, West J, Zhange Y, Anenberg SC, Lamarque JF, Shindell DT. Global premature mortality due to anthropogenic outdoor air pollution and the contribution of past climate change. Environ Resrch Lettrs. 2013; 8(3):034005.
4. World Health Organization. Health aspects of air pollution: results from the WHO project “systematic review of air pollution in Europe”. Copenhagen, Denmark: 2004.
5. Laden F, Schwartz J, Speizer FE. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am J of Respir Crit Care Med. 2006; 173:667–72. [PubMed: 16424447]
6. U.S. EPA. Air quality criteria for ozone and related photochemical oxidants. Washington, DC: United States Environmental Protection Agency; 2006.
7. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L. Descriptive epidemiological features of bronchiolitis in a population-based cohort. Pediatrics. 2008; 122(6):1196–203. [PubMed: 19047234]
8. Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM. Otitis media. Lancet. 2004; 363(9407):465–73. [PubMed: 14962529]
9. Bacharier LB, Cohen R, Schweiger T, Yin-Declue H, Christie C, Zheng J, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2012; 130(1): 91–100. [PubMed: 22444510]
10. Karr CJ, Demers PA, Koehoorn MW, Lencar CC, Tamburic L, Brauer M. Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. Am J Respir Crit Care Med. 2009; 180(10):995–1001. [PubMed: 19713450]
11. Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. PLoS One. 2011; 6(7):e22425. [PubMed: 21811609]
12. Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr. 2000; 137(6):865–70. [PubMed: 11113845]
13. Karr C, Lumly T, Sheperd K, Davis R, Larson T, Ritz B, et al. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ Health Perspect. 2006; 114(2): 227–81.

14. Karr C, Lumley T, Schreuder A, Davis R, Larson T, Ritz B, et al. Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am J Epidemiol. 2007; 165(5):553–60. [PubMed: 17158471]

15. Vandini S, Corvaglia L, Alessandroni R, Aquilano G, Marsico C, Spinelli M, et al. Respiratory syncytial virus infection in infants and correlation with meteorological factors and air pollutants. Ital J Pediatr. 2013; 39(1):1. [PubMed: 23311474]

16. Coker TR, Chan LS, Newberry SJ, Limbos MA, Suttorp MJ, Shekelle PG, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. JAMA. 2010; 304:2161. [PubMed: 21081729]

17. Soni, A. Ear infections (otitis media) in children (0-17) use and expenditures. Agency for Healthcare Research and Quality; 2006. Statistical Brief No. 228 Available at: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st228/stat228.pdf (Accessed on January 12, 2011).

18. Teele DW, Klein JO, Rosner B. Epidemiol of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J Infect Dis. 1989; 160:83–94. [PubMed: 2732519]

19. Costa JL, Navarro A, Neves JB, Martin M. Household wood and charcoal smoke increases risk of otitis media in childhood in Maputo. Int J Epidemiol. 2004; 33:583–78.

20. Daigler GE, Markello SJ, Cummings KM. The effect of indoor air pollutants on otitis media and asthma in children. Laryngoscope. 1991; 101(3):293–96. [PubMed: 2000018]

21. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children’s health. Pediatrics. 2004; 113(4 Suppl):1007–15. [PubMed: 15060193]

22. Lambert AL, Mangum JB, DeLorme MP, Everitt JL. Ultrafine carbon black particles enhance respiratory syncytial virus-induced airway reactivity, pulmonary inflammation, and chemokine expression. Toxicol Sci. 2003; 73:339–46. [PubMed: 12700399]

23. Brauer M, Gehring U, Bruneckreef B, de Jongste J, Gerritsen J, Rovers M, et al. Traffic-related air pollution and otitis media. Environ Health Perspect. 2006; 114(9):1414–8. [PubMed: 16966098]

24. MacIntyre EA, Karr CJ, Koehoorn M, Demers PA, Tamburic L, Lencar C, et al. Residential air pollution and otitis media among the first two years of life. Epidemiol. 2011; 22(1):81–9.

25. Aguilera I, Pedersen M, Garcia-Esteban R, Ballester F, Basterrechea M, Esplugues A, et al. Early-life exposure to outdoor air pollution and respiratory health, ear infections, and eczema in infants from the INMA study. Environ Health Perspect. 2013; 121(3):387–92. [PubMed: 23221880]

26. Goldman GT, Mulholland JA, Russell AG, Srivastava A, Strickland MJ, Klein M, et al. Ambient air pollutant measurement error: characterization and impacts in a time-series epidemiologic study in Atlanta. Environ Sci Technol. 2010; 44(19):7692–7698.

27. Shapiro-Mendoza CK, Tomashek KM, Kotchuck M, Barfield W, Nannini A, Weiss J, et al. Effect of late-preterm birth and maternal medical conditions on newborn morbidity risk. Pediatr. 2008; 121:223–227.

28. Girguis MS, Strickland MJ, Hu X, Liu Y, Bartell SM, Vieira VM. Maternal exposure to traffic-related air pollution and birth defects in Massachusetts. Environ Res. 2016; 146:1–9. [PubMed: 26705853]

29. Liu Y, Paciorek CJ, Koutrakis P. Estimating regional spatial and temporal variability of PM2.5 concentrations using satellite data, meteorology, and land use information Environ. Health Perspect. 2009; 117:886–892.

30. Lee HJ, Liu Y, Coull BA, Schwartz J, Koutrakis P. A novel calibration approach of modis aod data to predict PM2.5 concentrations. Atmos Chem Phys. 2011; 11:7991–8002.

31. Kloog I, Nordio F, Coull BA, Schwartz J. Predicting spatiotemporal mean air temperature using MODIS satellite surface temperature measurements across the Northeastern USA. Remote Sens Environ. 2014; 150:132–139.
32. Cosgrove BA, Lohmann D, Mitchell KE, Houser PR, Wood EF, Schaake JC, et al. Real-time and retrospective forcing in the North American Land Data Assimilation System (NLDAS) project. J Geophys Res Atmos. 2003:108.

33. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiol. 2001; 12(2):186–92.

34. Navidi W, Weinhardt E. Risk set sampling for case–crossover designs. Epidemiol. 2002; 13:100–5.

35. 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. [PubMed: 15546133]

36. Tristram, DA., Welliver, RC. Respiratory Syncytial Virus. In: Long, SS. Pickering, LK., Prober, CG., editors. Principles and practice of pediatric infectious diseases. 2nd. New York, NY: Churchill Livingstone; 2003. p. 213-218.

37. The Global Burden of Preterm Birth. The Lancet. 2009; 374(9697):1214.

38. World Health Organization. Air Pollution Ranking. 2015. 2014Website http:faq/2015-05-16/world-health-organization-2014-air-pollution-ranking

39. Glasser JR, Mallampalli RK. Surfactant and its role in the pathobiology of pulmonary infection. Microbes Infect. 2012; 14(1):17–25. [PubMed: 21945366]

40. Nkadi PO, Merritt TA, Pillers D-AM. An Overview of Pulmonary Surfactant in the Neonate: Genetics, Metabolism, and the Role of Surfactant in Health and Disease. Molecular genetics and metabolism. 2009; 97(2):95–101. [PubMed: 19299177]

41. Shukla A, Timblin C, Berube K, Gordon T, McKinney W, Driscoll K, et al. Inhaled particulate matter causes expression of nuclear factor (NF)-kappaB-related genes and oxidant-dependent NF-kappaB activation in vitro. Am J Respir Cell Mol Biol. 2000; 23:182–187. [PubMed: 10919984]

42. Zemek R, Szyszkowicz M, Rowe BH. Air pollution and emergency department visits for otitis media: a case-crossover study in Edmonton, Canada. Environ Health Perspect. 2010; 118:1631–1636. [PubMed: 20663739]

43. Cowling TE, Cecil EV, Soljak MA, Lee JT, Millett C, Majeed A, et al. Access to Primary Care and Visits to Emergency Departments in England: A Cross-Sectional, Population-Based Study. PLoS ONE. 2013; 8(6):e66699. [PubMed: 23776694]

44. Lesser J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. The Lancet Infect Dises. 2009; 9:291–300.
Table 1
Demographic characteristics of infant bronchiolitis and otitis media cases diagnosed in Massachusetts, 2001–2009 included in analysis.

|                       | Bronchiolitis n (%) | Otitis Media n (%) |
|-----------------------|---------------------|--------------------|
| Total Cases           | 20 017              | 42 336             |
| **Infant Sex**        |                     |                    |
| Male                  | 11 985 (59.9)       | 23 591 (55.7)      |
| Female                | 8032 (40.1)         | 18 745 (44.3)      |
| **Maternal Age**      |                     |                    |
| <20 years             | 2057 (10.3)         | 4997 (11.8)        |
| 21–24 years           | 4356 (21.8)         | 9913 (23.4)        |
| 25–29 years           | 4796 (23.9)         | 10 316 (24.4)      |
| 30–34 years           | 5204 (26.0)         | 10 395 (24.5)      |
| 35+ years             | 3604 (18.0)         | 6715 (15.9)        |
| **Parity**            |                     |                    |
| 0                     | 6923 (34.6)         | 19 021 (44.9)      |
| 1                     | 7362 (36.8)         | 13 902 (32.8)      |
| 2 or more             | 5679 (28.3)         | 9345 (22.1)        |
| missing               | 53 (0.2)            | 68 (0.2)           |
| **Adequacy of Prenatal Care** |                 |                    |
| Adequate              | 15 163 (75.8)       | 32 406 (76.5)      |
| Intermediate          | 3936 (19.7)         | 8261 (19.5)        |
| Inadequate            | 617 (3.1)           | 1263 (2.9)         |
| Unknown               | 251 (1.2)           | 299 (0.7)          |
| None                  | 50 (0.2)            | 107 (0.2)          |
| **Smoking During Pregnancy** |                |                    |
| Yes                   | 2445 (12.2)         | 5106 (12.1)        |
| No                    | 17 550 (87.7)       | 37 190 (87.9)      |
| missing               | 22 (0.1)            | 40 (0.1)           |
| **Drinking During Pregnancy** |              |                    |
| Yes                   | 311 (1.6)           | 670 (1.6)          |
| No                    | 19 684 (98.3)       | 41 629 (98.3)      |
| missing               | 22 (0.1)            | 37 (0.1)           |
| **Season of Conception** |                  |                    |
| Winter                | 3307 (16.5)         | 10 440 (24.7)      |
| Spring                | 4372 (21.8)         | 11 078 (26.2)      |
| Summer                | 6438 (32.2)         | 10 898 (25.7)      |
| Fall                  | 5892 (29.4)         | 9902 (23.4)        |
| missing               | 8 (0.1)             | 18 (0.1)           |
| Category                                      | Bronchiolitis n (% \(\Delta\)) | Otitis Media n (% \(\Delta\)) |
|----------------------------------------------|---------------------------------|--------------------------------|
| **Gestational Age**                          |                                 |                                |
| >37 weeks                                    | 17 123 (85.5)                   | 38 067 (89.9)                  |
| ≥37–32 weeks                                 | 2266 (11.3)                     | 3559 (8.4)                     |
| <32 weeks                                    | 620 (3.1)                       | 692 (1.6)                      |
| missing                                      | 8 (0.1)                         | 18 (0.1)                       |
| **Small for Gestational Age**                |                                 |                                |
| Yes                                          | 2484 (12.4)                     | 4855 (11.5)                    |
| No                                           | 17 436 (87.1)                   | 37 288 (88.1)                  |
| missing                                      | 97 (0.5)                        | 193 (0.5)                      |
| **Maternal Race/Ethnicity**                  |                                 |                                |
| Non Hispanic White                           | 12 012 (60.0)                   | 25 900 (61.2)                  |
| Non Hispanic Black                           | 2003 (10.0)                     | 4099 (9.7)                     |
| Hispanic                                     | 4642 (23.1)                     | 9301 (22.0)                    |
| Asian/Pacific Islander                       | 798 (3.9)                       | 1729 (4.1)                     |
| Other                                        | 547 (2.7)                       | 1282 (3.0)                     |
| Missing                                       | 15 (0.1)                        | 25 (0.1)                       |
| **Maternal Education**                       |                                 |                                |
| <12th grade                                  | 3549 (17.7)                     | 7714 (18.2)                    |
| High school graduation                       | 6489 (32.4)                     | 14 892 (35.1)                  |
| Some college                                 | 9945 (49.7)                     | 19 670 (46.4)                  |
| Missing                                       | 34 (0.1)                        | 60 (0.1)                       |
| **Breastfeeding**                            |                                 |                                |
| Yes                                          | 14 488 (72.4)                   | 30 170 (71.3)                  |
| No                                           | 5475 (27.4)                     | 12 084 (28.5)                  |
| missing                                       | 54 (0.3)                        | 82 (0.2)                       |
| **Maternal Language Preference**             |                                 |                                |
| English                                      | 17 095 (85.4)                   | 35 797 (84.5)                  |
| Spanish                                      | 1832 (9.2)                      | 3682 (8.7)                     |
| Portuguese                                   | 576 (2.9)                       | 1621 (3.8)                     |
| Other                                        | 442 (2.2)                       | 1121 (2.6)                     |
| missing                                       | 72 (0.4)                        | 115 (0.3)                      |
| **Household Income**                         |                                 |                                |
| <$20,000                                     | 1502 (7.5)                      | 3091 (7.3)                     |
| $20,000–$70,000                              | 11 220 (56.1)                   | 24 865 (58.7)                  |
| ≥$70,000                                     | 7291 (36.4)                     | 14 372 (34.0)                  |
| missing                                       | 4 (0.02)                        | 8 (0.02)                       |
| **Delivery Source of Payment**               |                                 |                                |
| Health Maintenance Organization              | 9071 (45.3)                     | 18 014 (42.5)                  |
|                        | Bronchiolitis n (%) | Otitis Media n (%) |
|------------------------|---------------------|--------------------|
| Medicaid/CommonHealth  | 7467 (37.3)         | 17,143 (40.5)      |
| Other                  | 3428 (17.1)         | 7097 (16.8)        |
| missing                | 51 (0.3)            | 82 (0.3)           |

*Percentages may not sum to 100% due to rounding.*
Table 2

Distribution of PM$_{2.5}$ as the difference between the index$^a$ and referent$^b$ measures for each lag.

| PM$_{2.5}$ μg/m$^3$ | N   | Mean | Standard Deviation | Median | Interquartile Range |
|---------------------|-----|------|--------------------|--------|---------------------|
| **Bronchiolitis**   |     |      |                    |        |                     |
| Lag 0               | 16359 | 0.17 | 7.34               | 0.13   | 8.20                |
| Lag 1               | 16357 | 0.06 | 7.28               | 0.48   | 8.17                |
| Lag 4               | 16281 | 0.11 | 7.37               | 0.10   | 8.11                |
| Lag 7               | 16295 | 0.01 | 7.21               | −0.02  | 8.10                |
| **Otitis Media**    |     |      |                    |        |                     |
| Lag 0               | 37040 | 0.01 | 7.64               | 0.03   | 8.11                |
| Lag 1               | 37114 | −0.08| 7.50               | −0.06  | 8.12                |
| Lag 4               | 37090 | 0.06 | 7.61               | 0.08   | 8.23                |
| Lag 7               | 37117 | 0.03 | 7.63               | 0.03   | 8.03                |

$^a$ Index days are days lagged in reference to date of clinical encounter of a case.

$^b$ Referent day for each case is randomly assigned as one week before or after index day.
Table 3

Associations between 10 ug/m$^3$ increase in PM$_{2.5}$ and infant bronchiolitis and otitis media on the day of clinical encounter (Lag 0), one day prior to clinical encounter (Lag 1), four days prior to clinical encounter (Lag 4) or seven days prior to clinical encounter (Lag 7).

|                    | OR (95% CI) | Lag 0      | Lag 1      | Lag 4      | Lag 7      |
|--------------------|-------------|------------|------------|------------|------------|
| **Infant Bronchiolitis** |             |            |            |            |            |
| Crude Model        | 1.02 (0.98, 1.07) | 1.07 (1.03, 1.11) | 1.04 (1.00, 1.09) | 1.00 (0.96, 1.05) |
| Adjusted Model*    | 1.03 (0.98, 1.07) | 1.07 (1.03, 1.11) | 1.04 (0.99, 1.08) | 1.00 (0.96, 1.05) |
| **Otitis Media**   |             |            |            |            |            |
| Crude Model        | 1.00 (0.98, 1.03) | 0.97 (0.95, 1.00) | 1.02 (0.99, 1.05) | 1.01 (0.98, 1.03) |
| Adjusted Model*    | 1.00 (0.97, 1.02) | 0.97 (0.95, 1.00) | 1.02 (0.99, 1.05) | 1.01 (0.99, 1.04) |
| Emergency Room and Observational Stays Only* | 0.97 (0.95, 1.00) | 0.99 (0.96, 1.02) | 1.02 (0.99, 1.05) | 1.01 (0.99, 1.04) |

*Model adjusted for lagged temperature, barometric pressure, humidity, and holiday indicator.
Table 4

Associations between 10 μg/m³ increase in PM$_{2.5}$ and infant bronchiolitis one day prior to clinical encounter (Lag 1) and four days prior to clinical encounter (Lag 4) stratified by susceptibility risk factors.

| Risk Factor                                      | Lag 1       | p-interaction$^b$ | Lag 4       | p-interaction$^b$ |
|--------------------------------------------------|-------------|-------------------|-------------|-------------------|
| **Season of Dx**                                 |             |                   |             |                   |
| Cold                                             | 1.08 (1.03, 1.13) | 0.188             | 1.04 (1.00, 1.09) | 0.489             |
| Warm                                             | 1.00 (0.80, 1.24) | –                 | 1.01 (0.90, 1.13) | –                 |
| **Gestational Age**                              |             |                   |             |                   |
| Term >37 weeks                                    | 1.04 (0.99, 1.09) | 0.018             | 1.04 (1.00, 1.09) | 0.978             |
| Preterm ≤37 weeks                                 | 1.17 (1.08, 1.28) | –                 | 1.04 (0.97, 1.13) | –                 |
| **Birthweight**                                   |             |                   |             |                   |
| Normal Weight ≥2500 g                             | 1.06 (1.02, 1.11) | 0.052             | 1.03 (0.99, 1.08) | 0.595             |
| Low Birth Weight <2500 g                         | 1.12 (0.98, 1.27) | –                 | 1.09 (0.95, 1.24) | –                 |
| **Breastfeeding Initiation in Hospital at Birth** |             |                   |             |                   |
| Yes                                              | 1.05 (0.99, 1.10) | 0.101             | 1.03 (0.98, 1.08) | 0.531             |
| No                                               | 1.13 (1.05, 1.22) | –                 | 1.06 (0.97, 1.15) | –                 |
| **Subsequent Infant Bronchiolitis Clinical Encounter** |             |                   |             |                   |
| No                                               | 1.07 (1.02, 1.12) | 0.459             | 1.04 (0.99, 1.07) | 0.375             |
| Yes                                              | 1.15 (1.01, 1.31) | –                 | 0.98 (0.85, 1.13) | –                 |
| **Infant Sex**                                    |             |                   |             |                   |
| Male                                             | 1.08 (1.02, 1.14) | 0.716             | 1.05 (1.00, 1.11) | 0.501             |
| Female                                           | 1.06 (0.99, 1.13) | –                 | 1.02 (0.95, 1.09) | –                 |
| **Age of Infant at Time of Clinical Encounter**   |             |                   |             |                   |
| 3 weeks–6months                                  | 1.06 (0.99, 1.12) | 0.659             | 1.09 (1.02, 1.15) | 0.027             |
| 6 months–1year                                   | 1.08 (1.02, 1.15) | –                 | 0.99 (0.93, 1.05) | –                 |
| **Delivery Payment Source**                      |             |                   |             |                   |
| Health Maintenance Organization                  | 1.04 (0.98, 1.10) | –                 | 1.04 (0.98, 1.10) | –                 |
| Medicaid/CommonHealth                            | 1.09 (1.02, 1.17) | 0.331             | 1.04 (0.97, 1.11) | 0.979             |
| Other                                            | 1.11 (1.00, 1.23) | 0.330             | 1.04 (0.96, 1.15) | 0.842             |
| **Median Income of Census Block Group**           |             |                   |             |                   |
| <$20 000                                         | 0.97 (0.83, 1.14) | 0.242             | 0.97 (0.83, 1.14) | 0.586             |
| $20 000–$70 000                                  | 1.09 (1.03, 1.15) | 0.534             | 1.04 (0.99, 1.10) | 0.987             |
| >$70 000                                        | 1.06 (0.99, 1.14) | –                 | 1.04 (0.97, 1.12) | –                 |
| **Maternal Race**                                |             |                   |             |                   |
| Non-Hispanic White                               | 1.06 (1.00, 1.12) | –                 | 1.06 (1.01, 1.12) | –                 |
| Non-Hispanic Black                               | 1.11 (0.97, 1.27) | 0.441             | 1.13 (0.99, 1.30) | 0.368             |
| Hispanic                                         | 1.06 (0.97, 1.15) | 0.845             | 0.96 (0.88, 1.05) | 0.054             |
| Asian                                            | 1.27 (1.02, 1.57) | 0.128             | 0.98 (0.79, 1.21) | 0.432             |
| Other                                            | 1.07 (0.83, 1.36) | 0.805             | 0.99 (1.75, 1.30) | 0.608             |
\(^a\) Model adjusted for lagged temperature, barometric pressure, humidity, and holiday indicator.

\(^b\) \(p\)-interaction generated from interaction term of susceptibility risk factor and PM\(_{2.5}\) in full model.

\(^c\) Warm months are May through October and cold months are January through April and November through December.
Table 5

Associations between 10 ug/m$^3$ increase in PM$_{2.5}$ and otitis media four days (Lag 4) and seven days (Lag 7) prior to clinical encounter stratified by susceptibility risk factors.

| Risk Factor                          | Lag 4 (95% CI) | p-interaction | Lag 7 (95% CI) | p-interaction |
|--------------------------------------|----------------|---------------|----------------|---------------|
| **Season of Dx**                     |                |               |                |               |
| Cold                                 | 1.02 (0.98, 1.06) | 0.963         | 1.01 (0.97, 1.04) | 0.879         |
| Warm                                 | 1.01 (0.98, 1.04) | –             | 1.02 (0.98, 1.06) | –             |
| **Gestational Age**                  |                |               |                |               |
| Term >37 weeks                       | 1.01 (0.98, 1.04) | 0.026         | 1.00 (0.97, 1.03) | 0.019         |
| Preterm ≤37 weeks                    | 1.09 (1.02, 1.16) | –             | 1.08 (1.02, 1.15) | –             |
| **Birthweight**                      |                |               |                |               |
| Normal Weight ≥2500 g                | 1.02 (0.99, 1.05) | –             | 1.01 (0.99, 1.04) | 0.377         |
| Low Birth Weight <2500 g             | 1.01 (0.91, 1.12) | 0.868         | 0.97 (0.88, 1.08) | –             |
| **Breastfeeding Initiation in Hospital at Birth** | | | | |
| Yes                                  | 1.02 (1.00, 1.06) | 0.508         | 1.02 (0.99, 1.05) | 0.555         |
| No                                   | 1.01 (0.96, 1.06) | –             | 1.00 (0.95, 1.05) | –             |
| **Subsequent Otitis Media Clinical Encounter** | | | | |
| No                                   | 1.02 (0.99, 1.05) | 0.624         | 1.01 (0.98, 1.04) | 0.678         |
| Yes                                  | 0.99 (0.82, 1.20) | –             | 0.99 (0.81, 1.20) | –             |
| **Infant Sex**                       |                |               |                |               |
| Male                                 | 1.04 (1.00, 1.08) | 0.205         | 0.99 (0.96, 1.03) | 0.146         |
| Female                               | 1.00 (0.96, 1.04) | –             | 1.04 (1.00, 1.08) | –             |
| **Age of Infant at Time of Clinical Encounter** | | | | |
| 0–1 year                             | 1.02 (0.99, 1.07) | –             | 1.04 (1.00, 1.08) | –             |
| 1–2 years                            | 1.02 (0.98, 1.07) | 0.972         | 0.98 (0.94, 1.03) | 0.0555        |
| 2–3 years                            | 1.00 (0.93, 1.07) | 0.489         | 1.00 (0.93, 1.07) | 0.270         |
| **Delivery Payment Source**          |                |               |                |               |
| Health Maintenance Organization      | 1.02 (0.98, 1.07) | –             | 0.99 (0.95, 1.04) | –             |
| Medicaid/CommonHealth                 | 1.01 (0.97, 1.17) | 0.593         | 1.04 (1.00, 1.09) | 0.097         |
| Other                                | 1.03 (0.97, 1.11) | 0.848         | 0.99 (0.93, 1.06) | 0.958         |
| **Median Income of Census Block Group** | | | | |
| <$20 000                              | 1.01 (0.91, 1.12) | 0.949         | 1.04 (0.94, 1.15) | 0.419         |
| $20 000–$70 000                       | 1.01 (0.98, 1.05) | 0.764         | 1.01 (0.97, 1.04) | 0.446         |
| >$70 000                              | 1.03 (0.98, 1.08) | –             | 1.01 (0.97, 1.06) | –             |
| **Maternal Race**                    |                |               |                |               |
| Non-Hispanic White                   | 1.03 (1.00, 1.07) | –             | 1.00 (0.96, 1.03) | –             |
| Non-Hispanic Black                   | 1.00 (0.92, 1.09) | 0.557         | 1.03 (0.94, 1.12) | 0.575         |
| Hispanic                             | 1.02 (0.96, 1.08) | 0.700         | 1.03 (0.98, 1.09) | 0.247         |
| Asian                                | 1.02 (0.89, 1.16) | 0.810         | 1.02 (0.89, 1.16) | 0.776         |
| OR (95% CI) | Lag4 | p-interaction<sup>b</sup> | Lag 7 | p-interaction<sup>b</sup> |
|------------|------|--------------------------|------|--------------------------|
| Other      | 0.89 (0.76, 1.05) | 0.136 | 1.12 (1.95, 1.31) | 0.149 |

<sup>a</sup> Model adjusted for lagged temperature, barometric pressure, humidity, and holiday indicator.

<sup>b</sup> p-interaction generated from interaction term of susceptibility risk factor and PM<sub>2.5</sub> in full model.

<sup>c</sup> Warm months are May through October and cold months are January through April and November through December.