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

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Abstract

Our aim is to estimate associations between acute increases in particulate matter with diameter of 2.5 µm or less ($PM_{2.5}$) 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. $PM_{2.5}$ 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^3 increase in $PM_{2.5.}$ We assessed effect modification to determine the most susceptible subgroups. Infant bronchiolitis risk was elevated for $PM_{2.5}$ 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 =

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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 $\mu g/m^3$), 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[13,23,24], limiting their study populations (particularly to the urban core) and raising concerns regarding exposure measurement error. [26]

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. [27] 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.[28] 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. [29]

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

$$PM_{2.5,\,st} = (\beta_0 + \beta_{0,\,t}) + (\beta_1 + \beta_{1,\,t})AOD_{st} + (\beta_2 + \beta_{2,\,t})Temperature_{st} + (\beta_3 + \beta_{3,\,t})Wind\ Speed_{st} + \beta_3 Elevation_s + \beta_4 Major\ Roads_s + \beta_5 Forest\ Cover_s + \beta_6 Point\ Emissions_s + \varepsilon_{st}(\beta_{0,\,t}\beta_{1,\,t}\beta_{2,\,t}\beta_{3,\,t}) \sim N[(0, 0, 0, 0), \psi]$$

where $PM_{2.5,st}$ is the measured ground level $PM_{2.5}$ concentration (μg/m^3) at site s in day t; β_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; β_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; β_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; β_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 Ψ 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.[30] 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.[31] Humidity and barometric pressure were obtained for each 14km grid of the geographic study location. [32] 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-μg/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[33,34] with narrow referent windows to minimize bias due to seasonal and longer-term confounding. Because $PM_{2.5}$ 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 $PM_{2.5}$ estimates were not available.[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 $PM_{2.5}$ 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 synctal 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.[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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ values ranged between 9.56–19.76 $\mu g/m^3$ for each lag. With the exception of 1 day lag among the otitis media cases, mean and median $PM_{2.5}$ 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 no 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 (Tables 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 very 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.[13] 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.[13] 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. [37] This finding is even more meaningful given that $PM_{2.5}$ levels in Massachusetts are relatively low compared to international levels[38]. 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.[13] Since surfactant has been shown to improve ciliary transport[39] and surfactant metabolism is slower in younger infants[40], 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.

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Table 1

Demographic characteristics of infant bronchiolitis and otitis media cases diagnosed in Massachusetts, 2001–2009 included in analysis.

	Bronchiolitis n (%)[a]	**Otitis Media n (%)**[a]
Total Cases	20 017	42 336
Infant Sex		
Male	11 985 (59.9)	23591 (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)

	Bronchiolitis n (%)[a]	Otitis Media n (%)[a]
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 (%)[a]	Otitis Media n (%)[a]
Medicaid/CommonHealth	7467 (37.3)	17 143 (40.5)
Other	3428 (17.1)	7097 (16.8)
missing	51 (0.3)	82 (0.3)

[a]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[a]	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[a]	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[a]	0.97 (0.95, 1.00)	0.99 (0.96, 1.02)	1.02 (0.99, 1.05)	1.01 (0.99, 1.04)

[a]Model adjusted for lagged temperature, barometric pressure, humidity, and holiday indicator.

Table 4

Associations between 10 ug/m^3 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.

OR (95%CI)[a]	**Lag1**	**p-interaction**[b]	**Lag 4**	**p-interaction**[b]
Season of Dx[c]				
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)	0.650	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.

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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.

OR (95% CI)[a]	**Lag4**	**p-interaction**[b]	**Lag 7**	**p-interaction**[b]
Season of Dx[c]				
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)[a]	Lag4	p-interaction[b]	Lag 7	p-interaction[b]
Other	0.89 (0.76, 1.05)	0.136	1.12 (1.95, 1.31)	0.149

[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.