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Chronic $PM_{2.5}$ exposure and risk of infant bronchiolitis and otitis media clinical encounters

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ABSTRACT

Chronic particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) exposure can leave infants more susceptible to illness. Our objective is to estimate associations of the chronic $PM_{2.5}$ exposure with infant bronchiolitis and otitis media (OM) clinical encounters. We obtained all first time bronchiolitis (n = 18,029) and OM (n = 40,042) clinical encounters among children less than 12 and 36 months of age, respectively, diagnosed from 2001 to 2009 and two controls per case matched on birthdate and gestational age from the Pregnancy to Early Life Longitudinal data linkage system in Massachusetts. We applied conditional logistic regression to estimate odds ratios (OR) and confidence intervals (CI) per 2-μg/m^3 increase in lifetime average satellite based $PM_{2.5}$ exposure. Effect modification was assessed by age, gestational age, frequency of clinical encounter, and income. We examined associations between residential distance to roadways, traffic density, and infant bronchiolitis and OM risk. $PM_{2.5}$ was not associated with infant bronchiolitis (OR = 1.02, 95% CI = 1.00, 1.04) and inversely associated with OM (OR = 0.97, 95% CI = 0.95, 0.99). There was no evidence of effect modification. Compared to infants living near low traffic density, infants residing in high traffic density had elevated risk of bronchiolitis (OR = 1.23, 95% CI = 1.14, 1.31) but not OM (OR = 0.98, 95% CI = 0.93, 1.02) clinical encounter. We did not find strong evidence to support an association between early-life long-term $PM_{2.5}$ exposure and infant bronchiolitis or OM. Bronchiolitis risk was increased among infants living near high traffic density.

1. Introduction

Infant bronchiolitis is a lower respiratory tract infection and the leading cause of hospitalizations among children during the first year of life (Koehoorn et al., 2008). Most bronchiolitis cases are caused by viral infection, specifically respiratory syncytial virus (RSV) infection. Although most infants are RSV seropositive, some infants experience mild symptoms whereas others are hospitalized (Bacharier et al., 2012). Otitis media (OM), or inflammation of the middle ear, is one of the most frequent infections among children less than 3 years of age (Rovers et al., 2004), 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 (Teele et al., 1989). OM can be caused by viral and bacterial infections. Much like bronchiolitis, OM results from a complex combination of pathogens, environmental exposures (such as tobacco smoke and indoor wood burning), and heredity (Costa et al., 2004; Daigler et al., 1991; DiFranza et al., 2004).

Symptomatic infants with bronchiolitis or OM have shown immunoregulatory and proinflammatory responses during the course of their illness (Bryan et al., 2007; Rosenberg and Domachowske, 2012; van Benten et al., 2003). Toxicological studies have demonstrated that chronic exposure to traffic related air

Abbreviations: PM2.5, particulate matter with diameter of 2.5 μm or less; OM, otitis media; km, kilometer; PELL, Pregnancy to Early Life Longitudinal; ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification; AOD, aerosol optical depth; OR, odds ratio; CI, confidence interval; RSV, respiratory synctal virus.

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pollution, such as particulate matter with a diameter of 2.5 μm or less (PM2.5) can trigger an inflammatory response in rats (Luo et al., 2014; Xu et al., 2008; Ying et al., 2012) and humans (Ostro et al., 2014). To date, there have been only a few studies investigating the effects of long term $PM_{2.5}$ exposure and bronchiolitis (de P Pablo-Romero et al., 2015; Karr et al., 2007; Karr et al., 2009a; Karr et al., 2009b) or OM (Brauer et al., 2006; MacIntyre et al., 2011; MacIntyre et al., 2014), indicating evidence of a possible association (Brauer et al., 2006; Karr et al., 2007; MacIntyre et al., 2011). Examining the association between $PM_{2.5}$ exposure and clinical encounters for infant bronchiolitis and OM may help better elucidate factors contributing to the occurrence and symptom severity of these common child morbidities.

In this study, we estimate the associations between satellite based chronic $PM_{2.5}$ exposure and risk of bronchiolitis during infancy and OM during early childhood. The use of satellite based $PM_{2.5}$ exposure allows for complete spatial coverage and reduced exposure misclassification compared to monitor based estimates. To rigorously control for confounding, we conducted analyses using a matched case-control design. The main analysis accounts for temporal trends and baseline health of the children based on gestational age and birthdate using matched controls. The secondary analysis uses siblings as controls to better control for confounding by unmeasured time-invariant factors that are shared among family members, such as parental propensity to seek health care, indoor pollution (such as wood burning), and family.

2. Methods

2.1. Study population

Eligible study participants were obtained from Pregnancy to Early Life Longitudinal (PELL), a partnership between the Boston University School of Public Health, the Massachusetts (MA) Department of Public Health, and the Centers for Disease Control and Prevention (Shapiro-Mendoza et al., 2008). PELL is a data linkage system which allows for the linkage of birth records to hospitalizations, emergency department visits and observational stays within the state of MA. Cases of infant bronchiolitis were selected among infants born between 2001 and 2008 and are defined as the first clinical encounter (hospitalization, observational stay, 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) experienced by infants greater than 3 weeks and less than 12 months of age. Cases of OM were selected among children born between 2001 and 2006 and are defined as the first clinical encounter with a primary or secondary diagnosis (ICD-9-CM 381-382) experienced by children greater than 3 weeks and less than 36 months of age. A minimum age of 3 weeks increases likelihood that infants have left the hospital and are exposed to $PM_{2.5}$ at home. Children are most susceptible to infant bronchiolitis and OM up until 12 months[1] and 36 months of age, respectively. Birth years for each outcome were determined based on exposure follow-up availability. There were 600,226 eligible infants born from 2001 to 2008 and 453,047 eligible infants born from 2001 to 2006 in Massachusetts. Cases with a different zip code at birth and time of clinical encounter (20%) were excluded to minimize exposure misclassification due to residential mobility. The Institutional Review Boards of the University of California at Irvine and the MA Department of Public Health approved this research.

To assess the influence of chronic $PM_{2.5}$ exposure on infant bronchiolitis and OM, a nested case-control design using random controls matched on birth date and gestational age was used. Two matched controls were selected for each case among infants in PELL with a non-respiratory related clinical encounter. Non-respiratory clinical encounters are mostly fever, gastroenteritis, head injury, dehydration, neonatal jaundice, and abnormal involuntary movements. Controls were eligible if they did not have a bronchiolitis or OM event before they were the same age as the case when the case was first diagnosed, were born within 6 days of the case, had the same gestational age (week) as the case, and had the same zip code at time of birth and time of PELL clinical encounter (to reduce risk of residential mobility among controls).

A secondary nested case control analysis was performed with sibling controls, utilizing PELL's data system tracking of families over time. Because important individual level risk factors such as indoor air pollution (including tobacco smoke), house dust, breastfeeding intensity and duration, frequency of wood burning in the home, and proclivity of parents to take their children to the emergency department are not assessed in PELL, using a sibling control helps adjust for these confounders as these variables are likely to be similar among siblings. Siblings of cases (individuals who had the same biological mother) were selected if they were single births with discordant outcomes from time of birth up until the case age.

Among all cases and controls, we excluded infants born with birth defects (4%) or whose birth address could not be successfully geocoded (2%).

2.2. Exposure assessment

We developed a three-stage statistical model to predict $PM_{2.5}$ throughout Massachusetts at a 4 km resolution from 2001 to 2009. For details see Girguis et al. (2016). Briefly, the first stage accounts for the temporally varying relationship between $PM_{2.5}$ and satellite based aerosol optical depth (AOD), a measurement of light transmission through atmospheric aerosols, after adjustment for relative humidity, wind speed, elevation, major roads, forest cover, and point emissions (Kloog et al., 2014; Lee et al., 2011; Liu et al., 2009). The second stage explains the spatially varying relationship between $PM_{2.5}$ and AOD accounting for geographic location (Hu et al., 2014). The third stage uses the first and second stage model predictions over the study area to estimate daily $PM_{2.5}$ concentrations in areas where AOD is not available. If AOD was completely missing for one day, there were no predications from any stage for that day.

For each case and control, daily $PM_{2.5}$ concentrations were averaged from birth until the age of case at time of clinical encounter. Birth addresses of infants were geocoded to the street level and assigned to a 4 km grid cell. Average daily $PM_{2.5}$ values were assigned to each child according to their birth grid cell and dates of exposure. We only included average $PM_{2.5}$ exposure measures of children who had $PM_{2.5}$ measure for over 70% of their exposure window.

Residential distance to major roadways and traffic density were calculated for each case and control. Using geographic information system software (ArcGIS, version 10.0; ESRI), we calculated the shortest distance between each birth address and the nearest Class 1 (limited access highways) or 2 (multilane highways without limited access) road segment to obtain residential distance to major roadways. Traffic density was calculated by summing the annual average daily traffic (AADT) for a 200 m grid of Class 1 and 2 road segments (Medina-Ramón et al., 2008). For further details, see Girguis et al. (2016).

2.3. Covariates

By matching on temporal variables such as birth date and gestational ages, secular time trends are accounted for ensuring children are compared across the same time period for the same duration. The following covariates were considered as poten-

Table 1
Demographic Characteristics of Infant Bronchiolitis and Otitis Media Cases Diagnosed in Massachusetts, 2001–2009 and Random Controls Matched on Birthdate (+/−6 days) and Gestational Week, Included in Analysis.

	Bronchiolitis Cases%[a]	Bronchiolitis Controls%[a]	p-value[b]	Otitis Media Cases%[a]	Otitis Media Controls%[a]	p-value[b]
Total	18,029	35,816		40,042	79,747	
Infant Sex			<0.001			<0.001
Male	60.0	52.8		59.9	55.8	
Female	40.0	47.3		40.1	44.2	
Maternal Age			<0.001			<0.001
<20 years	10.3	7.0		11.7	6.2	
21–24 years	21.8	16.2		23.3	15.1	
25–29 years	24.2	24.0		23.4	23.3	
30–34 years	26.1	30.1		24.6	32.4	
35+years	17.7	22.5		16.9	23.0	
Parity			<0.001			<0.001
0	34.9	44.7		44.9	44.1	
1	36.8	34.4		32.9	34.5	
2	28.1	20.8		22.0	21.3	
Missing	0.2	0.2		0.1	0.1	
Adequacy of Prenatal Care			<0.001			<0.001
Adequate	75.8	78.1		76.5	79.5	
Intermediate	19.6	17.9		19.5	17.0	
Inadequate	3.1	2.9		3.0	2.6	
Unknown	1.2	0.9		0.7	0.6	
None	0.3	0.2		0.3	0.2	
Smoking During Pregnancy			<0.001			<0.001
Yes	12.2	8.6		12.0	8.7	
No	87.8	91.3		87.9	91.9	
Missing	0.1	13.1		0.1	0.1	
Season of Conception			0.754			0.425
Winter	30.4	40.0		24.4	25.1	
Spring	20.2	16.3		25.8	26.6	
Summer	19.5	13.2		27.5	25.5	
Fall	29.8	29.9		22.3	22.2	
Gestational Age			0.410			0.937
≥37 weeks	85.5	86.1		89.9	90.2	
36–32 weeks	11.4	11.5		8.4	8.5	
<32 weeks	3.1	2.4		1.6	1.3	
Maternal Race/Ethnicity			<0.001			<0.001
NH White	59.5	68.8		61.3	71.1	
NH Black	10.1	8.3		9.7	7.2	
Hispanic	23.5	14.4		21.9	12.8	
Asian/Pacific Islander	3.9	6.2		4.0	6.0	
Other	2.8	2.3		3.0	2.2	
Missing	0.0	0.1		0.1	0.1	
Maternal Education			<0.001			<0.001
<12th grade	17.8	11.4		18.1	10.3	
High school graduation	32.5	27.9		35.2	26.7	
Some college	49.5	60.5		46.6	62.9	
Missing	0.1	0.2		0.1	0.1	
Maternal Language Preference			<0.001			<0.001
English	85.1	87.9		84.6	89.0	
Spanish	9.4	6.0		8.6	5.5	
Portuguese	3.0	2.7		3.9	2.3	
Other	2.2	3.1		2.6	2.9	
Missing	0.3	0.3		0.3	0.3	
Household Income[c]			<0.001			<0.001
Quartile 1	18.0	25.0		15.7	25.0	
Quartile 2	23.2	25.0		20.9	25.0	
Quartile 3	28.2	25.0		27.7	24.9	
Quartile 4	30.4	25.0		35.5	24.9	
Delivery Source of Payment			<0.001			<0.001
HMO	45.1	54.9		42.6	58.9	
Medicaid/Commonhealth	37.6	27.8		40.4	24.4	
Other	17.1	17.2		16.9	16.5	
Missing	0.2	0.2		0.2	0.2	
Use Wood for Fuel[b]			<0.001			<0.001
Yes	22.3	28.5		25.7	29.5	
No	77.1	71.4		74.2	70.5	

Table 1 (*Continued*)

	Bronchiolitis Cases%[a]	Bronchiolitis Controls%[a]	p-value[b]	Otitis Media Cases%[a]	Otitis Media Controls%[a]	p-value[b]
Birth Year			0.981			0.994
2001	13.4	13.4		20.0	20.0	
2002	9.9	9.9		14.3	14.3	
2003	12.1	12.1		17.0	17.0	
2004	11.4	11.4		16.3	16.3	
2005	13.4	13.4		16.3	16.3	
2006	14.8	14.7		16.0	16.0	
2007	12.3	12.3		–	–	
2008	12.7	12.8		–	–	

[a] Percentages may not sum to 100% due to rounding.
[b] Pearson Chi-square test (with continuity correction for variables with only two categories).
[c] Measured at the census block group level. Median income of census block group quartiles based on control distribution; quartile 1 = <$37,188, quartile 2 = $37,189–$56,579, quartile 3 = $56,580–$81,740, and quartile 4 = >$81,740 for infant bronchiolitis and quartile 1 = <$36,543, quartile 2 $36,544–$55,125, quartile 3 = $55,126–$78,929, and quartile 4 = >$78,929 for otitis media.

tial confounders in the time-matched analysis: plurality, parity, maternal race/ethnicity, maternal education, maternal language preference, delivery payment source, smoking during pregnancy, alcohol consumption during pregnancy, adequacy of prenatal care (measured by the Adequacy of Prenatal Care Utilization Index), marital status, maternal age, breastfeeding initiation in hospital, risky pregnancy, and birthweight. We used geocoded addresses to determine median household income and proportion of homes that use wood for fuel by census block group from the American Community Survey 2006–2010, 5 year estimates. Directed Acyclic Graphs (DAGs) were used for covariate selection and subsequent change-in-estimate procedures (5%) were used to simplify the final model (Evans et al., 2012; Weng et al., 2009).

Since sibling control studies only necessitate adjustment for potential confounders that differ between siblings, the following variables were considered for adjustment in the sibling control models: parity, smoking during pregnancy, alcohol consumption during pregnancy, adequacy of prenatal care (measured by the Adequacy of Prenatal Care Utilization Index), maternal age, season of conception, breastfeeding initiation in hospital, risky pregnancy, birthweight, birth year, and gestational age. Such control selection provides aggressive control for family level risk factors and reduces residual confounding by family-level risk factors.

2.4. Statistical analysis

Conditional logistic regression models clustered by census block group (to obtain robust sandwich variances estimators accounting for correlation with census block groups) were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for bronchiolitis and OM clinical encounters per 2 $\mu g/m^3$ increase in lifetime $PM_{2.5}$. Bronchiolitis and OM hospitalizations, emergency department visits, and observational stays were combined into a single analysis. A sensitivity analysis was run with hospitalizations only since a hospitalization diagnosis may represent more severe cases with comorbidities which may have different etiologies from individuals taken to the emergency department or admitted for observational stays.

Effect modification was assessed by income, frequency of clinical encounters within the first 12 or 36 months of life, gestational age, and age of child at time of diagnosis in the age matched analysis. In the sibling matched analysis, effect modification was assessed by maternal language preference and maternal education.

Studies have suggested that concentrations of traffic-related pollutants demonstrate consistent pollutant gradients where concentrations fall to background concentrations within a few hundred meters away from roads (Lipfert and Wyzga, 2008). To assess the relationship between distance to major roadways and risk of bronchiolitis and OM in our cohort, we used penalized splines to model log distance (meters). Traffic density was modeled using quartiles.

Table 2
Distribution of $PM_{2.5}$[a] Exposure in Massachusetts for Infant Bronchiolitis and Otitis Media Cases and Controls.

$PM_{2.5}$ $\mu g/m^3$	Bronchiolitis		Otitis Media	
	Cases	Controls	Cases	Controls
Mean (standard deviation)	9.7 (2.5)	9.6 (2.2)	10.1 (1.6)	10.0 (1.5)
Maximum	19.9	20.1	19.2	17.8
Median	9.9	9.8	10.3	10.2
Interquartile range	2.2	2.2	1.8	1.8

[a] $PM_{2.5}$ average from birth to time of clinical encounter for cases and from birth to age (days) of matched case at time of clinical encounter for controls.

We also fit a conditional poison regression to model counts of clinical encounter and assess rates of morbidity using the gnm R package (Armstrong et al., 2014). Counts of clinical encounters included the total number of bronchiolitis clinical encounters experienced by each child during the first 12 months of life. Controls were non-nested randomly selected infants matched on date of birth and gestational age among individuals in PELL with a non-respiratory clinical encounter. Analysis was adjusted for the same variables as the matched analysis above.

3. Results

We obtained 18,029 bronchiolitis and 40,042 OM first time clinical encounter cases diagnosed from 2001 to 2009. Demographic characteristics of cases and controls are presented in Table 1. A larger proportion of cases were male (60%) while controls were more evenly distributed across sex. For both cases and controls, the majority of mothers were between 30 and 34 years old. Among OM cases and controls, 45% were first born infants, while 35% and 45% of bronchiolitis cases and controls, respectively, were first born infants. Approximately half of the mothers attended at least some college and 86–90% of infants were full term. See Appendix, Table 1 for demographic information of matched sibling cases and controls.

Mean $PM_{2.5}$ was 9.7 and 9.6 $\mu g/m^3$ for bronchiolitis cases and controls, respectively and 10.1 and 10.0 $\mu g/m^3$ for OM cases and controls respectively (Table 2). The maximum lifetime $PM_{2.5}$ average was between 19.2-19.9 $\mu g/m^3$ and IQR was 2.2 $\mu g/m^3$ for bronchiolitis cases and controls and 1.8 $\mu g/m^3$ for OM cases and controls. See Appendix, Table 2 for $PM_{2.5}$ distribution of matched sibling cases and controls.

Crude analysis, controlling for the matching factors only, indicated positive associations between lifetime $PM_{2.5}$ exposure and bronchiolitis (OR = 1.05, 95% CI = 1.02, 1.07) and OM (OR = 1.08, 95% CI = 1.06, 1.10) (Table 3). After adjusting for risky pregnancy, maternal age, birthweight, smoking during pregnancy, maternal education, adequacy of prenatal care, parity, income and insurance type, the association between $PM_{2.5}$ and bronchiolitis was

Table 3
Odds Ratios (OR) and 95% Confidence Intervals (95% CI) for 2 ug/m^3 Increase in Lifetime Average $PM_{2.5}$ Exposure and Infant Bronchiolitis and Otitis Media.

	N	Bronchiolitis OR (95%CI)	N	Otitis Media OR (95%CI)
Crude[a]	53,845	1.05 (1.02, 1.07)	119,789	1.08 (1.06, 1.10)
Adjusted[b]	53,492	1.02 (1.00, 1.04)	119,072	0.97 (0.95, 0.99)
Adjusted + wood burning[b,c]	53,492	1.00 (0.98, 1.03)	119,072	0.96 (0.94, 0.98)
Hospitalizations only[b,d]	19,374	1.09 (1.05, 1.13)	3976	1.07 (0.96, 1.19)

[a] Crude models adjusted for matching variables; date of birth (+/− 6 days) and gestational week.
[b] Adjusted for risky pregnancy, maternal age, birthweight, smoking during pregnancy, maternal education, adequacy of prenatal care, parity, income and insurance type; matched on date of birth (+/− 6 days) and gestational week.
[c] Wood burning is a block group level variable obtained from census data.
[d] Analysis limited only to infants born between 2004 and 2009.

attenuated (OR = 1.02, 95% CI = 1.00, 1.04). Further adjustment for wood burning in the home yielded a null association (OR = 1.00, 95% CI = 0.98, 1.03). After adjustment (with and without wood burning), an inverse association was observed between OM and $PM_{2.5}$ exposure (OR = 0.96, 95% CI = 0.94, 0.98). When only using hospitalization clinical encounters, risk estimates were elevated for OM (OR = 1.07, 95% CI = 0.96, 1.19) and bronchiolitis (OR = 1.09, 95% CI = 1.05, 1.13) hospitalizations.

Results of effect modification by age at time of clinical encounter, income, frequency of clinical encounter and gestational age are displayed in Table 4. None of the stratified analyses indicated statistically meaningful differences across groups based on interaction *p*-values and Wald test *p*-values (used when comparing more than 2 groups), except for age at time of clinical encounter (p = 0.05). For both infant bronchiolitis and OM, elevated ORs were observed among the youngest age groups. Infants from households in the lowest quartile of median income by census block group (<$36,543) had stronger associations with increased lifetime exposure to $PM_{2.5}$ and OM (OR = 1.03, 95% CI = 0.96, 1.11) compared to households of the highest quartile of median income by census block group (>$78,929) (OR = 0.92, 95% CI = 0.85, 0.98), but with overlapping confidence intervals. In our analysis modeling the number of clinical encounters experienced for each child, we found no significant association between $PM_{2.5}$ exposure and the rate of bronchiolitis (results not shown).

We found a positive association with traffic density near the home and bronchiolitis, but not with OM (Table 5). Compared to individuals living in the least traffic-dense quartile, those living in the second (OR = 1.10, 95% CI = 1.05, 1.17), third (OR = 1.24, 95% CI = 1.17, 1.32) and fourth quartiles (OR = 1.23, 95% CI = 1.14, 1.31) had elevated ORs for bronchiolitis. Similar to results from traffic density analyses, bronchiolitis ORs decrease with increasing residential distance to major roadways (Fig. 1). There is a non-linear association between OM and distance to major roadways (Fig. 2).

Results of our secondary analysis using sibling matched controls were consistent with the age matched results (Table 6). After adjustment for variables that could differ across time, including season of conception, parity, birth year, maternal age, and adequacy of prenatal care, we found no association between lifetime $PM_{2.5}$ exposure and risk of bronchiolitis (OR = 1.00, 95% CI = 0.98, 1.03) or OM (OR = 0.96, 95% CI = 0.91, 1.00). The only evidence of effect modification in the sibling analyses was between maternal education and OM, with higher ORs among children whose mothers had less than a high school education (*p*-interaction = 0.005).

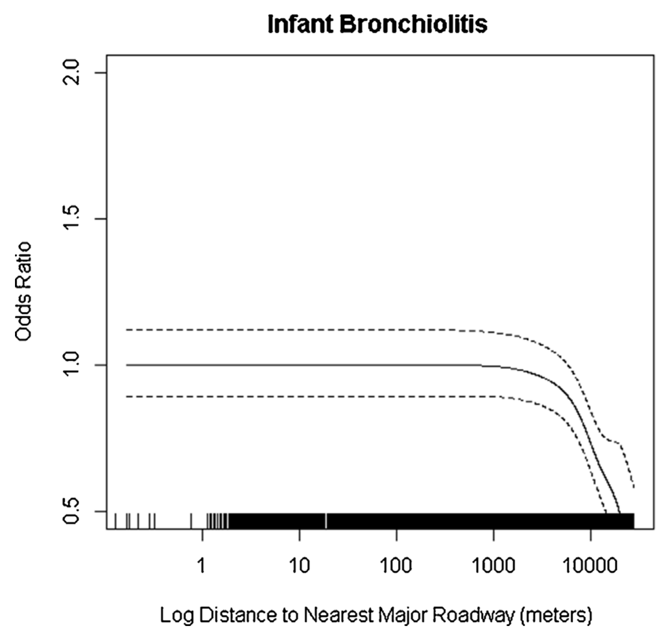

Fig. 1. Exposure Response Curve Using Penalized Splines to Determine Effect of Distance to Major Roadways and Risk of Infant Bronchiolitis.
Exposure response curve showing odds ratio (solid line) and 95% Confidence Interval (dashed line) to model the association between log residential distance to major roadways and bronchiolitis clinical encounter diagnosed in Massachusetts from 2001 to 2009 among infants less than 1 year of age. Odds ratios were estimated using penalized splines with the reference being individuals living closest to major roadways. The association between odds of infant bronchiolitis and residential distance to major roadways was significant (p = 0.002). Analysis adjusted for risky pregnancy, maternal age, birthweight, smoking during pregnancy, maternal education, adequacy of prenatal care, parity, income and insurance type and matched on date of birth (+/− 6 days) and gestational week.

4. Discussion

We report results from our large nested case-control study on the association of $PM_{2.5}$ and traffic related air pollution with bronchiolitis and OM clinical encounters. This study utilizes a unique data linkage system to apply two control groups: a random sample matched on birthdate and gestational age and a sibling matched design to carefully control for common sources of unmeasured confounding. The first study design controls for secular trends in air pollution, while sibling matched controls better control for familial factors which are commonly unaccounted for in traditional environmental epidemiology analyses. Sibling matched controls is a technique frequently used in cancer epidemiology but has rarely been used in air pollution epidemiology (Witte et al., 1999). A major strength and contribution to the literature of this study is the use of satellite based $PM_{2.5}$ measures that provide complete spatial coverage throughout Massachusetts and enable full advantage of the statewide birth cohort. Our findings suggest little evidence of consistent associations between chronic $PM_{2.5}$ exposure during early life and bronchiolitis clinical encounter risk, but positive significant associations with local residential traffic metrics. We did observe consistently protective associations with OM clinical encounters. Such protective associations with $PM_{2.5}$ and residential distance to major roadways may be indicative of incomplete adjustment due to access to care issues, especially since our study only included diagnosis in the most extreme clinical settings.

Table 4
Odds ratio (OR) and 95% confidence interval (95% CI) for 2 ug/m^3 increase in lifetime average $PM_{2.5}$ exposure and infant bronchiolitis and otitis media by susceptibility risk factors.

	Bronchiolitis OR (95%CI)[a]	N	p-value-interaction		Otitis Media OR (95%CI)[a]	N	p-value-interaction
Gestational age				**Gestational age**			
<37 weeks	1.05 (0.97, 1.13)	5989		<37 weeks	0.97 (0.95, 0.99)	8933	
≥37 weeks	1.02 (1.00, 1.05)	47,667	0.81	≥37 weeks	1.00 (0.90, 1.10)	11,0370	0.77
Frequency of clinical encounter				**Frequency of clinical encounter**			
1	1.04 (1.01, 1.07)	40,763		1	0.97 (0.95, 0.99)	11,7190	
≥2	1.02 (0.96, 1.08)	5370	0.29	≥2	0.82 (0.70, 0.96)	2481	0.08
Income[b]				**Income**[b]			
<$37,188	0.98 (0.92, 1.04)	4069		<$36,543	1.03 (0.96, 1.11)	7470	
$37,189–$56,579	0.98 (0.91, 1.05)	5282		$36,544–$55,125	0.94 (0.87, 1.00)	10,436	
$56,580–$81,740	0.99 (0.91, 1.07)	6774		$55,126–$78,929	0.97 (0.91, 1.04)	14,998	
>$81,740	1.07 (0.97, 1.18)	7608	0.09[c]	>$78,929	0.92 (0.85, 0.98)	20,563	0.08[c]
Age at time of clinical encounters				**Age at time of clinical encounters**			
0–6 months	1.04 (1.01, 1.07)	34,454		<1 year	0.98 (0.95, 1.01)	51,143	
6–12 months	1.02 (1.00, 1.04)	19,391	0.05	1–2 years	0.97 (0.94, 1.00)	49,657	
				2–3 years	0.94 (0.90, 0.98)	20,040	0.05[c]

[a] Adjusted for risky pregnancy, maternal age, birthweight, smoking during pregnancy, maternal education, adequacy of prenatal care, parity, income and insurance type; matched on date of birth (+/− 6 days) and gestational week.
[b] Median Income of census block group categorized by quartiles based on control distribution.
[c] *p*-value based on the Wald Test.

Table 5
Odds Ratio (OR) and 95% Confidence Interval (95% CI) for Residential Traffic Density and Infant Bronchiolitis and Otitis Media.

Traffic Density[a]	Bronchiolitis OR (95% CI)[b]	N	Otitis Media OR (95% CI)[b]	N
Q1 (least dense)	1.00	8462	1.00	20,688
Q2	1.10 (1.05, 1.17)	15,494	1.01 (0.98, 1.06)	35,577
Q3	1.24 (1.17, 1.32)	17,084	1.03 (0.99, 1.07)	37,381
Q4 (most dense)	1.23 (1.14, 1.31)	12,803	0.98 (0.93, 1.02)	26,128

[a] Traffic density modeled in quartiles (Q1–Q4) based on annual average daily traffic (AADT); Q1 is 0–12.7, Q2 is 12.8–23.0, Q3 is 23.1–79.0, and Q4 is 79.1–652 AADT. Categorized by quartiles based on control distribution.
[b] Adjusted for risky pregnancy, maternal age, birthweight, smoking during pregnancy, adequacy of prental care, maternal education, parity, income and insurance type; matched on date of birth (+/− 6 days) and gestational week.

Table 6
Odds Ratio (OR) and 95% Confidence Interval (95% CI) for 2 ug/m^3 Increase in Lifetime Average $PM_{2.5}$ Exposure and Infant Bronchiolitis and Otitis Media Using Sibling Matched Controls.

	Bronchiolitis OR (95% CI)	p-interaction	Otitis Media OR (95% CI)	p-interaction
Crude	0.88 (0.86, 1.05)		1.12 (1.07, 1.16)	
Adjusted[a]	1.00 (0.98, 1.03)		0.96 (0.91, 1.00)	
Maternal Education				
Less than high school	0.99 (0.92, 1.07)		1.01 (0.90, 1.13)	
High school	0.95 (0.88, 1.02)		0.99 (0.91, 1.09)	
More than high school	0.98 (0.93, 1.04)	0.96[b]	0.85 (0.78, 0.92)	0.005[b]
Maternal Language Preference				
English	0.98 (0.93, 1.02)		0.95 (0.90, 1.00)	
Not English	0.97 (0.87, 1.06)	0.65	0.95 (0.85, 1.06)	0.98

[a] Adjusted for season of conception, parity, year of birth, maternal age, gestational age, maternal education and adequacy of prenatal care; matched by mother.
[b] *p*-value based on the Wald Test.

We present both the crude (only accounting for the matched designs) and more adequately adjusted results to highlight the influence of confounders. In all analyses, there exists a disparity between the crude and adjusted estimates regardless of matching strategy, especially for OM models. In the time matched analysis, we found that income, as measured by the median income of census block group, shifted the risk estimate across the null for OM and most strongly influenced the effect estimate towards the null for bronchiolitis. To account for correlated income among infants within the same census block group and minimize Berkson Error from utilizing group level data (income and wood burning), we used marginal models by including a cluster specification for census block groups. As we only partially controlled for income and wood burning, we suspect there remains residual confounding by individual income, socioeconomic status, or wood burning in the home. In the sibling matched analysis, for both infant bronchiolitis and OM, year of birth and parity of the mother at time of birth most strongly shifted the effect estimate towards the null for infant bronchiolitis and across the null for OM, indicating the presence of strong temporal trends. Although we included year of birth and season of conception in the model to account for temporal trends, we suspect that the sibling analysis may be subject to residual confounding or selection bias by time and birth order (Sudan et al., 2014). We view the two analyses (time matched and sibling matched) as comple-

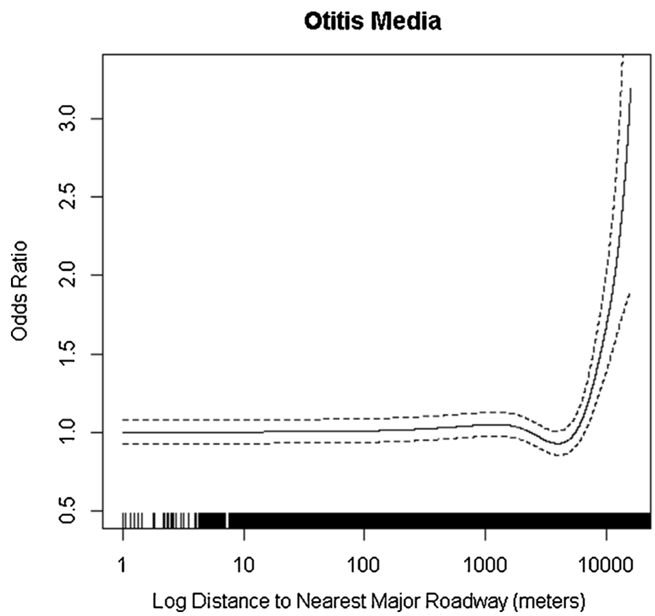

Fig. 2. Exposure Response Curve Using Penalized Splines to Determine Effect of Distance to Major Roadways and Risk of Otitis Media.
Exposure response curve showing odds ratio (solid line) and 95% Confidence Interval (dashed line to model the association between log residential distance to major roadways and otitis media clinical encounter diagnosed in Massachusetts from 2001 to 2009 among infants less than 3 years old). Odds ratios were estimated using penalized splines with the reference being individuals living closest to major roadways. The association between odds of OM and residential distance to major roadways was significant (p = 0.01). Analysis adjusted for risky pregnancy, maternal age, birthweight, smoking during pregnancy, maternal education, adequacy of prenatal care, parity, income and insurance type and matched on date of birth (+/− 6 days) and gestational week.

mentary, with better control for time-varying confounders such as season in the time matched analysis but better control of time-invariant confounders such as health care utilization in the sibling matched analysis.

Our analyses assessed both inpatient and outpatient clinical encounter types. Hospitalizations are inpatient services for which an infant or child is admitted to a hospital on doctor's orders. Outpatient encounters are made up of emergency department visits, where individuals seek emergency services in an emergency room, and observational stays, where individuals are being observed for some time until the doctors decide if the patient needs to be admitted as an inpatient or can be discharged. Our analyses of only hospitalization clinical encounters indicated elevated significant associations with infant bronchiolitis hospitalizations and lifetime $PM_{2.5}$ exposure. Infant bronchiolitis hospitalizations made up 36% of our cases (with emergency room visits and observational stays making up 50% and 14%, respectively). Such findings may be due to multiple comparisons or may indicate that $PM_{2.5}$ exposure may be associated with only the most extreme cases of bronchiolitis. Previous analyses (Karr et al., 2007; Karr et al. 2009a; Karr et al., 2009b; de P Pablo-Romero et al., 2015), which found null and positive associations, were conducted using only hospitalization cases. We also examined emergency room and observational stay clinical encounters separately and found risk and precision estimates were similar to our main findings using all types of encounters. Our results suggest that future studies would benefit from investigating associations between $PM_{2.5}$ exposure and different clinical encounter types if sufficient data are available.

Final models were adjusted for wood burning. Wood burning in the home is used as an alternate fuel source among individuals living in rural areas and contributes to $PM_{2.5}$ (Wu et al., 2007; Saarikoski et al., 2008) (see Appendix, Fig. 1). However, it is still unclear if wood burning increases risk of bronchiolitis (Morris et al., 1990) or OM (Daigler et al., 1991; Pettigrew et al., 2004), independent of the effects of $PM_{2.5}$. Given that wood burning is associated with risk of bronchiolitis and OM independent of $PM_{2.5}$ (as seen in our study when both variables were included in the model) and is also a source of $PM_{2.5}$, then wood burning is a classic confounder and estimates generated from models adjusted for wood burning should be more accurate. However, our study is limited by the lack of individual-level data on wood burning in the home.

Our findings are consistent with studies that assessed the association between chronic $PM_{2.5}$ exposure and risk of infant bronchiolitis. Two of the four previous studies also found null associations between chronic $PM_{2.5}$ and bronchiolitis in Washington, USA and Canada (Karr et al., 2009a; Karr et al., 2009b). Another study conducted in the South Coast Air Basin, a geographic region with high background $PM_{2.5}$ level (mean $PM_{2.5} = 24\ \mu g/m^3$) detected a positive association between lifetime $PM_{2.5}$ exposure and infant bronchiolitis (OR = 1.09, 95% CI = 1.04, 1.14) (Karr et al., 2007). The South Coast Air Basin statistical models did not adjust for income, which in our analysis, strongly influenced the effect estimates towards the null. Differences in results also may be due to differing levels and composition of $PM_{2.5}$ in the South Coast Air Basin compared to Massachusetts (Bell et al., 2007) or differing exposure assessment methods. Another analysis in Spain indicated a positive association, but this analysis was limited to a single monitor station for the entire region (de P Pablo-Romero et al., 2015).

Our findings indicate inverse associations between $PM_{2.5}$ exposure and risk of OM. The direction of the estimate was consistent across epidemiological designs. In Canada, a geographic location with low background $PM_{2.5}$ levels (mean $PM_{2.5}$ = 3.9-5.5), associations were similar to ours (OR = 0.91, 95% CI = 0.89, 0.93) when land-use regression was used to model $PM_{2.5}$ (McIntyre et al., 2011). The same study, using multipollutant models including $PM_{2.5}$ (measured using inverse distance weight) and wood burning predictions found positive significant associations (OR = 1.02, 95% CI = 1.01, 1.04) for $PM_{2.5}$ and OM (McIntyre et al., 2011). Although this study only accounted for physician visits, which were not accounted for in our study, and utilized more sophisticated measures of wood burning, similar to our study, they did see effect estimates for $PM_{2.5}$ decrease when including wood burning in the model. Another study found a marginal positive association in a Netherlands cohort and a null association in a German cohort between $PM_{2.5}$ and OM among young children living in areas of higher background $PM_{2.5}$ levels (mean $PM_{2.5}$ = 16.4 and 13.4 ug/m3) (Brauer et al., 2006). Lastly, another study utilizing 10 different European cohorts found no evidence of an association between annual $PM_{2.5}$ levels and risk of OM during an infant's first or second year of life (MacIntyre et al., 2014).

This study has several strengths, including the large sample size, the ability to link cases within the PELL data system to examine associations using both sibling and time matched controls, control of important confounders such as time, parity, income and wood burning, and the use of sophisticated satellite based $PM_{2.5}$ exposure measures which yield exposure predictions across the entire geographic region of MA. Such exposure assessments have not been used in previous studies and help reduce risk of differential exposure misclassification compared to previous studies that have relied on measures from stationary monitoring systems to estimate exposure over large areas.

A major strength of our study was the ability to use a comprehensive data linkage system to assess chronic exposure to traffic related air pollution on infant bronchiolitis and OM risk. PELL's longitudinal design, allowed for comparisons of zip code between birth and time of clinical encounter, an indicator of residential mobility. By excluding individuals who moved between birth and clinical encounter, the generalizability of our study is limited. To assess the influence of residential mobility, we compared characteristics of infants who moved to those who did not move and found that mothers of infants who moved were slightly older and of higher income groups. All other characteristics such as maternal education, race, healthcare insurance, etc. were similar.

We investigated the effects of traffic related air pollution at various scales. Distance to major roadways and traffic density were assessed at the local level and satellite based air pollution exposure was assessed to capture regional levels. As we found positive and significant associations with local measures but not regional measures we conclude that if associations between traffic related air pollution and infant bronchiolitis exist, they are at the local level. Marginal bronchiolitis and OM risk was observed among infants born to mothers of lower income and/or education. These findings may be indicative of exposure disparities among vulnerable populations with infants born to mothers of lower socioeconomic status living closer to local traffic pollutant sources, such as major roadways. Our findings in the analysis stratified by age at time of clinical encounter indicate that younger infants have higher risk of bronchiolitis and OM compared to their older counterparts ($p = 0.05$). Although effect estimates for younger infants were elevated for OM, they were still protective. Future studies assessing respiratory illness and air pollution should consider age in determining susceptible subgroups.

A limitation of satellite based $PM_{2.5}$ exposure is incomplete temporal coverage due to snowy conditions (Liu et al., 2009), satellite error, cloud coverage (Paciorek and Liu, 2012), or broken satellites. Therefore, we only included average measures which had exposure estimates for over 70% of the days assessed (< 10% of observations excluded). Another limitation of this analysis was the potential for spurious associations due to multiple testing. Although the primary analyses regarding $PM_{2.5}$, bronchiolitis, and OM using both types of matched designs were *a priori* hypotheses, our secondary analyses and investigations of effect modification were numerous and likely less well powered. Lastly, we were limited because we were not able to include primary care visit diagnosis of bronchiolitis or OM which is a likely place for repeat visits and would capture a more stable patient population. Therefore, our findings are only generalizable to hospitalizations, emergency room visits and observational stays. In summary, our results do not support a positive association between $PM_{2.5}$ exposure and risk of severe bronchiolitis and OM after adjustment for confounders, although there is suggestion of increased susceptibility among younger infants born to mothers with less education. Our findings do support an exposure response association between residential traffic density and infant bronchiolitis.

5. Conclusions

After controlling for unmeasured confounding using various epidemiological designs, this study did not provide evidence to support an association between early-life long-term $PM_{2.5}$ exposure and infant bronchiolitis or otitis media. There is consistent evidence to support an association between residential traffic density and distance to major roadways and infant bronchiolitis.

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