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Associations of mobile source air pollution during the first year of life with childhood pneumonia, bronchiolitis, and otitis media

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Abstract

Background—Exposure to pollution from motor vehicles in early life may increase susceptibility to common pediatric infections.

Methods—We estimated associations between residential exposure to primary fine particulate matter (PM_{2.5}), nitrogen oxides (NO_x), and carbon monoxide (CO) from traffic during the first year of life and incident pneumonia, bronchiolitis, and otitis media events by age two years in 22,441 children from the Kaiser Air Pollution and Pediatric Asthma Study, a retrospective birth cohort of children born during 2000–2010 and insured by Kaiser Permanente Georgia. Time to

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first clinical diagnosis of each outcome was defined using medical records. Exposure to traffic pollutants was based on observation-calibrated estimates from A Research LINE-source dispersion model for near surface releases (RLINE) and child residential histories. Associations were modeled using Cox proportional hazards models, with exposure as a continuous linear variable, a natural-log transformed continuous variable, and categorized by quintiles.

Results—During follow-up 2,181 children were diagnosed with pneumonia, 5,533 with bronchiolitis, and 14,373 with otitis media. We observed positive associations between early-life traffic exposures and all three outcomes; confidence intervals were widest for pneumonia as it was the least common outcome. For example, adjusted hazard ratios for a 1-unit increase in NO_x on the natural log scale (a 2.7-fold increase) were 1.19 (95% CI 1.12, 1.27) for bronchiolitis, 1.17 (1.12, 1.22) for otitis media, and 1.08 (0.97, 1.20) for pneumonia.

Conclusions—Our results provide evidence for modest, positive associations between exposure to traffic emissions and common pediatric infections during early childhood.

Keywords

pneumonia; bronchiolitis; otitis media; air pollution; traffic

Introduction

Pneumonia, bronchiolitis, and otitis media are common pediatric infections with a large economic burden. Pneumonia is the second leading cause of infant mortality globally and in 2009 was the leading cause of pediatric hospitalization in the U.S. with associated medical costs amounting to almost \$1 billion^{1, 2}. In 2002, an estimated 149,000 children under the age of two in the U.S. were hospitalized for bronchiolitis resulting in \$543 million in direct medical costs and \$1.4 billion in hospital charges³. An estimated 8.7 million children are diagnosed with otitis media annually in the U.S., with an associated cost of \$2.88 billion in health care utilization⁴.

Due to their size, inhalation rates, incomplete development of the respiratory and immune systems, and time spent outdoors, children are more vulnerable to urban air pollutants than adults⁵. Recent epidemiologic evidence suggests traffic-related air pollution may be a risk factor for respiratory infections and related comorbidities in infants and children^{6–12}. Secondary pollutants including ozone and particulate matter were found to be significantly associated with increased risk for bronchitis, pneumonia, and otitis media in a case crossover study of Georgia pediatric emergency department visits during 2002–2008¹³. Jedrychowski and colleagues reported a dose-response relationship between recurrent bronchiolitis and pneumonia infections and $\text{PM}_{2.5}$ at the child's prenatal residence in Krakow, Poland¹⁴. In British Columbia, Canada, infants living within 50 meters of a highway had a 6% higher risk of bronchiolitis diagnosis, and infants living within 150 m of a highway had a 14% higher risk of hospitalization for respiratory syncytial virus (RSV) bronchiolitis infection; however, the confidence intervals for both estimates included the null^{15, 16}. Another proximity study observed a statistically significant increased risk of bronchiolitis clinical encounters for infants living in areas of dense traffic, but found chronic $\text{PM}_{2.5}$ exposure alone was not meaningfully associated with infant bronchiolitis¹⁷. A meta-analysis of 10 European birth

cohorts found elevated and statistically significant associations between NO₂ and PM₁₀ with pneumonia in early childhood, but not PM_{2.5}¹⁸. Reductions in traffic emissions over a 20-year period [1993–2012] were associated with decreases in pediatric bronchitis diagnosis and hospitalizations in Southern California¹⁹. Modest, positive associations between NO_x, PM_{2.5}, and PM₁₀ with otitis media among children have been reported in several studies^{18, 20, 21,22,23} but not others^{11,24}.

In this paper, we report estimated associations between fine particulate matter (PM_{2.5}), carbon monoxide (CO), and nitrogen oxides (NO_x) concentrations from traffic during the first year of life and childhood pneumonia, otitis media, and bronchiolitis by age two in a cohort of insured children in Atlanta, Georgia.

Methods

Ambient air quality model

We modeled hourly concentrations of primary PM_{2.5} (µg/m³), CO (ppm), and NO_x (ppb) contributed by mobile sources for 2002–2011 in metropolitan Atlanta at 250 meter resolution using A Research LINE-source dispersion model for near surface releases (RLINE)²⁵. This model is designed to estimate air quality emissions from traffic in the direct vicinity of the roadway by numerically integrating point source emissions while also accounting for local meteorological conditions that affect dispersion patterns. Model inputs included emissions data for roadway segments based on 2010 traffic data from the Atlanta Regional Commission's Atlanta Roadside Emissions Exposure Study and surface meteorology data for 2002–2010 from AERMET, the meteorological processors of AERMOD^{26,27}. We created annual averages from the hourly estimates, and these averages were used in the epidemiologic analyses. The averages were calibrated using observational data from stationary air pollution monitors to adjust for overestimation of spatial gradients. Estimates of NO_x and CO were calibrated directly to observations because an estimated 73% and 88% of these pollutants, respectively, are contributed by mobile sources²⁸. A smaller proportion of PM_{2.5} is contributed by mobile sources, so primary PM_{2.5} was calibrated to source apportionment estimates based on monitoring data that were created using a chemical mass balance model with gas constraints²⁹. Annual average pollutant concentrations were created for years 2002–2011. Because the spatial characteristics of the study area (number/location of highways, traffic density, etc.) did not change meaningfully between 2000 and 2002, we assigned the year 2002 estimates to the study years prior to 2002, i.e., 2000 and 2001²⁸. RLINE does not include mechanisms forming secondary PM_{2.5}, so only the associations with the primary portion of the PM_{2.5} are assessed here. Further details about the creation of these air pollution estimates are available²⁸.

KAPPA cohort data

The Kaiser Air Pollution and Pediatric Asthma Study (KAPPA) is a retrospective birth cohort of children insured by Kaiser Permanente Georgia (KPGA) Health Maintenance Organization who were born between 2000 and 2010 in metropolitan Atlanta, Georgia. There were 24,608 children in the KAPPA cohort and 22,441 were included in this analysis. Children were excluded if they were not enrolled in KPGA at day 29 of life (the start of the

outcome period of interest) (n=489); were diagnosed with pneumonia, bronchiolitis, or otitis media in the first 28 days of life (n=223); had no residential history information in the first year of life (n=721); or had one or more residence during the exposure period outside the region for which pollutant concentrations were available (n=734).

The three health outcomes examined in this study were childhood pneumonia (ICD-9 codes 480–486), otitis media (ICD-9 codes 382.XX), and acute bronchitis and bronchiolitis (ICD-9 codes 466.XX). Because 80% of the events in the acute bronchitis and bronchiolitis outcome group were bronchiolitis (ICD-9 codes 466.1X), we refer to this outcome henceforth as “bronchiolitis.” For each outcome we followed children from day 29 of life (to exclude neonatal infections) until time of the first diagnosis, censorship (e.g., they ceased to be insured by the HMO), or the child’s second birthday. Ambient concentrations of primary PM_{2.5}, CO, and NO_x from traffic were assigned to each child based on residential location. We calculated separate estimates for each outcome using residences between the child’s birth date and date of diagnosis of the outcome of interest, censorship, or their first birthday (whichever came first). When a child moved during the exposure period we calculated a time-weighted average of the estimated concentrations at each location.

Description of covariates

We adjusted for neighborhood socioeconomic status (SES), city region, child race, child sex, maternal asthma, maternal education, maternal prenatal smoking, birth year and maternal age in the analyses. Because the RLINE estimates are for annual averages, there is no seasonality in exposure concentrations, and hence no confounding by season. Neighborhood SES was characterized at the census block group level by demographic clusters created by the Georgia Department of Public Health³⁰. These clusters were created using 2010 U.S. Census data on 25 variables related to age, income, family structure, housing, education attainment and employment. Neighborhood SES was determined for each child based on residence at birth. City region described the location of the child’s residence in Atlanta: inside metropolitan Atlanta (defined as inside the I-285 highway that surrounds the city), less than or equal to 16 kilometers outside I-285, and more than 16 kilometers outside I-285. Categorizations of other covariates were: child race (white, black, other, unknown), maternal asthma status (no, yes, missing), maternal education (less than 12th grade, high school or GED, at least some college, missing), maternal smoking during pregnancy from birth certificate data (no, yes, missing), birth year indicator variables (2000–2010), maternal age dichotomized at the mean, and child sex (male, female).

Statistical modeling

We used Cox proportional hazards (PH) regression to estimate associations between first year of life exposure to primary PM_{2.5}, CO and NO_x from traffic emissions and time to first diagnosis of pneumonia, bronchiolitis, or otitis media (up until age two). The PH assumption was evaluated using Kaplan Meier log-log curves, goodness of fit (GOF) tests using Schoenfeld residual p values, and extended Cox models to test each variable’s interaction with survival time. Variables satisfying the PH assumption according to (at least) 2 of these three approaches in univariate models were deemed to satisfy the PH assumption. Variables not satisfying the PH assumption were further evaluated in adjusted PH models. We used

stratified Cox models to accommodate variables that did not satisfy the PH assumption. As expected, the pollutant exposure distributions were right skewed, which motivated an examination of modeling exposures as continuous linear variables (scaled to 1 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$, 20 ppb NO_x , and 1 ppm CO), as natural log-transformed continuous variables, and by quintiles. Data were analyzed using SAS 9.4 (Cary, NC) allowing for non-independence due to sibling clustering via the robust sandwich estimator implemented by the “covs(aggregate)” statement in PROC PHREG.

Results

Annual average estimates for primary $\text{PM}_{2.5}$, NO_x , and CO from traffic are shown in Figure 1, eFigure 1, and eFigure 2. Concentrations of the three examined air pollutants decreased over the course of the study period. Descriptive statistics on first year of life air pollution exposures from traffic are shown in Table 1. Pollutant concentrations were highly correlated because they were modeled using the same emissions data.

Cohort characteristics are shown in Table 2. The cohort was racially diverse, with 39.5% of children classified as white, 34.9% as black, and the remaining classified as unknown or other race. The majority of children were born to mothers who attended at least some college and lived in neighborhoods classified as high SES. Out of the three outcomes examined by the second birthday, otitis media was the most common; during follow-up 2,181 children (9.7%) were diagnosed with pneumonia, 5,533 children (24.7%) were diagnosed with bronchiolitis, and 14,374 children (64.1%) were diagnosed with otitis media. Males were more likely than females to be diagnosed with a respiratory or ear infection by age two. Examining differences by race, black children were more likely to be diagnosed with pneumonia, and white children were more likely to be diagnosed with bronchiolitis or otitis media. Seasonal variation in diagnosis was observed, with the highest proportion of diagnoses occurring in winter for all outcomes (38% of pneumonia cases, 44% of bronchiolitis cases, and 34% of otitis media cases).

Neighborhood SES violated the proportional hazards assumption for both bronchiolitis and otitis media, child race violated the PH assumption for bronchiolitis, and city region violated the PH assumption for otitis media. No variables violated the PH assumption for pneumonia. We therefore implemented stratified Cox models for the bronchiolitis and otitis media analyses.

Although the magnitude of the hazard ratios varied, overall conclusions were consistent from Cox models when exposure was modeled as a continuous linear variable (eTable 1) and as a natural log-transformed continuous variable (Table 3). For a log increase in exposure, unadjusted hazard ratios for all pollutants with pneumonia, bronchiolitis and otitis media ranged from 0.95 to 1.05 with confidence intervals including the null ($\text{HR}=1.0$) in all but one instance (Table 3). The association estimates were elevated after statistical adjustment for covariates. In the adjusted models for bronchiolitis, the hazard ratios ranged from 1.16 (95% CI 1.08, 1.25) for a 2.7-fold increase in CO (a 1-unit increase on the natural log scale), to 1.23 (95% CI 1.15, 1.32) for a 2.7-fold increase in $\text{PM}_{2.5}$. Adjusted hazard ratios were similar for otitis media. The adjusted HRs for pneumonia were also positive, but 95%

confidence intervals were wider because pneumonia was the least common outcome. For example, the adjusted HR for pneumonia for a 2.7-fold increase in log-transformed PM_{2.5} was 1.08 (95% CI 0.97, 1.20).

When exposure was modeled using quintiles, we observed a general trend where the association estimates between primary PM_{2.5}, NO_x, and CO from traffic and bronchiolitis and otitis media by age 2 tended to increase as the exposure quintiles increased (Figure 2). This pattern was not evident for pneumonia. For bronchiolitis and otitis media, the shape of the exposure-response relationship across quintiles varied slightly, with the HRs increasing more rapidly for bronchiolitis than for otitis media.

Discussion

These results provide evidence for modest, positive associations between exposure to traffic emissions and bronchiolitis and otitis media diagnoses in the first two years of life. The estimated associations with pneumonia were positive but less elevated, and the confidence intervals were wider. Our findings add to evidence from earlier studies suggesting that early life exposures to traffic may increase susceptibility to childhood infections.

Misclassification of residential location in the KAPPA study is likely a small concern because the Kaiser Permanente Georgia HMO retains information on previous addresses, which enabled us to create time-weighted air pollution metrics. Although there is imprecision in the date of address change, simulations performed using KAPPA data to investigate the consequences of exposure measurement error due to residential mobility suggest that in this cohort this source of error likely causes only a small (2–10%) bias towards the null³¹. The calibrated RLINE estimates were shown in Zhai et al. (2016) to have good accuracy and precision; the calibration reduced normalized mean bias for all pollutants when compared to raw RLINE estimates (29% to 0.3% for PM_{2.5}, 22% to –1% for CO, and 303% to 43% for NO_x). A limitation of this model is that traffic emissions data were only available for 2010. Although we used the network of regulatory monitors to calibrate the pollutant concentrations for the earlier years of the study, our air quality model would not have captured meaningful variability in traffic dynamics or intensity in the early years of our study period (2002–2009). However, we do not expect large changes in the spatial distribution of emissions to have occurred during or prior to this period as there were no major changes in freeways or major highways (calibration captures temporal changes, including impacts from the recession and emission controls). Additionally, due to the high correlation between estimates of PM_{2.5}, NO_x, and CO, we were unable to isolate their individual impacts. Our epidemiologic results are indicative of associations between traffic exposure and early life outcomes in this cohort rather than of the specific pollutants.

The outcomes of interest in this study were defined using ICD-9 codes from clinical diagnosis instead of parental self-report, which lessens the potential for recall bias and outcome misclassification. This is a strength of our study; much of the prior literature has relied either on parental self-report^{6, 24, 32, 33, 34, 35} or on emergency department visits and hospitalizations^{11, 15, 20, 23, 36, 37} which do not capture the less-severe morbidities that are treated in pediatric care offices. Even with these clinical records, however, it is very likely

that some children had one or more of the outcomes but were never seen by a doctor particularly due to the similar symptoms that these conditions can have to cold or flu. As such, the true incidence of these pediatric conditions is likely somewhat higher than what was captured by the medical records.

We used Cox proportional hazards regression to analyze the data, wherein we considered children to be at risk for illness until the date of their illness diagnosis or censorship (which occurred when a child reached age two or when they were no longer insured by Kaiser Permanente Georgia). Due to skewed exposure distributions, we modeled exposure as an untransformed continuous variable, transformed by the natural log, and by quintile to allow for a potential linear or non-linear relationship between exposure and outcome. Results from all modeling techniques led to similar conclusions.

The KAPPA cohort is not a random sample of children, as membership was limited to children with health insurance through Kaiser Permanente Georgia HMO. Broadly, the KAPPA children tended to be of higher SES than the general population, with 59% of mothers having at least some college education and 62% of children residing in neighborhoods classified as having the highest of the four SES categories (Table 2). We do not know if the estimated associations with traffic pollutants would have been different had our cohort consisted of a more socioeconomically diverse group of children. However, it is probable that certain factors that could plausibly lessen the exposure effects in this cohort, e.g., air conditioning use and good nutrition, were likely more common among KAPPA cohort children. One advantage of a relatively uniformly high socioeconomic cohort is that risk of bias from residual confounding by socioeconomic factors might be lower than if the cohort consisted of a more diverse sample of Atlanta children.

In this large urban birth cohort, we observed positive associations between concentrations of primary PM_{2.5}, NO_x, and CO from traffic emissions and childhood bronchiolitis and otitis media diagnoses. Associations with pneumonia were also positive, although the effect estimates were of relatively smaller magnitude, and the confidence intervals were wider. Our study, which integrates calibrated RLINE outputs with a rich dataset of pediatric clinical encounters from Kaiser Permanente Georgia, provides further evidence regarding the associations between traffic pollution and pediatric respiratory disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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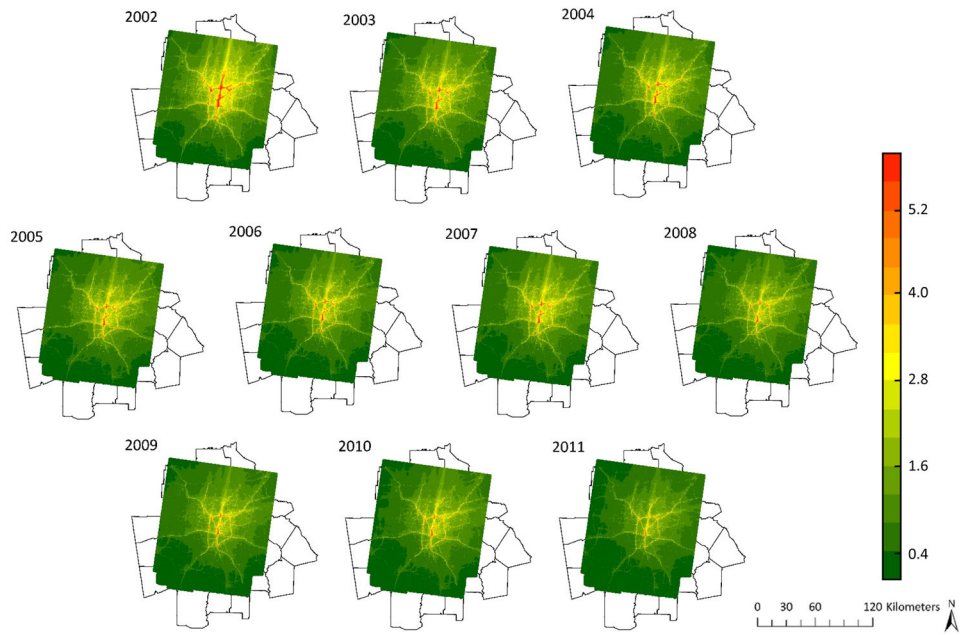


Figure 1.
2002–2011 Primary PM_{2.5} ($\mu\text{g}/\text{m}^3$) concentrations contributed by mobile sources.

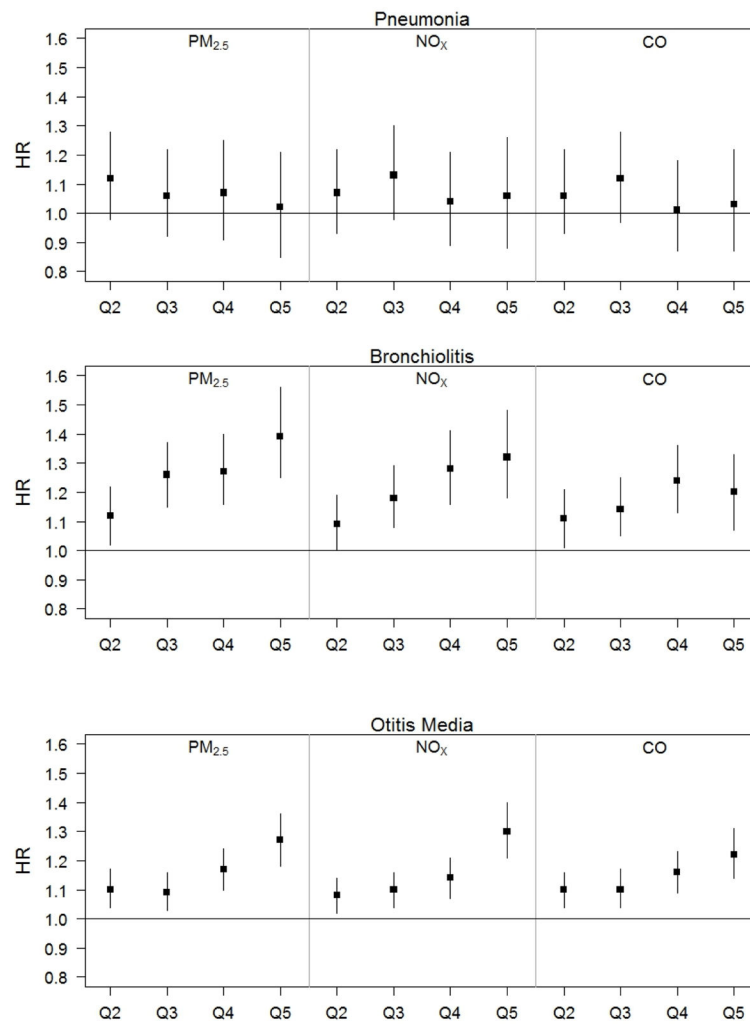


Figure 2. Adjusted hazard ratios and 95% confidence intervals per quintile of primary PM_{2.5}, NO_x and CO from traffic and pneumonia, bronchiolitis, and otitis media by age 2 (using quintile 1 as the reference group). Numeric results for this figure are available in eTable 2.

Table 1

First year of life exposure to primary PM_{2,5}, NO_x and CO from traffic (N=22,441)

Pollutant	Minimum	Median (IQR)	Maximum
PM _{2,5} (µg/m ³)	0.06	1.41 (0.93)	13.76
NO _x (ppm)	0.01	0.06 (0.04)	0.59
CO (ppm)	0.10	0.59 (0.38)	5.13

Exposures were estimated separately for each outcome, but were extremely similar across outcomes. To avoid unnecessary repetition only exposures calculated for pneumonia are displayed.

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Table 2

Descriptive statistics for children born between 2000–2010 and enrolled in Kaiser Permanente in the Atlanta, Georgia metropolitan area (n=22,441)

Characteristic (n, %)	Pneumonia (%)	Bronchiolitis (%)	Otitis Media (%)
% Diagnosed	9.7	24.7	64.1
Child Sex			
Male (11,409, 50.8%)	10.6	27.8	66.0
Female (11,032, 49.2%)	8.9	21.4	62.0
Neighborhood SES¹			
Highest SES (14,012, 62.4%)	9.6	25.9	65.6
Urban/Suburban (2,225, 9.9%)	10.1	20.6	57.9
Rural, average to low SES (1,087, 4.8%)	11.8	24.9	63.8
Lowest SES (5,114, 22.8%)	9.4	23.0	62.6
Child Race			
White (8,857, 39.5%)	9.6	27.4	68.2
Black (7,833, 34.9%)	10.7	25.1	63.7
Other ² (2,720, 12.1%)	8.2	17.8	58.7
Unknown (3,031, 13.5%)	8.9	21.8	57.7
Maternal Asthma Status			
No (17,736, 79.0%)	9.5	24.2	63.7
Yes (2,450, 10.9%)	11.8	30.8	71.2
Missing (2,255, 10.0%)	9.4	21.7	58.5
Maternal Education			
At least some college (13,270, 59.1%)	9.6	25.3	65.6
Less than 12 th grade (280, 1.2%)	14.3	22.9	66.8
High School or equivalent (2,564, 11.4%)	9.6	25.8	62.3
Missing (6,327, 28.2%)	9.9	22.9	61.4
Prenatal Smoking Status			
No (17,636, 78.6%)	9.8	24.9	64.8
Yes (450, 2.0%)	12.0	27.8	64.2
Missing (4,355, 19.4%)	9.3	23.5	61.2
City Region³			
Metro Atlanta (2,348, 10.5%)	9.5	20.4	60.6
16 km from metro Atlanta (9,629, 42.9%)	9.8	23.0	62.7
>16 km from metro Atlanta (10,464, 46.6%)	9.7	27.2	66.1
Maternal Age			
Less than 28, or missing (6,963, 31.0%)	10.0	23.1	60.9
Between 28 and 31 (4,435, 19.8%)	9.6	26.5	65.3
Between 31 and 35 (5,922, 26.4%)	9.3	26.2	66.5
Greater than 35 (5,121, 22.8%)	9.9	23.4	64.4

¹Neighborhood SES classified using demographic clusters created by Georgia Department of Public Health.

²Includes Asian, American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, and children identifying with more than one racial group.

³Metro Atlanta defined as inside the I-285 perimeter that encircles Atlanta.

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Hazard ratios per natural log increase in primary PM_{2.5}, NOx and CO from traffic and child outcomes by age two (n=22,441)

Table 3

Outcome	Exposure	Unadjusted HR (95% CI)	Adjusted ^{1,2} HR (95% CI)	Adjusted, ³ Females Only HR (95% CI)	Adjusted, ³ Males Only HR (95% CI)
Pneumonia	PM _{2.5}	0.96 (0.89, 1.04)	1.08 (0.97, 1.20)	1.04 (0.89, 1.23)	1.10 (0.95, 1.26)
	NOx	0.95 (0.88, 1.02)	1.08 (0.97, 1.20)	1.04 (0.90, 1.21)	1.10 (0.96, 1.26)
	CO	0.95 (0.87, 1.03)	1.06 (0.95, 1.18)	1.03 (0.87, 1.21)	1.07 (0.93, 1.24)
Bronchiolitis	PM _{2.5}	1.00 (0.95, 1.05)	1.23 (1.15, 1.32)	1.13 (1.03, 1.25)	1.32 (1.20, 1.44)
	NOx	1.01 (0.96, 1.06)	1.19 (1.12, 1.27)	1.10 (1.01, 1.21)	1.27 (1.16, 1.38)
	CO	0.97 (0.92, 1.02)	1.16 (1.08, 1.25)	1.07 (0.97, 1.18)	1.24 (1.13, 1.36)
Otitis media	PM _{2.5}	1.03 (1.00, 1.06)	1.17 (1.11, 1.22)	1.14 (1.07, 1.21)	1.19 (1.12, 1.26)
	NOx	1.05 (1.02, 1.08)	1.17 (1.12, 1.22)	1.14 (1.08, 1.21)	1.19 (1.13, 1.26)
	CO	1.02 (0.99, 1.06)	1.15 (1.10, 1.21)	1.13 (1.06, 1.20)	1.17 (1.10, 1.25)

¹ Adjusted models controlled for child sex, child race, maternal asthma, maternal age, neighborhood SES, city region, maternal education, maternal prenatal smoking, and year of birth.

² Stratified Cox models selected based on a priori modeling strategy for bronchiolitis and otitis media outcomes: bronchiolitis models were stratified on neighborhood SES and child race; otitis media models were stratified on neighborhood SES and city region.

³ Adjusted model, data limited to only females (or only males).

Hazard ratios represent the relative change in hazard rate per 2.7-fold increase in mobile source pollutant concentration.