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Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution☆

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Abstract

Few studies investigate the impact of air pollution on the leading cause of infant morbidity, acute bronchiolitis. We investigated the influence of $PM_{2.5}$ and other metrics of traffic-derived air pollution exposure using a matched case–control dataset derived from 1997 to 2003 birth and infant hospitalization records from the Puget Sound Region, Washington State. Mean daily $PM_{2.5}$ exposure for 7, 30, 60 and lifetime days before case bronchiolitis hospitalization date were derived from community monitors. A regional land use regression model of NO_2 was applied to characterize subject's exposure in the month prior to case hospitalization and lifetime average before hospitalization. Subject's residential proximity within 150 m of highways, major roadways, and truck routes was also assigned. We evaluated 2604 (83%) cases and 23,354 (85%) controls with information allowing adjustment for mother's education, mother's smoking during pregnancy, and infant race/ethnicity. Effect estimates derived from conditional logistic regression revealed very modest increased risk and were not statistically significant for any of the exposure metrics in fully adjusted models. Overall, risk estimates were stronger when restricted to bronchiolitis cases attributed to respiratory syncytial virus (RSV) versus unspecified and for longer exposure windows. The adjusted odds ratio (OR_{adj}) and 95% confidence interval per 10 mcg/m^3 increase in lifetime $PM_{2.5}$ was 1.14, 0.88–1.46 for RSV bronchiolitis hospitalization. This risk was also elevated for infants who resided within 150 m of a highway (OR_{adj} 1.17, 0.95–1.44). This study supports a developing hypothesis that there may be a modest increased risk of bronchiolitis attributable to chronic traffic-derived particulate matter exposure particularly for infants born just before or during peak RSV season. Future studies are needed that can investigate threshold effects and capture larger variability in spatial contrasts among populations of infants.

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Keywords

Bronchiolitis; Particulate matter; Traffic; Air pollution; Respiratory disease

1. Introduction

Bronchiolitis is the most common cause of hospitalization in the first year of life with respiratory syncytial virus (RSV) the most important etiologic agent (Panitch, 2001). Many studies have linked increased exposure to ambient air pollution with increased risk of pediatric respiratory conditions including respiratory infections; however, few epidemiologic data on the infant period and bronchiolitis are available (Karr et al., 2006, 2007). Nonetheless, there is consistent epidemiological evidence of increased infant post-neonatal mortality due to respiratory causes associated with increased exposure to ambient air pollution (Ritz et al., 2006; Woodruff et al., 1997; Bobak and Leon, 1999).

Toxicological studies demonstrate that exposure to air pollutants such as particulate matter increases the severity of pulmonary pathology associated with viral respiratory infection in animal and *in vitro* models (Harrod et al., 2003; Castranova et al., 2001). As such, we hypothesize that infants who reside in settings of elevated ambient air pollutants may develop subclinical pulmonary compromise that places them at risk of developing more severe bronchiolitis when these infants encounter the common etiologic respiratory viruses in their communities, such as RSV. This was previously examined in a region of relatively high ambient air pollution in the Los Angeles area of California (South Coast Air Basin) (Karr et al., 2007). In that setting, a case–control analysis of infant bronchiolitis hospitalization and ambient air pollutant exposure found modestly increased risk for subchronic (30 day) and chronic (lifetime) fine particulate matter ($PM_{2.5}$) exposure but not with other criteria air pollutants investigated (nitrogen dioxide, ozone, carbon monoxide) and not with shorter, more acute exposure periods investigated. For a 10 mcg/m^3 increase in chronic $PM_{2.5}$ exposure, the risk of hospitalization increased approximately 9% (adjusted OR 1.09, 95% confidence interval: 1.04, 1.14).

Here we investigate the influence of $PM_{2.5}$ and metrics of traffic-derived air pollution exposure in the Puget Sound region of Washington State, where ambient concentrations of pollutants are generally low and are on average approximately half those experienced in the Los Angeles area (Karr et al., 2007).

While traffic predominates as a source in ambient air pollution in both areas and most US cities, woodsmoke is also a prominent air pollutant in the Puget Sound, particularly in wintertime, coinciding with the annual winter epidemic of RSV bronchiolitis. Observational studies have linked woodsmoke exposure with increased respiratory health events including acute lower respiratory tract infections in children (Naeher et al., 2007). We used the approach of linking population-based data on infant hospitalization for bronchiolitis with available community-based regulatory network monitor data for $PM_{2.5}$ to test the primary hypothesis that increased exposure to ambient $PM_{2.5}$ in infants in the Puget Sound region is associated with increased hospitalization for bronchiolitis. This approach is commonly employed in air pollution epidemiological studies and the density of $PM_{2.5}$ monitors in this region provides an opportunity to capture community-wide spatial contrasts in $PM_{2.5}$ specifically. In addition, we applied a NO_2 land use regression (LUR) model to improve spatial heterogeneity regarding exposure to traffic exhaust, recognizing the potential increased toxicity of traffic-derived particulate matter in the ultrafine size range (<0.1 μm) and the observation that exposure to traffic-derived particulate can vary considerably at the

neighborhood scale (US EPA, 2008). Lastly, we evaluated proximity to major highways and roadways as an additional proxy for traffic-derived air pollution exposure.

2. Methods

The study procedures were approved by the University of Washington and Washington State Department of Health Institutional Review Boards.

2.1. Subject characterization

The Washington State Birth Events Registry Database (BERD) contains data from Washington State birth certificates with linkage to mother/infant first year of life hospitalization records and includes geocoded birth address information. Using BERD, we identified all livebirths with a birth residence in Puget Sound, Washington (defined as King, Snohomish, Pierce, and Kitsap counties) for 1997–2003. Eligible subjects included those with data on length of gestation and a $PM_{2.5}$ ambient monitor within 20 km of their birth residence. From this population-based sample, we developed a nested case–control dataset. Cases were defined as all infants who had a hospitalization discharge record for bronchiolitis in the first year of life. Two ICD 9 CM codes represented all bronchiolitis cases in these data; 466.11—bronchiolitis due to respiratory syncytial virus or 466.19—bronchiolitis due to other infectious organisms. Coding was done by the treating physician or hospital and may or may not include laboratory confirmation. For each case, up to 10 controls were randomly selected from the subjects who did not have a hospitalization discharge record for bronchiolitis in their first year of life. Controls were matched within 7 days to their case's date of birth, gestational length, and length of birth hospitalization stay.

2.2. Exposure characterization

The Puget Sound Clean Air Agency provided data on daily average $PM_{2.5}$ from the ambient monitor regulatory network for the years representing the first year of life for our study subjects (1997–2004). For most monitors during this study period, daily average $PM_{2.5}$ measurements were conducted at least every third day. The number of ambient $PM_{2.5}$ monitors in the region was 4, 9, 16, and 17 for the years 1997–2000, respectively, and 18 in subsequent study years. Subjects' geocoded birth address was the basis of assignment to the most proximal $PM_{2.5}$ monitor. Means of daily average $PM_{2.5}$ concentrations for the period 7 days prior to case hospitalization date were calculated to represent an acute exposure window. If a subject had more than one hospitalization record for bronchiolitis, the first event was used as the reference date. Similarly, means of $PM_{2.5}$ daily average concentrations 30 and 60 days prior to case hospitalization date were determined as subacute/subchronic–chronic exposure periods. Lastly, mean of $PM_{2.5}$ for all days between discharge from birth hospitalization to case hospitalization date was determined to represent lifetime exposure. A subject had to have been at risk, based on their age, during an exposure window for exposure to be assessed. For example, subjects in case/control groups with a case diagnosed at age 1 month did not have 60 day exposure windows assessed but would be included in the lifetime average analysis.

Exposure assessment was also performed based on a regionally developed LUR model of nitrogen dioxide (NO_2) ambient concentrations which included characterization of subject's proximity to major roadways, highways, or truck routes. The basic LUR model followed the form of a model initially developed for Vancouver, Canada in which regression methods are used to model pollutant concentrations measured at specific sites based on variables that characterize surrounding land use, population density, and traffic patterns (Henderson et al., 2007). An NO_2 dataset collected in Seattle to refine a field sampling protocol, with the majority of sampling locations placed to capture concentration gradients, was used in a

model transferability exercise to derive the LUR model for the Seattle area (Poplawski et al., 2009). The specific model was calibrated based on 2-week field measurements of average ambient NO_2 using passive Ogawa samplers conducted at 26 sites during March 2005 in Seattle. The NO_2 field measurements were annualized through comparison of annual and 2-week NO_2 at a Washington Department of Ecology continuous NO_2 analyzer where one of the passive samplers was collocated. The land use variables and associated effect distances, or buffers, were selected according to the strength of their correlation with NO_2 and a stepwise regression analysis. Model predictors included the following land use variables: area in hectares of transportation, communications, and utilities land use within 750 m; length in kilometers of expressways and highways within 100m; length in kilometers of major roads and arterials within 300m; and population density per hectare within 2500 m.

The LUR model with these variables was derived with a restriction that required all variable coefficients to be positive, so the model could be extrapolated into lower population density areas of the four-county region without predicting negative NO_2 concentrations. Values of the predictor variables were generated from data obtained from the Puget Sound Regional Council, county road networks, the US Environmental Protection Agency, and the US Census for all of the birth residence sites. The corresponding annual NO_2 concentration was then estimated from the Seattle LUR model. Monthly NO_2 exposure estimates were generated from comparison of each month's average NO_2 with that of the annualized prediction based on the Ecology continuous monitoring data. A proximity analysis for each of the residence sites classified all sites according to whether or not they are within 50 or 150 m of roads categorized as either expressways or highways (Rd1) or major roads and arterials (Rd2). The same network of streets and roads which were significant for the NO_2 model within 100 and 300 m buffers, respectively, were used in the proximity classification but with effect distances of 50 and 150 m from each residence site. Specifically, a circular buffer of 50 and 150m was constructed around the latitude/longitude for the birth residence of each subject using Arc-GIS. If the intersection of that buffer with the network of Rd1 or Rd2 roadways produced a non-zero length, the subject was classified as "exposed".

In summary, subjects had individually computed exposure assessment for ambient $PM_{2.5}$ average exposure in the period 7, 30, 60, or all days (lifetime) between birth hospitalization to case hospitalization. They also had individually estimated lifetime and month prior average traffic-associated NO_2 exposure and classification of their residence as yes/no within 150 m of a major roadway, highway, or truck route.

2.3. Data analysis

Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals associated with a 10 mcg/m^3 increase in $PM_{2.5}$, a 1 ppb increase in NO_2, and quartile increases in both (STATA 8). The risks associated with classification of residential proximity within 150 m of major roadways, highways, and truck routes were also evaluated with this model. In addition to the matching variables, models were initially adjusted for known strong risk factors for bronchiolitis hospitalization available in these data: mother's self-reported smoking during pregnancy and infant race/ethnicity (non-Hispanic white, black, Native American, Pacific Islander, and Hispanic). (Bronchiolitis rates are higher for infants who are not identified as non-Hispanic white). Socioeconomic factors were suspected as likely important confounders so maternal education was also included in all adjusted models (<high school, high school, >high school). Other available covariates representing measures of socioeconomic factors were also considered but had no meaningful effect on risk estimates so were not retained (e.g. insurance and public assistance program status did not change the risk estimate by more than 10%). Additional potential confounders considered which also lacked a consequential influence on observed effect estimates were infant sex, parity (potential proxy for household crowding and exposure to viruses from

siblings), and prenatal care utilization. We investigated the potential susceptibility of subgroups of infants by stratified analysis based on age at diagnosis and gestational age at birth, hypothesizing those younger infants and those born prematurely would be at greatest risk. We performed sensitivity analysis by investigating the effect of increased air pollution exposure on those cases coded as RSV bronchiolitis specifically, as this may represent a more precise case definition and represents the majority of the disease burden. Additional sensitivity analyses based on restricted subject groups with more proximal ambient monitors were performed to explore the impact of distance to monitor on risk estimates.

3. Results

In total, 3124 infants met the case definition for bronchiolitis and we identified 27,340 matched controls (Table 1). We constructed exposure windows to represent mean daily average $PM_{2.5}$ for the 7, 30, and 60 days prior to case date of hospitalization for 99.8%, 86.2%, and 64.7% of our matched case–control subjects, respectively (Table 2). Those missing these exposure windows represent those not at risk (age at case diagnosis less than the length of the total exposure time window). A lifetime average $PM_{2.5}$ concentration starting from time of birth hospitalization discharge was constructed for all subjects. All subjects were classified regarding whether their residential address was within 150 m of a major highway or truck route. Inputs for land use regression modeling of NO_2 exposures were available for 2986 (96%) cases and 25,824 (94%) controls. About 67.3% of our identified bronchiolitis hospitalizations were coded as due to RSV bronchiolitis specifically (ICD 9 CM 466.11).

Consistent with known risk factors for infant bronchiolitis, our cases were more likely to be male and have mothers who smoked during pregnancy (Table 1). Birth month, birth year, and gestational age were comparable, reflecting our matching criteria for date of birth and length of gestation. Mothers of case subjects were less likely to have completed high school. Our controls were more likely to be white or Asian compared with the other race/ethnic categories.

The distribution of distance to monitors was similar for cases and controls; the mean (SD) was 8.4 km (4.6) and 8.5 km (4.7), respectively. The maximum distance from subjects' birth residence to the nearest $PM_{2.5}$ monitor was 20 km, based on initial eligibility requirements.

Table 2 shows the distribution of calculated mean $PM_{2.5}$ and NO_2 exposures for case and control subjects for the exposure windows of interest. On average, $PM_{2.5}$ exposures were slightly higher for cases than controls for all exposure windows, with mean exposures for the various exposure window analyses between 11.6 and 12.6 mcg/m^3. The NO_2 land use regression estimates (NO_2–LUR) were very similar among cases and controls with means for month prior and lifetime average between 14.8 and 15 ppb. The interquartile ranges of assigned exposures for the study population were approximately 4 mcg/m^3 for $PM_{2.5}$ and 3 ppb for NO_2

As expected for the Puget Sound region, air pollution concentrations were low relative to air quality standards and international guidelines. The US EPA Federal Ambient Air Quality standard for daily $PM_{2.5}$ during the study period was 65 mcg/m^3, although it has recently been reduced to 35 mcg/m^3. The national standard for *annual* average NO_2 is 53 ppb.

In general, the adverse air pollution exposure effects observed in these data were observed among those infants hospitalized with a code indicating RSV bronchiolitis, specifically. Point estimates were attenuated for RSV and non-RSV bronchiolitis combined ((Table 3) compared with RSV bronchiolitis only). The estimated odds ratios demonstrated non-statistically significant increased risk for RSV bronchiolitis hospitalization associated with

$PM_{2.5}$ for all exposure windows evaluated. Land use regression NO_2 estimates were not associated with an increase risk in linear models although some effect was observed in quartile-based assessment. However, adjustment for potentially confounding factors decreased all of these estimates such that they were no longer statistically significant (Table 3). The odds ratio point estimates for a 10 mcg/m^3 increase in all $PM_{2.5}$ exposure windows investigated for RSV bronchiolitis cases were in the range of 1.12–1.20, with the latter estimated for a 60-day (subchronic–chronic) exposure window. Adjusted point estimates for increasing quartiles of lifetime average NO_2 exposure were 1.17, 1.16, and 1.04, respectively. All of these analyses yielded confidence intervals spanning 1.00 and trend analyses for all quartile-based analyses did not reach statistical significance.

Evaluation of 7-day, 30-day and 60-day exposure windows demonstrate increasing risk estimates with increasing exposure averaging time. Similarly, for LUR–NO_2 models, lifetime average exposure yielded a stronger association with risk of bronchiolitis hospitalization as compared to exposure in the month prior.

Infants whose birth address was within 150 m of a freeway or highway had a higher adjusted risk estimate for bronchiolitis hospitalization overall (OR_{adj} 95% CI: 1.07, 0.90–1.27) as well as RSV bronchiolitis hospitalization (OR_{adj} 95% CI: 1.17, 0.95–1.44) (Table 4). Increased risk was also observed for bronchiolitis hospitalization among infants who lived within 150 m of a designated truck route but not for infants hospitalized with RSV bronchiolitis (Table 4).

For $PM_{2.5}$ exposure, stratified analysis by age at diagnosis yielded positive point estimates for the youngest (age 0–3 months) infants in contrast to infants diagnosed at older ages, although not statistically significant (Fig. 1). Stratification based on prematurity revealed a positive point estimate for infants born at or near term (⩾37 weeks) in contrast to infants born prematurely, contrary to our hypothesis (Fig. 1).

Half of the subjects were within 5 km of the assigned $PM_{2.5}$ monitor which provided the basis of exposure characterization. Analyses based on proximity to ambient monitor suggested elevated risk estimates for subjects whose exposure assessment was based on more proximal monitors (within 5 km of birth residence) (Fig. 1).

4. Discussion

Few air pollution epidemiologic investigations address the impact of specific endpoints of respiratory morbidity in the infant period. We focused on the prominent respiratory disease of concern in infancy, bronchiolitis, in a region of modest air pollution exposure. For lifetime exposure to $PM_{2.5}$, quartile-based exposure assessment suggested an increased risk in RSV bronchiolitis hospitalization as exposure increased. In addition, longer exposure windows yielded higher risk estimates than short-term exposure windows for this outcome (OR_{adj}, 95% CI: 1.14, 0.88–1.46 per 10 mcg/m^3 increase in lifetime exposure). However, overall, effect estimates were very modest and were not statistically significant for infant bronchiolitis hospitalization and exposure to $PM_{2.5}$, traffic, or NO_2 in the Puget Sound region of Washington State for any of the exposure windows (acute, subacute, subchronic, and chronic) investigated in fully adjusted models.

Cases and controls were contemporaneous by design to remove temporal variability and the potential for seasonally varying confounding. The remaining spatial variability for subjects in this study region was limited. The interquartile range of monitor-based $PM_{2.5}$ exposures in this study was less than a third of that observed in a similar study conducted in the Los Angeles area where significant effects were observed. Other differences in these studies that may explain lack of effect observed include potential differing toxicity of the particulate

matter composition. For example, woodsmoke is an important source of exposure in the wintertime in Puget Sound. Also, housing may be "leakier" in LA (windows open in milder weather) such that ambient air pollution exposure is more reflective of personal exposure (indoor plus outdoor) and thereby reduces exposure misclassification. While these limitations made detection of significant effects challenging in this study, exploration of these data allows novel preliminary investigation of bronchiolitis attributed to RSV, the prominent viral etiologic agent.

RSV bronchiolitis occurs in annual wintertime epidemics. Diagnosis is typically based on clinical presentation, although laboratory confirmative methods are available. Designation of RSV bronchiolitis based on ICD 9 CM coding in the hospitalization record reflects the attribution of the clinical provider/hospital which may or may not be based on laboratory confirmation. Analysis of air pollution effects in the peak RSV season (November–April) regardless of ICD 9 CM viral etiologic identity (i.e., all cases) yielded similar findings to the RSV only analyses. Our finding regarding higher effect estimates for the RSV subgroup may reflect an enhanced ability to discern air pollutant effects in the wintertime when exposure to fine particulate matter is more variable and higher compared with the warm season, rather than a specific viral agent–air pollution interactive effect. Wintertime PM composition may also vary due to the importance of wood burning in this region. Another possible explanation is that RSV-attributed cases may be less misclassified than bronchiolitis not otherwise specified and the more homogeneous case definition may improve detection of an effect on this disease. However, experimental data argue against this as the pathological processes incited by RSV as well as other viral agents such as influenza can be augmented with concurrent exposure to particulate matter air pollution (Castranova et al., 2001; Fujii et al., 2002).

The observation of higher risk estimates observed for the longer term exposure windows versus more acute exposure effects is consistent with findings on bronchiolitis and fine particulate air pollution exposure windows investigated in Southern California (Karr et al., 2006, 2007). $PM_{2.5}$ exposure effect estimates increased across exposure windows of 7 days to 30 days to 60 days. Lifetime average NO_2–LUR exposure risk estimates also exceeded those estimated for the month prior. The chronic or lifetime exposure window represents a mix of averaging times, dependent upon the age of the child at diagnosis. Available investigations of the effects of ambient air pollution on young children's respiratory health have largely relied on acute exposure models such as time series and case crossover designs. The potential for chronic exposure to increase the vulnerability of young infants to significant respiratory health compromise when encountering common respiratory infections such as RSV deserves more attention in other large population-based studies and experimental models.

Our risk estimate for the youngest infants (diagnosis age 0–3 months) was positive in contrast to the risk estimates for older infants, which is consistent with our hypothesis that relative pulmonary immaturity increases risk. It may also reflect the fact that the disease peaks in wintertime and infants diagnosed at these young ages have exposure windows assessed in the wintertime when fine particulate matter concentrations have the highest concentrations and greatest variability. Contrarily, we did not observe an increased risk for a fine particulate effect on infants born prematurely. Overall, premature infants have not been investigated as a vulnerable subgroup for air pollution exposure post-natally. The impact of prematurity was investigated in the Los Angeles area-based study of infant bronchiolitis where no increased risk for this potentially vulnerable subgroup was observed for chronic exposure (unpublished), although increased risk was observed for very premature infants and *short-term* increases in $PM_{2.5}$ (Karr et al., 2006).

Premature birth is among the most significant risk factors for hospitalization for bronchiolitis. At risk subgroups of premature infants routinely receive immunoprophylaxis with an RSV monoclonal antibody. This intervention may explain the lack of air pollution risk. In addition, the increased medical fragility of premature infants may influence their mobility and exposure to ambient air pollutants. The observed elevated risk estimate for term infants suggests that the vulnerability to ambient air pollution effects on bronchiolitis occurs via a pathway outside of the link between maternal (infant *in utero*) exposure to ambient air pollution and premature birth which has been reported in some studies (Brauer et al., 2008).

The opportunity to use the population's proximity to regulatory monitoring stations to estimate community based and personal exposure in regions with relatively dense networks of routinely collected data has proved useful in large epidemiological studies. However, critiques of this method note the potential misclassification of assigning individuals to the most proximal monitor. Capturing the local heterogeneity of $PM_{2.5}$ based on monitors that were placed to represent community-wide exposure will be dependent on the extent of population proximity to these monitors. Wind vectors and topographical features that may influence the dispersion of pollutants are not incorporated into this simple proximity exposure assessment. In a Los Angeles based birth outcome study, effect estimates clearly diminished with increasing distance between homes and PM_{10} and CO monitoring stations with strongest effects were among subjects within 1 mile (1.6 km) (Wilhelm and Ritz, 2005). In our data, effect estimates diminished when analyses included subject's residing more than 5 km (approximately 3 miles) of a monitoring station. The density of $PM_{2.5}$ monitors in our study region precludes an adequate sample size for analyses less than this distance.

Ambient monitoring network limitations have led to recent development of alternative efficient approaches for large-scale studies. Increasingly, estimates of traffic-derived ambient air pollutants using modeled spatiotemporal surfaces of traffic exposure such as we have used here are being employed. Comparisons of health risk estimates using a monitor-based approach versus a land use regression approach in a similar airshed (Georgia Air Basin of British Columbia) suggest these approaches capture somewhat independent aspects of the spatiotemporal variability in ambient air pollutants (Brauer et al., 2008). In our study, using the $PM_{2.5}$ ambient monitoring network provided slightly greater variability among subject's exposure estimates and more consistent associations with health risk. For $PM_{2.5}$ exposure, elevated risk estimates were observed only at the highest two quartiles of exposure. For NO_2, higher risks were observed in all quartiles but point estimates were higher in the middle quartiles. If there is a threshold for an adverse effect of $PM_{2.5}$ and NO_2, our opportunity to observe a significant effect may be further limited in this region of relatively low concentrations of pollutants in addition to the limited spatial variability. Since the NO_2 data were collected predominantly to characterize gradients near major roadways, they may not have captured enough range in NO_2 concentrations or the explanatory variables to enable a robust LUR model for NO_2 that could more accurately depict spatial variability, especially in outlying regions with very different land use pattern than those which prevail in Seattle.

Using straightforward and reliable metrics of proximity of residence to major roadways and highways has proven to be a consistently good predictor of adverse respiratory outcomes associated with ambient air pollution in epidemiological studies (Morgenstern et al., 2007). This occurs despite their limitations. For example, the latitude and longitude do not reflect differences that may occur in distance between an actual residence and the geocoded address for subjects. Such metrics have the advantage of being easily translatable to land use policy. New policies restricting siting of new schools to distances of greater than 150 m of busy

freeways or traffic corridors are being implemented (State of California 2004 Senate Bill 352 http://www.cde.ca.gov/LS/fa/sf/sb352.asp). We found increased point estimates of risk of bronchiolitis hospitalization and specific RSV bronchiolitis hospitalization for infants who reside within 150 m of a freeway or highway (not statistically significant). We did not observe an effect on RSV hospitalization in relation to proximity to a truck route (proxy for diesel exposure) or within 150 m of major road or arterial (data not shown).

Given the high prevalence of illness attributed to RSV bronchiolitis in infancy and the widespread population exposure to $PM_{2.5}$ and traffic, even a small relative risk, if real, translates to large public health relevance. This study lends some support to a developing hypothesis that there may be a modest increased risk attributable to chronic traffic-derived exposure particularly for infants born just before or during peak RSV season. However, the lack of statistically significant findings limits interpretation. Future studies that can capture larger variability in spatial contrasts among populations of infants and investigate threshold effects are needed. Clearly, additional studies that focus on respiratory health in infancy are important given the lack of therapeutic modalities for bronchiolitis (primarily supportive care), where the need for prevention strategies is paramount. While not particularly sophisticated, the utility of traffic proximity measures as a marker of adverse exposure in population-based studies is underscored given their widespread availability throughout municipalities and the straightforward translation to land use planning policies.

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References

Bobak M, Leon D. The effect of air pollution on infant mortality appears specific for respiratory causes in the postneonatal period. Epidemiology 1999;10:666–670. [PubMed: 10535778]

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ. Health Perspect 2008;116:680–686. [PubMed: 18470315]

Castranova V, Ma JYC, Yang HM, Antonini JM, Butterworth L, Barger MW, Roberts J, Ma JKH. Effect of exposure to diesel exhaust particles on the susceptibility of the lung to infection. Environ. Health Perspect 2001;109(Suppl 4):609–612. [PubMed: 11544172]

Fujii T, Hogg JC, Keicho N, Vincent R, VanEeden SF, Hayashi S. Adenoviral EIA modulates inflammatory mediator expression by lung epithelial cells exposed to PM 10. Am. J. Physiol. Lung Cell Mol. Physiol 2002;284:L290–L297. [PubMed: 12388335]

Harrod KS, Jaramillo RJ, Rosenberger CL, Wang S-Z, Berger JA, McDonald JD, Reed MD. Increased susceptibility to RSV infection by exposure to inhaled diesel engine emissions. Am. J. Respir. Cell Mol. Biol 2003;28:451–463. [PubMed: 12654634]

Henderson SB, Beckerman B, Jerrett M, Brauer M. Application of land use regression to estimate long-term concentrations of traffic-related nitrogen oxides and fine particulate matter. Environ. Sci. Technol 2007;41:2422–2428. [PubMed: 17438795]

Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, Kaufman J. A case crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ. Health Perspect 2006;114:277–281. [PubMed: 16451867]

Karr C, Lumley T, Schreuder A, Davis R, Larson T, Ritz B, Kaufman J. Effect of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am. J. Epidemiol 2007;165:553–560. [PubMed: 17158471]

Morgenstern V, Zutavern A, Cyrys J, Brockow I, Gehring U, Koletzo S, Bauer CP, Reinhardt D, Wichmann HE, Heinrich J. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. Occ. Environ. Med 2007;64:8–16.

Naeher LP, Brauer M, Lipsett M, Zelikoff JT, Simpson CD, Koenig JQ, Smith KR. Woodsmoke health effects: a review. Inhal. Toxicol 2007;19:67–106. [PubMed: 17127644]

Panitch H. Bronchiolitis in infants. Curr. Opin. Pediatr 2001;13:256–260. [PubMed: 11389361]

Poplawski K, Gould T, Setton E, Allen R, Su J, Larson T, Henderson S, Brauer M, Hystad P, Lightowlers C, Keller P, Cohen M, Silva C, Buzzelli M. Intercity transferability of land use regression models for estimating ambient concentrations of nitrogen dioxide. J. Exp. Anal. Environ. Epidemiol 2009;19:107–117.

Ritz B, Wilhelm M, Zhao X. Air pollution and infant death in Southern California, 1989–2000. Pediatrics 2006;118:493–502. [PubMed: 16882800]

US Environmental Protection Agency. Research program particulate matter health effects. [accessed July 10, 2008]. <http://www.epa.gov/NHEERL/research/pm/research_area05.html>

Wilhelm M, Ritz B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. Environ. Health Perspect 2005;113:1212–1221. [PubMed: 16140630]

Woodruff TJ, Grillo J, Schoendorf KC. The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. Environ. Health Perspect 1997;105:608–612. [PubMed: 9288495]

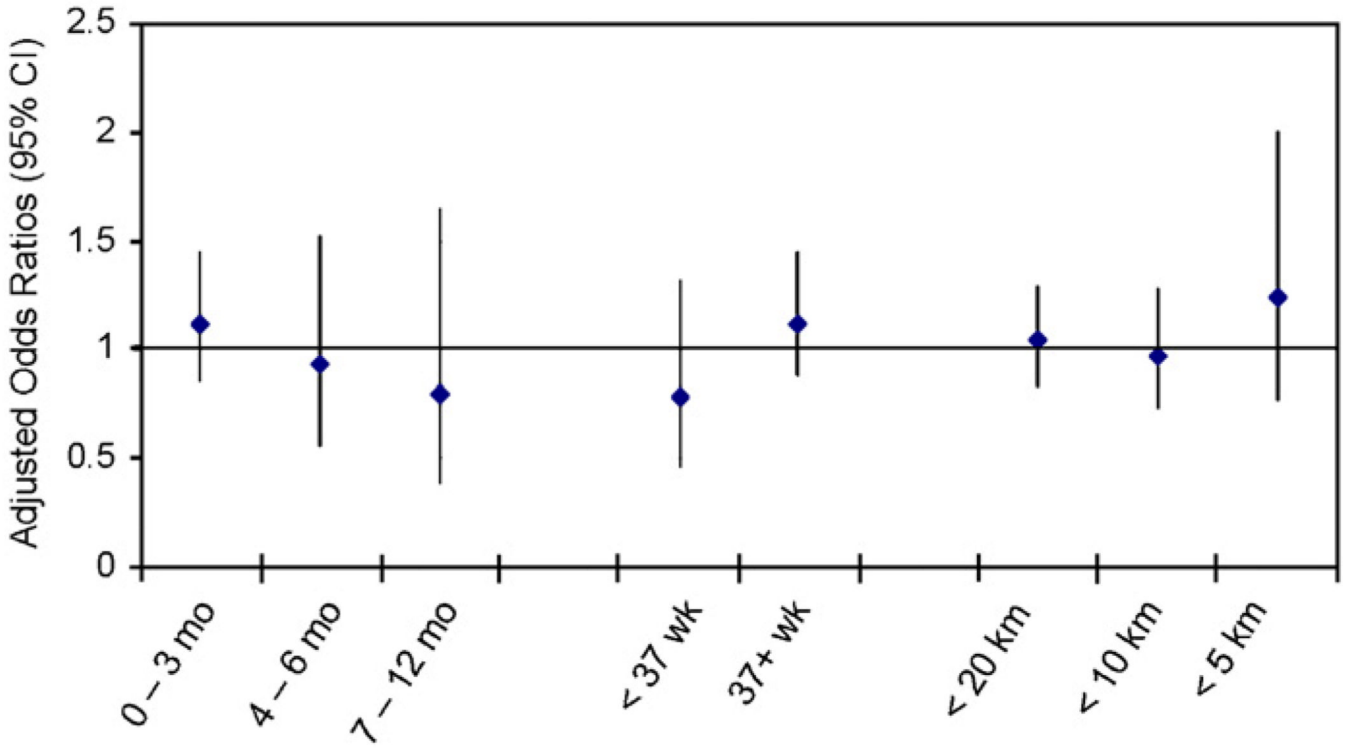

Fig. 1.

Modification of $PM_{2.5}$ effect on infant bronchiolitis (adjusted odds ratio (OR) and 95% confidence intervals (CI) based on age at diagnosis (months), gestational age (weeks), and monitor proximity (km).

Table 1

Selected characteristics of bronchiolitis case and control study subjects.

Characteristic	Case *N* (%)	Control *N* (%)
All subjects	3124 (10.2)	27,340 (89.8)
Sex		
Male	1871 (59.9)	13,925 (50.9)
Female	1253 (40.1)	13,415 (49.1)
Child's race/ethnicity[a]		
White	1786 (57.1)	17,150 (62.7)
Black	356 (11.4)	2417 (8.8)
Native American	128 (4.1)	496 (1.8)
Asian	303 (9.7)	3410 (12.5)
Pacific islander	53 (1.7)	199 (0.7)
Hispanic	353 (11.3)	2328 (8.5)
Other or unknown	148 (4.7)	1340 (4.9)
Maternal smoking during pregnancy[a]		
Yes	579 (18.5)	2668 (9.8)
No	2450 (78.4)	24,134 (88.3)
Missing	95 (3.0)	538 (2.0)
Gestational age[2] (weeks), mean (SD)	38.5 (2.1)	38.8 (1.7)
25–29 weeks	17 (0.5)	23 (0.1)
30–34 weeks	118 (3.8)	565 (2.1)
35–37 weeks	538 (17.2)	4146 (15.2)
>37 weeks	2451 (78.5)	22,606 (82.7)
Maternal education[a]		
< High school	620 (19.9)	3133 (11.5)
High school	910 (29.1)	6695 (24.5)
> High school	1228 (39.3)	14,733 (53.9)
Missing high school	366 (11.7)	2779 (10.2)
Birth year[b]		
1997	360 (11.5)	2423 (8.9)
1998	343 (11.0)	2581 (9.4)
1999	508 (16.3)	4206 (15.4)
2000	533 (17.1)	5199 (19.0)
2001	582 (18.6)	5617 (20.5)
2002	444 (14.2)	3983 (14.6)
2003	354 (11.3)	3331 (12.2)
Birth month[b]		
1	428 (13.7)	3669 (13.4)
2	307 (9.8)	2793 (10.2)
3	234 (7.5)	2288 (8.4)

Characteristic	Case *N* (%)	Control *N* (%)
4	167 (5.4)	1564 (5.7)
5	154 (4.9)	1294 (4.7)
6	148 (4.7)	1219 (4.5)
7	171 (5.5)	1414 (5.2)
8	220 (7.0)	1728 (6.3)
9	233 (7.5)	2006 (7.3)
10	311 (10.0)	2545 (9.3)
11	343 (11.0)	3059 (11.2)
12	408 (13.1)	3761 (13.8)
Distance to $PM_{2.5}$ monitor (km), mean (SD)	8.4 (4.6)	8.5 (4.7)
25th percentile	4.7	4.9
50th percentile	7.7	7.8
75th percentile	11.6	11.7
Maximum	20.0	20.0
Case diagnosis, month		
November–April	2854 (91.4)	
May–October	270 (8.6)	
Case age at diagnosis		
0–3 months	1801 (57.7)	
4–6 months	713 (22.8)	
7–12 months	610 (19.5)	

[a] Covariates in adjusted models.

[b] Matching variable.

Table 2

Distribution of subject's estimated exposure to $PM_{2.5}$ based on proximal community ambient monitor or traffic using an NO_2-based land use regression model (mean, standard deviation).

	Cases (*N*)	Case exposures	Controls (*N*)	Control exposures
Lifetime average $PM_{2.5}$ (mcg/m^3)	3124	12.2 (3.3)	27,340	12.0 (3.3)
Minimum		2.9		1.9
25th percentile		10.1		9.9
50th percentile		11.9		11.7
75th percentile		13.9		13.8
Maximum		32.5		36.9
7-Day average $PM_{2.5}$ (mcg/m^3)	3117	11.8 (5.3)	27,304	11.6 (5.2)
30-Day average $PM_{2.5}$ (mcg/m^3)	2701	12.2 (3.9)	23,503	12.1 (3.9)
60-Day average $PM_{2.5}$ (mcg/m^3)	2051	12.6 (3.7)	17,663	12.4 (3.7)
Lifetime average NO_2 (ppb)	2993	14.8 (2.3)	26,154	14.8 (2.3)
Minimum		9.2		8.5
25th percentile		13.2		13.2
50th percentile		14.6		14.5
75th percentile		16.0		16.0
Maximum		29.5		38.8
30 Day average NO_2 (ppb)	2993	15.0 (2.7)		14.9 (2.6)

Table 3

Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for infant bronchiolitis hospitalization in relation to community $PM_{2.5}$ and traffic NO_2 exposure during specific time windows.

	All bronchiolitis				RSV bronchiolitis			
	Crude OR	**95% CI**	**Adj. OR**	**95% CI**	**Crude OR**	**95% CI**	**Adj. OR**	**95% CI**
Lifetime average $PM_{2.5}$ (mcg/m^3)—per 10 mcg/m^3 increase	1.49	1.22, 1.81	1.04	0.83, 1.29	1.55	1.23,1.95	1.14	0.88, 1.46
Quartile 1 (2.0, 10.1)	1.00	Referent	1.00		1.00	Referent	1.00	
Quartile 2 (10.1, 12.0)	1.07	0.94, 1.21	0.94	0.82, 1.09	1.05	0.90, 1.22	0.97	0.81, 1.15
Quartile 3 (12.0, 14.0)	1.12	0.97, 1.29	0.93	0.79, 1.09	1.21	1.02, 1.44	1.06	0.87, 1.29
Quartile 4 (14.0, 36.9)	1.30	1.10, 1.54	0.99	0.82, 1.20	1.38	1.13, 1.68	1.10	0.88, 1.37
Linear trend	$p = 0.003$		$p = 0.84$		$p = 0.001$		$p = 0.33$	
60-Day average $PM_{2.5}$ (mcg/m^3)—per 10 mcg/m^3 increase	1.46	1.18, 1.80	0.98	0.77, 1.24	1.70	1.31, 2.20	1.20	0.89, 1.61
30-Day average $PM_{2.5}$ (mcg/m^3)—per 10 mcg/m^3 increase	1.35	1.13, 1.61	1.00	0.82, 1.22	1.47	1.18, 1.83	1.15	0.90, 1.47
7-Day average—per 10 mcg/m^3 increase $PM_{2.5}$ (mcg/m^3)	1.23	1.08,1.40	1.04	0.90, 1.20	1.26	1.07,1.47	1.12	0.94, 1.33
Lifetime average NO_2—per 1 ppb increase	1.02	1.00–1.04	1.01	0.99–1.03	1.02	1.00–1.05	1.00	0.96–1.04
Quartile 1 (8.5–13.1)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Quartile 2 (13.2–14.4)	1.06	0.95, 1.19	0.99	0.88, 1.13	1.14	0.99, 1.31	1.17	0.93, 1.46
Quartile 3 (14.5–15.9)	1.14	1.01,1.28	1.03	0.91, 1.18	1.22	1.06, 1.42	1.16	0.92, 1.45
Quartile 4 (16.0–38.8)	1.15	1.02,1.31	1.02	0.88, 1.17	1.22	1.04, 1.43	1.04	0.81, 1.36
Linear trend	$p = 0.02$		$p = 0.71$		$p = 0.01$		$p = 0.09$	
Average NO_2 in the month before hospitalization—per 1 ppb increase	1.02	1.00–1.04	1.01	0.99–1.03	1.02	1.00–1.04	1.00	0.96–1.04
Quartile 1 (8.5–13.1)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Quartile 2 (13.2–14.6)	1.03	0.92–1.16	0.96	0.84–1.09	1.08	0.93–1.25	1.08	0.86–1.35
Quartile 3 (14.7–16.4)	1.03	0.91–1.18	0.92	0.79–1.07	1.08	0.91–1.27	1.04	0.80–1.34
Quartile 4 (16.5–38.8)	1.17	1.01–1.35	1.04	0.89–1.23	1.18	0.99–1.40	1.02	0.77–1.36
Linear trend	$p = 0.04$		$p = 0.64$		$p = 0.09$		$p = 0.98$	

Table 4

Adjusted odds ratios and 95% confidence intervals (OR_{adj}, CI) for infant bronchiolitis hospitalization (all cases and RSV only) in relation to proximity traffic metrics.

Residential proximity to traffic	All cases (*N*)	Controls (*N*)	OR_{adj}. CI	RSV cases (*N*)	Controls (*N*)	OR_{adj}.CI
Within 150 m of a freeway or highway?						
No	2914	1561	1.00	1959	17,493	1.00
Yes	210	25,779	1.07 (0.90–1.27)	144	1037	1.17 (0.95–1.44)
Within 150 m of a designated truck route?						
No	2372	21575	1.00	1609	22338	1.00
Yes	232	1779	1.06 (0.91–1.23)	147	1864	1.00 (0.83–1.21)