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Original Contribution

Effects of Subchronic and Chronic Exposure to Ambient Air Pollutants on Infant Bronchiolitis

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Ambient air pollutant exposure has been linked to childhood respiratory disease, but infants have received little study. The authors tested the hypotheses that subchronic and chronic exposure to fine particulate matter (particulate matter $\leq$2.5 μm in aerodynamic diameter ($PM_{2.5}$)), nitrogen dioxide, carbon monoxide, and ozone increases risk of severe infant bronchiolitis requiring hospitalization. Study subjects were derived from linked birth–hospital-discharge records of infants born in 1995–2000 in the South Coast Air Basin of California. Cases with a hospital discharge for bronchiolitis in infancy were matched to 10 age- and gestational-age-matched controls. Exposures in the month prior to hospitalization (subchronic) and mean lifetime exposure (chronic) referenced to the case diagnosis date were assessed on the basis of data derived from the California Air Resources Board. In conditional logistic regression, only subchronic and chronic $PM_{2.5}$ exposures were associated with increased risk of bronchiolitis hospitalization after adjustment for confounders (per 10-μg/m^3 increase, adjusted odds ratio = 1.09 (95% confidence interval: 1.04, 1.14) for both). Ozone was associated with reduced risk in the single-pollutant model, but this relation did not persist in multipollutant models including $PM_{2.5}$. These unique US data suggest that infant bronchiolitis may be added to the list of adverse effects of $PM_{2.5}$ exposure.

air pollutants; bronchiolitis; case-control studies; infant; respiratory tract diseases

Abbreviations: CI, confidence interval; OR, odds ratio; $PM_{2.5}$, particulate matter $\leq$2.5 μm in aerodynamic diameter.

A number of regulated outdoor air pollutants have been consistently linked to adult and pediatric respiratory diseases. Among children, asthma has received much study, and exacerbations have been associated with increases in ozone, particulate matter, nitrogen dioxide, carbon monoxide, and sulfur dioxide (1–6). These pollutants have also been linked to increased hospitalization for respiratory infections or all respiratory diseases considered as a whole (7–9). In addition, negative effects on normal lung function growth have been associated with exposure to particulate matter, ozone, and nitrogen dioxide (10). Most pediatric studies focus on school-age and preschool-age children. Some studies include infants, but only as part of an aggregate category including older children and with aggregated

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diagnostic categories. There are few data on the effects of air pollution in infancy or specific diagnostic categories in infancy.

Studies investigating overall and respiratory-specific infant mortality during the postneonatal period have been undertaken in the Czech Republic, South Korea, and the United States and in Mexico City, Mexico (11–15). These studies have demonstrated the most consistent and sizeable increased risk for exposure to particulate matter air pollution. Effects in both acute and longer-term exposure scenarios have been investigated. In a recent California-based case-control study, Woodruff et al. (15) evaluated the effect of chronic exposure to ambient fine particulate matter (particulate matter $\leq$2.5 μm in aerodynamic diameter ($PM_{2.5}$)). A modest increase (10 $\mu g/m^3$) was associated with an odds ratio of 2.13 (95 percent confidence interval (CI): 1.20, 4.05) for respiratory mortality among normal-birth-weight infants.

Bronchiolitis is the leading cause of hospitalization in the first year of life (16, 17), and respiratory syncytial virus is the etiologically responsible agent in up to 90 percent of cases (18, 19). It occurs in annual wintertime epidemics and induces pathophysiologic responses similar to asthma, including excess inflammation and subsequent airway obstruction. Approximately 40 percent of affected infants go on to develop recurrent wheezing and to receive a subsequent diagnosis of asthma (19). Data specifically evaluating the role of air pollution in bronchiolitis are rare.

In a cohort of Chilean infants followed monthly from age 4 months to 1 year, short-term increases in $PM_{2.5}$ were associated with clinical evaluation for ''wheezy bronchitis'' (20). In that study, results for nitrogen dioxide and sulfur dioxide were less consistent. In a Netherlands-based cohort study that modeled young children's (age $\leq$2 years) chronic exposure to fine particulate matter and nitrogen dioxide, an increase in physician-diagnosed asthma in the first year of life (as reported by parents) was observed for an interquartile-range increase in $PM_{2.5}$ (3.2 $\mu g/m^3$) and soot but not nitrogen dioxide ($PM_{2.5}$ odds ratio (OR) = 1.35, 95 percent CI: 1.02, 1.61) (21). In both of these studies, the outcomes evaluated, ''wheezy bronchitis'' and asthma, are likely to overlap with infant bronchiolitis, given the descriptions and clinical presentation of these respiratory conditions during infancy. Recently, we reported results from a US-based study of infant bronchiolitis and air pollution (22). The findings of our study, a case-crossover analysis of the effect of short-term exposure to fine particulate matter, carbon monoxide, and nitrogen dioxide on infant bronchiolitis hospitalization in the South Coast Air Basin of southern California, were largely null.

In the current study, we sought to evaluate the effect of longer-term exposures that could not be assessed with a case-crossover design. We performed a matched case-control study of infant bronchiolitis and subchronic (month prior to hospitalization) and chronic (lifetime average) exposure to particulate and gaseous ambient air pollutants in the South Coast Air Basin of southern California, a region known for its relatively high and heterogeneous exposure to ambient air pollutants.

The proinflammatory properties of ambient air pollutants, especially ozone and particulate matter, have been described previously, as well as their potential to modulate immune responses to respiratory viruses in human in vitro and animal in vivo models (23–25). Thus, we hypothesized that longer-term exposures (subchronic and chronic) to increased levels of ambient air pollutants may influence pulmonary response to subsequent respiratory syncytial virus infection and increase the severity of the illness (i.e., result in hospitalization for bronchiolitis).

MATERIALS AND METHODS

Study subjects

We identified cases and controls from a data set created by the California Office of Statewide Health Planning and Development. This data set linked birth records for infants born between 1995 and 2000 with hospital discharge records from the first year of life. Infants with a birth residence in a South Coast Air Basin zip code represented by an ambient air pollution monitor were eligible (see ''Exposure assessment'' below). This included all in-hospital livebirths (excluding birthing centers, home births, and military facilities). Approval for access to these data was provided by the California Committee for the Protection of Human Subjects and the University of Washington Human Subjects Division.

Cases included subjects with a record of a single hospitalization with a discharge diagnosis of acute bronchiolitis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 466.1) at age 3 weeks to 1 year during the annual respiratory syncytial virus epidemic season (November through March). For each case, 10 controls matched on date of birth (within 14 days) and gestational age were randomly selected from subjects with birth records who did not have a linked hospital discharge record with a diagnosis of bronchiolitis. Nearly all controls (99.6 percent) had a birth date and gestational age within 7 days of those of their matched case.

Exposure assessment

The residential zip code of each subject's birth record was assigned to a representative California Air Resources Board ambient monitor using a preexisting schema. The linkage of monitors to zip codes was described by Ritz et al. (26). In this study of birth defects in the region, a study team member and a researcher from the California Air Resources Board manually assigned the most relevant monitoring station for all zip codes on the basis of knowledge of distance, topography, major wind direction, and air flow in the South Coast Air Basin.

During the study period, several air monitoring stations provided data on the US Environmental Protection Agency criteria air pollutants of interest: carbon monoxide (36 monitors), nitrogen dioxide (34 monitors), and ozone (40 monitors); and in 1999, 17 monitoring stations initiated data collection for $PM_{2.5}$. Nearly daily measures were available for all pollutants except $PM_{2.5}$, for which measures were taken every third day. Occasional lapses in data collection by the regulatory authority occurred, and in some cases entire months of data were missing for a particular monitor,

precluding exposure characterization for some subjects (approximately 20 percent of cases and controls for each pollutant analysis). Weather monitoring information was obtained from the National Weather Service and the Environmental Protection Agency's Aerometric Information Retrieval System. These agencies provided daily data on humidity and temperature, and the data were similarly linked to subjects on the basis of proximity to residential zip code.

Case-subject and matched control-subject air pollution exposures were assessed in relation to the hospitalization date for cases. Subchronic exposure was calculated as the average of all daily measured pollutant levels for the 30 days prior to hospitalization, excluding measurements from the most proximal 9 days (i.e., excluding acute exposure data). Chronic exposure was calculated as the mean of monthly average air pollution levels over a subject's lifetime from birth to the hospitalization date. Monitor-derived 24-hour average measures of particulate matter and carbon monoxide, 1-hour maximum measures of nitrogen dioxide, and 8-hour maximum average ozone measures were used to construct the exposure periods of interest.

Data analysis

We used conditional logistic regression to estimate the relative risk of hospitalization for bronchiolitis per interquartile-range increase in gaseous air pollutants and per 10-$\mu g/m^3$ increase in $PM_{2.5}$. The latter estimate was designed to allow comparability with previous air pollution studies.

The potentially divergent vulnerability of infant subgroups was considered. Stratified analysis of infants of differing gestational ages and ages at diagnosis was undertaken to evaluate effect modification based on gestational maturity and age. An interaction term for underlying cardiopulmonary disease conditions was included in the models to assess the potential for risk modification in these infants. Gestational age was determined from birth records, and the presence of cardiopulmonary disease was determined from both birth records and first-year-of-life hospitalization records.

We included a number of potential confounders in the models based on a priori, recognized risk factors for infant bronchiolitis hospitalization (gender, parity (used as a proxy for household crowding), chronic lung disease, and cardiac or pulmonary anomalies, including congenital diaphragmatic hernia). Age, gestational age, and season of birth are among the strongest recognized risk factors and were controlled for by matching. Poorer infants are also more likely to be hospitalized for bronchiolitis, and socioeconomic factors are also potentially associated with exposures to ambient air pollution. Several socioeconomic covariates were available and were selected in an attempt to address this, including insurance category (MediCal, private/health maintenance organization/preferred provider organization, other), ethnicity (Hispanic vs. not Hispanic), and mother's highest level of education (0, 1–6, 7–12, or $\geq$13 years). We also linked zip-code-level information on median family income from the 2000 US Census in an effort to further control residual socioeconomic confounding.

TABLE 1. Characteristics of infants hospitalized for bronchiolitis and their age- and gestational-age-matched controls, South Coast Air Basin, California, 1995–2000

	Cases* (n = 18,595)		Controls (n = 169,472)	
	No.	%	No.	%
Age (days) at case admission				
21–90	7,999	43.0	72,922	43.0
91–180	5,692	30.6	51,863	30.6
181–270	3,103	16.7	28,270	16.7
271–365	1,801	9.7	16,417	9.7
Gestational age (weeks)				
37$^1/_7$–44	15,849	85.2	142,773	84.3
34$^1/_7$–37	1,824	9.8	19,046	11.2
29$^1/_7$–34	697	3.8	6,006	3.5
25–29	225	1.2	1,647	1.0
Gender				
Male	11,057	59.5	86,786	51.2
Female	7,538	40.5	82,685	48.8
Unknown	0	0	1	<0.1
Ethnicity				
Hispanic	12,512	67.3	95,838	56.6
Non-Hispanic	5,789	31.1	68,408	40.4
Unknown	294	1.6	5,226	3.0
Cardiopulmonary conditions				
Respiratory distress syndrome	556	3.0	3,135	1.9
Bronchopulmonary dysplasia	85	0.5	305	0.2
Pulmonary anomalies	65	0.4	368	0.2
Any pulmonary disease	631	3.4	3,508	2.1
Cardiac anomalies	491	2.6	1,720	1.0
Maternal parity at subject's birth				
1	5,940	31.9	64,268	38.0
2–3	9,561	51.4	82,006	48.4
≥4	3,082	16.6	23,111	13.6
Unknown	12	0.1	87	<0.1
Payment source				
MediCal	11,722	63.0	82,359	48.6
Private insurance, health maintenance organization, or preferred provider organization	6,154	33.1	78,991	46.6
Other	719	3.9	8,122	4.8
Mother's highest level of education (years)				
≥13	4,182	22.5	53,990	31.8
7–12	11,244	60.5	91,628	54.1
1–6	2,920	15.7	21,651	12.8
0	102	0.5	709	0.4
Unknown	147	0.8	1,494	0.9

* Includes infants meeting the study case definition of being hospitalized once at age 3 weeks to 1 year with an admission date falling during the period November through April.

TABLE 2. Distribution of daily air pollution measures among infants hospitalized for bronchiolitis and their matched controls, South Coast Air Basin, California, 1995–2000

Pollutant and exposure window	Minimum	Percentile				Maximum*	Mean	Interquartile range
		25%	50%	75%	90%			
Fine particulate matter ($PM_{2.5}$†) ($\mu g/m^3$)‡								
Chronic§	6	19	23	29	36	111	25	10
Subchronic¶	6	19	23	29	36	111	25	10
Nitrogen dioxide (ppb†)#								
Chronic	12	51	58	67	78	204	60	16
Subchronic	12	50	57	65	75	152	59	15
Ozone (ppb)**								
Chronic	2	15	22	29	38	96	23	14
Subchronic	2	15	22	29	38	96	23	14
Carbon monoxide (ppb)‡								
Chronic	120	1,180	1,630	2,130	2,880	8,300	1,770	960
Subchronic	130	1,170	1,610	2,080	2,750	5,070	1,720	910

* The regulatory levels for these pollutants under US National Ambient Air Quality Standards (29) are as follows: $PM_{2.5}$ annual average, 15 $\mu g/m^3$; nitrogen dioxide annual average, 53 ppb; ozone 8-hour average, 80 ppb; and carbon monoxide 8-hour average, 9,000 ppb.

† $PM_{2.5}$, particulate matter $\leq$2.5 μm in aerodynamic diameter; ppb, parts per billion.

‡ 24-hour daily average.

§ Lifetime monthly average from birth, referenced to the case's hospitalization date.

¶ Average for the 30 days preceding the case's hospitalization date, excluding measures made during the acute exposure period (i.e., the most proximal 9 days).

1-hour daily maximum.

** 8-hour daily average maximum.

Daily mean temperature and humidity were also entered into the models. All analysis was done using Stata 8 (Stata Corporation, College Station, Texas).

RESULTS

Characteristics of the 18,595 infants who met the case definition for bronchiolitis and their age- and gestational-age-matched controls ($N = 169{,}472$) are presented in table 1. Case infants were more likely to be male, to be Hispanic, and to have underlying cardiopulmonary conditions. The state Medicaid program (MediCal) paid for a larger proportion of case subjects' birth hospitalizations, consistent with previous reports that infants of lower socioeconomic status have a higher risk of hospitalization for bronchiolitis (27, 28). Case mothers were less likely to have education beyond high school and were more likely to be multiparous at the case subject's birth.

Subchronic and chronic exposure assessments for carbon monoxide, $PM_{2.5}$, nitrogen dioxide, and ozone are summarized in table 2. During the study period, there were occasional, rare exceedances of the Environmental Protection Agency's regulatory standards (29) for ozone, carbon monoxide, and $PM_{2.5}$ but not for nitrogen dioxide or ozone.

For most subjects (90 percent), the residential zip code centroid at birth was within 11 miles (17.7 km) of the air pollutant and meteorologic monitors used to assign exposure. The mean distance between the subject's residential zip code centroid and the assigned monitor was in the range of 4–6 miles (6.4–9.6 km), with a maximum distance of 30 miles (48.2 km).

Among the pollutants evaluated, only increases in fine particulate matter ($PM_{2.5}$) were found to be consistently and significantly associated with increased risk of hospitalization for infant bronchiolitis. For 10-$\mu g/m^3$ increases in both subchronic and chronic $PM_{2.5}$ exposure, we observed an adjusted odds ratio of 1.09 and a 95 percent confidence interval of 1.04, 1.14 (table 3). This model included terms for gender, ethnicity, insurance category, maternal education, any lung disease, any cardiac anomalies, daily mean temperature, and daily mean humidity. Further adjustment for socioeconomic factors using census data on zip-code-level median family income had no effect on these estimates and was not included in the final model (data not shown).

While crude analyses also demonstrated modestly increased risks for interquartile-range increases in subchronic and chronic carbon monoxide and nitrogen dioxide exposures, the models including the important potential confounders listed above decreased the point estimate such that there was no demonstrated effect on risk of bronchiolitis hospitalization (table 3). Adjustment did not affect the width of the confidence intervals.

Contrary to our hypothesis of increased risk, both crude and adjusted models of chronic and subchronic exposure to ozone demonstrated lowered risk estimates for infants per

TABLE 3. Adjusted odds ratio* for bronchiolitis hospitalization according to subchronic and chronic increases in ambient air pollution exposures, South Coast Air Basin, California, 1995–2000

Pollutant and exposure window	Definition of exposure interval	Increment of increase†	No. of cases	No. of controls‡	Odds ratio	95% confidence interval
Carbon monoxide						
Subchronic§	Mean of 24-hour daily averages in the month prior to case's hospitalization	910 ppb¶	12,627	114,199	1.00	0.97, 1.03
Chronic#	Mean of 24-hour daily averages from birth	960 ppb	13,670	122,717	1.00	0.97, 1.03
Nitrogen dioxide						
Subchronic	Mean of 1-hour daily maximums in the month prior to case's hospitalization	15 ppb	12,152	111,534	1.04	1.00, 1.08
Chronic	Mean of 1-hour daily maximums from birth	16 ppb	13,138	119,718	1.03	0.99, 1.07
Ozone						
Subchronic	Mean of daily 8-hour maximum averages in the month prior to case's hospitalization	14 ppb	12,180	111,977	0.92	0.88, 0.97
Chronic	Mean of daily 8-hour maximum averages from birth	14 ppb	13,165	120,170	0.92	0.88, 0.97
Fine particulate matter ($PM_{2.5}$¶)						
Subchronic	Mean of 24-hour daily averages in the month prior to case's hospitalization	10 $\mu g/m^3$	6,230	57,334	1.09	1.04, 1.14
Chronic	Mean of 24-hour daily averages from birth	10 $\mu g/m^3$	6,360	56,166	1.09	1.04, 1.14

* Adjusted for gender, ethnicity (Hispanic vs. not Hispanic), insurance category (medical, private/health maintenance organization/preferred provider organization, other), mother's highest level of education (0, 1–6, 7–12, or ≥13 years), any lung disease (chronic lung disease and pulmonary anomalies, including congenital diaphragmatic hernia), any cardiac anomalies, daily mean temperature, and daily mean humidity.

† Risk estimates per interquartile-range increase are shown for all pollutants, except estimates for $PM_{2.5}$, which are per 10-$\mu g/m^3$ increase.

‡ Controls were matched to cases on gestational age and date of birth.

§ Subchronic exposure was based on the mean of all available daily measures of the pollutant in the 30 days prior to the case's hospitalization date, excluding the acute exposure period (i.e., the most proximal 9 days).

¶ ppb, parts per billion; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter.

Chronic exposure was defined as the lifetime monthly average of all available daily measures of the pollutant from birth to the case's hospitalization date.

interquartile-range increase in this pollutant (table 3). Adjusted odds ratios and 95 percent confidence intervals were both 0.92 and 0.88, 0.97.

Stratified analysis by age at diagnosis or gestational age group did not reveal a pattern of differential risk based on these factors (data not shown). Inclusion of an effect-modifier term for infants with underlying pulmonary disease revealed consistently elevated point estimates for affected infants for all pollutants except ozone. However, the effect modification term was not statistically significant (data not shown). The confidence intervals were relatively wide, because of the small number of infants identified as having these conditions. A very small number of infants were identified as having cardiac anomalies. Analyses of the effect modification in these infants were less consistent, showing some elevated point estimates but no consistent pattern and very wide confidence intervals.

Statistically significant effect modification for infants with cardiac anomalies or pulmonary disease was observed in the ozone models. A more pronounced reduction of risk for these infants was observed. The adjusted odds ratio for an interquartile-range increase in chronic exposure among infants with pulmonary disease was 0.75 (95 percent CI: 0.61, 0.92), and that for infants with cardiac anomalies was also 0.75 (95 percent CI: 0.61, 0.92), as compared with infants without these conditions (adjusted OR = 0.92, 95 percent CI: 0.88, 0.97).

DISCUSSION

In this study, subchronic and chronic exposures to $PM_{2.5}$ were found to be significantly associated with an increased risk of hospitalization for bronchiolitis in infants. For each 10-$\mu g/m^3$ increase in $PM_{2.5}$, the risk of hospitalization increased approximately 9 percent. None of the other ambient air pollutants investigated demonstrated increased risk for increases in exposure. This is consistent with the air pollution literature in general, where accumulating evidence implicates fine particulate matter in cardiopulmonary health outcomes. This recognition is reflected in the most recent air quality regulatory responses, which have strengthened the standards for exposure to $PM_{2.5}$ (30).

The limited relevant data on air pollution effects on infant respiratory disease are also most suggestive of a particulate matter effect. Adverse effects have been observed in both short-term and chronic exposure models, but most data are not US-based, and outcome definitions vary. In the Introduction, we described the observed association with physician-diagnosed asthma in the first year of life (as reported by

parents) for a cohort of infants in the Netherlands in relation to chronic $PM_{2.5}$ and soot exposure but not nitrogen dioxide (21). Interestingly, this relation was not statistically significant for children who had been diagnosed with asthma in the second year of life ($PM_{2.5}$ OR = 1.60, 95 percent CI: 0.83, 1.50). In the United States, asthma is not frequently diagnosed in children less than 1 year of age; the term ''asthma'' is generally reserved for children with recurrent episodes (usually three or more). However, bronchiolitis is a clinical diagnosis with features similar to those of asthma, and the case definition used in this study probably included cases which could be termed bronchiolitis. In Chile, in a longitudinal cohort study of infants evaluated from age 4 months to 1 year, Pino et al. (20) also reported positive associations for increased episodes of ''wheezy bronchitis'' with increased $PM_{2.5}$ but not consistently for other pollutants investigated (nitrogen dioxide, sulfur dioxide). This diagnosis was based on a constellation of symptoms and, as in the Netherlands cohort study, probably included both bronchiolitis and asthma. Unlike the Netherlands cohort study, in which exposure was based on a chronic model (land use regression), the exposure effects evaluated related to short-term increases (days before episodes). To our knowledge, our own assessment of short-term exposure effects represents the only published US-based data on this disease. We used a case-crossover analysis based on temporal variability in exposure among subjects in this study. Our analyses did not support an adverse impact of elevated exposures in the days prior to bronchiolitis events (22).

One other published study addressed bronchiolitis specifically but did not evaluate individual pollutants. Ciccone et al. (31) described findings in a cohort of Italian children exposed to differing levels of truck (lorry) traffic near their residence as based on parental reports. Odds ratios for bronchiolitis during the first 2 years of life were estimated as 1.52 (95 percent CI: 1.05, 2.18) for ''sometimes'' being exposed to truck traffic near the residence and 1.74 (95 percent CI: 1.09, 2.77) for ''often'' being exposed to truck traffic near the residence, as compared with ''never'' being exposed. Many trucks have diesel engines, which are an important source of fine particulate matter and nitrogen dioxide.

We found an unexpected risk reduction with increasing ozone exposure. A variety of explanations may be considered. One possibility may be that on high-ozone days, parents or caregivers elect to keep infants indoors, lessening their exposure to ambient air pollution and risk. There are no data to support or refute this. Alternatively, the relation between ambient and personal exposures to $PM_{2.5}$ and ozone may underlie this discrepancy—as confounders or alternatively as surrogates.

Multipollutant modeling is one approach to controlling for the potentially confounding influence of other pollutants. In our study, the protective effects of ozone were not sustained (became null) when fine particulate matter exposure was included in the models (table 4). In addition, the $PM_{2.5}$ effects were not lessened when ozone or other pollutants were included in the models (table 4).

Another view is to consider ozone (and other gaseous ambient air pollutants) as surrogates for particulate matter exposure during winter months. In our South Coast Air Basin study area, ozone peaks occur in the summer and the level of fine particulate matter is highest in winter (in 1995–2000, the Pearson correlation coefficient for November through April was −0.24). The ''protective'' effect of relatively high ozone may simply be a reflection of the relatively low level of particulate matter when ozone is high. In support of this notion, data derived from a Baltimore, Maryland-based cohort demonstrated that *ambient* levels of the gaseous air pollutants were associated with *personal* fine particulate concentrations but not with personal measures of gaseous air pollutants (32). The association was

TABLE 4. Estimates of the effects of exposure to ozone and fine particulate matter ($PM_{2.5}$*) on an infant's risk of bronchiolitis hospitalization in single-pollutant and multipollutant models, South Coast Air Basin, California, 1995–2000

Pollutant and model	Subchronic exposure†		Chronic exposure‡	
	OR*,§	95% CI*	OR§	95% CI
Ozone¶				
Single-pollutant model	0.92	0.88, 0.97	0.92	0.88, 0.96
Adjusted for $PM_{2.5}$	0.98	0.91, 1.07	1.02	0.94, 1.10
Adjusted for carbon monoxide and nitrogen dioxide	0.90	0.84, 0.96	0.89	0.84, 0.95
Adjusted for $PM_{2.5}$, carbon monoxide, and nitrogen dioxide	0.96	0.86, 1.08	1.00	0.90, 1.11
$PM_{2.5}$#				
Single-pollutant model	1.09	1.04, 1.14	1.09	1.04, 1.14
Adjusted for ozone	1.10	1.04, 1.16	1.09	1.03, 1.15
Adjusted for carbon monoxide and nitrogen dioxide	1.14	1.07, 1.21	1.12	1.06, 1.20
Adjusted for ozone, carbon monoxide, and nitrogen dioxide	1.15	1.08, 1.22	1.13	1.06, 1.21

* $PM_{2.5}$, particulate matter $\leq$2.5 μm in aerodynamic diameter; OR, odds ratio; CI, confidence interval.

† Subchronic exposure was defined as the monthly average of all available daily measures of the pollutant in the 30 days prior to the case's hospitalization date, excluding the acute exposure period (i.e., the most proximal 9 days).

‡ Chronic exposure was defined as the lifetime monthly average of all available daily measures of the pollutant from birth to the case's hospitalization date.

§ Adjusted for gender, ethnicity (Hispanic vs. not Hispanic), insurance category (medical, private/health maintenance organization/preferred provider organization, other), mother's highest level of education (0, 1–6, 7–12, or $\geq$13 years), any lung disease (chronic lung disease and pulmonary anomalies, including congenital diaphragmatic hernia), any cardiac anomalies, daily mean temperature, and daily mean humidity.

¶ Based on daily maximum 8-hour average ozone measurements and interquartile-range increases of 14 parts per billion (subchronic) and 14 parts per billion (chronic).

Based on daily 24-hour average $PM_{2.5}$ measurements, per 10-μg/m^3 increase.

strongest for ambient ozone and personal $PM_{2.5}$ in both summer and winter. In addition, *ambient* levels of gaseous pollutants were significantly correlated with *ambient* levels of fine particulate matter. As such, we viewed ozone as a surrogate with strong collinearity, which argues against the use of multipollutant modeling.

We were also interested in evaluating vulnerable subgroups of infants. Our data suggest that for pollutants besides ozone, infants with underlying lung disease may be more vulnerable, although the effect modification terms for these analyses were not statistically significant. The number of affected infants in these analyses was small and probably represented a subset of all affected infants. In relying on administrative data for this study (birth and hospitalization records), we would have identified only infants with heart or lung disease that was noted at birth or resulted in a later hospitalization and was coded as such. Thus, our ability to determine the effects on the subset of children with heart and lung conditions was limited.

We were also limited to the control of potentially confounding factors that could be captured by data elements available in these administrative data sets. Socioeconomic factors are of special concern. We were able to use a number of proxies to address this. We first adjusted for relevant information available in the primary data set (maternal education, ethnicity, and insurance category). Adjustment for these factors did reduce the point estimates of the estimated crude odds ratios for carbon monoxide, nitrogen dioxide, and $PM_{2.5}$, with only $PM_{2.5}$ risks remaining statistically significantly elevated after adjustment. The effect on ozone was to increase the point estimate such that it became less protective. In summary, control for socioeconomic status served to shift the point estimates toward the null. Residual confounding was possible. As such, we further augmented our control for socioeconomic status by assigning zip-code-level information on family median income available from the 2000 US Census and found that this did not change the estimates further. These same proxies probably helped address other important factors that share a relation to socioeconomic status for which we did not have individual-level data, including exposure to environmental tobacco smoke, day-care attendance, and extent of breastfeeding.

By design, our study was based on zip-code-level spatial discrepancies in air pollution for case and control subjects. Unaccounted-for spatial clustering of response may occur in our study design, and thus the related confounding is an additional concern. We evaluated this by addition of a spatial area component to the modeling of the association between air pollution exposure based on zip-code-level information and outcome (bronchiolitis hospitalization). Specifically, we performed sensitivity analyses to investigate the addition of the spatial area component, defined as county. This resulted in modest (3–4 percent) changes in risk estimates that were, in general, slightly further from the null. (Details are available in a supplement posted on the *Journal*'s website (http://aje.oxfordjournals.org/).)

This study adds to the evidence of adverse effects of fine particulate matter, even at levels below current regulatory limits. Infants are a potentially vulnerable subgroup that has received relatively little attention in epidemiologic studies. These data are unique in homing in on this important disease, bronchiolitis, in a US infant population. Infants who are exposed to relatively higher levels of particulate matter over a period of weeks to months are more likely to develop bronchiolitis severe enough to warrant hospitalization. Although bronchiolitis is a relatively acute episodic event, a high proportion of infants who are hospitalized with bronchiolitis go on to develop chronic respiratory symptoms of recurrent wheezing and asthma. Attempts at vaccine development have been largely unsuccessful and treatment is largely supportive rather than curative, underscoring the importance of primary prevention. Our study suggests that infant bronchiolitis may be added to the list of adverse effects of ambient air pollution and that reducing exposure to fine particulate matter may be a viable strategy for reducing the burden of this disease.

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