Original Contribution

Assessing the Influence of Traffic-related Air Pollution on Risk of Term Low Birth Weight on the Basis of Land-Use-based Regression Models and Measures of Air Toxics

Jo Kay C. Ghosh*, Michelle Wilhelm, Jason Su, Daniel Goldberg, Myles Cockburn, Michael Jerrett, and Beate Ritz

* Correspondence to Dr. Jo Kay C. Ghosh, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Soto Street Building, 2001 North Soto Street, 3rd Floor, MC 9239, Los Angeles, CA 90089-9239 (e-mail: jokay@ucla.edu).

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Few studies have examined associations of birth outcomes with toxic air pollutants (air toxics) in traffic exhaust. This study included 8,181 term low birth weight (LBW) children and 370,922 term normal-weight children born between January 1, 1995, and December 31, 2006, to women residing within 5 miles (8 km) of an air toxics monitoring station in Los Angeles County, California. Additionally, land-use-based regression (LUR)-modeled estimates of levels of nitric oxide, nitrogen dioxide, and nitrogen oxides were used to assess the influence of small-area variations in traffic pollution. The authors examined associations with term LBW (≥ 37 weeks' completed gestation and birth weight $< 2,500$ g) using logistic regression adjusted for maternal age, race/ethnicity, education, parity, infant gestational age, and gestational age squared. Odds of term LBW increased 2%–5% (95% confidence intervals ranged from 1.00 to 1.09) per interquartile-range increase in LUR-modeled estimates and monitoring-based air toxics exposure estimates in the entire pregnancy, the third trimester, and the last month of pregnancy. Models stratified by monitoring station (to investigate air toxics associations based solely on temporal variations) resulted in 2%–5% increased odds per interquartile-range increase in third-trimester benzene, toluene, ethyl benzene, and xylene exposures, with some confidence intervals containing the null value. This analysis highlights the importance of both spatial and temporal contributions to air pollution in epidemiologic birth outcome studies.

air pollution; benzene; fetal growth retardation; hydrocarbons, aromatic; infant, low birth weight; pregnancy

Abbreviations: BTEX, benzene, toluene, ethyl benzene, and xylenes; CARB, California Air Resources Board; CI, confidence interval; IQR, interquartile range; LBW, low birth weight; LUR, land-use-based regression; PAH(s), polycyclic aromatic hydrocarbon(s); $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; PM_{10} , particulate matter < 10 μm in aerodynamic diameter.

For over a decade, epidemiologic studies have linked prenatal air pollution exposure to adverse birth outcomes, including low birth weight (LBW), small size for gestational age, preterm birth, and birth defects (1–4). Links between prenatal exposure to carbon monoxide, particles (particulate matter < 10 μm in aerodynamic diameter (PM_{10}), particulate matter < 2.5 μm in aerodynamic diameter ($PM_{2.5}$)), and polycyclic aromatic hydrocarbons (PAHs) and intrauterine growth restriction point to toxins in motor vehicle exhaust as possible causative agents (2, 5, 6).

Most of these studies relied on data from government air pollution monitoring stations, which typically measure only

“criteria” air pollutants (carbon monoxide, nitric oxide, nitrogen dioxide, nitrogen oxides, ozone, and particulate matter) monitored for regulatory purposes, and exposure estimates are often assigned on the basis of residential zip codes (2–5, 7, 8). This method of exposure assessment results in limited spatial resolution for primary traffic pollutants (9, 10), and toxic air pollutants (air toxics) coming from the same sources as criteria pollutants may be the causative agents for these birth outcomes (11, 12). Few epidemiologic birth outcome studies have examined air toxics as potentially better markers of vehicle exhaust, most likely because these data are not commonly available.

Figure 1. Locations of California Air Resources Board toxic air pollutant monitoring stations in the Los Angeles Basin, California. The monitoring stations are shown as small dots, with a 5-mile (8-km) radius circular buffer around each station.

To achieve better spatial resolution for primary traffic pollutants, some recent birth outcome studies have employed land-use-based regression (LUR) methods to model traffic-related prenatal air pollution exposures on a finer spatial scale (13–21). Only 4 studies compared results from LUR-estimated exposures with other exposure assessment methods or examined the importance of both spatial and temporal variations in pollution for the same population (18–21). Two of these studies were recently conducted by our research group (20, 21), and they included births spanning 22 months in 2004–2006, corresponding to monitoring data from the Multiple Air Toxics Exposure Study (22). For this brief period, we reported increased risks of term LBW and preterm birth with increased exposure to traffic-related air pollution, estimated using LUR models, measured air toxics, and source-specific PM_{2.5} estimates (20, 21). While these studies evaluated a large number of air toxics, we could not address the influence of temporal exposure variations versus spatial exposure variations or confidently identify pregnancy periods of greater sensitivity, because of sample size and time span limitations.

In this study, we extended our research using data on ambient air toxics and criteria pollutants provided by a network of monitors managed by the California Air Resources Board (CARB) to estimate exposures for a larger number of births and a time span of 12 years (1995–2006). We also compared these effect estimates for exposures based on monitoring station data with LUR-modeled estimates of traffic-related air pollution. Our goal was to examine whether these measured

and modeled air pollution metrics showed consistent associations with term LBW, indicating a role for traffic exhaust exposures.

MATERIALS AND METHODS

Birth certificate data and outcome assessment

We used electronic birth certificate data from the State of California to identify women who gave birth between January 1, 1995, and December 31, 2006, while residing in Los Angeles County, California ($n = 1,745,754$). These data included the mother's residential address at delivery and information about maternal age, race/ethnicity, education, parity, prenatal care initiation and payment source, multiplicity of gestation, baby's gestational age at birth, birth weight, sex, birth defects, and date of birth. We excluded births with recorded defects ($n = 85,114$), missing ($n = 81,072$) or extreme (<140 days or >320 days) gestational ages ($n = 19,139$), extreme birth weights (<500 g or $>5,000$ g) ($n = 3,125$), and multiple gestations ($n = 32,425$).

The University of Southern California GIS Research Laboratory geocoding engine (23) successfully geocoded 1,522,267 addresses; 2,612 nongeocodeable addresses were excluded. A sensitivity analysis excluding the poorer-quality geocodes (<7%) did not change our results (see Web Table 1 (<http://aje.oxfordjournals.org/>) for quality flags). Address locations were mapped in ESRI ArcGIS software (ESRI, Redlands, California) and overlaid with the geocoded locations of

CARB air toxics stations in Los Angeles County. Among women with geocoded addresses ($n = 1,522,267$), we included those who resided ≤ 5 miles (≤ 8 km) from a CARB air toxics station ($n = 415,531$; 27.3%) (Web Table 2). This radius was selected to balance sample size needs and the potential for exposure misclassification with increasing distances from stations.

We compared term infants born LBW ($< 2,500$ g; $n = 8,181$) with term infants born normal birth weight ($\geq 2,500$ g; $n = 370,922$); preterm births (< 259 completed days of gestation) were excluded ($n = 36,428$). A subset of 2000–2006 births (for the LUR analyses) included 4,895 term LBW cases and 217,717 noncases.

Exposure assessment

The CARB maintains 4 air toxics monitoring stations in Los Angeles County. Three stations (downtown Los Angeles, Burbank, and North Long Beach) were active throughout the entire study period, while the Azusa station provided measurements from 2000–2006 only (Figure 1). Measurements of benzene, toluene, ethyl benzene, and xylenes (BTEX) were available for the entire study period, but PAH measurement ceased in December 2004 and vanadium measurement in February 2003. These stations collected data on criteria air pollutants throughout the study period, except for $PM_{2.5}$, for which data collection started in January 1999.

Exposure estimates were created for the entire pregnancy, the first (first day of the last menstrual period to day 92), second (days 93–185) and third (day 186 to birth) trimesters, and the last month of pregnancy (the 30 days before birth) for criteria pollutants (carbon monoxide, nitric oxide, nitrogen dioxide, nitrogen oxides, ozone, PM_{10} , and $PM_{2.5}$) and air toxics. For the gaseous criteria pollutants (hourly data), 24-hour averages were created and averaged over the pregnancy periods. For air toxics (measured every 12 days), averages were created for benzo[*a*]pyrene, benzo[*g,h,i*]perylene, total PAHs (detailed in Table 1), benzene, ethyl benzene, *m,p*-xylenes, *o*-xylene, toluene (BTEX), and vanadium. We applied exclusion criteria based on having $\geq 50\%$ of measurements available in each exposure period (Web Table 3).

For the 3,506 women (0.9%) who lived within 5 miles (8 km) of 2 stations (Burbank and downtown Los Angeles), we created daily averages when data were available from one or both stations, weighted by the inverse of the distance to the station.

LUR model and seasonalization

We used our LUR models, previously developed for the Los Angeles Basin, to represent traffic-related air pollution (24). Because these models were based on measurements collected in 2006–2007, we restricted the LUR analyses to births taking place during the years 2000–2006. The LUR model was based on more than 200 monitoring locations throughout Los Angeles County and explained 81%, 86%, and 85% of the variance in measured nitric oxide, nitrogen dioxide, and nitrogen oxide concentrations, respectively (24). The LUR model represents long-term spatial patterns and approximate annual average concentrations, and we expect

spatial contrasts to be maintained despite year-to-year changes in land use, meteorology, and other factors (25, 26).

We overlaid the geocoded residential addresses from the birth certificate with the LUR surfaces to assign estimated exposures. In addition to the LUR annual average estimates (“unseasonalized estimates”), we created “seasonalized” LUR measures using measurement data from the air monitoring station(s) within 5 miles (8 km) of the woman’s home address, using the same weighted average approach as for criteria pollutants for women assigned to 2 stations. We multiplied the LUR estimates to generate pregnancy-month-specific LUR values, as follows: first-month seasonalized nitrogen oxides average = LUR nitrogen oxides $\times$ (first-month air monitoring station average nitrogen oxides/2006 air monitoring station annual average nitrogen oxides). These “seasonalized” pregnancy-month LUR values were then averaged over the pregnancy periods of interest. We restricted the data to those with $\geq 50\%$ of possible measurements available in the averaging month.

Statistical analysis

All analyses were conducted using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina). We plotted pollutant measures to examine trends across time and monitoring stations. Pearson’s correlation coefficients were used to assess collinearity across pollutants and pregnancy periods.

Standard logistic regression methods were used to estimate increases in odds of term LBW per unit or interquartile-range (IQR) increase in pregnancy-period exposures. Regression analyses using exposure quartiles and splines confirmed the assumption of linearity between the log odds of term LBW and exposure. We adjusted for several potential confounders identified in our previous studies (27)—maternal age, race/ethnicity, education, parity, gestational age (weeks), and gestational age squared—and examined changes in effect estimates with additional adjustment for mother’s birthplace and a Census-based metric of socioeconomic status (28, 29). Because the birthplace and socioeconomic status variables did not change the air pollution effect estimates by more than 5%, these variables were not included in the final models.

RESULTS

Seasonal trends and correlations across air pollutants

All air toxics except vanadium showed strong seasonal variations, with peak levels occurring in winter (results not shown). Benzene and PAH levels declined approximately 65% and 40%, respectively, over the study period. The highest BTEX levels were measured at the Burbank and downtown Los Angeles stations, while PAH levels were highest in Burbank. Vanadium levels were generally highest in North Long Beach.

Seasonalized LUR-based exposure estimates were moderately correlated with most measured air toxics (Table 1), probably because these pollutants are important components of traffic exhaust—a major contributor to air pollution in the Los Angeles Basin (30). Unseasonalized LUR exposure estimates correlated only with seasonalized LUR estimates ($r = 0.56$ – 0.75) (Table 1). Levels of air toxics were strongly

Table 1. Distributions of Air Pollutant Exposure Estimates and Pearson's Correlation Coefficients for Entire-Pregnancy Averages in Term Low Birth Weight Cases and Term Normal-Weight Noncases Among Births to Women Living Within 5 Miles (8 km) of a California Air Resources Board Air Toxics Monitoring Station, Los Angeles County, California, 1995–2006

Pollutant	No. of Births	Pollutant Level			Pearson Correlation Coefficient					
					Unseasonalized LUR ^a			Seasonalized LUR ^b		
		Mean	IQR	SD	NO	NO ₂	NO _x	NO	NO ₂	NO _x
Unseasonalized LUR ^c										
NO, ppb	222,612	32.9	11.2	10.5	1.00					
NO ₂ , ppb	222,612	27.8	5.2	4.5	0.79	1.00				
NO _x , ppb	222,612	60.4	15.5	13.7	0.98	0.83	1.00			
Seasonalized LUR										
NO, ppb	211,808	39.5	19.0	16.8	0.75	0.61	0.73	1.00		
NO ₂ , ppb	211,808	34.1	9.8	7.4	0.56	0.64	0.58	0.79	1.00	
NO _x , ppb	211,808	73.3	27.3	22.5	0.71	0.59	0.72	0.97	0.87	1.00
Measured pollutant										
BAP, ng/m ³	302,516	0.1	0.1	0.1	−0.03	−0.09	−0.04	0.21	0.05	0.19
BGP, ng/m ³	302,516	0.6	0.4	0.3	−0.02	−0.04	−0.03	0.37	0.21	0.35
Total PAHs, ^d ng/m ³	302,516	1.2	0.8	0.5	−0.02	−0.05	−0.03	0.36	0.23	0.35
Benzene, ppbV	358,751	1.1	0.8	0.6	0.00	0.10	−0.02	0.49	0.61	0.53
Ethyl benzene, ppbV	358,751	0.4	0.2	0.2	0.00	0.16	−0.01	0.41	0.49	0.42
Toluene, ppbV	358,751	3.0	1.6	1.3	−0.03	0.19	−0.02	0.37	0.57	0.42
<i>m,p</i> -Xylene, ppbV	358,751	1.5	0.9	0.6	0.00	0.14	−0.01	0.41	0.56	0.45
<i>o</i> -Xylene, ppbV	358,751	0.5	0.3	0.2	−0.01	0.17	−0.02	0.41	0.55	0.44
Vanadium, ng/m ³	186,547	11.9	6.5	5.2	−0.04	−0.24	−0.04	−0.34	−0.40	−0.34
CO, ppm	364,146	1.1	0.6	0.4	0.00	0.09	−0.02	0.48	0.60	0.52
NO, ppb	338,898	41.6	24.1	17.1	0.03	0.10	0.00	0.53	0.46	0.51
NO ₂ , ppb	338,890	34.8	10.4	6.7	0.00	0.17	−0.01	0.44	0.72	0.53
NO _x , ppb	338,890	76.3	31.2	21.8	0.02	0.13	0.00	0.53	0.57	0.55
Ozone, ppb	366,191	35.4	8.4	6.1	−0.04	0.19	−0.02	−0.36	−0.09	−0.34
PM ₁₀ , µg/m ³	351,562	38.4	8.5	5.9	−0.02	0.11	0.00	0.33	0.58	0.42
PM _{2.5} , µg/m ³	219,975	19.8	4.6	2.8	0.01	0.16	0.01	0.34	0.59	0.41

Table continues

correlated within each pollutant class (PAHs, BTEX), but vanadium showed moderate negative correlations with all other air toxics (r ranged from -0.27 to -0.64) (Table 1).

Pollutant estimates were correlated across pregnancy periods, with moderate-to-strong positive correlations between second-trimester and entire-pregnancy averages and between third-trimester and last-pregnancy-month averages (Table 2). First-trimester averages for nitric oxide and benzo[*a*]pyrene were negatively correlated with their respective third-trimester averages but were positively correlated with entire-pregnancy averages. Entire-pregnancy nitrogen dioxide was positively correlated with nitrogen dioxide in each trimester ($r = 0.69$ – 0.88) for both measured criteria pollutants and LUR-modeled averages.

Term LBW

The largest numbers of births occurred in downtown Los Angeles (3,505 cases, 150,384 noncases) and North Long

Beach (1,827 cases, 79,920 noncases). Approximately 70% of mothers were Hispanic, of whom 60% were foreign-born (Table 3). Most women initiated prenatal care during the first trimester (86.6%); 61.8% were multiparous, 69.3% had an educational level of high school or less, and 52.8% were aged 20–29 years at delivery. The overall prevalence of term LBW was 2.2%. Over the 12-year study period, we observed increases in older maternal age, Asian race/ethnicity, and years of education, while the prevalence of term LBW and the distribution of the socioeconomic status quintile scores remained relatively consistent.

Univariate models indicated higher odds of term LBW for infants born to mothers who were under age 20 years, were nulliparous, received late or no prenatal care, were US-born, and used public insurance or had no insurance coverage for prenatal care. African-American mothers had double the odds of term LBW compared with non-Hispanic white mothers. While Hispanic mothers were 25% more likely to deliver a term LBW baby than non-Hispanic white mothers,

Table 1. Continued

Pearson Correlation Coefficient															
Measured Pollutant															
BAP	BGP	Total PAHs	Benzene	Ethyl Benzene	Toluene	m,p-Xylene	o-Xylene	Vanadium	CO	NO	NO ₂	NO _x	Ozone	PM ₁₀	PM _{2.5}
1.00															
0.88	1.00														
0.91	0.99	1.00													
0.52	0.81	0.79	1.00												
0.40	0.66	0.64	0.89	1.00											
0.42	0.71	0.69	0.89	0.78	1.00										
0.39	0.61	0.61	0.85	0.79	0.86	1.00									
0.45	0.70	0.68	0.91	0.86	0.89	0.92	1.00								
−0.27	−0.50	−0.45	−0.56	−0.64	−0.49	−0.32	−0.45	1.00							
0.47	0.76	0.74	0.94	0.85	0.86	0.82	0.89	−0.61	1.00						
0.49	0.64	0.65	0.69	0.68	0.59	0.68	0.70	−0.58	0.70	1.00					
0.31	0.59	0.57	0.83	0.78	0.82	0.81	0.85	−0.64	0.84	0.62	1.00				
0.46	0.66	0.66	0.77	0.75	0.69	0.76	0.78	−0.62	0.80	0.97	0.79	1.00			
−0.34	−0.28	−0.29	−0.07	0.03	0.10	0.02	0.03	−0.03	−0.06	−0.45	0.12	−0.31	1.00		
0.11	0.28	0.30	0.52	0.53	0.52	0.60	0.53	−0.09	0.49	0.15	0.63	0.32	0.29	1.00	
−0.11	−0.02	0.04	0.74	0.49	0.68	0.80	0.78	−0.04	0.78	0.54	0.82	0.66	0.04	0.75	1.00

Abbreviations: BAP, benzo[a]pyrene; BGP, benzo[g,h,i]perylene; CO, carbon monoxide; IQR, interquartile range; LUR, land-use-based regression; NO, nitric oxide; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; PAHs, polycyclic aromatic hydrocarbons; PM_{2.5}, particulate matter <2.5 μm in aerodynamic diameter; PM₁₀, particulate matter <10 μm in aerodynamic diameter; ppbV, parts per billion volume; SD, standard deviation.

^a Unseasonalized LUR estimates for births occurring during the years 2000–2006 only.

^b Seasonalized LUR estimates for births occurring during the years 2000–2006 only.

^c Regression models with LUR exposure estimates included only those births occurring during the years 2000–2006.

^d Includes benzo[a]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene.

Mexican-born Hispanics had a lower risk than US-born Hispanics (results not shown).

Seasonalized LUR exposure estimates were associated with increased odds of term LBW for the entire pregnancy and for each trimester, with stronger associations for the entire-pregnancy and third-trimester averages. For the third trimester, adjusted odds ratios for nitric oxide were 1.01 (95% confidence interval (CI): 1.00, 1.02) per 10-ppb increase in seasonalized LUR-estimated nitric oxide levels (Table 4) and 1.05 (95% CI: 1.01, 1.08) per IQR increase (Table 5); results for nitrogen dioxide and nitrogen oxides were similar. Results for nitric oxide, nitrogen dioxide, and nitrogen oxides based on monitoring station data were similar

to seasonalized LUR results (Table 4). Additionally, odds of term LBW increased 6% per IQR increase in unseasonalized LUR-estimated nitric oxide, nitrogen dioxide, and nitrogen oxide levels (Table 5).

Several measured air toxics were associated with odds of term LBW, particularly benzene, xylenes, and toluene exposures in the third trimester (Table 5) and the last month of pregnancy (results not shown). PAH exposures in the last pregnancy month were associated with 3%–5% increased odds of term LBW per IQR increase in pollutant concentration (not shown). All measured air toxics showed null associations for first-trimester, second-trimester, and entire-pregnancy exposure averages (not shown). Consistent with

Table 2. Pearson's Correlation Coefficients for Correlations Between Exposures to Select Air Pollutants Across Pregnancy Periods in Term Low Birth Weight Cases and Term Normal-Weight Noncases Among Births to Women Living Within 5 Miles (8 km) of a California Air Resources Board Air Toxics Monitoring Station, Los Angeles County, California, 1995–2006

Pollutant and Pregnancy Period	Measured Pollutant Levels					Seasonalized LUR-Estimated Exposure				
	First Trimester	Second Trimester	Third Trimester	Entire Pregnancy	Last Month of Pregnancy	First Trimester	Second Trimester	Third Trimester	Entire Pregnancy	Last Month of Pregnancy
Nitric oxide										
First Trimester	1					1				
Second Trimester	0.10	1				0.13	1			
Third Trimester	−0.47	0.16	1			−0.42	0.12	1		
Entire pregnancy	0.45	0.79	0.35	1		0.45	0.77	0.41	1	
Last month of pregnancy	−0.37	−0.23	0.80	0.06	1	−0.34	−0.19	0.84	0.18	1
Nitrogen dioxide										
First Trimester	1					1				
Second Trimester	0.52	1				0.53	1			
Third Trimester	0.11	0.48	1			0.19	0.54	1		
Entire pregnancy	0.72	0.87	0.69	1		0.73	0.88	0.73	1	
Last month of pregnancy	0.11	0.22	0.87	0.51	1	0.18	0.32	0.87	0.59	1
Benzo[a]pyrene										
First Trimester	1									
Second Trimester	−0.04	1								
Third Trimester	−0.46	0.04	1							
Entire pregnancy	0.47	0.71	0.32	1						
Last month of pregnancy	−0.34	−0.26	0.68	−0.01	1					
Benzene										
First Trimester	1									
Second Trimester	0.55	1								
Third Trimester	0.25	0.52	1							
Entire pregnancy	0.78	0.87	0.71	1						
Last month of pregnancy	0.23	0.28	0.83	0.53	1					

Abbreviation: LUR, land-use-based regression.

previous studies using criteria pollutant data (7, 31, 32), ambient carbon monoxide, nitric oxide, nitrogen dioxide, nitrogen oxides, PM₁₀, and PM_{2.5} exposures also increased the odds of term LBW for third-trimester and entire-pregnancy averages.

In adjusted models stratified by closest monitoring station, higher unseasonalized LUR-estimated nitric oxide, nitrogen oxide, and nitrogen dioxide exposures increased term LBW odds at the North Long Beach and downtown Los Angeles stations (Table 5). For seasonalized LUR estimates, women assigned to the downtown Los Angeles station had 4%–5% increased odds per IQR increase for the entire pregnancy and the third trimester. For women living near the North Long Beach station, term LBW odds increased 7%–10% with IQR increases in vanadium exposure in each trimester, as well as with entire-pregnancy averages (adjusted odds ratio = 1.07, 95% CI: 0.98, 1.17). Results for air toxics analyses at the Azusa station are not shown, because of small case counts leading to unstable estimates.

Analyses stratified by decade of birth (1995–1999 vs. 2000–2006) showed few differences across strata (results not shown).

DISCUSSION

Our results provide additional evidence for a contribution of traffic exhaust to risk of term LBW, including longer- and shorter-term local exposures (represented by unseasonalized and seasonalized LUR estimates) and shorter-term regional exposures (represented by trimester average air toxics and criteria pollutant exposures). Mothers residing in Los Angeles who delivered at term had greater odds of delivering a low-weight baby when exposed to higher levels of traffic exhaust pollutants in the third trimester. We observed approximately 5% increased odds of term LBW per IQR increase in seasonalized and unseasonalized LUR-estimated levels of nitric oxide,

Table 3. Demographic Characteristics of Term Low Birth Weight Cases and Noncases Among Births to Women Living Within 5 Miles (8 km) of a California Air Resources Board Air Toxics Monitoring Station, Los Angeles County, California, 1995–2006

Parameter	Term Low Birth Weight Cases (n = 8,181)		Noncases (n = 370,922)		Crude Odds Ratio	95% Confidence Interval
	No. or Mean (SD)	%	No. or Mean (SD)	%		
Mean gestational age, days	273.6 (10.9)		278.7 (10.3)			
Mean birth weight, g	2,288.5 (241.0)		3,429.4 (429.7)			
Maternal age, years						
<20	1,317	16.1	42,083	11.4	1.30	1.22, 1.39
20–24	2,252	27.5	93,655	25.3	0.78	0.73, 0.83
25–29 (reference)	1,920	23.5	102,654	27.7	1.00	
30–34	1,557	19.0	81,809	22.1	0.79	0.74, 0.85
≥35	1,135	13.9	50,721	13.7	0.93	0.87, 1.00
Maternal race/ethnicity						
Hispanic	5,341	65.3	259,561	70.0	1.25	1.16, 1.35
White, non-Hispanic (reference)	825	10.1	50,131	13.5	1.00	
African-American	865	10.6	20,969	5.7	2.51	2.28, 2.76
Asian	586	7.2	22,895	6.2	1.56	1.40, 1.73
Other ^a	549	6.7	16,698	4.5	2.00	1.79, 2.23
Missing data	15	0.2	668	0.2		
Maternal education, years						
≤8	1,536	18.8	70,099	18.9	0.93	0.88, 0.99
9–12 (reference)	4,406	53.9	186,785	50.4	1.00	
13–15	1,221	14.9	59,506	16.0	0.87	0.82, 0.93
≥16	918	11.2	51,305	13.8	0.76	0.71, 0.82
Missing data	100	1.2	3,227	0.9		
Parity						
0	3,931	48.1	140,832	38.0	1.51	1.45, 1.58
≥1 (reference)	4,245	51.9	230,006	62.0	1.00	
Missing data	5	0.1	84	0.02		

Table continues

nitrogen dioxide, and nitrogen oxides, and 1%–3% increased odds per IQR increase in measured levels of PAHs, benzene, xylenes, and toluene, although some confidence intervals included the null value.

The consistent associations found for the LUR-based estimates highlight the importance of spatial contrasts in air pollution in Los Angeles, while monitoring station-based air toxics results underscore the contributions of seasonal and regional influences within each local area. That is, stratifying the analysis by monitoring station effectively restricts comparisons to seasonal contrasts only, while our unseasonalized LUR exposure estimates rely solely on small-area spatial variations. Because we observed positive associations using temporal and spatial resolutions despite low correlations across these measures, these results suggest that both spatial and temporal variability are important. In previous studies of criteria air pollution and term LBW or intrauterine growth restriction, investigators reported increased risks with third-trimester and/or entire-pregnancy average exposures, similar to our results, and suggested that these pollutants could be acting as markers of traffic exhaust (7, 31, 32). Few studies

used LUR techniques to model pregnancy exposure to traffic pollution, and most were unable to identify critical windows of exposure for term LBW or birth weight decreases. Only 2 studies were conducted in North America, including our analysis based on the Multiple Air Toxics Exposure Study (21), where we found increased odds of term LBW with LUR-estimated levels of nitric oxide, nitrogen dioxide, and nitrogen oxides, similar to the current study.

The second North American study was conducted in Vancouver, Canada. In that study, Brauer et al. (18) compared exposure estimates from LUR models (based on residential postal code) and monitoring station data (including an inverse distance-weighted approach using the 3 closest stations within 50 km of the residential postal code). LUR-estimated entire-pregnancy average PM_{2.5} exposure was associated with risk of small size for gestational age and term LBW; nitric oxide was associated with small size for gestational age. Comparing results from LUR modeling with estimates based on inverse distance weighting, the authors reported similar results for nitric oxide but dissimilar results for nitrogen dioxide, for both small size for gestational age and

Table 3. Continued

Parameter	Term Low Birth Weight Cases (n = 8,181)		Noncases (n = 370,922)		Crude Odds Ratio	95% Confidence Interval
	No. or Mean (SD)	%	No. or Mean (SD)	%		
Initiation of prenatal care						
No prenatal care or started after first trimester	1,305	16.0	48,066	13.0	1.28	1.21, 1.36
First trimester (reference)	6,819	83.4	321,411	86.7	1.00	
Missing data	57	0.7	1,445	0.4		
Mother's birthplace (United States vs. elsewhere)						
US-born (reference)	3,090	37.8	132,748	35.8	1.00	
Foreign-born	5,080	62.1	237,399	64.0	0.92	0.88, 0.96
Missing data	11	0.1	775	0.2		
Primary payment method for prenatal care						
Private insurance, HMO, Blue Cross Blue Shield (reference)	2,493	30.5	138,183	37.3	1.00	
Medicare, Medi-Cal, government program, other nongovernment program	5,401	66.0	222,329	59.9	1.35	1.28, 1.41
No prenatal care, self-payment, no charge, medically indigent, other	279	3.4	10,152	2.7	1.52	1.34, 1.73
Missing data	8	0.1	258	0.1		
Quintile of Census-based SES index ^b						
1 (reference)	4,901	59.9	206,567	55.7	1.00	
2	1,669	20.4	78,237	21.1	0.90	0.85, 0.95
3	924	11.3	45,960	12.4	0.85	0.79, 0.91
4	489	6.0	28,184	7.6	0.73	0.67, 0.80
5	197	2.4	11,880	3.2	0.70	0.61, 0.81
Missing data	1	0.01	94	0.03		

Abbreviations: HMO, health maintenance organization; SD, standard deviation; SES, socioeconomic status.

^a Native American/American Indian, Indian, Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander, or other (specified).

^b The SES metric was based on Census block group data, where principal component analysis was used to combine 7 indicator variables into a single SES score. Each block group was assigned a score, and then the block groups were divided into quintiles. Census-based indicator variables for SES included in the score are: mean years of education; median household income; percentage living 200% below the federal poverty level; percentage of blue-collar workers; percentage of residents aged ≥ 16 years without a job; median monthly rent; and median house value.

term LBW. In contrast, we observed similar results using LUR-estimated and monitoring-based exposure estimates (Table 4), perhaps because of better predictive capabilities with our LUR model (higher R^2 values), and less exposure misclassification within a maximum 5-mile (8-km) radius from the monitoring stations.

All other LUR-based studies examining intrauterine growth restriction metrics were conducted in Europe and covered very short time periods (approximately 1–2 years). Two Spanish studies used LUR models based on nitrogen dioxide and BTEX measurements (16, 17). In one study, Aguilera et al. (17) reported birth weight reductions with entire-pregnancy average BTEX and second-trimester and entire-pregnancy nitrogen dioxide levels, but only for women who spent less than 2 hours in nonresidential outdoor locations. In the other study, Ballester et al. (16) reported decreased birth weight and length and increased risk of small size for gestational age with first-trimester and entire-pregnancy nitro-

gen dioxide levels, although exposure estimates were strongly correlated across pregnancy periods. In a German cohort study, Slama et al. (13) reported increased risk of term LBW with LUR-estimated entire-pregnancy average nitrogen dioxide, $PM_{2.5}$, and $PM_{2.5}$ absorbance. Two Dutch studies used seasonalized LUR models in large cohorts; in one study, Gehring et al. (14) reported no increased risk of small size for gestational age or term birth weight reductions with LUR-estimated nitrogen dioxide levels, while in the other, Gehring et al. (15) reported detrimental effects on term birth weight with LUR-estimated nitrogen dioxide, $PM_{2.5}$, and soot exposures, with 95% confidence intervals spanning the null value.

While specific causative agents have not yet been identified, there are some animal and epidemiologic data pointing to motor vehicle toxins in the risk of adverse birth outcomes, with the strongest evidence indicating a role for PAHs (33). PAHs can cross through the human placenta and disrupt placental perfusion, leading to intrauterine growth restriction

Table 4. Adjusted Odds Ratios for Term Low Birth Weight According to Maternal Air Pollution Exposure, Comparing Seasonalized LUR-Modeled Exposure Estimates With Measured Criteria Pollutant Estimates, Among Births to Women Living Within 5 Miles (8 km) of a California Air Resources Board Air Toxics Monitoring Station, Los Angeles County, California, 1995–2006

Pregnancy Period and Pollutant	Seasonalized LUR Exposure Estimate				Monitoring Station Criteria Pollutant			
	No. of Cases ^a	No. of Noncases ^a	OR ^b	95% CI	No. of Cases	No. of Noncases	OR ^b	95% CI
Entire pregnancy								
NO	4,608	205,235	1.02	1.01, 1.04	4,665	208,331	1.01	0.99, 1.03
NO ₂	4,608	205,235	1.04	1.00, 1.08	4,665	208,331	1.02	0.97, 1.07
NO _x	4,608	205,235	1.02	1.00, 1.03	4,665	208,331	1.01	1.00, 1.02
First trimester								
NO	4,766	212,920	1.00	0.99, 1.01	4,766	212,920	1.00	0.99, 1.01
NO ₂	4,766	212,920	1.02	0.99, 1.05	4,766	212,920	1.00	0.96, 1.03
NO _x	4,766	212,920	1.00	1.00, 1.01	4,766	212,920	1.00	0.99, 1.01
Second trimester								
NO	4,757	212,551	1.01	1.00, 1.02	4,757	212,551	1.01	1.00, 1.02
NO ₂	4,757	212,551	1.03	1.00, 1.06	4,757	212,551	1.01	0.98, 1.05
NO _x	4,757	212,551	1.01	1.00, 1.01	4,757	212,551	1.01	1.00, 1.01
Third trimester								
NO	4,735	211,206	1.01	1.00, 1.02	4,758	212,737	1.01	1.00, 1.02
NO ₂	4,735	211,206	1.04	1.00, 1.07	4,758	212,737	1.02	0.99, 1.06
NO _x	4,735	211,206	1.01	1.00, 1.02	4,758	212,737	1.01	1.00, 1.02

Abbreviations: CI, confidence interval; LUR, land-use-based regression; NO, nitric oxide; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; OR, odds ratio.

^a Small differences in the numbers of participants between seasonalized LUR estimates and monitoring station estimates are due to minor differences in the way the exclusions were implemented, since monitoring station estimates were based on averages of daily averages measured over the pregnancy period, while the seasonalization method for the LUR metrics was based on averaging of monthly averages.

^b Odds ratios and 95% confidence intervals were calculated per 10-ppb change in the level of each pollutant. Results were adjusted for maternal age, race/ethnicity, education, parity, infant gestational age, and gestational age squared.

(34–42). As Perera et al. (43) summarized, current hypotheses on PAH mechanisms include antiestrogenic effects (44), binding of constituents to the human aryl hydrocarbon receptor to induce production of cytochrome P-450 enzymes (45), and DNA damage resulting in activation of apoptotic pathways (42, 46, 47).

Some epidemiologic studies support a role for PAHs in small size for gestational age (42) and term LBW (48, 49). The only US studies were based on a small birth cohort in New York City (12, 43, 50), which linked third-trimester PAH exposures (including benzo[a]pyrene and benzo[*g,h,i*]perylene) to reduced birth weight and head circumference and to higher risks of preterm birth and small size for gestational age among African Americans but not Dominicans (11, 12). While we observed slightly increased odds of term LBW with benzo[a]pyrene, benzo[*g,h,i*]perylene, and total PAH exposure, our “total PAH” measure did not include naphthalene, the most abundant PAH in the Los Angeles Basin (51), because CARB air toxics stations do not measure it.

Very few birth outcome studies have examined specific air toxics, aside from PAHs. In a small study of 271 non-smoking women, Slama et al. (52) assessed benzene exposure using personal monitoring and reported decreases in head circumference and birth weight with second- and third-trimester exposures, although confidence intervals included

the null for the birth weight associations. A Spanish population-based study using a LUR model (53) and a Chinese occupational study (54) found negative effects of benzene on gestational age. In animal and experimental studies, benzene has been shown to cross the placenta (55–57) and is associated with reduced fetal weight (58). While specific biologic mechanisms are unknown, benzene has been shown to form DNA adducts, which could alter enzyme formation and lead to cell death (58), and benzene metabolites cause oxidative stress and negatively affect fetal blood cell development (59–62).

The major strengths of our study include the use of long-term air toxics monitoring data and LUR-modeled exposure estimates and a large, diverse population spread over a large geographic area, allowing us to assess both spatial and temporal variations in pollutant concentrations. Analyses stratified by monitoring station allowed us to investigate seasonal effects of air pollution; seasonal effects are less likely to be affected by residual confounding by socioeconomic status and related factors (e.g., smoking), which tend to be spatially distributed. With many years of data, we were also able to examine pregnancy-period-specific exposures and identify the third trimester as a possibly sensitive exposure window for term LBW, consistent with some previous studies (3, 31, 63–65).

Table 5. Adjusted Odds Ratios for Term Low Birth Weight According to Maternal Air Pollution Exposure, Using Unseasonalized LUR Exposure Estimates and Third-Trimester Exposure Estimates for Seasonalized LUR, Air Toxics, and Criteria Pollutants, Among Births to Women Living Within 5 Miles (8 km) of a California Air Resources Board Air Toxics Monitoring Station, Los Angeles County, California, 1995–2006

Pollutant	All CARB Stations				CARB Monitoring Station			
					North Long Beach			
	No. of Cases	No. of Noncases	OR ^b	95% CI	No. of Cases	No. of Noncases	OR ^b	95% CI
Unseasonalized LUR ^c								
NO	4,825	215,721	1.06	1.03, 1.09	1,359	58,137	1.06	0.98, 1.13
NO ₂	4,825	215,721	1.06	1.02, 1.09	1,359	58,137	1.09	0.99, 1.21
NO _x	4,825	215,721	1.06	1.03, 1.10	1,359	58,137	1.06	0.98, 1.14
Third trimester								
Seasonalized LUR								
NO	4,735	211,206	1.05	1.01, 1.08	1,353	57,888	1.05	0.98, 1.13
NO ₂	4,735	211,206	1.04	1.00, 1.08	1,353	57,888	1.04	0.97, 1.11
NO _x	4,735	211,206	1.05	1.01, 1.09	1,353	57,888	1.04	0.98, 1.11
Benzo[a]pyrene	6,150	277,153	1.01	0.98, 1.04	1,767	77,722	1.01	0.95, 1.06
Benzo[<i>g,h,i</i>]perylene	6,150	277,153	1.01	0.98, 1.05	1,767	77,722	1.00	0.93, 1.07
Total PAHs ^d	6,150	277,153	1.02	0.98, 1.05	1,767	77,722	1.00	0.94, 1.07
Benzene	7,689	346,999	1.03	1.00, 1.05	2,123	92,923	1.00	0.94, 1.07
Ethyl benzene	7,689	346,999	1.01	1.00, 1.03	2,123	92,923	1.02	0.97, 1.08
<i>m,p</i> -Xylenes	7,689	346,999	1.03	1.01, 1.06	2,123	92,923	1.04	0.97, 1.11
<i>o</i> -Xylene	7,689	346,999	1.03	1.01, 1.05	2,123	92,923	1.01	0.97, 1.06
Toluene	7,689	346,999	1.02	1.00, 1.05	2,123	92,923	1.02	0.95, 1.10
Vanadium	4,668	211,698	0.98	0.95, 1.02	1,266	55,422	1.07	0.98, 1.17
Carbon monoxide	7,932	360,858	1.04	1.01, 1.07	2,062	89,671	1.03	0.96, 1.11
NO	7,604	344,858	1.05	1.02, 1.09	2,062	89,671	1.04	0.96, 1.13
NO ₂	7,604	344,854	1.04	1.01, 1.07	2,062	89,671	1.02	0.95, 1.09
NO _x	7,604	344,854	1.06	1.02, 1.09	2,062	89,671	1.03	0.96, 1.11
Ozone	7,944	361,348	0.97	0.94, 1.01	2,062	89,672	0.95	0.85, 1.06
PM ₁₀	7,833	354,638	1.03	1.00, 1.06	2,058	89,439	1.03	0.97, 1.10
PM _{2.5}	5,221	234,865	1.04	1.00, 1.07	1,505	65,285	1.03	0.96, 1.10

Table continues

While the exposure modeling methods employed in this study added new information in comparison with most previous studies, we acknowledge potential issues regarding exposure misclassification. Exposure estimates were assigned on the basis of the birth certificate address. While approximately 20% of Los Angeles County women move during pregnancy (27), they typically stay within the same neighborhood, so monitoring station-based exposure estimates do not change substantially (66, 67). The effect of residential mobility on LUR-estimated exposures is not known. Additionally, exposure estimates were potentially less valid for women who lived further from monitoring stations. When restricting the data to women living within 3 miles (4.8 km) of the monitoring stations, we found somewhat stronger associations but large overlap in confidence intervals, suggesting some exposure misclassification due to residential distance from the monitoring station. Another source of misclassification stems from air toxics monitoring data being available

only every 12 days, and we may have missed some peaks in toxin levels because of unusual events. We expect this limitation to have affected shorter-term averages more strongly than longer-term averages.

There are also limitations related to using birth certificate data, which do not include ultrasound measurements of fetal growth. Without prenatal measurements, we could not distinguish babies born LBW because of growth restriction from those born LBW because of early delivery. Thus, we restricted this study to term babies to help distinguish growth-restricted babies. This exclusion introduced an unknown degree of selection bias, because the preterm growth-restricted infants who were excluded may have been more highly exposed to air pollution. Including preterm babies would create a mixed case group with both etiologies, which is also problematic. Finally, we could be missing potentially important confounders for which data are not available through public records (e.g., smoking, alcohol consumption,

Table 5. Continued

CARB Monitoring Station											
Azusa ^a				Burbank				Downtown Los Angeles			
No. of Cases	No. of Noncases	OR ^b	95% CI	No. of Cases	No. of Noncases	OR ^b	95% CI	No. of Cases	No. of Noncases	OR ^b	95% CI
507	26,477	0.94	0.81, 1.09	579	31,367	1.02	0.92, 1.13	2,380	99,740	1.07	1.03, 1.10
507	26,477	0.88	0.77, 1.02	579	31,367	1.01	0.91, 1.13	2,380	99,740	1.08	1.03, 1.13
507	26,477	0.94	0.82, 1.09	579	31,367	1.01	0.91, 1.13	2,380	99,740	1.08	1.04, 1.12
506	26,368	1.04	0.87, 1.26	568	30,615	1.06	0.96, 1.18	2,308	96,335	1.04	0.99, 1.08
506	26,368	1.02	0.90, 1.16	568	30,615	1.02	0.91, 1.14	2,308	96,335	1.06	1.00, 1.12
506	26,368	1.05	0.87, 1.28	568	30,615	1.06	0.95, 1.18	2,308	96,335	1.05	1.00, 1.10
				849	45,892	1.00	0.95, 1.06	3,454	149,124	1.02	0.98, 1.07
				849	45,892	1.01	0.94, 1.09	3,454	149,124	1.02	0.97, 1.07
				849	45,892	1.01	0.94, 1.08	3,454	149,124	1.02	0.98, 1.07
				1,016	53,831	1.05	1.00, 1.12	4,041	173,635	1.02	0.98, 1.05
				1,016	53,831	1.04	1.00, 1.09	4,041	173,635	1.00	0.98, 1.02
				1,016	53,831	1.05	0.99, 1.12	4,041	173,635	1.01	0.98, 1.05
				1,016	53,831	1.05	0.99, 1.11	4,041	173,635	1.02	0.98, 1.06
				1,016	53,831	1.05	0.99, 1.12	4,041	173,635	1.01	0.98, 1.04
				646	34,917	1.01	0.90, 1.13	2,535	109,211	1.01	0.95, 1.07
873	46,495	1.03	0.89, 1.20	1,004	53,342	1.06	0.99, 1.14	3,993	171,350	1.03	0.98, 1.07
873	46,495	1.17	0.77, 1.75	950	49,997	1.05	0.96, 1.14	3,719	158,695	1.02	0.98, 1.07
873	46,495	1.01	0.92, 1.10	950	49,993	1.08	0.98, 1.20	3,719	158,695	1.04	0.99, 1.09
873	46,495	1.06	0.83, 1.36	950	49,993	1.06	0.97, 1.16	3,719	158,695	1.03	0.99, 1.07
873	46,495	0.99	0.92, 1.08	1,016	53,831	0.97	0.89, 1.06	3,993	171,350	0.99	0.94, 1.04
816	42,930	1.03	0.97, 1.10	965	51,295	1.07	0.97, 1.18	3,994	170,974	1.04	0.99, 1.08
551	28,552	1.06	0.94, 1.19	556	29,695	0.99	0.89, 1.10	2,609	111,333	1.04	0.98, 1.11

Abbreviations: CARB, California Air Resources Board; CI, confidence interval; NO, nitric oxide; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons; PM_{2.5}, particulate matter <2.5 µm in aerodynamic diameter; PM₁₀, particulate matter <10 µm in aerodynamic diameter.

^a The Azusa station measured levels of toxic air pollutants only from 2000 to 2006, and the small numbers of cases caused unstable estimates; those effect estimates have been omitted from the table.

^b Exposure estimates were scaled by the interquartile range for each pollutant from the total data set. Results were adjusted for maternal age, race/ethnicity, education, parity, gestational age, and gestational age squared.

^c Unseasonalized LUR metrics represent annual average exposures; that is, all pregnancy periods would receive the same annual value.

^d Includes benzo[a]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene.

maternal stature). However, because we observed associations with both spatial and temporal comparisons and it is unlikely that a residual confounder would bias both comparisons simultaneously, this makes residual confounding a less compelling explanation.

In this article, we have provided evidence that air toxics may play a role in fetal growth restriction and have highlighted the potential for LUR modeling techniques to capture important spatial variations in air pollution. Future studies should further explore the utility of air toxics and modeling techniques based on geographic information systems to more

accurately characterize traffic-related air pollution exposures across large geographic regions, study both spatial and temporal contributions to air pollution, and provide information on vulnerable pregnancy periods.

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Author affiliations: Department of Epidemiology, School of Public Health, University of California, Los Angeles, Los

Angeles, California (Jo Kay C. Ghosh, Michelle Wilhelm, Beate Ritz); Center for Occupational and Environmental Health, School of Public Health, University of California, Los Angeles, Los Angeles, California (Beate Ritz); Department of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, California (Jason Su, Michael Jerrett); Spatial Sciences Institute, College of Letters, Arts and Sciences, University of Southern California, Los Angeles, California (Daniel Goldberg, Myles Cockburn); and Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California (Jo Kay C. Ghosh, Myles Cockburn).

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