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The effects of air pollution on adverse birth outcomes

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Abstract

Background—Air pollution has been shown to have adverse effects on many health outcomes including cardiorespiratory diseases and cancer. However, evidence on the effects of prenatal exposure is still limited. The purpose of this retrospective cohort study is to evaluate the effects of prenatal exposure to air pollutants including particulate matter with aerodynamic diameter less than 2.5 micrometer ($PM_{2.5}$) and ozone (O_3) on the risk of adverse birth outcomes (ABOs) including term low birth weight (LBW), preterm delivery (PTD) and very PTD (VPTD).

Methods—Singleton births from 2004–2005 in Florida were included in the study (N=423,719). Trimester-specific exposures to O_3 and $PM_{2.5}$ at maternal residence at delivery were estimated using the National Environmental Public Health Tracking Network data, which were interpolated using Hierarchical Bayesian models.

Results—After adjustment for potential confounders such as demographics, medical and lifestyle factors $PM_{2.5}$ exposures in all trimesters were found to be significantly and positively associated with the risk of all ABOs. Second-trimester exposure had the strongest effects. For an interquartile range (IQR) increase in $PM_{2.5}$ during the second trimester, the risk of term LBW, PTD and VPTD increased by 3% [95% confidence interval (CI): 1–6%)], 12% (11–14%) and 22% (18–25%), respectively. O_3 was also found to be positively associated with PTD and VPTD with the strongest effects over the whole pregnancy period [3% (1–5%) for PTD and 13% (7–19%) for VPTD for each IQR increase]. However, O_3 was observed to have protective effects on term LBW. Results were consistent for multi-pollutant models.

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Conclusion—$PM_{2.5}$ has consistent adverse effects on ABOs whereas O_3 has inconsistent effects. These findings warrant further investigation.

Keywords

air pollution; low birth weight; preterm delivery; birth outcomes

BACKGROUND

Adverse birth outcomes including preterm delivery (PTD), very preterm delivery (VPTD) and low birth weight (LBW) are associated with higher risk of subsequent morbidity and higher health care expenditure. Specifically, infants with these outcomes are more likely to have subsequent respiratory complications including both respiratory failures shortly after birth, and childhood asthma (Escobar et al., 2006; Sonnenschein-van der Voort et al., 2014). Additionally, they are associated with a higher risk of neurobehavioral problems (Aarnoudse-Moens et al., 2009). According to a nationally representative cross-sectional analysis using the Nationwide Inpatient Sample database from the Healthcare Cost and Utilization Project, hospitalization cost for infants with PTD or LBW in 2001 was 5.8 billion dollars, which represents almost 50% of the costs of all infant hospitalization in the United States (Russell et al., 2007). This analysis also reported that on average, infants with PTD or LBW have longer hospital stays with a mean length of stay of 12.9 days and a cost of approximately $15,100 compared to an uncomplicated birth with an average of 1.9 days in the hospital and a cost of $600 (Russell et al., 2007). Due to the serious impact of these two adverse birth outcomes, efforts towards their prevention remain a critical part of Healthy People 2020 (Heathy People 2020).

In recent years, there has been a growing interest in focusing on environmental determinants of adverse birth outcomes including air pollution. Air pollutants that have commonly been studied in relation to adverse birth outcomes are particulate matter with aerodynamic diameter of less than 2.5 micrometer ($PM_{2.5}$) and ozone (O_3). However, studies have yielded inconsistent results. For example, some studies have found that $PM_{2.5}$ is positively associated with the risk of PTD (Geer et al., 2012; Hyder et al., 2014; Pereira et al., 2014). Others have found no difference (Fleischer et al., 2014; Rudra et al., 2011; Shah et al., 2011). Similar contradictory results have been found for O_3 (Shah et al., 2011; Stieb et al., 2012; Vinikoor-Imler et al., 2013). Due to these inconsistent findings, further investigation of the relationship between these air pollutants and birth outcomes is warranted. Moreover, previous studies mostly relied on air pollution data from fixed monitor sites for exposure assessment, which likely lack spatial coverage as fixed monitors only provide the information about air pollution at the sites where the monitors are located. Thus, there are no air pollution data available at locations without monitors. In previous studies, some houses were located very far from sparsely located air monitors; therefore, relying solely on the closest monitor value may not accurately represent individual air pollution exposure. The interpolated air pollution data from statistical modeling can address this weakness by additionally taking into account meteorological patterns, emission and photochemical properties of pollutants. Therefore, the purpose of this retrospective cohort study is to use a more sophisticated exposure assessment based on Hierarchical Bayesian Modeling to

determine the association between prenatal exposure to $PM_{2.5}$ and O_3 and the risk of adverse birth outcomes (ABOs) including term low birth weight (LBW), preterm delivery (PTD), and very preterm delivery (VPTD).

MATERIAL AND METHODS

Participants

Study participants included all singleton live births born in Florida from January 01, 2004 through December 31, 2005 identified from Florida Vital Statistics (FVS) (N=445,028). After excluding births that had addresses outside of Florida (n=4,672), missing address (423), unable to geocode (e.g. only PO Box available) (n=563), missing gestational age (n=937), multiple births (n=13,686), those with birth weight out of range (i.e. less than 500 and more than 5,000 grams) (n=903), and those with gestational age out of range (i.e. less than 140 days and more than 320 days) (n=125), 423,719 births remained for analyses.

Exposure assessment

Air pollution data was obtained from the US Environmental Protection Agency's (USEPA) Hierarchical Bayesian Prediction Model (HBM) output. The HBM combines $PM_{2.5}$ and O_3 data from the EPA's Air Quality System (AQS) and the gridded output from the Models-3/Community Multi-scale Air Quality Model (CMAQ), which is based on the National Emission Inventory and meteorological and geographical factors. The methodology for the HBM model is described elsewhere (McMillan, 2010). The HBM model output includes 12×12 km gridded estimates of $PM_{2.5}$ (daily average) and O_3 (daily 8-hr maximum) surfaces. For the purpose of this study, we extracted data for the state of Florida during the period 2003–2005.

To obtain exposure, we geocoded each mother's residential address at delivery and overlaid this layer with the HBM output layer. Individual exposure during pregnancy was then estimated using daily concentrations in the grid in which the residential address falls. We determined pregnancy period and each trimester period by using gestational age given in the data by FVS. On Florida birth certificates, gestational age in weeks is typically determined by ultrasound measurements. When ultrasound is not available, fundal height—determined by clinical examination—or menstrual history is used to estimate gestational age. Exposures were calculated as daily concentrations averaged over each trimester. First, second and third trimester were defined as the first 13 weeks of gestation, week 14 through 26 and week 27 through birth, respectively.

Outcome assessment

The outcomes of interest were term LBW, PTD and VPTD; all of which are assessed using FVS. Term LBW is defined as a birth that occurred on or after the 37^{th} week of gestation with weight less than 2,500 grams. PTD is defined as a birth that occurred before 37 weeks of gestation. VPTD is defined as a birth that occurred before 32 weeks of gestation.

Covariates

Covariates from this study come from FVS. They included infant's gender (female or male), maternal age in years (continuous), gestational age in weeks (continuous), maternal education (<high school, high school graduate and/or some college, college graduate, graduate school), maternal race (White, Black, Hispanic, Asian/Pacific Islander, and Others), marital status (married or unmarried), prenatal care (yes or no), pregnancy tobacco use (yes <10/day, yes>10/day, quit and no), pregnancy alcohol drink (yes or no), maternal risk factors (yes or no), maternal infection (yes or no), maternal complications (yes or no), season of conception, urbanicity and year of birth. Season of conception was defined as warm (May through October) or cold (November to April). The presence of maternal risk factors was defined as whether or not the mother had previous ABOs, gestational/chronic diabetes or hypertension, or pre-eclampsia. Maternal infection was defined as whether the mother was diagnosed with an infection at the time of delivery or was treated during pregnancy for an infection. Maternal complications were defined as whether mother needed transfusion, had third or fourth degree perineal laceration, ruptured uterus, unplanned hysterectomy, admission to ICU or unplanned surgery. Since income was not available on the birth certificate, we obtained census block group level median household income information from the 2000 Census for each birth and categorized into quartiles. We also considered unemployment rate at the county level with two levels, high or low, defined as above or below the median.

Statistical analysis

T-tests and chi-square tests were performed to compare continuous and categorical characteristics for participants with and without ABOs. Univariate and multivariate logistic regression models were used to investigate the effects of $PM_{2.5}$ and O_3 on the risk of LBW, PTD, and VPTD. In the univariable models, we obtained the unadjusted effects of air pollutants. In the adjusted models, we selected confounders that have been found or reported to be associated with both the exposure and the outcomes to estimate the effects of air pollutants. Finally, multi-pollutant models were applied to estimate the effects after adjusting for their potential effects on each other. For all analyses, we compared births with a defined outcome with "healthy" births without any of the outcomes in this study. Data analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Statistical significance was set at $p<0.05$.

Sensitivity analysis

We also performed a capture area analysis by which we included only births within 5 miles of air O_3 and $PM_{2.5}$ monitor stations. We estimated individual exposure for each trimester using average daily concentrations from the nearest monitor.

RESULTS

Table 1 summarizes the characteristics of study participants by ABO status. Compared to the Controls (20.7%), the percentages of mothers with less than high school education were significantly higher among term LBW (27.8%), PTD(23.7%) and VPTD mothers (25.2%), respectively. Additionally, among the ABO groups, the percentages of mothers who were

Black, lived in census block with income in the lowest quartile, unmarried, had no prenatal care, smoked or used alcohol during pregnancy, and had maternal risk factors (e.g. had previous ABOs, gestational/chronic diabetes or hypertension, or pre-eclampsia,) were significantly higher than Controls. Additionally, a higher percentage of term LBW infants were female (59.9% vs. 48.7%). However, the percentages of males were higher for PTD and VPTD. Unemployment status was not associated with any ABOs.

Table 2 displays summary statistics for the distribution of prenatal exposure to $PM_{2.5}$ and O_3 by trimester and the whole pregnancy period. The mean daily average concentrations of $PM_{2.5}$ during the first, second and third trimesters were 9.7, 9.9 and 10.2 $\mu g/m^3$, respectively. Additionally, the mean daily average concentrations of O_3 were 37.2, 37.6, and 37.4 ppb for the first, second and third trimester, respectively. There were significant but weak correlations between $PM_{2.5}$ and O_3 exposures during pregnancy periods with Pearson correlation coefficients ranging from 0.10 for the whole pregnancy to 0.39 during the first trimester.

Table 3 shows the unadjusted and adjusted odds ratio (OR) for the associations between prenatal exposure to $PM_{2.5}$ and O_3 and ABOs by trimester and the whole pregnancy period. In the unadjusted models, exposure to $PM_{2.5}$ in all trimesters and the whole pregnancy significantly increase the unadjusted risk of term LBW. After adjustment for potential confounders, exposure to $PM_{2.5}$ during the second trimester was significantly associated with a 3.4% higher odds (CI 0.7%–6.1%) of term LBW for each IQR increase in exposure but its effects during other periods were no longer significant (Table 3). On the other hand, in both adjusted and unadjusted analysis, O_3 exposure during the third trimester and the whole pregnancy period had an inverse effect on risk of term LBW (Table 3). Each IQR increase in O_3 exposure showed approximately 6% decrease in risk of LBW during the third trimester and a 6% decrease for the whole pregnancy period after adjusting for other covariates.

For PTD, the unadjusted odds ratios indicate that higher exposure to both $PM_{2.5}$ and O_3 during the first trimester, second trimester and the entire pregnancy period were associated with higher risk. After adjustment for potential confounders, results remained consistent. Specifically, for each IQR increase in O_3 exposure during the second trimester and entire pregnancy, the risk of PTD increases by 2.3% and 2.8%, respectively. Similar findings were observed for $PM_{2.5}$, with specifically stronger association for exposure during the second trimester corresponding to a 12.3% increase in risk per IQR increase. The effects of $PM_{2.5}$ and O_3 were similar for VPTD.

Consistent findings were also observed when the models were adjusted for co-pollutant effects (Table 4). In the multi-pollutant models, O_3 still has negative associations (protective effect) with term LBW but positive associations with PTD and VPTD, only for full pregnancy. Meanwhile, $PM_{2.5}$ is still shown to increase risk of all outcomes.

We also performed sensitivity analyses using exposures from the nearest monitor station for all births within 5 miles of monitor stations. In our sensitivity analyses using the same inclusion/exclusion criteria, there were 112,500 and 123,207 singleton live births living

within 5 miles from O_3 and $PM_{2.5}$ monitor stations, respectively. Among those living within 5 miles from O_3 stations, there were 2,569 cases of term LBW (2.51%), 10,193 cases of PTD (9.06%) and 1,499 cases of VPTD (1.33%). When repeating the same analyses but using closest monitors values as exposures, results remained consistent with main analyses. One exception is the inverse association between O_3 and ABOs became insignificant. Specifically, after adjustment for covariates, an IQR increase in O_3 exposures during the first, second and third trimester and the entire pregnancy were associated with 0.97 (95% CI: 0.91–1.03), 1.02 (0.96–1.08), 0.96 (0.91–1.02) and 0.97 (95% CI: 0.92–1.03) times the odds of having term LBW, respectively (Table 5).

DISCUSSION

The purpose of this retrospective cohort study was to use a more sophisticated exposure assessment based on Hierarchical Bayesian Modeling to determine the association between prenatal exposure to $PM_{2.5}$ and O_3 and the risk of adverse birth outcomes (ABOs). Our results indicate that higher exposures to $PM_{2.5}$ increase the risk of all ABOs. While it may have a protective effect on term LBW, O_3 exposure has a negative effect on PTD and VPTD.

Our observation that O_3 exposures increase the risk of PTD and VPTD are consistent with many previous reports. Other studies from different regions of the world have found that O_3 exposures increase the risk of PTD (Hansen et al., 2006; Lee et al., 2013; Olsson et al., 2013). For example, among 120,755 singleton births during 1998 to 2006 in Greater Stockholm, Sweden, Olsson et al. 2013 observed an association between first trimester O_3 and preterm birth (OR 1.04, 95% CI 1.01 to 1.08) per 10 $\mu g/m^3$ increase in O_3 (Olsson et al., 2013). This finding is similar to our data with 3% increase in risk during the first trimester. The association between pollution and specifically VPTD has received less attention. Most studies have focused on PTD. Since VPTD infants have higher rates of morbidity and mortality compared to PTD infants, it is also important to investigate the potential association between pollution within this particularly vulnerable group. Our study showed there is a stronger association between pollution and VPTD compared to PTD.

Unlike previous studies, we observed a protective association between O_3 and term LBW during the third trimester and the entire pregnancy. This finding is inconsistent with previous studies with some reporting positive associations (Geer et al., 2012; Gray et al., 2014; Morello-Frosch et al., 2010) and others showing no association (Liu et al., 2003). To ensure that our results were not due to chance, we performed a sensitivity analysis for births with the same inclusion criteria to women who resided within 5 miles of monitor stations. Results remained consistent but the protective association between O_3 and term LBW became insignificant perhaps due to a smaller sample size. Thus, the observed finding is unlikely to be explained by random error. One possible explanation of the main finding may be due to unselected confounders such as diet, which may account for these results. Other studies have shown that O_3 can activate the antioxidant system, decrease tissue hypoxia, and increase the host immunity and characteristics of microcirculation and general health status of the exposed population (Elvis and Ekta, 2011). The protective properties of non-toxic dose exposure to O_3 on health outcomes including cardiovascular complications, liver

injuries, renal injuries, diabetes and its related complications, and radiation induced toxicity have been documented (Delgado-Roche et al., 2013; Ajamieh et al., 2002; Gul et al., 2012; Oztosun et al., 2012; Al-Dalain et al., 2001; Gultekin et al., 2013). However, we can only speculate that our findings reflect negative association of term LBW with O_3 exposure. Finally, our O_3 exposure mainly relied on the statistically modeled data or the data from the monitor close to residential area. These methods may result in misclassification, which could possibly account for the observed inverse association. Therefore, more research with personal exposure monitors may be needed to confirm this association.

Our findings regarding the negative effects of $PM_{2.5}$ on ABOs are consistent with the literature. An extensive systematic review by Shah et al. 2011 found that exposure to $PM_{2.5}$ increases the risk of both LBW and PTD (Shah et al., 2011). More importantly, our results were also consistent with two similar studies using Florida births by Salihu et al. and Mainolfi et al. (Salihu et al., 2012; Mainolfi et al., 2013). Specifically, using exposure based on Euclidean minimum distance from air pollution monitoring sites, Salihu et al. found that Florida women above the median exposure to particulate matter had a statistically significant 9% increase in risk of LBW, 5% increase in risk of PTD and 13% increase in VPTD (Salihu et al., 2012). Additionally, the fact that we observed the strongest effects for second trimester exposure is consistent with a recent study that found that the effects of criteria pollutants on adverse birth outcomes among 145,445 singleton live births in Hillsborough County, Florida were strongest in the second trimester from similar study periods (Mainolfi et al., 2013). According to the U.S. Census, many characteristics in this county are comparable to those of the state of Florida (US Census, 2013).

Though our results show relatively weak magnitude of association, they have an important clinical significance due to the omnipresent nature of air pollution. Although the exact mechanism between air pollution and adverse birth outcomes has not been well-established, some studies have suggested that air pollutants can invade the body through direct diffusion or active transport. Upon entrance, it may affect the body in several ways. The chief mechanisms underlying the association between air pollution and adverse birth outcomes have been suggested to involve oxidative stress and inflammation, changes in hemodynamic and rheological factors, endocrine disruption, and genetic and epigenetic changes (Ghio et al., 2012; Slama et al., 2008; Brook and Rajagopalan, 2012; Peters et al., 1997; Furuta et al., 2004; Takeda et al., 2004; Tran et al., 1996; Jafarabadi, 2007; Rubes et al., 2005; Somers and Cooper, 2009; Baccarelli et al., 2009; Barthauer, 1990). These changes are believed to ultimately affect maternal-fetal exchange in nutrients and oxygen, which subsequently affect fetal growth.

Our study offers some strength. While many existing studies relied on fixed site monitor stations, our study utilized the predicted $PM_{2.5}$ and O_3 estimates form the HBM model, which combined EPA's AQS monitor measurements and the gridded output from the CMAQ models. These models predict air pollution concentrations at unknown locations using known samples after accounting for photochemical properties of the pollutants as well as meteorological factors. Consequently, this data has an increased spatial and temporal resolution compared to the monitored data.

Our study also has several limitations. First, the only address available is that at time of birth. However, many women may have lived at a different address during pregnancy. Therefore, we were unable to adjust our analyses for residential mobility of mothers during pregnancy. This assignment of exposure may lead to non-differential misclassification of exposure, which could bias the results towards the null. Additionally, a study assessing exposure misclassification due to residential mobility during pregnancy showed that the majority of pregnant women did not move throughout their pregnancy (Chen et al., 2010). Furthermore, among those who moved, they stayed close enough that their exposure estimates were similar to what they would have been if they had not reported relocation. Therefore, mobility is not likely to have profoundly affected our results.

Additionally, we did not have activities pattern data for these women. Therefore, we could not adjust our analysis for this potential source of misclassification. Women may reside at a certain address and work or have activities in other locations, which may have different exposures. Daily multiple locations may result in exposure misclassification. However, we have no reason to believe that activities pattern would result in differential misclassification. Thus, our result, if biased by activities patterns, is in a conservative direction.

Finally, since the resolution of our air pollution data is 12×12km, we were unable to account for variation at a smaller scale. Furthermore, despite the HBM model's ability to incorporate more information (e.g. weather, emission) relevant for prediction, there are still limitations associated with its estimates. Specifically, this model relies on CMAQ outputs using monitoring observations. Therefore, the prediction error is likely to be larger in areas farther away from monitors. This error may introduce some bias as the populations living near monitors are potentially different from those living far from monitors (Bravo et al., 2012). However, we performed sensitivity analyses including only births within 5 miles from monitoring stations. The results were consistent suggesting that error associated with distance from air monitors did not differentially affect our results. Furthermore, in the main analyses, we adjusted for characteristics (e.g. urbanicity, unemployment, age, race, education, income), which Bravo et al. suggested could have affected our results. Therefore, our results are not likely confounded by these factors. Nevertheless, we cannot exclude the possibility of residual confounding and other sources of prediction error given that CMAQ model has the tendency to overestimate O_3 and underestimate $PM_{2.5}$ (Bravo et al., 2012).

CONCLUSIONS

We found that $PM_{2.5}$ exposure increases the risk of adverse birth outcomes including term LBW, PTD and VPTD among singleton births born in Florida from 2004–2005. We also found that O_3 increases the risk of PTD and VPTD while it decreases the risk of term LBW. The study adds to the existing evidence on the negative health effects of particulate matter. Furthermore, it supports the importance of minimizing population exposure to air pollution in order to reduce risks of adverse birth outcomes. Studies with personal exposure assessment will be needed to confirm these associations, especially for the inverse association between O_3 and term LBW.

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Abbreviations

LBW	Low birth weight
PTD	Preterm delivery
VPTD	Very preterm delivery
$PM_{2.5}$	Particulate matter with aerodynamics diameter less than 2.5 micrometer
O_3	ozone
$\mu g/m^3$	microgram per cubic meter
ppb	parts per billion
AQS	EPA's Air Quality System
CMAQ	Models-3/Community Multi-scale Air Quality Model
HBM	Hierarchical Bayesian Prediction Model

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Highlights

- Prenatal exposure to $PM_{2.5}$ may increase the risk of term LBW, PTD and VPTD.
- The effects of $PM_{2.5}$ on ABOs are strongest during the second trimester.
- Prenatal O_3 exposure may increase the risk of PTD and VPTD.

The protective association between O_3 and term LBW needs further investigation.

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Table 1

Characteristics of singleton births in Florida 2004–2005 (N=423,719) by adverse birth outcomes.

Characteristics	Term LBW n(%) or mean(SD)		PTD n(%) or mean(SD)		VPTD n(%) or mean(SD)		Controls n(%) or mean(SD)
	9320 (2.42)	p-value*	39082 (9.43)	p-value*	5680(1.49)	p-value*	375317
Maternal age (years)	26.7 (7.1)	<0.001	27.6 (7.0)	0.0019	27.4 (7.3)	0.5857	27.4 (6.4)
Gestational age (weeks)	38.0 (1.0)	<0.001	34.0 (2.9)	<0.001	27.9 (2.6)	<0.001	39.0 (1.1)
Mother education		<0.001		<0.001		<.0001	
<High school	2560 (27.8)		9127 (23.7)		1397 (25.2)		77011 (20.7)
HS grad/some college	4749 (51.6)		19616 (50.9)		2942 (53.1)		183225 (49.3)
College degree	1504 (16.4)		7880 (20.4)		984 (17.8)		88270 (23.7)
Graduate school	394 (4.3)		1925 (5.0)		215 (3.9)		23343 (6.3)
Maternal race		<0.001		<0.001		<.0001	
White	3344 (36.4)		16479 (42.6)		1864 (33.3)		176354 (47.4)
Black	2756 (30.0)		9642 (24.9)		1932 (34.5)		62419 (16.8)
Hispanic	1881 (20.5)		7606 (19.7)		1155 (20.6)		83470 (22.4)
Asian/PI	324 (3.5)		1026 (2.7)		124 (2.2)		10605 (2.9)
Others	894 (9.6)		3952 (10.2)		522 (9.3)		39483 (10.6)
Census block group annual income		<0.001		<0.001		<0.001	
First quartile (≤$29,643.00)	3026 (32.5)		11066 (28.3)		1892 (33.3)		92338 (24.6)
Second quartile ($29,643.00–38,095.00]	2401 (25.8)		9748 (24.9)		1461 (25.7)		94213 (25.1)
Third quartile ($38,095.00–49,457.00]	2152 (23.1)		9608 (24.6)		1320 (23.2)		94303 (25.1)
Fourth quartile ≥$49,457.00	1741 (18.7)		8660 (22.2)		1007 (17.7)		94463 (25.2)
Urbanicity		0.0006		0.0020		0.0015	
Urban	8160 (87.6)		33958 (86.89)		4986 (87.8)		323992 (86.3)
County unemployment		0.7244		0.0463		0.9073	
High (≥ median (11%))	6079 (65.2)		25225 (64.5)		3699 (65.12)		244140 (65.1)
Infant sex		<0.001		<0.001		0.0128	
Female	5578 (59.9)		18565 (47.5)		2655 (46.7)		182823 (48.7)
Marital status		<0.001		<0.001		<.0001	

Characteristics	Term LBW n(%) or mean(SD)		PTD n(%) or mean(SD)		VPTD n(%) or mean(SD)		Controls n(%) or mean(SD)
	9320 (2.42)	**p-value***	**39082 (9.43)**	**p-value***	**5680(1.49)**	**p-value***	**375317**
Married	4408 (47.4)		21180 (54.2)		2631 (46.4)		224450 (59.8)
Prenatal care		<0.001		<0.001		<0.001	
Yes	9055 (97.2)		37438 (95.8)		5224 (92.0)		370271 (98.7)
Tobacco use		<0.001		<0.001		<.0001	
Yes <10/day	1519 (16.3)		5991 (15.3)		1031 (18.2)		51941 (13.8)
Yes ≥10/day	1128 (12.1)		3058(7.8)		472 (8.3)		22611 (6.0)
Quit	190 (2.0)		647 (1.7)		99 (1.7)		5952 (1.6)
No	6483 (69.6)		29386 (75.2)		4078 (71.8)		294813 (78.6)
Alcohol		<0.001		<0.001		<.0001	
Yes	69 (0.7)		192 (0.5)		32 (0.6)		1180 (0.3)
Maternal risk factors		<0.001		<0.001		<.0001	
Yes	3611 (38.7)		18488 (47.3)		2836 (49.9)		114943 (30.6)
Maternal infection		0.006		0.7907		0.3025	
Yes	1951 (20.9)		7724 (19.8)		1093 (19.2)		74283 (19.8)
Maternal morbidity		0.0791		<0.001		<.0001	
Yes	1090 (11.7)		5066 (13.0)		960 (16.9)		41721 (11.1)
Season of conception		0.0040		0.8694		0.7374	
Warm	4382 (47.0)		18964 (48.5)		2743 (48.3)		182090 (48.5)
Cold	4938 (53.0)		20118 (51.5)		2937 (51.7)		193227 (51.5)
Year of birth		0.5500		0.2007		0.1745	
2004	4548 (48.8)		19061(48.8)		2738 (48.2)		184325 (49.1)
2005	4772 (51.2)		20021 (51.2)		2942 (51.8)		190992 (50.9)

*Denotes p-values for t-tests (for continuous variables) and chi-square tests (for categorical variables) comparing the differences between those with outcomes and those without any.

Table 2

Summary statistics for the distribution of pollutants during pregnancy by trimesters.

Pollutants	Summary Statistics							
	Min	P25	P50	P75	Max	IQR	Mean	SD
O_3 (ppb)								
Trimester 1	20.4	33.1	36.5	41.0	56.2	7.8	37.2	6.0
Trimester 2	20.9	33.3	37.0	41.3	57.3	8.1	37.6	6.1
Trimester 3	18.5	33.1	37.0	41.1	69.2	8.0	37.4	6.1
All pregnancy	22.8	33.9	37.9	41.0	51.3	7.1	37.4	4.1
$PM_{2.5}$ ($\mu g/m^3$)								
Trimester 1	2.6	8.2	9.6	11.0	26.6	2.6	9.7	2.1
Trimester 2	2.3	8.5	9.8	11.1	25.2	2.6	9.9	2.1
Trimester 3	1.8	8.7	10.0	11.5	44.3	2.8	10.2	2.3
All pregnancy	4.5	8.9	9.9	10.9	22.2	2.0	9.9	1.7

Abbreviations: P25: 25^{th} percentile, P50: 50^{th} percentile (median), P75: 75^{th} percentile, IQR: Interquartile Range; SD: standard deviation.

Table 3

Unadjusted and adjusted odds ratio for the association of air pollutants and adverse birth outcomes for every interquartile (IQR)[a] increase in exposure.

	Term LBW		PTD		VPTD	
Exposure period	**Unadjusted**	**Adjusted[b]**	**Unadjusted**	**Adjusted[c]**	**Unadjusted**	**Adjusted[c]**
O_3 (ppb)						
Trimester 1	1.002 (0.976,1.029)	0.994 (0.967,1.023)	1.026 (1.012,1.039)*	1.012 (0.998,1.027)	1.022 (0.988,1.057)	1.054 (1.016, 1.093)*
Trimester 2	0.980 (0.954,1.007)	0.978 (0.950,1.007)	1.026 (1.012,1.040)*	1.023 (1.008,1.039)*	1.014 (0.980,1.050)	1.072 (1.033, 1.113)*
Trimester 3	0.954 (0.928,0.980)*	0.940 (0.912,0.969)*	1.003 (0.989,1.017)	0.993 (0.978,1.008)	0.963 (0.924,1.004)	0.984 (0.940, 1.030)
Pregnancy	0.959 (0.926,0.994)*	0.938 (0.900,0.977)*	1.039 (1.020,1.058)*	1.028 (1.007, 1.050)*	1.018 (0.973,1.066)	1.125 (1.067, 1.186)*
$PM_{2.5}$ (μg/m^3)						
Trimester 1	1.037 (1.011,1.064)*	1.007 (0.981, 1.034)	1.046 (1.032,1.059)*	1.029 (1.016, 1.043)*	1.090 (1.055,1.126)*	1.063 (1.028, 1.098)*
Trimester 2	1.059 (1.032,1.087)*	1.034 (1.007, 1.061)*	1.139 (1.124,1.154)*	1.123 (1.109, 1.138)*	1.252 (1.214,1.291)*	1.215 (1.177, 1.253)*
Trimester 3	1.035 (1.010,1.061)*	1.005 (0.980, 1.031)	1.039 (1.026,1.052)*	1.026 (1.012, 1.039)*	1.038 (1.000,1.078)	1.010 (0.972, 1.049)
Pregnancy	1.050 (1.024,1.076)*	1.015 (0.989, 1.041)	1.071 (1.057,1.084)*	1.053 (1.040, 1.067)*	1.116 (1.082,1.151)*	1.082 (1.048, 1.117)*

[a] Interquartile range for O_3 in ppb: 7.8 for trimester 1, 8.0 for trimester 2, 8.0 for trimester 3, 7.1 for the entire pregnancy; for $PM_{2.5}$ in μg/m^3: 2.6 for trimester 1, 2.6 for trimester 2, 2.8 for trimester 3, and 2.0 for the entire pregnancy.

[b] Adjusted for maternal education, ethnicity, marital status, maternal age, infant gender, prenatal care status, alcohol, smoking, season of conception, census group income, urbanicity, presence or absence of maternal risk factor, infection, PTD status, or co-morbidity.

[c] Adjusted for maternal education, ethnicity, marital status, age, infant gender, prenatal care status, alcohol, smoking, census group income, urbanicity, presence or absence of maternal risk factor, LBW status, or co-morbidity.

* Indicates statistical significance at $p<0.05$

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Table 4

Adjusted odds ratio for the association of air pollutants and adverse birth outcomes for every interquartile (IQR)[a] increase in exposure after adjustment for co-pollutant effects.

Pollutants	Term LBW[b]	PTD[c]	VPTD[c]
O_3 (ppb)			
Trimester 1	0.990 (0.960, 1.021)	1.012 (0.997, 1.028)	1.021 (0.983, 1.061)
Trimester 2	0.960 (0.931, 0.990) *	0.990 (0.975, 1.005)	0.985 (0.949, 1.024)
Trimester 3	0.936 (0.907, 0.965) *	1.001 (0.986, 1.016)	0.987 (0.943, 1.033)
Pregnancy	0.930 (0.892, 0.970) *	1.034 (1.014, 1.055) *	1.075 (1.022, 1.131) *
$PM_{2.5}$ ($\mu g/m^3$)			
Trimester 1	1.013 (0.984, 1.042)	1.030 (1.015, 1.045) *	1.053 (1.016, 1.091) *
Trimester 2	1.047 (1.018, 1.076) *	1.132 (1.117, 1.148) *	1.217 (1.177, 1.257) *
Trimester 3	1.020 (0.994, 1.047)	1.030 (1.017, 1.044) *	1.020 (0.981, 1.061)
Pregnancy	1.026 (1.000, 1.053)	1.052(1.038, 1.066) *	1.069 (1.035, 1.105) *

[a] Interquartile range for O_3 in ppb: 7.8 for trimester 1, 8.0 for trimester 2, 8.0 for trimester 3, 7.1 for the entire pregnancy; for $PM_{2.5}$ in $\mu g/m^3$: 2.6 for trimester 1, 2.6 for trimester 2, 2.8 for trimester 3, and 2.0 for the entire pregnancy.

[b] Adjusted for maternal education, ethnicity, marital status, age, infant gender, prenatal care status, season of conception, alcohol, smoking, census tract income, urbanicity, presence or absence of maternal risk factor, infection, PTD status, or co morbidity.

[c] Adjusted for maternal education, ethnicity, marital status, age, infant gender, prenatal care status, alcohol, smoking, census group income, urbanicity, presence or absence of maternal risk factor, LBW status, or comorbidity.

* Indicates statistical significance at $p<0.05$

Table 5

Adjusted odds ratio for the association between air pollutants and adverse birth outcomes for every interquartile (IQR)[a] increase in exposure using closest monitor values among births within 5 miles from a monitor station.

Pollutants	Term LBW[b]		PTD[c]		VPTD[c]	
	n(LBW/total)	Adjusted OR	n(PTD/total)	Adjusted OR	n(VPTD/total)	Adjusted OR
O_3 (ppb)						
Trimester 1	2,569/112,500	0.966 (0.911, 1.025)	10,193/112,500	1.047 (1.015, 1.079)*	1,499/112,500	1.123 (1.041, 1.212)*
Trimester 2	2,569/112,500	1.017 (0.961, 1.075)	10,193/112,500	1.056 (1.023, 1.089)*	1,499/112,500	1.121 (1.037, 1.212)*
Trimester 3	2,569/112,500	0.960 (0.907, 1.016)	10,193/112,500	0.985 (0.956, 1.015)	1,499/112,500	0.972 (0.888, 1.063)
Pregnancy	2,569/112,500	0.974 (0.920, 1.031)	10,193/112,500	1.057 (1.023, 1.091)*	1,499/112,500	1.171 (1.079, 1.271)*
$PM_{2.5}$ (μg/m^3)						
Trimester 1	2,887/123,207	1.027 (0.977, 1.080)	11,656/123,207	1.060 (1.037, 1.084)*	1,867/123,207	1.101 (1.047, 1.159)*
Trimester 2	2,887/123,207	1.054 (1.005, 1.106)*	11,656/123,207	1.149 (1.125, 1.173)*	1,867/123,207	1.226 (1.169, 1.285)*
Trimester 3	2,887/123,207	1.031 (0.988, 1.075)	11,656/123,207	1.052 (1.031, 1.073)*	1,867/123,207	1.031 (0.975, 1.090)
Pregnancy	2,887/123,207	1.048 (0.989, 1.110)	11,656/123,207	1.110 (1.081, 1.141)*	1,867/123,207	1.146 (1.077, 1.220)*

[a] Interquartile range for O_3 in ppb: 8.9 for trimester 1, 9.1 for trimester 2, 8.5 for trimester 3, 5.9 for the entire pregnancy; for $PM_{2.5}$ in μg/m^3: 2.4 for trimester 1, 2.5 for trimester 2, 2.5 for trimester 3, and 2.5 for the entire pregnancy.

[b] Adjusted for maternal education, ethnicity, marital status, age, infant gender, prenatal care status, season of conception, alcohol, smoking, census tract income, urbanicity, presence or absence of maternal risk factor, infection, PTD status, or co morbidity.

[c] Adjusted for maternal education, ethnicity, marital status, age, infant gender, prenatal care status, alcohol, smoking, census group income, urbanicity, presence or absence of maternal risk factor, LBW status, or comorbidity.

* Indicates statistical significance at $p<0.05$