



Prenatal airshed pollutants and preterm birth in an observational birth cohort study in Detroit, Michigan, USA

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ABSTRACT

Detroit, Michigan, currently has the highest preterm birth (PTB) rate of large cities in the United States. Disproportionate exposure to ambient air pollutants, including particulate matter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), $\text{PM} \leq 10 \mu\text{m}$ (PM_{10}), nitrogen dioxide (NO_2) and benzene, toluene, ethylbenzene, and xylenes (BTEX) may contribute to PTB. Our objective was to examine the association of airshed pollutants with PTB in Detroit, MI. The Geospatial Determinants of Health Outcomes Consortium (GeoDHOC) study collected air pollution measurements at 68 sites in Detroit in September 2008 and June 2009. GeoDHOC data were coupled with 2008–2010 Michigan Air Sampling Network measurements in Detroit to develop monthly ambient air pollution estimates at a spatial density of 300 m^2 . Using delivery records from two urban hospitals, we established a retrospective birth cohort of births by Detroit women occurring from June 2008 to May 2010. Estimates of air pollutant exposure throughout pregnancy were assigned to maternal address at delivery. Our analytic sample size included 7961 births; 891 (11.2%) were PTB. After covariate adjustment, PM_{10} ($P = 0.003$) and BTEX ($P < 0.001$), but not $\text{PM}_{2.5}$ ($P = 0.376$) or NO_2 ($P = 0.582$), were statistically significantly associated with PTB. In adjusted models, for every 5-unit increase in PM_{10} there was a 1.21 times higher odds of PTB (95% CI 1.07, 1.38) and for every 5-unit increase in BTEX there was a 1.54 times higher odds of PTB (95% CI 1.25, 1.89). Consistent with previous studies, higher PM_{10} was associated with PTB. We also found novel evidence that higher airshed BTEX is associated with PTB. Future studies confirming these associations and examining direct measures of exposure are needed.

1. Introduction

Despite decades of efforts to prevent preterm birth (PTB), the United States, and Detroit, Michigan in particular, has staggeringly high rates of PTB (9.9% and 14.5%, respectively, in 2018) (March of Dimes, 2018; Shi et al., 2004; Martin et al., 2017). A recent study of 4.1 million births demonstrated a paucity of identified risk factors for PTB (Ferrero et al., 2016). While there is evidence that genetic factors (both maternal and fetal) influence length of gestation, environmental factors during pregnancy also account for a large proportion in the variation of gestational

duration, and the environmental contribution may be greater in pregnancies in black women (York et al., 2014). Efforts to decrease PTB have not fully considered the complex interrelationships of environmental, medical and social determinants of risk. This lack of consideration has likely contributed to persistent racial disparities in PTB: compared to white women, black women have 2.0 (95% CI 1.8, 2.2) times greater odds of PTB (Schaaf et al., 2013). Additional studies of the role of environmental exposures on risk of PTB, especially among black women, are needed.

There is growing evidence that air pollutants impact birth outcomes

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(Nieuwenhuijsen et al., 2013; Sapkota et al., 2012; Shah and Balkhair, 2011; Bolden et al., 2015). Guo et al. (2019) in a meta-analysis of 40 studies found that nitrogen dioxide (NO₂) was inversely associated with PTB (pooled odds ratio [OR] = 0.98, 95% CI 0.97, 0.99) and particulate matter ≤ 10 μm (PM₁₀) was positively associated with PTB (pooled OR = 1.05, 95% CI 1.02, 1.07); in contrast, particulate matter ≤ 2.5 μm (PM_{2.5}) was not associated with PTB (pooled OR = 1.00, 95% CI 0.98, 1.01) (Guo et al., 2019). In a large Canadian study of nearly 350,000 births, xylene and toluene were each associated with greater odds of PTB (Serrano-Lomelin et al., 2019) and in the Infancia y Medio Ambiente (INMA) cohort in Spain, women exposed to benzene levels > 2.7 μg/m in the air were at increased risk of PTB (Llop et al., 2010).

The goal of this study was to examine if airshed pollutants (benzene, toluene, ethylbenzene, and xylenes [BTEX], NO₂, PM_{2.5} or PM₁₀), estimated through high resolution spatial monitoring of air pollution by the Geospatial Determinants of Health Outcomes Consortium (GeoDHOC) (Miller et al., 2010a, 2019; Lemke et al., 2014), were associated with PTB in a study of births that occurred in Detroit. We additionally examined whether associations between airshed pollutants and PTB varied by infant sex, maternal race, or trimester of exposure.

2. Materials and methods

2.1. Study population

A cohort of women with a singleton delivery between June 8, 2008 and May 9, 2010, at Henry Ford Hospital (HFH) and Detroit Medical Center (DMC) were identified. Deliveries were limited to women residing within Detroit. For HFH, deliveries were identified from the hospital discharge abstract using the Diagnosis-Related Group (DRG) for vaginal and Caesarean section deliveries. For the DMC, Wayne State University (WSU) Physicians' Group Department of Obstetrics and Gynecology maintained a database (the Women, Infant, Neonatal Database [WIND]) with all deliveries that was used for population identification; data were also populated using the hospital discharge abstract. Collection of the pregnancy outcomes for the HFH cohort was done by manual abstraction of the electronic medical record. For DMC, these data were gleaned from WIND.

Prior to statistical analysis, we excluded 1 woman with an infant of undetermined sex as we could not include her in sex-specific analysis; 4 with gestational age at delivery ≤ 23 weeks as this was before the time of viability; 1 woman who was 62 years old at delivery, as this was outside the expected window of reproductive age; and 5 with gestational age at delivery ≥ 42.9 weeks, as this was outside the typical bounds of gestational length that a pregnancy is clinically allowed to continue, suggesting inaccuracy with the estimated date of pregnancy onset. We also excluded 7 women who were of race American Indian, Native Hawaiian, or Pacific Islander, as this sub-group was too small for statistical inferences. Three women who had addresses in regions not covered by the pollutant location data were also excluded. The final analytic sample size was 7961. The Institutional Review Boards at HFH, DMC and WSU approved the study and waiver of consent was obtained.

2.2. Preterm birth (PTB)

Gestational age was abstracted from the infant's medical record at delivery. PTB was defined as birth occurring < 37 weeks gestation.

2.3. Covariates

Data were obtained from the administrative databases at HFH and from the WIND for DMC, including maternal age, race/ethnicity, marital status, parity, mode of delivery, and pregnancy complications. Low birthweight was defined as birthweight < 2500 g. Parity was defined as the number of previous pregnancies and classified as 0, 1, 2–3 or 4+. Pregnancy-induced hypertension (PIH) and gestational diabetes mellitus

(GDM) were identified using International Classification of Diseases, 9th edition, Clinical Modification.

To obtain a measure of socioeconomic status during the 2008–2010 period coinciding with air pollution data collection and modeling, maternal addresses at delivery were geocoded and grouped by the 2010 U.S. census tracts. Neighborhood-level poverty was defined as the proportion of residents in a census tract living below the federal poverty level. Estimates of the association of neighborhood contextual factors, based on census level variables, on health outcomes may result in biased estimates if the continuously-distributed factor is used; however, use of quantiles results in unbiased estimates (Mooney et al., 2014). Thus, we calculated sample quartiles of neighborhood-level poverty.

2.4. Air pollution estimation

The GeoDHOC performed high resolution spatial monitoring of air pollution at 68 sites in Detroit and 32 sites in the adjacent city of Windsor, Ontario, Canada during the periods of September 5–20, 2008 and May 29–June 13, 2009 (Miller et al., 2010a, 2019; Lemke et al., 2014). During the sampling period, 100 passive samplers measured NO₂ and volatile organic compounds (including BTEX) creating a spatial sampling density of approximately 5 km (Shi et al., 2004) per sample. Particulate matter (PM) was measured using 50 active samplers distributed across both cities creating a spatial sampling density of approximately 10 km² per sample. Ordinary kriging (i.e., geostatistical interpolation) was used to model individual air pollutant content across Detroit. The geospatial resolution of our air pollution models (i.e., 300 m × 300 m) generates an approximate city block scale exposure estimate which exceeds that of any published, synoptic study for an area the size of Detroit. The perinatal data are Detroit-based and this study utilized the Detroit NO₂, BTEX, PM_{2.5}, and PM₁₀ models.

As described in O'Leary and Lemke, these spatially detailed GeoDHOC air pollutant models were combined with 3-year air contaminant time series data from the Michigan Air Sampling Network. The combined datasets were then used to generate monthly contaminant concentration maps for the city of Detroit covering January 2008 through December 2010 (O'Leary and Lemke, 2014). As a result, a pollutant concentration can be calculated for each month, at any location within Detroit, during 2008–2010. Similar approaches of combining spatial and temporal pollutant data have been utilized in other cities (Ross et al., 2013).

2.5. Assignment of estimated exposures

For each woman, we defined the bounds of the pregnancy by the last menstrual period (LMP) date (lower bound) and the delivery date (upper bound). LMP date was calculated by subtracting the delivery medical record entry of gestational age from the date of delivery. The first and second trimesters were defined as the periods ending 13 weeks (91 days) and 27 weeks (189 days) after LMP, respectively.

Exposures for pregnancies with a LMP date on or before the 15th of each month were considered to begin in that month. Exposures for pregnancies with a LMP date after the 15th of a month were considered to begin the following month. Total exposures for each delivery in the cohort were estimated by averaging the monthly exposure estimates for each month of the pregnancy falling within the modeled exposure period (2008–2010). Trimester-specific pollution estimates were assigned by averaging modeled concentrations at the location of the maternal residential address over each month of that trimester. For example, for a 9-month pregnancy with LMP beginning on September 1, 2007 and ending with delivery on June 8, 2008, no exposure estimate is assigned to the first trimester due to it falling outside our pollution modeling timeframe; the second trimester is estimated as the average of January and February 2008; the third trimester exposure is the average of March, April, and May 2008; and the total exposure is estimated as the average of the first 5 months of 2008.

2.6. Statistical analysis

SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses. Pearson correlation coefficients were calculated to estimate the correlation across the 4 pollutants. Logistic models were used to obtain crude ORs for PTB. Generalized estimating equation logistic models were used to examine the association of air pollutants with PTB accounting for clustering within zip code. Race-by-pollutant and infant sex-by-pollutant interaction terms were fit to examine if there were race- or sex-specific associations between each pollutant and PTB. Linear regression models using generalized estimating equations were also fit to examine the association of each pollutant and continuously distributed gestational age at delivery. All models were fit (I) unadjusted; (II) adjusted for delivery hospital and basic demographic and clinical characteristics known to be associated with PTB (i.e., maternal age at delivery, maternal marital status, maternal race, and parity); (III) adjusted for II plus pregnancy complications (i.e., PIH, GDM); and (IV) adjusted for III plus a measure of neighborhood-level SES (i.e., neighborhood level poverty).

Population attributable risk was calculated using PROC STDRATE in SAS. To calculate the population attributable risk, for each pollutant the highest quartile was compared against the lower 3 quartiles combined. Given that exposures to pollutants do not occur in isolation, we fit a fully-adjusted model including all 4 pollutants. For each pollutant, paired Pearson correlation coefficients were calculated to estimate the

correlations between the different trimesters. Trimester-specific associations of the air pollutants with PTB were investigated using logistic models with a multiple informant approach (Sanchez et al., 2011; Stacy et al., 2017).

Finally, given that this was a retrospective birth cohort design based on births within a pre-specified calendar period matched with dates of air pollution measurement, we are at risk for fixed cohort bias (shorter pregnancies missed at the beginning and longer pregnancies missed at the end of the study period) (Strand et al., 2011). We conducted a sensitivity analysis, using the approach of Strand et al. (2011), where we limited the cohort to pregnancies with LMP dates between 19 weeks before the cohort started and 43 weeks before the cohort ended (Strand et al., 2011) and fit the models using this adjusted cohort.

3. Results

A total of 7961 singleton deliveries were included in this analysis of which 891 (11.2%) were PTB. There was variation in the proportion of PTB across the geographic region of the study (Detroit, MI), ranging from <5% to 30% within a census tract (Fig. 1). Table 1 provides descriptive statistics of the study population. The mean age of the mothers at delivery was 25.0 ± 6.4 years; most mothers were Black (76.2%), had at least 1 prior pregnancy (89.1%), and were not married at the time of delivery (82.5%). Most deliveries were vaginal (70.6%); 5.0% of women had GDM and 5.4% had PIH.

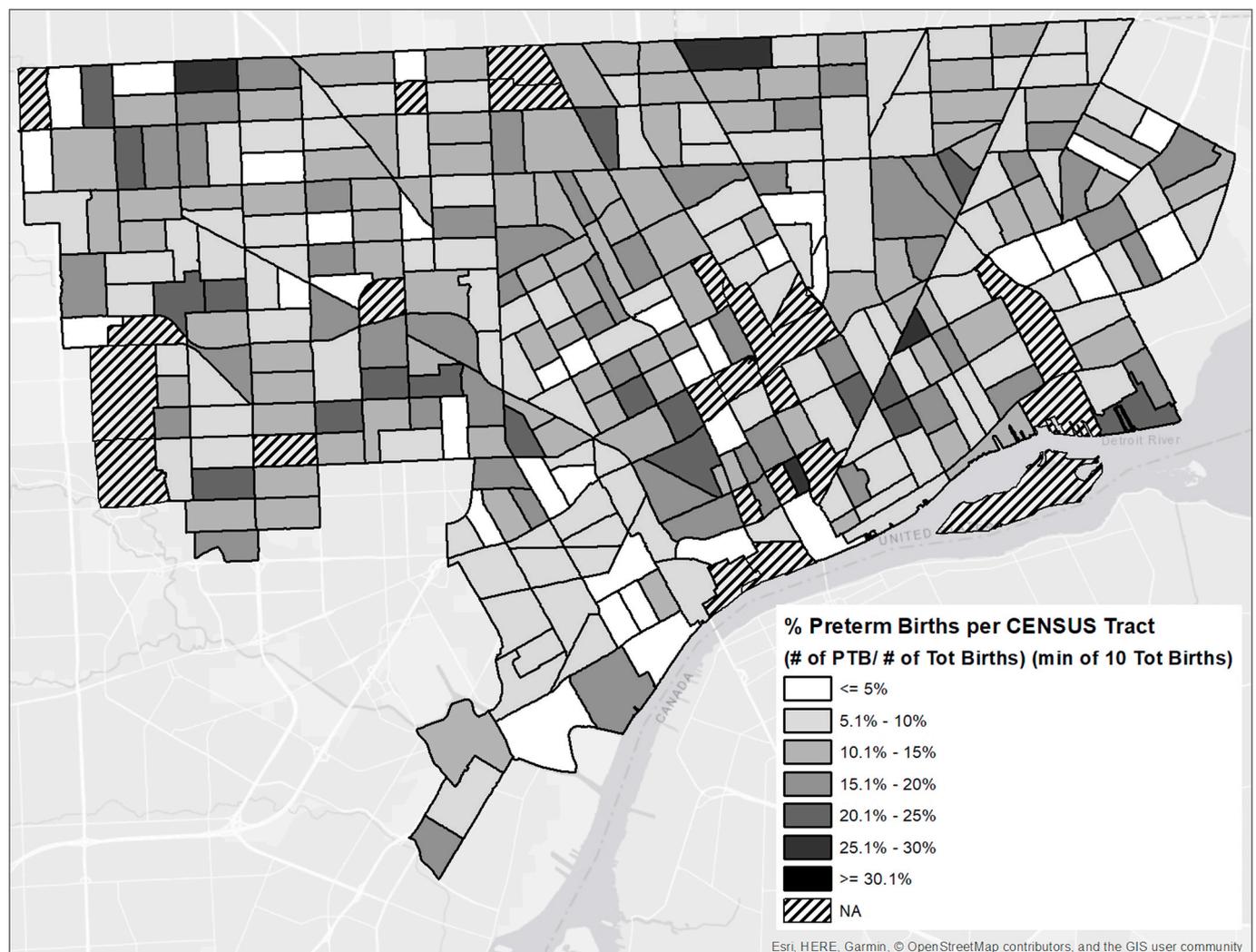


Fig. 1. Proportion of preterm (PTB) within 2010 Census tracts across the city of Detroit, MI. Census tracts with <10 total (Tot) births were set to not available (NA).

Table 1
Descriptive characteristics of the overall cohort and those with preterm birth (PTB).

Parameter	All Cases (N = 7961) N(%) or mean ± SD	PTB (N = 891) N(%) or mean ± SD	OR (95% CI)
Gestational age (weeks)	38.9 ± 2.3	34.0 ± 3.1	–
Birthweight (grams)	3138.8 ± 599.6	2214.6 ± 733.2	–
Low birth weight			–
No	7099 (89.2%)	347 (39.0%)	
Yes	862 (10.8%)	544 (61.1%)	
Maternal age (years)	25.0 ± 6.4	25.9 ± 6.8	1.03 (1.01, 1.04)
Maternal age < 20 years	1801 (22.6%)	183 (20.5%)	0.93 (0.75, 1.16)
20–24 years	2490 (31.3%)	249 (28.0%)	0.92 (0.75, 1.12)
25–29 years	1755 (22.0%)	190 (21.3%)	1.00 (reference)
30–34 years	1159 (14.6%)	149 (16.7%)	1.22 (0.97, 1.53)
≥ 35 years	756 (9.5%)	120 (13.5%)	1.55 (1.22, 1.99)
% Below poverty level	43.0 ± 13.3	42.8 ± 12.9	0.99 (0.99–1.00)
% Below poverty level ^a			
Quartile 1	1988 (25.0%)	237 (26.7%)	1.01 (0.83, 1.22)
Quartile 2	1984 (24.9%)	211 (23.7%)	0.89 (0.73, 1.08)
Quartile 3	1988 (25.0%)	204 (23.0%)	0.85 (0.70, 1.04)
Quartile 4	1999 (25.1%)	237 (26.7%)	1.00 (reference)
Maternal race/ethnicity			
Black	6063 (76.2%)	758 (85.1%)	1.20 (0.88, 1.63)
Hispanic	741 (9.3%)	47 (5.3%)	0.57 (0.37, 0.86)
White	440 (5.5%)	39 (4.4%)	1.00 (reference)
Other	717 (9.0%)	47 (5.3%)	0.48 (0.31, 0.75)
Parity			
0	871 (10.9%)	72 (8.1%)	0.81 (0.62, 1.06)
1	3422 (43.1%)	343 (38.5%)	1.00 (reference)
2–3	2627 (33.0%)	309 (34.7%)	1.20 (1.02, 1.41)
4+	1030 (12.9%)	167 (18.7%)	1.74 (1.43, 2.13)
Marital status			
Married	1395 (17.5%)	117 (13.1%)	1.00 (reference)
Not married	6566 (82.5%)	774 (86.9%)	1.46 (1.19, 1.79)
Delivery mode			
Cesarean section	2338 (29.4%)	347 (39.0%)	1.63 (1.41, 1.88)
Vaginal	5622 (70.6%)	544 (61.1%)	1.00 (reference)
PIH			
No	7528 (94.6%)	727 (81.6%)	1.00 (reference)
Yes	433 (5.4%)	164 (18.4%)	5.70 (4.63, 7.03)
GDM			
No	7564 (95.0%)	836 (93.8%)	1.00 (reference)
Yes	397 (5.0%)	55 (6.2%)	1.30 (0.97, 1.74)
Infant's sex			
Female	3841 (48.3%)	409 (45.9%)	0.90 (0.78, 1.03)
Male	4120 (51.8%)	482 (54.1%)	1.00 (reference)

Note: Odds ratio (OR) is for the association of each parameter with PTB. GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension.

^a Quartile 1: <33.7%; Quartile 2: 33.7- < 42.2%; Quartile 3: 42.2- < 52.2%; Quartile 4: ≥52.2%.

Maternal factors associated with PTB are also presented in Table 1. Women age ≥35 years at the time of delivery had 1.55 (95% CI OR 1.22, 1.99) times higher odds of PTB compared to women ages 25–29 years at delivery. Compared to women with 1 previous pregnancy, women with 2–3 previous pregnancies had a 1.20 (95% CI 1.02, 1.41) times higher odds of PTB and women with 4+ previous pregnancies had a 1.74 (95% CI 1.43, 2.13) times higher odds of PTB. Women who were not married at the time of delivery had 1.46 (95% CI 1.19, 1.79) times higher odds of PTB than women who were married. Women with PIH had a 5.70 (95% CI 4.63, 7.03) times higher odds of PTB than women without PIH. Cesarean section delivery was also associated with PTB (OR = 1.63; 95% CI 1.41, 1.88).

Variations in exposure estimates (overall, and by trimester) resulted from differences in the spatial locations of the maternal residences as well as the timing of the onset of each pregnancy evaluated in our study cohort (Table 2). These data show a large range of exposure estimates during each trimester but relatively little variation across trimesters and the total term for each individual pollutant. Because exposure estimates are averaged over multiple months in each trimester or term, these results highlight the importance of neighborhood scale variability in air pollutant concentrations measured in the GeoDHOC study (Miller et al., 2010a; Lemke et al., 2014). Additionally, there was evidence that total exposure estimates for the four pollutants were correlated (Table 3). The strongest correlation was between PM_{2.5} and NO₂ (r = 0.52, P < 0.001). The weakest correlation, which was also the only inverse correlation, was between PM_{2.5} and BTEX (r = -0.06, P < 0.001).

3.1. Association of air pollution estimates across pregnancy with PTB

Mean exposure estimates for the four air pollutants by PTB status are presented in Fig. 2. Women who experienced PTB had higher mean BTEX exposure than women who did not (Fig. 2A). In contrast, mean NO₂ exposure was lower in women who experienced PTB compared to those who did not (Fig. 2B). Mean PM₁₀ (Fig. 2C) and PM_{2.5} (Fig. 2D) did not differ between women who did and did not experience PTB.

Table 4 presents the association of the air pollutants (total exposure over pregnancy) with PTB in the entire cohort. After full covariate adjustment, for every 5-unit increase in airshed BTEX, there was a 1.54 (95% CI 1.25, 1.89) times higher odds of PTB. Similarly, for every 5-unit increase in PM₁₀ the odds of PTB increased by 1.21 (95% CI 1.07, 1.38). PM_{2.5} (OR = 0.86, 95% CI 0.62, 1.20) and NO₂ (OR = 0.94, 95% CI 0.76, 1.17) were not associated with PTB occurring in the entire cohort.

We estimated the population attributable risk for BTEX and PM₁₀ with PTB. To estimate the population attributable risk, we categorized the pollutants into quartiles and compared the highest quartile to the other 3 quartiles combined. In the fully-adjusted model, women in the highest quartile of BTEX exposure had 1.30 (95% CI 1.14, 1.47) times higher odds of PTB than women in the other 3 quartiles. Under the strong assumption of a causal association between BTEX and PTB, 7.4% (95% CI 4.0%, 10.7%) of all PTB in the total population is attributable to the higher BTEX exposure. Similarly, in the fully-adjusted model, women in the highest quartile of PM₁₀ exposure had a 2.46 (95% CI 0.99, 6.12) times higher odds of PTB compared to women in the other quartiles of PM₁₀ exposure, although the CI includes 1.00. Assuming a causal relationship, 3.6% (95% CI 0.3%, 6.8%) of all PTB in the total population is attributable to the higher PM₁₀ exposure.

Results were similar when we examined the association of each pollutant with gestational age at delivery. In the fully-adjusted model, neither PM_{2.5} (mean change in gestational age [weeks] = 0.14 ± 0.12; P = 0.255) nor NO₂ (mean change in gestational age [weeks] = 0.11 ± 0.09; P = 0.245) were associated with gestational age at delivery. There was an inverse association between PM₁₀ and gestational age at delivery (P = 0.006); for every 5-unit increase in PM₁₀, there was a mean decrease in gestational age at delivery of 0.22 ± 0.08 weeks. There was also an inverse association of BTEX with gestational age at delivery (P = 0.005); for every 5-unit increase in BTEX, there was a mean decrease in

Table 2
Statistical summary of air pollutant exposure estimates.

Pollutant	Min	Mean	Median	Max	Standard Deviation	Coefficient of Variation (%)
BTEX ($\mu\text{g}/\text{m}^3$)						
1st trimester	1.7	8.0	7.7	23.0	2.2	27.7
2nd trimester	2.0	8.2	7.8	23.0	2.4	29.4
3rd trimester	2.1	8.2	7.9	23.0	2.4	29.3
Total	2.8	8.1	8.2	19.2	1.7	20.4
NO₂ (ppb)						
1st trimester	9.8	18.6	18.3	26.9	3.2	17.5
2nd trimester	9.5	18.7	18.6	26.5	3.1	16.5
3rd trimester	9.6	18.5	18.4	28.0	3.0	16.2
Total	11.6	18.5	18.6	25.7	2.1	11.3
PM₁₀ ($\mu\text{g}/\text{m}^3$)						
1st trimester	5.1	14.7	13.7	28.2	5.6	37.7
2nd trimester	5.1	13.9	12.8	28.1	5.2	37.4
3rd trimester	4.1	13.4	11.8	29.5	5.4	40.3
Total	7.2	14.2	13.4	24.5	3.9	27.4
PM_{2.5} ($\mu\text{g}/\text{m}^3$)						
1st trimester	5.8	11.0	10.6	17.2	2.5	22.9
2nd trimester	5.9	10.9	10.4	17.2	2.4	22.2
3rd trimester	3.8	10.3	9.8	17.8	2.0	19.8
Total	7.2	10.7	10.7	16.5	1.3	11.9

BTEX, benzene, toluene, ethylbenzene, and xylenes; NO₂, nitrogen dioxide, PM_{2.5}, particulate matter $\leq 2.5 \mu\text{m}$; PM₁₀, particulate matter $\leq 10 \mu\text{m}$; min, minimum, max, maximum.

Table 3
Correlation matrix of the four pollutants (total estimated exposure during pregnancy).

Pollutant	BTEX ($\mu\text{g}/\text{m}^3$)	NO ₂ (ppb)	PM ₁₀ ($\mu\text{g}/\text{m}^3$)	PM _{2.5} ($\mu\text{g}/\text{m}^3$)
BTEX ($\mu\text{g}/\text{m}^3$)	1.00000	$r = 0.10$ $p < 0.0001$	$r = 0.38$ $p < 0.0001$	$r = -0.06$ $p < 0.0001$
NO ₂ (ppb)	$r = 0.10$ $p < 0.0001$	>1.00000	$r = 0.09$ $p < 0.0001$	$r = 0.52$ $p < 0.0001$
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	$r = 0.38$ $p < 0.0001$	$r = 0.09$ $p < 0.0001$	1.00000	$r = 0.40$ $p < 0.0001$
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	$r = -0.06$ $p < 0.0001$	$r = 0.52$ $p < 0.0001$	$r = 0.40$ $p < 0.0001$	1.00000

BTEX, benzene, toluene, ethylbenzene, and xylenes; NO₂, nitrogen dioxide, PM_{2.5}, particulate matter $\leq 2.5 \mu\text{m}$; PM₁₀, particulate matter $\leq 10 \mu\text{m}$; r, Pearson correlation coefficient.

gestational age at delivery of 0.32 ± 0.11 weeks.

3.2. Race and infant sex-specific association of air pollutants with PTB

There was no evidence to suggest that there were differences in the association of BTEX, NO₂, or PM₁₀ with PTB by infant sex (all interaction $P > 0.130$; Supplemental Tables 1–4). There was evidence for a potential sex-specific association of PM_{2.5} with PTB (interaction $P = 0.032$; Supplemental Table 2). In male infants, after full covariate adjustment, there was no association of PM_{2.5} with PTB (OR = 1.06, 95% CI 0.64, 1.75). In contrast, in female infants there was an inverse association between PM_{2.5} and PTB (OR = 0.51, 95% CI 0.34, 0.74). There was no evidence to suggest that there were race specific effects of any of the measured pollutants on PTB (all interaction $P > 0.102$; Supplemental Tables 1–4).

3.3. Multi-pollutant model for PTB

After adjusting for maternal age, parity, marital status, race, site, PIH and GDM and including all 4 pollutants in the same model, BTEX remained associated with PTB (Supplemental Table 5). For every 5-unit increase in BTEX there was a corresponding increased odds of PTB of 1.32 (95% CI 1.04, 1.68). PM₁₀ was no longer associated with PTB in the model adjusted for the other pollutants (OR = 1.19, 95% CI 0.99, 1.42). In the fully-adjusted model accounting for all pollutants neither PM_{2.5} (OR = 0.72, 95% CI 0.46, 1.12) nor NO₂ (OR = 1.03, 95% CI 0.79, 1.33)

were associated with PTB.

3.4. Trimester-specific analysis of air pollution and PTB

While the grouped analysis showing the distributions of the pollutants across trimester showed little overall variability (Table 2), for each woman, there was evidence that the pollution level in one trimester differed from that in another trimester, with the magnitude of the relationship between each trimester varying by pollutant (Supplemental Table 6). There was evidence of a weak to moderate correlation for each pollutant between measures across trimester (Supplemental Table 6), with the weakest correlation between 1st and 3rd trimester PM_{2.5} levels ($r = 0.04$, $P < 0.001$) and the strongest correlation between 2nd and 3rd trimester NO₂ levels ($r = 0.42$, $P < 0.001$). There was evidence of a trimester-specific effect of some pollutants with PTB (Supplemental Table 7). After full covariate adjustment, there was a statistically significant interaction between trimester of exposure and BTEX (interaction $P = 0.003$). For every 5-unit increase in BTEX in the first trimester the odds of PTB increased by 1.29 (95% CI 1.10, 1.51); similarly, for every 5-unit increase in BTEX in the third trimester the odds of PTB increased by 1.23 (95% CI 1.05, 1.45). Second trimester BTEX was not associated with PTB (OR = 1.12, 95% CI 0.97, 1.29). There was also evidence of a trimester-specific effect of PM₁₀ on PTB risk (interaction $P = 0.007$). For every 5-unit increase in PM₁₀ in the third trimester the odds of PTB increased by 1.21 (95% CI 1.05, 1.38); neither first trimester (OR = 1.00, 95% CI 0.94, 1.06) nor second trimester PM₁₀ (OR = 1.02, 95% CI 0.95, 1.09) were associated with PTB. There was no evidence for a trimester-specific effect of PM_{2.5} (interaction $P = 0.378$) or NO₂ (interaction $P = 0.549$) on PTB.

3.5. Sensitivity analysis accounting for fixed cohort bias

To account for potential bias due to fixed cohort effects, we conducted a sensitivity analysis by further restricting the cohort to women with a LMP at least 19 weeks before the first delivery date or at least 43 weeks before the cohort ended (last delivery date) and refitting the main model (Supplemental Table 8). Our adjusted cohort consisted of $N = 7690$ women (96.6% of the original cohort). In the adjusted cohort 818 (10.6%) were PTB. In the fully-adjusted model, BTEX remained statistically significantly and positively associated with PTB ($P = 0.006$); for every 5-unit increase in BTEX the odds of PTB increased by 1.36 (95% CI 1.09, 1.69). Similarly, PM₁₀ also remained statistically significantly

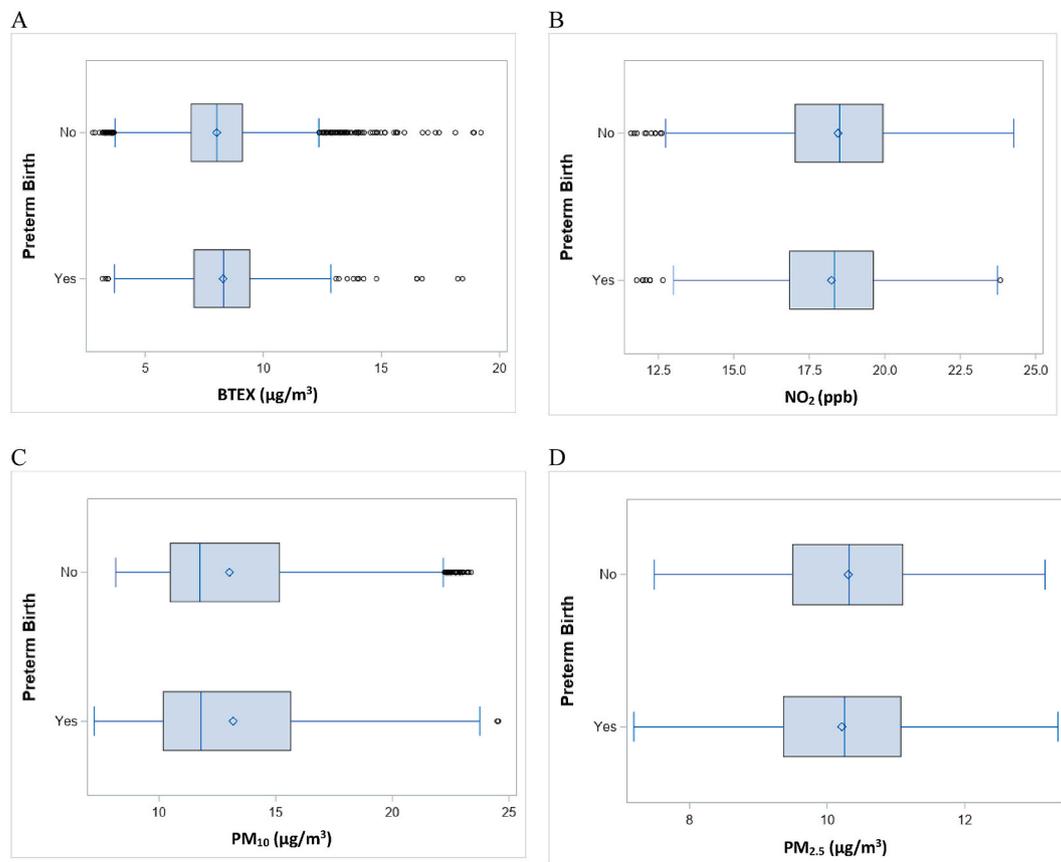


Fig. 2. Box plots of the distribution of each pollutant by preterm birth status for (A) benzene, toluene, ethylbenzene, and xylenes (BTEX); (B) nitrogen dioxide (NO_2); (C) particulate matter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$); and (D) particulate matter $\leq 10 \mu\text{m}$ (PM_{10}).

Table 4
Association of each pollutant with preterm birth.

Pollutant	Model I ^a OR (95% CI) P	Model II ^b OR (95% CI) P	Model III ^c OR (95% CI) P	Model IV ^d OR (95% CI) P
BTEX ($\mu\text{g}/\text{m}^3$)	1.61 (1.31, 1.98) p < 0.001	1.51 (1.23, 1.84) p < 0.001	1.55 (1.26, 1.90) p < 0.001	1.54 (1.25, 1.89) p < 0.001
$\text{PM}_{2.5}$ ($\mu\text{g}/\text{m}^3$)	0.82 (0.58, 1.16) p = 0.260	0.89 (0.64, 1.23) p = 0.476	0.86 (0.62, 1.19) p = 0.372	0.86 (0.62, 1.20) p = 0.376
NO_2 (ppb)	0.80 (0.62, 1.03) p = 0.080	0.96 (0.79, 1.19) p = 0.734	0.95 (0.77, 1.17) p = 0.618	0.94 (0.76, 1.17) p = 0.582
PM_{10} ($\mu\text{g}/\text{m}^3$)	1.14 (1.03, 1.27) p = 0.014	1.19 (1.04, 1.35) p = 0.009	1.21 (1.07, 1.38) p = 0.003	1.21 (1.07, 1.38) p = 0.003

Note: OR interpretation is for a 5-unit increase in pollutant. BTEX, benzene, toluene, ethylbenzene, and xylenes; CI, confidence interval; NO_2 , nitrogen dioxide; OR, odds ratio; $\text{PM}_{2.5}$, particulate matter $\leq 2.5 \mu\text{m}$; PM_{10} , particulate matter $\leq 10 \mu\text{m}$.

^a Model I: Unadjusted.

^b Model II: Adjusted for maternal age, parity, marital status, race, and clinical site.

^c Model III: Adjusted for Model II covariates and additionally adjusted for pregnancy-induced hypertension and gestational diabetes mellitus.

^d Model IV: Adjusted for Model II and III covariates and additionally adjusted for poverty quartile.

associated PTB ($P < 0.001$); for every 5 unit increase in PM_{10} , the odds of PTB increased by 1.30 (95% CI 1.14, 1.49).

4. Discussion

In this study of births in Detroit, MI, we found novel evidence showing higher exposure to airshed BTEX is associated with PTB in women residing in Detroit, MI, which remained even after accounting for the other pollutants. Consistent with prior estimates (Guo et al., 2019), we also found that higher PM_{10} , but not NO_2 or $\text{PM}_{2.5}$, were associated with greater odds of PTB.

BTEX compounds are volatile organic compounds in the atmosphere originating largely from motor vehicle exhaust and local stationary sources (Hinwood et al., 2007; Brunekreef and Holgate, 2002). The components of BTEX have each been shown to act as endocrine disrupting hormones and a small but growing body of evidence suggests both the individual components and combined BTEX may be associated with adverse birth outcomes (Bolden et al., 2015; Llop et al., 2010; Slama et al., 2009; Zahran et al., 2012). Fewer studies have examined if BTEX or its components are associated with PTB but the limited data support our findings. Data from the INMA cohort suggest that women exposed to benzene levels $>2.7 \mu\text{g}/\text{m}^3$ in the air were at increased risk of PTB (Llop et al., 2010). Higher xylene and toluene exposure was associated with greater risk of PTB in a large study in Canada (Serrano-Lomelin et al., 2019). Using birth certificate and publicly available pollution data in Brazil, higher cumulative exposure in the 5 days before delivery to benzene (OR = 1.12; 95% CI = 1.01–1.23) and toluene (OR = 1.12; 95% CI = 1.01–1.23) were each associated with increased risk of preterm birth (Santos and Nascimento, 2019). To our knowledge, ours is the first study to examine ambient BTEX levels and PTB. Of relevance, because indoor BTEX levels can be greater than outdoor levels (Bolden

et al., 2015), additional study is needed to fully understand the contribution of BTEX to adverse birth outcomes.

While additional studies are needed to establish a causal relationship between BTEX and PTB, potential mechanisms underlying the BTEX-PTB associations include disruption of the maternal or fetal immune system. In the EDEN cohort, higher maternal benzene exposure was associated with decreased cord blood CD4⁺CD25⁺ T-regulatory cells, suggesting that benzene could impact fetal immune development (Baiz et al., 2011). Benzene exposure is also associated with altered cytokine levels in humans (Minciullo et al., 2014). Intrauterine infection is a well described risk factor for PTB (Agrawal and Hirsch, 2012; Goldenberg et al., 2000); thus, if BTEX exposure disrupts the maternal or fetal immune response, this may lead to increased risk of PTB. Specific studies to address potential mediation of the BTEX-PTB association by immune dysfunction or infections are needed.

Our results were also consistent with a recent meta-analysis by Guo et al. (2019) showing that PM₁₀ is associated with PTB. PM₁₀ includes both coarse, fine and ultrafine PM (Guo et al., 2019). Globally, traffic contributes the greatest proportion of PM₁₀; in the US, however, unspecified sources of human origin are the largest source of PM₁₀ (44%) followed by traffic (30%) (Karagulian et al., 2015). As described elsewhere, PM may influence risk of PTB via mechanisms related to oxidative stress, inflammation, coagulation, endothelial function and hemodynamic responses (Kannan et al., 2006). Additional studies to further understand the mechanisms linking PM₁₀ and PTB are needed.

Similar to other studies (Guo et al., 2019), we did not find an association between PM_{2.5} and PTB. In the current study, the sampling density of approximately 5 km (Shi et al., 2004) per sample and collection of three size fractions (PM₁, PM_{1-2.5}, PM_{2.5-10}) to calculate PM_{2.5} and PM₁₀ suggests a robust approach to measurement. In Detroit, we have shown that at each sampling site, there were statistically significant correlations between PM measurements from 2008 to 2009 (Miller et al., 2019). PM_{2.5} and PM₁₀ have different sources (Miller et al., 2019) and methods of formation; PM_{2.5} is formed by combustion or photochemical reactions and PM₁₀ is formed by mechanical grinding and resuspension of solid materials (Adar et al., 2014). The composition of the finer PM_{2.5} (primarily elemental and black carbon, sulfate, nitrate and metals) and the coarser PM₁₀ (primarily crustal elements, metals from road dust, organic material) also differ (Adar et al., 2014). Particle size influences where the matter is deposited in the body; PM₁₀ primarily in the upper airway and PM_{2.5} in the lower airway (Falcon-Rodriguez et al., 2016). Adar et al. (2014) suggest that both the differences in composition and deposition may lead to differential health effects of PM₁₀ vs. PM_{2.5} (Adar et al., 2014). Additionally, PM_{2.5} and PM₁₀ are indicators or surrogates of fine and coarse pollution, respectively, not direct measures (Wilson and Suh, 1997); studies of the compositional properties of fine and coarse air pollutants on PTB are needed to better understand potential mechanisms as well as reasons for differences in association.

Because of the rapid development of the fetus over pregnancy, there may be critical windows of exposure to pollutants that may alter the risk of PTB. In the current study, first and third trimester BTEX was associated with higher odds of PTB, which may suggest that BTEX could impact placentation (early) or inflammation (late) (Ferguson et al., 2013). Additional studies on the timing of BTEX exposures across pregnancy and their impact on PTB are needed. We also found evidence that increasing PM₁₀ exposure in the third but not first or second trimester was associated with increased odds of PTB. While an earlier meta-analysis showed similar results of higher odds of PTB for higher exposure to PM₁₀ in the third but not first trimester (Sapkota et al., 2012), the meta-analysis by Guo et al. (2019) found that PM₁₀ exposure in the first but not second or third trimester was associated with PTB. Sapkota et al. (2012) suggest that variation in trimester-specific estimates may be due to reduced sample size/number of studies with available exposure data within trimesters or increased chance of exposure misclassification when assigning exposure estimates to first

compared to third trimester (i.e., exposure estimates based on address at delivery may better reflect address in the third compared to the first trimester) (Sapkota et al., 2012). Additional studies that quantify direct exposure to pollutants over gestation may be needed to better understand if critical windows of exposure exist.

Our study population was chosen based on a woman residing in the city of Detroit and delivering at one of two major medical centers in the city of Detroit, and represents ~40% of all deliveries to women residing in Detroit during the study period. Between 2008 and 2010, the rate of PTB in the city of Detroit was between 12 and 13% (Data Driven Detroit and the Skillman Foundation, 2012). Our rate of 11.2% was slightly lower than the average for the city of Detroit, and likely reflects that our sample was identified through hospital records (and thus may reflect women who obtained more prenatal care) rather than birth certificates. Between 2008 and 2009, rates of PTB and low birth weight in the United States were ~12% and ~8%, respectively (Martin et al., 2010, 2011), which is similar to the rates in our study population of 11.2% PTB and 10.8% low birth weight. The rates of PIH (5.6%) and GDM (5.0%) in our study population were also similar to the rates in the United States; PIH affects between 5% and 8% of pregnancies (Roberts et al., 2011), and GDM affects between 2% and 10% of pregnancies in the United States (Centers for Disease Contr, 2011). Finally, although historically Detroit is one of the most polluted cities in the United States (Morishita et al., 2006; Club, 2018), air quality data from the US Environmental Protection Agency suggest that air pollution for components such as PM_{2.5} in the Detroit region was comparable to other major Midwestern cities (Cleveland, OH; Chicago, IL; Cincinnati, OH; Columbus, OH; and Fort Wayne, IN) over the years of this study (United States Environmental Protection Agency, 2019). Consequently, findings from the current study should be relevant to other populations residing in large, urban cities in the United States.

In the current study we did not find evidence that maternal race modified associations of the measured ambient pollutants with PTB; similar results have been reported previously (Rappazzo et al., 2014). In contrast, however, while a previous study showed no effect modification by infant sex on the association between PM_{2.5} and PTB (Rappazzo et al., 2014), we found evidence that in girls, but not boys, higher PM_{2.5} was associated with lower odds of PTB. Male fetuses are at higher risk for PTB and for adverse effects of environmental exposures (DiPietro and Voegtline, 2017); thus, we had expected that if there were sex-specific effects, there would have been a larger, adverse effect in males, not a protective effect in females. Spontaneous abortion happens more frequently in male fetuses (Byrne and Warburton, 1987); our study population was identified through live birth, thus our sex-specific findings could be biased by this selection criterion. Alternatively, our sex-specific findings could be spurious; additional study of potential infant sex-specific associations of ambient pollutants on PTB is needed.

4.1. Strengths and limitations

Our definition of PTB is based on the delivery medical record entry of gestational age at delivery. Both obstetrical estimate of gestational age and LMP estimated gestational age have limitations; Rappazzo et al. (2017) have shown that using obstetrical estimation of gestational age at delivery results in higher effect estimates of associations between pollutants and PTB compared to those using LMP estimates (Rappazzo et al., 2017). It is possible that our use of obstetric estimated gestational age at delivery to define PTB in the current study led to biased effect estimates. Further, we did not have information to distinguish between spontaneous and induced preterm delivery; these may have different underlying mechanisms and future studies should examine associations of ambient pollutants with different PTB subtypes.

Our analyses were based on maternal address reported at the time of delivery. Change in maternal residence during pregnancy may result in incorrect estimation of pollution exposures in pregnancy. Several studies have shown little impact of maternal residential mobility during

pregnancy on estimates of air pollution exposure (Chen et al., 2010; Lupo et al., 2010). However, Bell et al. (2018) recently showed that residential mobility may detrimentally impact studies of spatially-varying exposures (Bell et al., 2018). To evaluate the potential impact of residential mobility, we randomly selected 50 women who delivered at HFH and compared address at birth to addresses listed within prenatal care records; of these, only 10 women (20%) moved over the pregnancy. This is similar to previous studies suggesting ~80% of women have 1 residence during pregnancy (Ritz and Wilhelm, 2008). Further, our women moved relatively short distances during pregnancy (mean driving distance between residences, an overestimate of actual distance, was 3.7 miles; longest distance was 10.2 miles). If there is misclassification, it would likely be non-differential (Miller et al., 2010b), resulting in weaker effect estimates. Similarly, we do not have information on mother's work or other addresses, thus we are unable to estimate exposure based on address other than residential address. Although we were able to adjust our analyses for some individual and population socioeconomic factors (e.g., maternal marital status, neighborhood-level poverty), residual confounding due to other unmeasured covariates is possible. For example, since the study utilized health system records, we were unable to adjust for maternal income or education level. Results from the current study may not be generalizable to other populations with different socioeconomic status compared to urban Detroit. Finally, population attributable risk estimates should be interpreted cautiously, as they make the strong assumption that a risk factor and health outcome are causally related (Rowe et al., 2004; Rockhill et al., 1998).

Strengths of the study include that our sample is comprised predominantly of black women; despite black women being at highest risk of PTB, the majority of current studies that have examined BTEX or its constituents have examined predominantly white cohorts. Our ability to control for several major confounding factors, including PIH and GDM, is also a strength of the current study. However, PIH and GDM could also be intermediate variables on the causal pathway between an air pollution exposure and PTB and thus including them in the model may be an overadjustment (Schisterman et al., 2009). In contrast to most previous studies, our estimates of ambient air pollution exposure have uniquely high spatial and temporal resolution capable of representing exposure variability during pregnancy. Such data may be critical to more accurately quantifying neighborhood scale and seasonally varying exposure levels (Ross et al., 2013). However, the influence of localized anomalously high or low air pollution measurements on environmental exposure models must also be evaluated (O'Leary et al., 2016). By defining our cohort based on date of delivery, our findings could be subject to bias due to fixed cohort effects (Strand et al., 2011); however, after conducting a sensitivity analysis restricting the sample to avoid over-inclusion of longer pregnancies at the start of the cohort and shorter pregnancies at the end of the cohort, inferences were the same suggesting our results were not due to fixed cohort bias.

5. Conclusions

In summary, in this cohort of births to women living in Detroit, Michigan, greater PM₁₀ and BTEX levels in the ambient air were associated with increased odds of PTB. Additional study on BTEX and birth outcomes is needed to better understand where intervention/remediation efforts could be targeted to reduce exposure and potentially improve maternal-child health. Further, because the influence of one pollutant may be dependent on the burden of another pollutant (e.g. in an area with lower or higher background ambient PM_{2.5} levels, the association between ambient BTEX and PTB may differ), additional studies in other geographic locations are also needed.

Author credit statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2020.109845>.

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