



# Article Benzene and NO<sub>2</sub> Exposure during Pregnancy and Preterm Birth in Two Philadelphia Hospitals, 2013–2017

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**Abstract:** Infants born preterm are at risk of neonatal morbidity and mortality. Preterm birth (PTB) can be categorized as either spontaneous (sPTB) or medically indicated (mPTB), resulting from distinct pathophysiologic processes such as preterm labor or preeclampsia, respectively. A growing body of literature has demonstrated the impacts of nitrogen dioxide (NO<sub>2</sub>) and benzene exposure on PTB, though few studies have investigated how these associations may differ by PTB subtype. We investigated the associations of NO<sub>2</sub> and benzene exposure with sPTB and mPTB among 18,616 singleton live births at two Philadelphia hospitals between 2013 and 2017. Residential NO<sub>2</sub> exposure was estimated using a land use regression model and averaged over the patient's full pregnancy. Benzene exposure was estimated at the census tract level using National Air Toxics Assessment (NATA) exposure data from 2014. We used logistic mixed-effects models to calculate odds ratios for overall PTB, sPTB, and mPTB separately, adjusting for patient- and tract-level confounders. Given the known racial segregation and PTB disparities in Philadelphia, we also examined race-stratified models. Counter to the hypothesis, neither NO<sub>2</sub> nor benzene exposure differed by race, and neither were significantly associated with PTB or PTB subtypes. As such, these pollutants do not appear to explain the racial disparities in PTB in this setting.

**Keywords:** NO<sub>2</sub>; nitrogen dioxide; benzene; preterm birth; Philadelphia; spontaneous preterm birth; medically indicated preterm birth

## 1. Introduction

Preterm birth (PTB) occurs in one in ten live births in the United States [1]. A major risk factor for infant mortality and future adverse health outcomes [2,3], PTB also occurs 1.5 times more often among Black individuals compared to White individuals [4], likely due to social, environmental and structural factors that continue to systemically differ by race [5]. There are two substantively different subtypes of PTB. Spontaneous PTB (sPTB) occurs after preterm labor or the premature rupture of membranes prior to 37 weeks of gestation. Medically indicated PTB (mPTB) is provider-initiated due to concern for maternal or fetal wellbeing from conditions such as preeclampsia or poor fetal growth prior to 37 weeks of gestation. Though certain risk factors for each subtype are shown to



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**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). differ (young maternal age is more strongly associated with sPTB, whereas obesity and hypertension are more strongly associated with mPTB) [6–10], few studies have considered how environmental exposure to factors such as air pollution may contribute differently to each PTB phenotype.

There is a growing body of literature demonstrating the impacts of NO<sub>2</sub> and benzene exposure during pregnancy on adverse birth outcomes [11–13]. NO<sub>2</sub> is primarily emitted from motor vehicles and power plants and is a ubiquitous, though varying, form of exposure in urban environments. Benzene, a volatile organic compound (VOC), is a carcinogen emitted from industrial sources such as oil refineries. Benzene was of particular interest in this setting due to a large oil refinery operating in South Philadelphia during this period, and several large oil refineries operating in the region. NO<sub>2</sub> exposure during pregnancy has been associated with adverse birth outcomes, including PTB [12,13], though some studies remain inconclusive [14,15]. While less studied, benzene exposure has also been associated with PTB [11,12]. The biological mechanism through which NO<sub>2</sub>, benzene and other air pollutants may lead to adverse birth outcomes is not fully understood, but may involve oxidative stress and impaired oxygen transport to the fetus [16–18].

This study aimed to examine the associations of  $NO_2$  and benzene exposure during pregnancy with PTB phenotypes in a cohort of singleton births at two Philadelphia hospitals between 2013 and 2017, after controlling for other characteristics. Due to ongoing residential segregation, which may co-vary with both pollutant exposure and PTB rates, we also explored race-stratified analyses.

#### 2. Materials and Methods

### 2.1. Study Population

We used a subset of the *GeoBirth* cohort, which includes all live singleton births at the Hospital of the University of Pennsylvania and Pennsylvania Hospital in Philadelphia, PA from 23 April 2013 to 4 March 2017 (n = 24,683 total) [19,20], for which we had curated electronic health records and air pollution data. We retained the 19,471 patients living in Philadelphia County for whom pollution exposure assignments were available. Infant records with unrealistic birth weights (<200 g or >7000 g) or who were at <20 weeks' or >45 weeks' gestation at birth were excluded from the analysis (n = 302). Additionally, patients (n = 513) missing covariate information were excluded, except for body mass index (BMI) (18%); given the high prevalence of missing BMI data, we created a categorical variable with a 'missing' category to retain these births in the analysis (Figure 1).

#### 2.2. Exposure Estimates

NO<sub>2</sub> exposure was estimated using the average predicted NO<sub>2</sub> concentration within a 300 m buffer around each patient's home on the date of delivery, averaged over each patient's entire pregnancy. We used a NO<sub>2</sub> surface developed using land use regression (LUR) modeling, based on spatial source covariates derived in ArcGIS and monitoring data collected in January 2018 at 48 sites distributed across Philadelphia County, plus 13 spatially representative sites monitored throughout 2018. After testing a large suite of GIS-based source covariates—including traffic density indicators, roadway descriptors, land use/built environment metrics, industrial emissions and transportation facilities—the final LUR covariates included impervious surface within 300 m of the sampling site, distance to the nearest bus stop, distance to a navigable river and kernel traffic density within 300 m (R<sup>2</sup> = 0.77). The final LUR surface was produced by predicting the NO<sub>2</sub> concentration at each centroid of a 30 m × 30 m grid.

The NO<sub>2</sub> estimates were temporally adjusted to the time period matching each patient's pregnancy using Equation (1), below, and daily NO<sub>2</sub> data from a Camden, New Jersey EPA Air Quality System (AQS) monitor, directly downwind of the Philadelphia area, and by providing more consistent data availability than did the Philadelphia AQS monitors for the period 2010–2018.

$$NO_{2} [loc x_{t=2}] = loc x_{t=1} - AQS_{t=1} + AQS_{t=2}$$
(1)

The predicted NO<sub>2</sub> exposure around a patient's home during pregnancy (NO<sub>2</sub> (loc  $x_{t=2}$ )) was calculated by averaging the LUR surface grid cell centroids within 300 m of each home, and was temporally adjusted by subtracting the mean NO<sub>2</sub> at the Camden monitor during the two-week air monitoring period (which provided the spatial data for the LUR model) in January 2018 (AQS<sub>t=1</sub> = 19.46 ppb) from the LUR-predicted NO<sub>2</sub> at the 300 m buffer around a patient's home in January 2018 (loc  $x_{t=1}$ ), replacing it with the mean NO<sub>2</sub> at the Camden monitor during a specific patient's pregnancy (AQS<sub>t=2</sub>). Each patient's period of pregnancy was estimated as the date of the last menstrual period (back-calculated using the best obstetric estimate of gestational age) until the date of birth. Trimesterspecific NO<sub>2</sub> exposure was calculated using the mean NO<sub>2</sub> exposure in the first 12 weeks for the first trimester, the mean NO<sub>2</sub> exposure between weeks 13 and 26 for the second trimester and the mean NO<sub>2</sub> exposure between 30 and <37 weeks were included in the third trimester cohort.

Benzene exposure was calculated using census tract-level National Air Toxics Assessment (NATA) exposure data from 2014, the latest NATA estimates available, and the only NATA year during our follow-up [21]. The NATA exposure estimates were tract-level benzene concentrations, combined with census data, climate data and human activity patterns, to estimate the average exposure for a person living in that tract [22]. We assigned NATA estimates based on the patient's census tract of residence. As Philadelphia is relatively dense, the patient census tracts were generally very small (mean area =  $0.86 \text{ km}^2$  (SD =  $0.93 \text{ km}^2$ )), suggesting better accuracy than in less dense regions of larger census tracts.



Figure 1. Analytic cohort development.

#### 2.3. Birth Outcomes and Covariate Ascertainment

The main outcome of interest was PTB, defined as birth before 37 weeks of gestation, with further distinction between spontaneous versus medically indicated PTB. sPTB was defined as birth following preterm labor or the spontaneous rupture of membranes. mPTB was defined as birth after labor induction or cesarian birth performed due to concern for maternal or fetal wellbeing. Each PTB was independently adjudicated by two blinded reviewers. Where there was disagreement, the chart went to a third senior reviewer for final assignment of the PTB phenotype. The covariates used in the models that may be associated with PTB included maternal race/ethnicity (Asian, Black non-Hispanic, Hispanic, other/unknown, White non-Hispanic), maternal age (<25, 25–34,  $\geq$ 35 years), BMI (<25, 25–<30,  $\geq$ 30 kg/m<sup>2</sup>, missing), insurance status (private, public/Medicaid/other), nulliparity (yes, no) and census tract-level percentage of poverty.

#### 2.4. Analysis

To estimate the associations of benzene and NO<sub>2</sub> exposure during pregnancy with PTB outcomes, we used logistic mixed-effects models with the birth hospital and the patient's census tract as random intercepts to account for clustering. NO<sub>2</sub> and benzene exposure were represented in parts per billion (ppb) and the models used standard deviation increments as the independent variables. Both pollutants were included in the models. We compared the unadjusted and adjusted associations of NO<sub>2</sub> and benzene with overall PTB, and with sPTB and mPTB separately. We also re-ran all the models stratified by race. Statistical analyses were run using R (Version 3.6.1, R Core Team: Vienna, Austria) [23] on RStudio (Version 1.2.5001, RStudio, PBC: Boston, MA, USA) [24]. Demographic and exposure data were mapped at the census tract level using qGIS3 (Version 3.18.3, QGIS Development Team) [25].

#### 3. Results

The demographic characteristics and air pollution estimates for the cohort are shown in Table 1. Of the 19,169 births, 1708 (8.9%) were PTB (n = 1035 (5.4%) sPTB and n = 657(3.4%) mPTB). There were 16 PTBs that were not able to be classified as either sPTB or mPTB. Patients with PTB were more likely to self-identify as Black and be publicly insured. With respect to characteristics and PTB phenotypes, patients with mPTB (but not sPTB) were older and had higher BMIs. The mean NO<sub>2</sub> and benzene exposure levels were similar among patients with term birth and PTB. The mean NO<sub>2</sub> and benzene exposure levels were similar among patients with sPTB and mPTB.

**Table 1.** Maternal demographics, environmental characteristics and birth outcomes of the study cohort, stratified by term birth, preterm birth (PTB), spontaneous PTB (sPTB) and medically indicated PTB (mPTB).

	Overall	Term	РТВ	sPTB	mPTB
Characteristics	n = 19,169	n = 17,461	n = 1708	n = 1035	<i>n</i> = 657
Maternal Age					
<25	26.9%	26.7%	29.1%	33.2%	22.7%
25–34	55.3%	55.5%	53.0%	51.5%	55.4%
$\geq$ 35	17.8%	17.8%	17.9%	15.5%	21.9%
Maternal Race					
White Non-Hispanic	28.2%	29.0%	19.4%	21.0%	17.0%
Black Non-Hispanic	52.6%	51.4%	64.4%	61.2%	69.7%
Asian	6.3%	6.4%	4.7%	6.3%	2.1%
Hispanic	8.4%	8.5%	7.6%	7.3%	7.6%
Mixed/Other/Unknown	4.2%	4.6%	3.9%	4.3%	3.5%

	Overall	Term	РТВ	sPTB	mPTB
BMI <sup>1</sup>					
<25	49.5%	50.2%	42.3%	49.2%	32.4%
25-<30	23.5%	23.5%	23.3%	23.2%	23.8%
<u>≥</u> 30	27.0%	26.3%	34.4%	27.7%	43.8%
Private Insurance <sup>2</sup>	45.1%	46.1%	35.8%	36.3%	35.4%
Nulliparity <sup>3</sup>	44.5%	44.8%	41.3%	41.1%	42.0%
Census Tract: Percentage of Poverty	28.0 (14.7)	27.7 (14.8)	30.35 (14.1)	29.9 (14.2)	30.9 (13.8)
Hospital of Birth					
Pennsylvania Hospital	54.8%	55.6%	47.2%	46.4%	47.5%
Hospital of the University of Pennsylvania	45.2%	44.4%	52.8%	53.6%	52.5%
Air Pollutants					
NO <sub>2</sub> (ppb)	17.2 (2.3)	17.2 (2.3)	17.1 (2.6)	17.2 (2.6)	17.0 (2.6)
Benzene (ppb)	0.22 (0.02)	0.22 (0.02)	0.22 (0.02)	0.22 (0.02)	0.22 (0.02)

#### Table 1. Cont.

<sup>1</sup> Missing values for BMI overall: 3484, term: 3152, PTB: 332, sPTB: 236, mPTB: 86. <sup>2</sup> Missing values for private insurance overall: 314, term: 271, PTB: 443, sPTB: 33, mPTB: 10. <sup>3</sup> Missing values for nulliparity overall: 238, term: 237, PTB: 1, sPTB: 0, mPTB: 0.

Benzene exposure estimates by census tract are mapped in Figure 2a. The benzene exposure map shows the highest exposure concentrations in west South Philadelphia and parts of North Philadelphia. The exposure decreases as the distance from these areas increases. The spatial component of the NO<sub>2</sub> LUR model shown in Figure 2b demonstrates higher exposure in Center City and South Philadelphia, as well as near highways and major roads.



Figure 2. (a) Benzene level by census tract in Philadelphia County; (b) spatial component of LUR model showing  $NO_2$ . This map does not account for temporal component, which is individualized to the patient.

Figure 3 shows the spatial distribution of the study cohort patients from the two hospitals. The majority of the patients at the Hospital of the University of Pennsylvania lived in West and Southwest Philadelphia (Figure 3a). The majority of the patients at Pennsylvania Hospital lived in Center City and South Philadelphia (Figure 3b). Figure 4 shows the racial distribution of the patients in the birth cohort. Black patients primarily lived in West and Southwest Philadelphia, in addition to west South Philadelphia, close to the oil refinery, while White patients lived in Center City and other parts of South Philadelphia.



**Figure 3.** Number of births per census tract by hospital: (**a**) Hospital of the University of Pennsylvania; (**b**) Pennsylvania Hospital.



Figure 4. Maternal race by census tract. (a) Patients who self-identified as Black, Non-Hispanic;(b) Patients who self-identified as White Non-Hispanic.

In the unadjusted models, we did not detect associations of benzene or  $NO_2$  with overall PTB (Table 2). In the adjusted models, we also did not detect associations of benzene or  $NO_2$  with overall PTB. When stratified by race, we also did not observe significant associations of benzene or  $NO_2$  and with overall PTB. With respect to associations with sPTB, in the unadjusted models, we observed no significant associations with benzene or  $NO_2$ . In the adjusted models, we also did not detect significant associations of benzene or  $NO_2$  with sPTB (Table 2). Race-stratified sPTB models also showed no association with benzene or  $NO_2$ . With respect to mPTB, the unadjusted analyses showed negative associations of benzene and  $NO_2$  with mPTB, but adjustment nullified the association. Models stratified by race also showed no association of benzene or  $NO_2$  with mPTB.

**Table 2.** Unadjusted and adjusted <sup>a</sup> odds ratios (ORs) of a standard deviation increment increase in NO<sub>2</sub> and benzene with preterm birth (PTB) outcomes, including spontaneous (sPTB) and medically indicated (mPTB).

	Birth Outcome: PTB OR (95% CI)	Birth Outcome: sPTB OR (95% CI)	Birth Outcome: mPTB OR (95% CI)			
Overall						
Unadjusted Benzene	0.96 (0.91, 1.01)	1.00 (0.94, 1.06)	0.89 (0.82, 0.97) *			
Adjusted Benzene	1.02 (0.96, 1.08)	1.05 (0.97, 1.13)	0.97 (0.89, 1.06)			
Unadjusted NO <sub>2</sub>	0.95 (0.90, 0.99) *	0.98 (0.92, 1.04)	0.90 (0.84, 0.97) *			
Adjusted NO <sub>2</sub>	0.975 (0.92, 1.03)	0.972 (0.90, 1.05)	0.97 (0.89, 1.06)			
Maternal race/ethnicity: Asian NH						
Unadjusted Benzene	1.06 (0.844, 1.33)	1.01 (0.78, 1.30)	1.26 (0.745, 2.04)			
Adjusted Benzene	1.05 (0.817, 1.34)	0.974 (0.735, 1.29)	1.36 (0.80, 2.30)			
Unadjusted NO <sub>2</sub>	1.11 (0.878, 1.42)	1.16 (0.891, 1.52)	0.925 (0.564, 1.63)			
Adjusted NO <sub>2</sub>	1.12 (0.857, 1.46)	1.20 (0.892, 1.62)	0.833 (0.47, 1.47)			
Maternal race/ethnicity: Black NH						
Unadjusted Benzene	1.04 (0.98, 1.10)	1.05 (0.97, 1.14)	1.01 (0.92, 1.11)			
Adjusted Benzene	1.01 (0.94, 1.09)	1.04 (0.94, 1.15)	0.97 (0.88, 1.08)			
Unadjusted NO <sub>2</sub>	1.01 (0.95, 1.09)	1.03 (0.94, 1.13)	1.00 (0.90, 1.11)			
Adjusted NO <sub>2</sub>	0.99 (0.92, 1.07)	0.99 (0.90, 1.10)	1.00 (0.893, 1.12)			
Maternal race/ethnicity: Hispanic						
Unadjusted Benzene	0.986 (0.782, 1.23)	1.09 (0.82, 1.43)	0.856 (0.58, 1.22)			
Adjusted Benzene	1.05 (0.816, 1.35)	1.19 (0.861, 1.64)	0.929 (0.623, 1.39)			
Unadjusted NO <sub>2</sub>	0.953 (0.78, 1.17)	0.980 (0.759, 1.29)	0.930 (0.684, 1.30)			
Adjusted NO <sub>2</sub>	0.905 (0.715, 1.15)	0.855 (0.625, 1.17)	0.966 (0.677, 1.38)			
Maternal race/ethnicity: White NH						
Unadjusted Benzene	0.96 (0.85, 1.08)	1.03 (0.89, 1.19)	0.82 (0.66, 1.00)			
Adjusted Benzene	0.99 (0.87, 1.13)	1.02 (0.88, 1.19)	0.94 (0.75, 1.18)			
Unadjusted NO <sub>2</sub>	0.95 (0.86, 1.05)	0.99 (0.88, 1.13)	0.87 (0.75, 1.02)			
Adjusted NO <sub>2</sub>	0.95 (0.85, 1.05)	0.983 (0.858, 1.13)	0.88 (0.74, 1.05)			
Maternal race/ethnicity: other						
Unadjusted Benzene	1.05 (0.815, 1.34)	1.02 (0.753, 1.38)	1.10 (0.719, 1.65)			
Adjusted Benzene	1.12 (0.852, 1.48)	1.22 (0.875, 1.70)	0.962 (0.594, 1.56)			
Unadjusted NO <sub>2</sub>	1.15 (0.911, 1.46)	1.03 (0.785, 1.37)	1.47 (0.971, 2.31)			
Adjusted NO <sub>2</sub>	1.11 (0.850, 1.45)	0.964 (0.698, 1.33)	1.58 (0.962, 2.58)			

<sup>a</sup> Adjusted models were logistic mixed models adjusting for age, race, BMI, nulliparity, insurance status and census tract-level percentage below poverty. Hospital and census tracts were included as random intercepts. Adjusted models mutually adjusted for the other pollutant. NH, non-Hispanic. \* Results were statistically significant.

The trimester-specific  $NO_2$  exposure models with benzene showed a negative association with mPTB in the unadjusted  $NO_2$  model that was nullified by adjustment, and all other trimester-specific adjusted models showed no association with overall PTB, sPTB or mPTB (Supplementary Table S1). The unadjusted and adjusted models stratified by hospital also showed no association with overall PTB, sPTB or mPTB (Appendix A Table A1).

## 4. Discussion

Our study did not find evidence that exposure to benzene and NO<sub>2</sub> during pregnancy was associated with PTB in a cohort of patients from two hospitals in Philadelphia. Adjusting for patient and census tract-level characteristics and including hospital and census tract as random intercepts nullified the negative unadjusted associations of benzene and NO<sub>2</sub> with mPTB. When stratified by race, we also found no association of benzene and NO<sub>2</sub> with PTB or PTB phenotypes. This suggests that other types of environmental exposure may be more likely candidates in explaining the racial disparities in PTB in Philadelphia, in addition to other health and socioeconomic factors.

The lack of association may have also been driven by other factors that we could not account for in the models. While we hypothesized that NO<sub>2</sub> and benzene may be toxic to pregnancies, it is likely that other factors have stronger effects. Certain individual- and health-level factors are more predictive of preterm birth outcomes. For example, high BMI and smoking are associated with preterm birth outcomes [26,27], in addition to health factors such as diabetes mellitus and high blood pressure [28,29]. However, we consciously chose not to adjust for variables that may be on the causal pathway between pollution and PTB, such as hypertension (Supplementary Figure S1).

These results are consistent with other studies, such as an NYC multi-center birth study from 2008 to 2010 that explored the relationship between LUR-predicted exposure to  $PM_{2.5}$  and  $NO_2$  and sPTB but found negative associations due to confounding by hospital characteristics [14]. A meta-analysis of several pollutant and birth outcome studies found a pooled OR for the association between  $NO_2$  and PTB that was not statistically significant [30]. Our study differs from other studies' findings, including those from a cohort of patients in Valencia, Spain from 2003 to 2005 that used LUR models to predict benzene and  $NO_2$  exposure and found a positive association between exposure to these pollutants and the risk of PTB [12]. In addition, a large study from Shanghai that examined the effects of LUR-predicted  $NO_2$  and PTB found a positive association between third-trimester  $NO_2$  exposure and PTB [31].

Multicenter studies such as this one are important for understanding the effect of environmental exposure on adverse birth outcomes because they provide a more representative sample of patients that give birth in an area. As shown in Figure 3, the spatial distribution of patients' addresses between the two hospitals in the birth cohort differ substantially. While the cohort had data from only two of the five birth hospitals in Philadelphia, the births at these hospitals together made up 47% of all Philadelphia births from 2013 to 2017 [32]. Although stratifying the results by hospital did not reveal associations between the pollutants and PTB outcomes (Figure 4), including the hospital as a random intercept in the final models reduced the between-hospital variability.

There were several factors that may have contributed to the lack of association seen in the study. Reliable smoking data were unavailable, though smoking affects health overall and impacts benzene and  $NO_2$  exposure during pregnancy, as both are present in cigarette smoke [33]. However, only 7.2% of pregnant people in 2016 reported smoking during pregnancy [34]. Alcohol consumption and drug use data were also unavailable. In addition, many White patients lived in the areas of Philadelphia, such as Center City, with the highest traffic emissions (Figure 4), but also had higher average socioeconomic status and better access to healthcare. While we had access to insurance data, we did not have other individual-level socioeconomic variables. It is also possible that buffering factors such as air conditioning in wealthier areas with high pollution could have reduced exposure to  $NO_2$  and benzene in these areas. The spatial distribution of wealthier White patients in areas with higher pollution may mask the possible effects of benzene and  $NO_2$ on PTB. Finally, benzene air monitoring data from 2014 was at the census tract level and relied on the average exposure in 2014. Thus, in contrast to the  $NO_2$  estimates, the benzene estimates were not specific to each patient's pregnancy period, which could have diluted associations that might have otherwise been detected during exposure peaks. Finally, we

did not have information on the patients' work addresses, and it is possible that patients moved residences during pregnancy, which may have led to exposure misclassification.

#### 5. Conclusions

In conclusion, an analysis of 18,616 births in Philadelphia did not reveal associations of ambient NO<sub>2</sub> or benzene exposure with PTB or its phenotypes, nor did it support the hypothesis that these exposures might partially explain the racial disparities in these outcomes. Our findings suggest that other types of exposure are likely responsible for the ongoing racial disparities in PTB in Philadelphia, while controlling for other socioeconomic factors. Ultimately, more thorough and consistent air monitoring of benzene, NO<sub>2</sub> and other air pollutants may improve our understanding of the relationships between air pollution and PTB and may provide more insight into the environmental factors that affect PTB disparities.

**Supplementary Materials:** The following supporting information can be downloaded at: https: //www.mdpi.com/article/10.3390/ijerph191610365/s1, Figure S1. Directed acyclic graph demonstrating the assumed relationships between different socioeconomic and health factors that may have an effect when studying the relationship between NO<sub>2</sub> and benzene exposure to preterm births. Certain medical comorbidities may be on the causal pathway between air pollution exposure and preterm birth; Table S1. Unadjusted and adjusted odds ratio (OR) of a standard deviation increment increase in benzene and trimester-level NO<sub>2</sub> exposure, with preterm birth (PTB) outcomes including spontaneous (sPTB) and medically indicated (mPTB).

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the University of Pennsylvania (protocol code 829674, 23 April 2018).

**Informed Consent Statement:** Patient consent was waived due to the use of existing data collected for clinical purposes and the minimal risk to the study subjects.

**Data Availability Statement:** Data may be requested from Burris, and, upon approval from the University of Pennsylvania, deidentified data may be made available to external investigators. The data are not publicly available due to their containing protected health information.

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## Appendix A

**Table A1.** Unadjusted and adjusted <sup>a</sup> odds ratios (OR) of a standard deviation increment increase in NO<sub>2</sub> and benzene with preterm birth (PTB), spontaneous PTB (sPTB) and medically indicated PTB (mPTB), stratified by hospital of birth.

	Birth Outcome: PTB OR (95% CI)	Birth Outcome: sPTB OR (95% CI)	Birth Outcome: mPTB OR (95% CI)		
HUP					
Unadjusted Benzene	1.01 (0.944, 1.09)	1.07 (0.982, 1.17)	0.920 (0.817, 1.03)		
Adjusted Benzene	1.02 (0.933, 1.11)	1.06 (0.953, 1.19)	0.931 (0.819, 1.06)		
Unadjusted NO <sub>2</sub>	1.04 (0.964, 1.12)	1.06 (0.970, 1.17)	1.02 (0.891, 1.18)		
Adjusted NO <sub>2</sub>	1.03 (0.942, 1.12)	1.03 (0.921, 1.14)	1.02 (0.900, 1.16)		
	PA	Н			
Unadjusted Benzene	0.971 (0.902, 1.05)	1.01 (0.915, 1.10)	0.920 (0.817, 1.03)		
Adjusted Benzene	1.02 (0.945, 1.11)	1.03 (0.935, 1.15)	1.01 (0.888, 1.14)		
Unadjusted NO <sub>2</sub>	0.909 (0.850, 0.973)	0.949 (0.870, 1.04)	0.974 (0.828, 1.15)		
Adjusted NO <sub>2</sub>	0.939 (0.868, 1.02)	0.941 (0.851, 1.04)	0.935 (0.826, 1.06)		

<sup>a</sup> Adjusted models were logistic mixed models adjusting for age, race, BMI, nulliparity, insurance status and census tract-level percentage below poverty. Hospital and census tracts were included as random intercepts. Adjusted models mutually adjusted for the other pollutant. NH, non-Hispanic. HUP, Hospital of the University of Pennsylvania. PAH, Pennsylvania Hospital.

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