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Acute ambient air pollution exposure and placental Doppler results in the NICHD Fetal Growth Studies – Singleton Cohort

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Abstract

Background: Increased placental vascular resistance is a proposed mechanism by which air pollution exposure during pregnancy lowers birth weight and increases pregnancy-induced hypertensive disorders.

Objective: To examine the impact of acute air pollution exposure during pregnancy on uterine and umbilical artery Doppler indicators of placental vascular resistance.

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Methods: After a first ultrasound to confirm gestational age, 2,562 pregnant women recruited in 12 clinics throughout the United States underwent up to five standardized ultrasounds with Doppler measurements. Exposures to 11 air pollutants were estimated for the hour of ultrasound and each of the two hours prior to ultrasound at the clinics using the National Air Quality Forecast Capability reanalysis products. We used mixed logistic regression to study the longitudinal odds ratio (OR) of any, uni- or bi-lateral systolic and diastolic uterine artery notching compared to nonotching and the longitudinal OR of abnormal end diastolic flow of the umbilical artery compared to forward flow. Uterine and umbilical artery resistance indexes were studied using linear mixed models.

Results: Each inter-quartile range (IQR) increase of particulate matter < 2.5 microns, nitrate, ammonium, primary organic matter (POM) and nitrogen dioxide during the hour of ultrasound was associated with a decreased risk of unilateral systolic notch and with increased resistance index of the left uterine artery. For the umbilical artery, each IQR increase in ozone was associated with decreased resistance index (b: - 0.26, 95% CI: -0.52, -0.01) and with a decreased risk of abnormal end diastolic flow (OR: 0.36, 95% CI: 0.14, 0.94); while each IQR increase of elemental carbon and POM was associated with increased risk of abnormal end diastolic flow (OR: 1.47, 95% CI: 1.02, 2.13 and OR: 1.67, 95% CI: 1.17, 2.39, respectively).

Discussion: Our results suggest acute air pollution exposure may influence placental vascular resistance.

Keywords

Ultrasound Doppler; Uterine artery notch; Air pollution; Particulate matter; Ozone; Vascular resistance; Placenta

1. INTRODUCTION

Maternal hypertensive disorders and preeclampsia are major complications during pregnancy that have been associated with lower birth weight (Odegard et al., 2000), which is an important predictor of the risk of cardiovascular and chronic disease in the later life of the offspring (Barker, 1993; Barker, 1998). An increasing number of studies highlight an association between air pollutant exposure and low birth weight (Lamichhane et al., 2015; Stieb et al., 2012), increased risk of preeclampsia (Pedersen et al., 2017), as well as increases in blood pressure during pregnancy (Pedersen et al., 2014) and at admission for delivery, including exposure within an hour of admission (Mannisto et al., 2015b). Maternal hypertensive disorders, preeclampsia and fetal growth restriction could be consequences of air pollution exposure to the placenta.

Placental vascularization and function can be assessed by ultrasound Doppler during pregnancy measuring uterine and umbilical arteries flow to assess vascular resistance (American College of Obstetricians and Gynecologists, 2014). Uterine arteries blood flow reflect the maternal side of placental resistance (the “up-stream” blood flow characterizing the uteroplacental resistance) while the umbilical artery blood flow can reflect the fetal side of placental resistance (the “down-stream” blood flow characterizing the fetoplacental resistance) (Sciscione et al., 2009). In non-pregnant women and early pregnancy, uterine

arteries are characterized by the presence of an early diastolic notch characterized by a reduced diastolic velocity and represent the arteries elasticity (Loupas et al., 1995). As normal pregnancy progresses, uterine resistance decreases resulting in the early diastolic notch loss after 26 weeks of gestation (Schulman et al., 1986). Persistence of early diastolic notch in late pregnancy, and the appearance of systolic notch are associated with a decrease in placenta vascularization (Sciscione et al., 2009), while abnormal diastolic flow in the umbilical artery indicates fetal vascular stress underlying placental insufficiency (Wang et al., 2009).

Altered placental vascularization/blood flow in relation to air pollution exposure has been seen in mice (Veras et al., 2008), yet evidence among humans is sparse (Carvalho et al., 2016; Contreras et al., 2018; Hettfleisch et al., 2017; van den Hooven et al., 2012). Previous studies considered only chronic exposure, i.e. from week before the ultrasounds (Carvalho et al., 2016; Hettfleisch et al., 2017) to whole pregnancy (Contreras et al., 2018), compared to acute exposure (i.e. hours before ultrasounds). Among previous studies, two were conducted in Sao Paulo, Brazil, using maternal personal exposure for the week prior to the ultrasound reported a negative association between nitrogen dioxide (NO₂) and placental vascularization indices (Hettfleisch et al., 2017) and between ozone (O₃) and umbilical pulsatility index (Carvalho et al., 2016). Other studies reported exposure to NO₂ associated with increased uterine resistance index (Contreras et al., 2018) and increased risk of bilateral uterine notch (van den Hooven et al., 2012). Studies have shown that pregnant women with a decrease in placental vascularization have higher risk of preeclampsia and fetal growth restriction (de Almeida Pimenta et al., 2014; Odeh et al., 2011; Odibo et al., 2011). Thus, placental vascularization could be a possible pathway between air pollution exposure and maternal pregnancy-induced hypertensive disorders and fetal growth restriction. In this exploratory study we aimed to examine the association between acute (i.e. hourly) maternal air pollution exposure and placental Doppler results in a population of pregnant women without chronic disease.

2. MATERIALS AND METHODS

2.1 Study population

This study was based on the NICHD Fetal Growth Studies – Singleton cohort that included 2,802 singleton pregnant women enrolled before 14 weeks' gestation between July 2009 and January 2013 from 12 U.S. clinical sites (Christina Care Health System, Newark, Delaware; Columbia University, New York, New York; Fountain Valley Hospital, Fountain Valley, California; Long Beach Memorial Medical Center, Long Beach, California; New York Hospital, Queens, Flushing, New York; Northwestern University, Chicago, Illinois; University of Alabama, Birmingham, Alabama; University of California, Irvine, Orange, California; Medical University of South Carolina, Charleston, South Carolina; Saint Peters University Hospital, New Brunswick, New Jersey; Tufts University, Medford, Massachusetts; and Women and Infants Hospital, Providence, Rhode Island) (Grewal et al., 2018). Among the participants, 2,334 (83.3%) had low-risk antenatal profiles (without pre-pregnancy hypertension, diabetes, renal/autoimmune disease, psychiatric disorder, cancer, and HIV or AIDs) and 468 (16.7%) were obese (body mass index (BMI) between 30.0 to

45.0 kg/m²) at the time of enrollment. Women were enrolled conditional on gestational age based on the date of the last menstrual period and confirmed by ultrasound; the difference between estimated gestational age from last menstrual period and from ultrasound was considered acceptable if it matched within five days for gestation estimated between 8 weeks (w) 0 days (d) and 10w6d, within six days for gestation estimated between 11w0d to 12w6d, or within seven days for gestation estimated between 13w0d to 13w6d.

Out of the 2,802 women, 240 women were excluded (18 were ineligible after enrolment, 211 were missing the time of ultrasounds, 9 had no air pollution information, and 2 had out-of-range resistance index measures > 1). The remaining 2,562 pregnant women contributed a total of 11,458 ultrasounds.

2.2 Outcomes

After enrollment, pregnant women were randomized to one of four schedules for five ultrasound visits (Grewal et al., 2018) to allow for weekly measures of fetal growth while minimizing the number of scans for each individual woman. Measurements were performed using standardized obstetrical ultrasonography protocols and identical equipment (Voluson E8; GE Healthcare, Milwaukee, WI). All sonographers underwent an intensive training and evaluation period (Fuchs and D'Alton, 2012). A quality control evaluation showed that measurements between site sonographers and experts were both accurate and reliable, with high correlations (Pearson's $r > 0.99$) and low coefficients of variation (< 3%) (Hediger et al., 2016).

Doppler measurements included a pulsed Doppler waveform evaluation of the bilateral maternal uterine arteries at enrollment and each follow-up visit, and the umbilical artery at each visit beyond 15 weeks. The ultrasound protocol specified that the waveform be obtained near the midpoint of the umbilical cord. For the uterine arteries we used the qualitative assessment of the flow velocity waveform (e.g. notching present or absent) and quantitative analysis of the resistance index as generated by the ultrasound software (Chan et al., 1995). For the umbilical artery, we used resistance index as generated by the ultrasound software and the qualitative waveform descriptions of the end diastolic flow recorded by the sonographer (e.g. forward, absent or reverse end-diastolic flow). All measurements were taken with both manual and auto trace in the beginning of the study and during the middle of the study changed to only with auto trace to simplify the protocol.

For the present analysis, we used uterine and umbilical resistance index as continuous variable, uterine artery Doppler notching categorized as: any notch (from right, left or both uterine arteries), unilateral notch and bilateral notch, and the end diastolic flow of the umbilical artery dichotomized as forward flow (normal) vs. absent or reversed flow (abnormal).

2.3 Exposure assessment

We assessed exposures during the hour of the ultrasound visit and at each of the two hours prior to the ultrasound visit at the clinical site using the air quality forecast model operated by the National Weather Service National Air Quality Forecast Capability (NAQFC) Program (Lee et al., 2017; Tong et al., 2016). Briefly, the NAQFC join

the Community Multiscale Air Quality (CMAQ) air pollution model from the U.S. Environmental Protection Agency's (EPA) and the meteorological model North American Model (NAM) Nonhydrostatic Multiscale Model with Arakawa B-grid staggering (NMMB) to calculate hourly and 24-h average pollution concentrations on a 12-km resolution horizontal grid. Evaluation of the NAQFC reanalysis product using the observations from the EPA's AIRNow surface monitoring network showed a high accuracy (fraction correct > 0.90). We used the hourly output from the NAQFC reanalysis of the 11 available air pollutants: ozone (O₃, part per billion, ppb), particulate matter < 2.5 microns (PM_{2.5}, µg/m³), particulate sulfate (SO₄, µg/m³), nitrate (NO₃, µg/m³), ammonium (NH₄, µg/m³), elemental carbon (EC, µg/m³), primary organic matter (POM, µg/m³), secondary organic aerosol (SOA, µg/m³), sulfur dioxide (SO₂, ppb), nitric oxide (NO, ppb) and nitrogen dioxide (NO₂, ppb).

At the same time points, hourly exposure to ambient temperature was assessed using the U.S. EPA Air Quality System (AQS) data nearest to the clinic sites, using the mean of AQS monitors in 10-km buffers around the clinical sites.

2.4 Statistical methods

Multiple imputation of covariates using fully conditional specification with 100 iterations was performed with the MICE package in R software (van Buuren and Groothuis-Oudshoorn, 2011). We used Pearson's correlation coefficients to quantify the association between resistance indices.

We used mixed logistic regression to assess the longitudinal odd ratio (OR) of any, uni- or bi-lateral systolic and diastolic uterine artery notching compared to no notching and the longitudinal OR of abnormal end diastolic flow compared to normal diastolic flow. Uterine and umbilical artery resistance index were modelled using linear mixed models. All regression analyses estimate odds based on the inter-quartile range (IQR) increase of air pollutant exposure and adjusted for maternal pre-pregnancy weight, height, race/ethnicity, parity, marital status, education, season of conception (to account for seasonality of air pollution and other traits that may be related to the season), fetal sex, gestational age at ultrasound, ambient temperature and clinical sites. Models had a random effect for mother-child pair to take into account the repeated measures across gestation. Models were run separately for each pollutant and each exposure timing.

We also conducted four sensitivity analyses: 1) Uterine notches are common in the first trimester but more likely to indicate pathology as the pregnancy progresses, to avoid this bias we stratified the data at 28 gestational weeks (i.e. before 28 gestational weeks vs. 28 gestational weeks and after) to study the impact of air pollution on placental Doppler earlier and later in pregnancy, when notching may be more associated with pathology, with adjustment for the same covariates; 2) we further assessed potential effect modification by fetal sex with adjustment for the same covariates; 3) we used a multiple pollutants model assessing the impact of O₃ and PM_{2.5} separately while mutually adjusting for the other. We have selected two common pollutants (one particle (PM_{2.5}) and one gas (O₃)) which are not highly correlated; 4) finally, we estimated the overall impact of pollutant mixtures on placental Doppler with a Bayesian kernel machine regression approach that accounts

for high correlation, potential interaction (synergy) and non-linear associations between air pollutants (Bobb et al., 2015).

Analyses were done using R software (R-version 3.5, R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1 Description of the dataset

The mean maternal age was 28.2 years (standard deviation (SD): 5.5 years), 47% were nulliparous and 74% were married or living with a partner (Table 1). Uterine artery diastolic notching was more common than systolic Doppler notching (34.1% diastolic notches vs. 6.4% systolic notches, Supplement Figure S1) and the resistance index of uterine and umbilical arteries decreased through the pregnancy (Supplement Table S1, Supplement Figure S2). Resistance index of right and left uterine artery were highly correlated with each other ($r = 0.62$, $p < 0.001$, Supplement Figure S3) but moderately correlated with umbilical artery resistance ($r = 0.28$, $p < 0.001$ and $r = 0.31$, $p < 0.001$). Abnormal end diastolic flow (i.e. absent or reversed flow) was present for 24 pregnant women representing 0.3% of the ultrasounds (Supplement Table S2).

Hourly O_3 was not correlated with SOA and SO_4 (Pearson's correlations range from -0.01 to 0.12) and inversely correlated with other pollutants (Pearson's correlations range from -0.65 to -0.17 , Supplement Table S3). The inter-quartile range (IQR) at the hour of exposure was 25.1 ppb for O_3 , $14.1 \mu\text{g}/\text{m}^3$ for $PM_{2.5}$, $2.6 \mu\text{g}/\text{m}^3$ for SO_2 , $2.8 \mu\text{g}/\text{m}^3$ for NO_3 , $1.6 \mu\text{g}/\text{m}^3$ for NH_4 , $1.4 \mu\text{g}/\text{m}^3$ for EC, $1.9 \mu\text{g}/\text{m}^3$ for POM, $0.7 \mu\text{g}/\text{m}^3$ for SOA, 3.0 ppb for SO_2 , 6.8 ppb for NO and 18.0 ppb for NO_2 .

3.2 Main analyses

$PM_{2.5}$, SO_4 , NO_3 , NH_4 , POM and NO_2 during the hour of ultrasound was significantly associated with a lower risk of unilateral systolic notch (Supplement Table S4), but SO_2 and NO_2 during the hour of ultrasound and NO one hour prior to the ultrasound were associated with higher risk of diastolic notch. O_3 was significantly associated with lower umbilical resistance indexes (b per each IQR increase in $O_3 = 0.26$, 95% CI: -0.52 , -0.01 during the hour of ultrasound and $b = -0.26$, 95% CI: -0.52 , -0.0 two hours before Figure 1, Supplement Table S5). Whereas, $PM_{2.5}$, NO_3 , NH_4 , POM and NO_2 during the hour of ultrasound and one hour before were associated with a higher resistance index of the left uterine artery, and NO_2 during the hour of ultrasound was associated with a higher resistance index of the right uterine artery (Figure 1, Supplement Table S5).

O_3 during the hour of ultrasound was associated with a lower risk of abnormal end diastolic flow of the umbilical artery (OR = 0.36, 95% CI: 0.14 – 0.94), whereas EC and POM for all studied hours were significant only associated with higher risk of abnormal end diastolic flow of the umbilical artery (Figure 2, Supplement Table S6).

3.3 Sensitivity analyses

Analysis stratified at 28 gestational weeks revealed similar results regardless of gestational age for uterine notches (Supplement Table S7), but results were significant only before 28 gestational weeks for resistance indexes (Supplement Table S8) and after 28 gestational weeks for abnormal end diastolic flow of the umbilical artery (Supplement Table S9).

Analysis by fetal sex revealed different patterns for uterine notches, with O₃ significantly associated with higher risk of systolic notch among males (Supplement Table S10), while results on resistance indexes were not conclusive (Supplement Table S11). Stratification analysis for the end diastolic flow of the umbilical artery revealed higher risk of abnormal flow among females exposed to PM_{2.5}, SO₄, NH₄, EC, POM and SO₂ while NO and NO₂ were associated with higher risk of abnormal end diastolic flow of the umbilical artery among males (Supplement Table S12).

Multipollutant models produced similar results, with PM_{2.5} during the hour of ultrasound showing association with lower risk of systolic notches and higher resistance index of the left uterine artery when mutually adjusted for O₃ (Supplement Table S13). PM_{2.5} during the hours before ultrasound was associated with higher risk of abnormal end diastolic flow of the umbilical artery when mutually adjusted for O₃ (Supplement Table S13).

In exposure mixture models, ambient air pollution exposure during the hour of ultrasound was associated with lower risk of any and bilateral systolic notches (Supplement Figure S4), while ambient air pollution mixture was not associated with resistance indexes (Supplement Figure S5). Ambient air pollution exposure 1 hour before ultrasound was associated with a lower risk of abnormal end diastolic flow of the umbilical artery (Supplement Figure S6).

4. DISCUSSION

Overall, we found increased exposure to air pollution (except O₃) was associated with qualitative and quantitative measures of increased placental resistance although heterogeneity in effects by pollutant, Doppler indices, and timing during pregnancy were observed. Exposures to PM_{2.5}, NO₃, NH₄, POM and NO₂ during the hour of ultrasound were associated with decreased risk of uterine artery systolic Doppler notching and with increased resistance index of the left uterine artery, while SO₂, NO₂ and NO were associated with higher risk of diastolic notch. EC and POM (PM_{2.5} compounds) were associated with increased risk of abnormal end diastolic flow of the umbilical artery, revealing placental insufficiency. In contrast, higher exposure to O₃ yielded inverse associations, including decreased resistance index of the umbilical artery and decreased risk of abnormal end diastolic flow of the umbilical artery, consistent with the inverse correlation between O₃ and all other air pollutants. When we evaluated for a differential effect by gestational age, we found an increase in the resistance index of the left uterine artery in response to exposure to PM_{2.5}, NO₃, NH₄, POM and NO₂ in the hour of ultrasound before 28 gestational weeks, while PM_{2.5}, EC, POM, NO and NO₂ were associated with increased risk of abnormal end diastolic flow of the umbilical artery after 28 gestational weeks.

In this study, air pollutant exposures (except O₃) were associated with decreased risk of systolic Doppler notching and increased risk of diastolic Doppler notching. Diastolic Doppler notching has relevance in a clinical setting which has been associated with pre-eclampsia and fetal growth restriction (Cnossen et al., 2008), while systolic Doppler notching importance is less clear (Thaler et al., 1992). Only one study investigated the relationship between air pollution exposure and uterine artery notching; within the Generation R study, Rotterdam, The Netherlands, NO₂ exposure during the 2-weeks and 2-months prior to the ultrasound were associated with third trimester uterine artery Doppler notching (van den Hooven et al., 2012); similarly, we found an increased risk of bilateral diastolic Doppler notching associated with exposure to NO₂ during the hour of ultrasound.

The impact of air pollution on placental resistance index had been investigated by only one study among 566 pregnant women in Los Angeles, U.S., NO₂ and NO_x were associated with increased resistance index of the uterine artery during the third trimester (Contreras et al., 2018), similarly we found that NO₂ during the hour of ultrasound was associated with increased resistance index in the right uterine artery and NO₂ and NO_x exposure during the hours and the two hours prior the ultrasound associated with increased resistance index in the left uterine artery. One study conducted in Sao Paulo, Brazil, studied the relationship between maternal personal exposure to NO₂ and O₃ the week before the ultrasound and Doppler results; they reported that exposure to O₃ in the second trimester of gestation was positively associated with umbilical artery velocimetry index at the 2nd trimester ultrasound, while this association became negative at the 3rd trimester ultrasound (Carvalho et al., 2016), similar to this last result we found a decrease in umbilical resistance index with acute exposure to O₃.

Several mechanisms have been proposed to explain the influence of O₃ in reducing placental resistance. Previous studies reported vasodilation after O₃ therapy to decrease damage of stroke (Frosini et al., 2012), and diabetes (Bocci et al., 2011) by improving the blood circulation (Akcilar et al., 2015) and oxygen delivery to ischemic tissues and increasing the level of prostacyclin, a known vasodilator (Elvis and Ekta, 2011; Smith et al., 2017). Another study comparing the morphology of the placenta collected at delivery from 12 pregnant women with fetoplacental insufficiency treated with O₃ therapy and 20 healthy pregnant women reported normalization of the placental microcirculation among treated women (Andikyan et al., 2000). Moreover, among hypertensive pregnant women, improvement of the umbilical blood flow with decreases in the resistance index have been reported after O₃ therapy (Tanbouli et al., 2009). No prior study has investigated the association between air pollution exposure and end diastolic flow of the umbilical artery.

Several studies have investigated the potential mechanisms underlying the effect of air pollution on adverse outcomes for pregnant women and their offspring. Some of the hypotheses are linked with deficiency in placentation and placental dysfunction. Studies in mice have reported smaller umbilical cord volumes and potentially reduction of umbilical flow (Veras et al., 2012) but also modification of the maternal side of the placenta with a decrease of the resistance on the fetal side to maintain the flow (Veras et al., 2008). Exposure to air pollution has also been associated with lower placental weight in mice (Rocha et al., 2008) and humans (Ghasemi-Tehrani et al., 2017; Rahmalia et al., 2012; van

den Hooven et al., 2012), suggesting that air pollution has an impact on placental exchange function (Salafia et al., 2006) through mechanisms that may not involve placental vascular resistance but through restricted placental exchange surface. Van den Hooven et al. also reported a higher level of anti-angiogenic factors and lower level of pro-angiogenic factors with higher exposure to NO₂ and PM₁₀ (van den Hooven et al., 2012). Furthermore, air pollution exposure has been associated with differential placental DNA methylation (Saenen et al., 2019) including *LEP*, a marker of oxidative stress (Saenen et al., 2015), *ADORA2B* and differentially methylated regions associated with preeclampsia (Abraham et al., 2018).

Most of the previous studies have used exposure metrics based on regulatory data (e.g., from the AQS) measured at air monitoring site(s) nearest to the home address or average of AQS within a buffer around the home. Studies based on the simultaneous use of several exposure models (e.g. AQS, land-use regression, dispersion model) have demonstrated that the amplitude of the measurement error may be large when AQS are used (Nerriere et al. 2005; Nethery et al. 2008). Exposure assessment approaches using publicly available monitoring data have the advantage that they are relatively easy to access and use, and are typically available in hourly measures. However, AQS monitoring stations are not spatially distributed to characterize an airshed but rather are usually placed in more polluted areas that need to be monitored for regulatory compliance. The NAQFC reanalysis product has the advantage of relying on observed emissions and meteorological predictions to simulate physical and chemical processes in the atmosphere to provide a high-quality assessment of exposure on large areas. However we were not able to account for indoor measurements and local mobility and will deviate from actual personal exposure (Ouidir et al., 2015). However, acute exposure in the hours prior to the ultrasound likely represents a more plausible scenario as the impact of air pollution on vascular resistance has been shown to operate acutely as well as chronically (Mannisto et al., 2015a; Mannisto et al., 2015b).

Our study has some limitations, such as potential unmeasured confounding and exposure misclassification. The interpregnancy interval for multiparous as well as low-aspirin intake may modify the risk of hypertension during pregnancy and preeclampsia and/or may impact placental vascular resistance; these factors were not assessed in our cohort. Unfortunately, we were unable to estimate chronic effects of our exposure as our study is limited by a lack of data on maternal residence and mobility in the hours/days prior to the ultrasound scan. Our previous study of maternal blood pressure (Mannisto et al., 2015b) found exposures up to four hours prior to admission for hospital delivery were associated with maternal blood pressure at admission. We assume that women were in similar exposure scenarios during the two hours prior to their scans, being near the clinics. This may be reasonable since all clinics were in urban areas and women agreed to repeated scans over the course of pregnancy. Finally, we would anticipate this misclassification would be non-differential with respect to placental vascular resistance and would bias our results towards the null.

The strengths of this study are our healthy population (without chronic disease or prior unfavorable pregnancy outcomes), the race/ethnic diversity of the cohort and the ultrasound Doppler data over the course of the entire pregnancy with more than 11,000 repeated measurements with acute high-quality air pollution exposures hours prior to the ultrasounds using the reanalysis products from the NAQFC. In conclusion, we observed that exposure

measured in hours prior to ultrasound was associated with decreased systolic notching but increased diastolic resistance index and increased risk of abnormal end of diastolic flow of the umbilical artery, suggesting the acute air pollution exposure may influence placental vascular resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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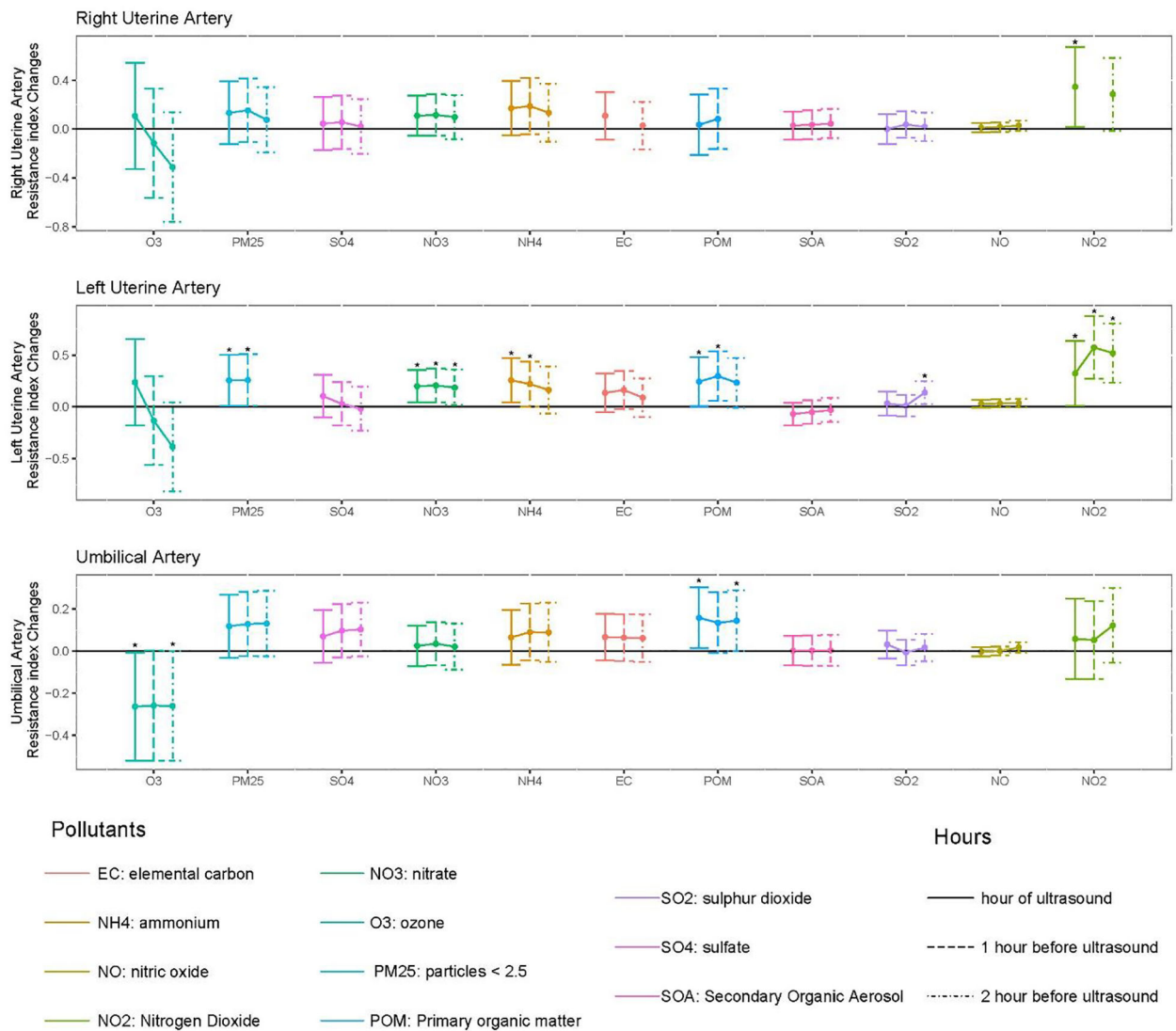


Figure 1:

Association between acute ambient air pollution exposure assessed at the clinic sites and longitudinal resistance index. All effect estimates (in %) correspond to an increase of IQR of exposure. Dots indicate the estimates; vertical lines, the 95% confidence intervals; horizontal lines, the null.

Adjusted for: maternal pre-pregnancy weight, height, education, race/ethnicity, parity, marital status, fetal sex, gestational age at ultrasound, clinical site, season of conception and concomitant hourly ambient temperature.

* denotes p-value < 0.05.

Abbreviation: O3: ozone; PM2.5: particles < 2.5 microns; SO4: sulfate; NO3: nitrate; NH4: ammonium; EC: elemental carbon; POM: Primary organic matter; SOA: Secondary Organic Aerosol; SO2: sulphur dioxide; NO: nitric oxide; NO2: Nitrogen Dioxide.

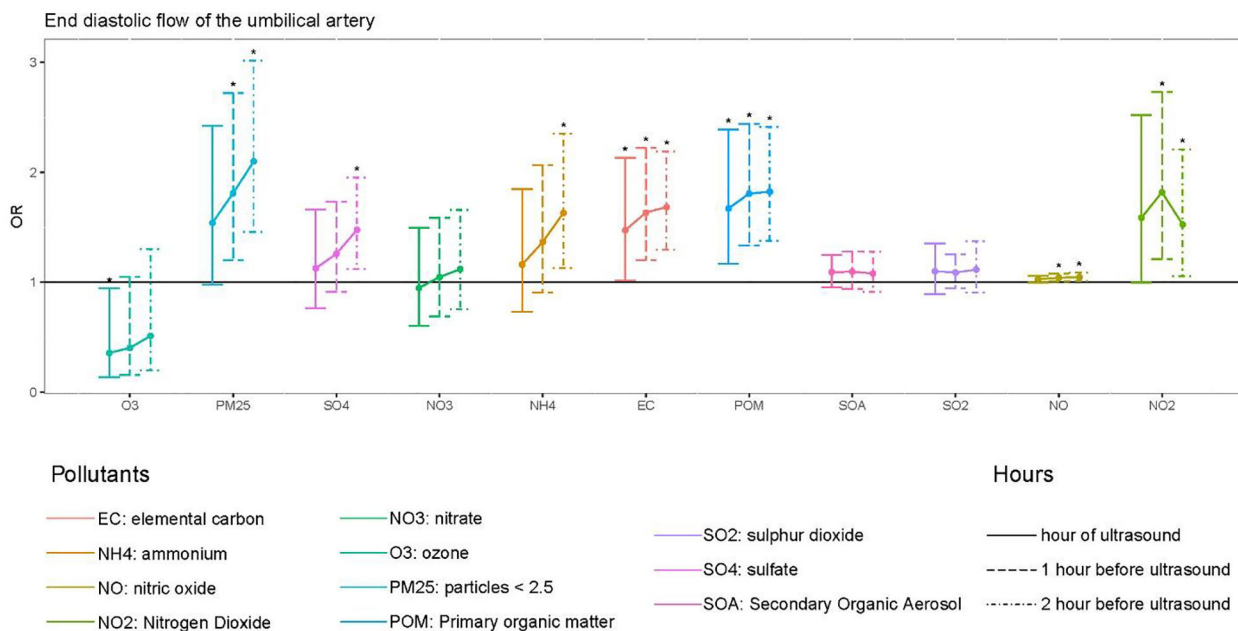


Figure 2: Association between acute ambient air pollution exposure assessed at the clinic sites and longitudinal end diastolic flow of the umbilical artery. All effect estimates correspond to an increase of an IQR of exposures. Dots indicate the estimates; vertical lines, the 95% confidence intervals; horizontal lines, the null.

Adjusted for: maternal pre-pregnancy weight, height, education, race/ethnicity, parity, marital status, fetal sex, gestational age at ultrasound, clinical site, season of conception and concomitant hourly ambient temperature.

* denotes p-value < 0.05.

Abbreviation: O3: ozone; PM2.5: particles < 2.5 microns; SO4: sulfate; NO3: nitrate; NH4: ammonium; EC: elemental carbon; POM: Primary organic matter; SOA: Secondary Organic Aerosol; SO2: sulphur dioxide; NO: nitric oxide; NO2: Nitrogen Dioxide.

Table 1:

Description of the study population (n=2,562 from the NICHD Fetal Growth Studies – Singleton cohort)

	N (%) or Mean \pm sd
Maternal age at enrollment, years	28.2 \pm 5.5
Maternal pre-pregnancy weight, kg	67.4 \pm 15.0
Maternal height, cm	162.8 \pm 7.0
Maternal race/ethnicity	
White	700 (27.3)
Black	742 (29)
Hispanic	695 (27.1)
Asian	425 (16.6)
Parity	
0	1202 (46.9)
1	869 (33.9)
2	331 (12.9)
3 or more	160 (6.2)
Marital Status	
Not married	666 (26.0)
Married or living with someone	1893 (73.9)
Missing*	3 (0.1)
Highest level of education	
Less than high school	284 (11.1)
High school diploma or GED or equivalent	465 (18.1)
College or Associate degree	776 (30.3)
Bachelor's degree	599 (23.4)
Masters or Advanced degree	437 (17.1)
Missing*	1 (0)
Season of conception	
January-March	608 (23.7)
April-June	620 (24.2)
July-September	725 (28.3)
October-December	609 (23.8)
Fetal sex	
Male	1206 (47.1)
Female	1149 (44.8)
Missing*	207 (8.1)

* Missing values have been imputed for the analysis