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Ambient air pollution exposure and blood pressure changes during pregnancy

Pei-Chen Lee^{a,*}, Evelyn O. Talbott^a, James M. Roberts^{a,b}, Janet M. Catov^{a,b}, Richard A. Bilonick^c, Roslyn A. Stone^d, Ravi K. Sharma^e, and Beate Ritz^f

^aDepartment of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

^bMagee-Womens Research Institute, Department of Obstetrics and Gynecology, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

^cDepartment of Ophthalmology, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

^dDepartment of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA USA

^eDepartment of Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

^fDepartment of Epidemiology, School of Public Health, University of California at Los Angeles, California, USA

Abstract

Background—Maternal exposure to ambient air pollution has been associated with adverse birth outcomes such as preterm delivery. However, only one study to date has linked air pollution to blood pressure changes during pregnancy, a period of dramatic cardiovascular function changes.

Objectives—We examined whether maternal exposures to criteria air pollutants, including particles of less than 10 μm (PM_{10}) or 2.5 μm diameter ($\text{PM}_{2.5}$), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3), in each trimester of pregnancy are associated with magnitude of rise of blood pressure between the first 20 weeks of gestation and late pregnancy in a prospectively followed cohort of 1684 pregnant women in Allegheny County, PA.

Methods—Air pollution measures for maternal ZIP code areas were derived using Kriging interpolation. Using logistic regression analysis, we evaluated the associations between air pollution exposures and blood pressure changes between the first 20 weeks of gestation and late pregnancy.

Results—First trimester PM_{10} and ozone exposures were associated with blood pressure changes between the first 20 weeks of gestation and late pregnancy, most strongly in non-smokers. Per interquartile increases in first trimester PM_{10} and O_3 concentrations were associated with mean increases in systolic blood pressure of 1.88 mmHg (95% CI = 0.84 to 2.93) and 1.84 (95% CI =

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*Corresponding author. Present address: Department of Epidemiology, School of Public Health, University of California at Los Angeles, 650 Charles E. Young Drive, Los Angeles, CA 90095-1772, USA. Fax: +1 310 206 6039. pel27@pitt.edu, pel27@ucla.edu (P.-C. Lee).

Conflict of interest

The authors have no competing financial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2012.05.011>.

1.05 to 4.63), respectively, and in diastolic blood pressure of 0.63 mmHg (95% CI= -0.50 to 1.76) and 1.13 (95% CI= -0.46 to 2.71) in non-smokers.

Conclusions—Our novel finding suggests that first trimester PM₁₀ and O₃ air pollution exposures increase blood pressure in the later stages of pregnancy. These changes may play a role in mediating the relationships between air pollution and adverse birth outcomes.

Keywords

Ambient air pollution; Pregnancy; Blood pressure changes

1. Introduction

Pregnancy-associated hypertension, defined as the new onset of systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg during the second half of pregnancy, is one of the leading causes of perinatal and maternal mortality and morbidity (Chesley, 1978; Laragh and Brenner, 1995; Saftlas et al., 1990). When pregnancy-associated hypertension is accompanied by proteinuria after 20 weeks of gestation, the disorder is termed preeclampsia, a pregnancy complication associated with an increased risk not only for preterm birth and intrauterine growth restriction (Goldenberg and Rouse, 1998; Xiong et al., 1999), but also cardiovascular disease in mothers later in life (Irgens et al., 2001). Although reduced placental perfusion, due to abnormal vascular remodeling of vessels that supply the placenta, is proposed as a root cause of preeclampsia, the pathophysiology of this disorder is poorly understood (Laragh and Brenner, 1995).

A growing body of research has linked changes in blood pressure to ambient air pollution, especially particulate matter, among elderly persons with preexisting cardiac disease and healthy individuals (Auchincloss et al., 2008; Sergio Chiarelli et al., 2011; Zanobetti et al., 2004). Some short-term exposure studies have reported positive associations between particulate air pollution and blood pressure (Auchincloss et al., 2008; Zanobetti et al., 2004), while others have reported the opposite; e.g., increases in particulate matter exposure are associated with decreases in blood pressure (Ebelt et al., 2005; Harrabi et al., 2006; Ibaldu-Mulli et al., 2004) or no association (Jansen et al., 2005; Madsen and Nafstad, 2006). To date, only one study has examined whether increases in particulate air pollution are associated with blood pressure changes in women who are pregnant (van den Hooven et al., 2011), even though pregnancy is a period of dramatic changes in maternal anatomy, physiology, and metabolism to support the development of the fetus.

Pregnancy hormones, including progesterone and prostaglandins, and components of the renin-angiotensin-aldosterone system influence blood pressure changes during pregnancy (Blackburn, 2003; Luppi, 1999). During normal pregnancy, blood volume, as well as cardiac output, begins to increase by 6 weeks of gestation to adequately perfuse and oxygenate the fetal and maternal tissues (Torgersen and Curran, 2006). These profound cardiovascular adaptations result in changes in blood pressure during gestation, with decreased systolic and diastolic blood pressure in early pregnancy. At approximately 20 weeks of gestation, blood pressure increases and returns to non-pregnancy levels by term in normal pregnancies (Clapp et al., 1988; Duvekot and Peeters, 1994).

To date, studies of air pollution and reproductive outcomes have primarily focused on outcomes such as preterm birth, low birth weight, and small for gestational age infants. Only three studies focused on preeclampsia (Rudra et al., 2011; Woodruff et al., 2008; Wu et al., 2009), and one study examined blood pressure changes during pregnancy (van den Hooven et al., 2011). Positive associations have been reported between air pollutants and

preeclampsia risk (Rudra et al., 2011; Woodruff et al., 2008; Wu et al., 2009). Increased blood pressure throughout pregnancy has also been observed in mothers who are exposed to air pollution (van den Hooven et al., 2011). However, no study has examined the influence of air pollution on the rise of blood pressure between early and late pregnancy. A greater increase in blood pressure between early pregnancy and mid-third trimester increased the risk of spontaneous preterm birth in a large prospective cohort study (~ 83,000 women) by Zhang et al. (2007). Based upon the findings of Zhang et al. (2007), we examined whether air pollution exposures during early pregnancy (i.e., first trimester) increased the magnitude of blood pressure rise between the first 20 weeks of gestation and late third trimester in a cohort of 1684 pregnant women followed throughout pregnancy to delivery. We chose to examine the effect of exposure prior to 20 weeks of gestation, since remodeling of the maternal vessels that supply the placenta takes place between 10 and 20 weeks' gestation. Inadequate remodeling of these vessels is proposed to be associated with adverse pregnancy outcomes, including preterm birth and preeclampsia (Kim et al., 2003; Roberts and Gammill, 2005; Salafia et al., 1998).

2. Materials and methods

2.1. Study population

Study subjects were selected from the Prenatal Exposures and Preeclampsia Prevention study that took place in Pittsburgh between 1997 and 2001. This study enrolled 2211 healthy women aged 14–44 years attending clinics and private practices in early pregnancy (< 16 weeks of gestation) and followed them until delivery. Women were interviewed twice, at the first visit and then again postpartum. Information collected in both interviews included socio-demographic characteristics, reproductive and medical histories at baseline, and information about diet, cigarette smoking and consumption of alcohol. From hospital records, we abstracted maternal residential ZIP codes at the time of delivery, maternal history of chronic hypertension and diabetes, blood pressure (both systolic and diastolic), and maternal weight during each prenatal care visit. Blood pressure was taken by the clinic nursing staff with the patient seated and the cuff at the level of the subject's heart. We excluded women with chronic hypertension and diabetes ($N=32$), because the blood pressure of these women may respond differently to an exposure challenge. We also excluded women without blood pressure measurements before 20 weeks of gestation or without at least two measurements after 20 weeks ($N=84$). Additionally, multiparous women who had already been surveyed once in the study and those with a maternal residential ZIP code outside of Allegheny County, PA were excluded. A total of 1684 women were included. Women excluded were an average of two years older than our study population and were more likely to be Caucasian. They also had higher average blood pressure measurements (about 2 mmHg higher for both systolic and diastolic) in the first 20 weeks of gestation. This study was approved by the Institutional Review Board at the University of Pittsburgh, and written informed consent was obtained from all participants.

2.2. Exposure assessment

Maternal exposure to ambient air pollution (including CO, NO₂, SO₂, O₃, PM₁₀, and PM_{2.5}) during prenatal care was estimated based on air monitoring data for Allegheny County and its neighboring counties (within 50 km of the Allegheny County boundary), collected by the Allegheny County Health Department and the US Environmental Protection Agency between 1996 and 2001. PM_{2.5} and PM₁₀ measurements were collected daily or every third or sixth day at 23 (including 13 monitoring stations in Allegheny County) and 40 (including 18 monitoring stations in Allegheny County) monitoring stations, respectively, from 1999 to 2001 (Fig. 1). For gaseous pollutants, SO₂ measurements were available from 32 stations (including 7 monitoring stations in Allegheny County), and O₃ from 15 stations (including 3

monitoring stations in Allegheny County). Only 11 stations measured NO₂ and CO during the study period (with 3 and 2 monitoring stations, respectively, in Allegheny County). The air pollution data included 1-h concentrations for CO, NO₂, O₃, and SO₂, and 24-h concentrations for PM_{2.5} and PM₁₀. Hourly temperature measurements were derived from the National Climate Data Center for the monitoring site located at the Pittsburgh International Airport during the study period.

We used space-time ordinary kriging, a geo-statistical technique optimizing spatial prediction, to estimate daily air pollution concentrations at each centroid of 13.4 m² grids in Allegheny County. Unlike conventional ordinary kriging, which relies on spatial variograms for prediction only, space-time ordinary kriging combines spatial and temporal variograms to model the joint space-time variogram for prediction. This increases mean precision as compared to ordinary kriging (Gething et al., 2007). We fitted the spatial and temporal variograms separately, using a spherical semivariogram model. We also combined the individual spatial and temporal variograms into one space-time variogram by fitting a general product-sum model (DeCesare et al., 2001). Parameters estimating spatial and temporal variograms for each pollutant are presented in Table SI of the Supplemental Materials, and these parameters include sill, range, and nugget.

To calculate exposure concentrations for each woman, we first calculated the date of each prenatal visit based upon gestational age (assessed by ultrasound and estimated day of delivery) at each visit and the date of the delivery of her infant. We then calculated exposure concentrations for each pollutant during each trimester by averaging the estimated daily concentrations for each trimester at each centroid of the grid within each ZIP code. First, second, and third trimesters were defined as the first 12 weeks, 13 to 27 weeks, and after 27 weeks of gestation, respectively. In addition, we calculated air pollutant concentrations 0 to 7 day (lag0–lag7) and mean concentrations for a period of 7 day (i.e., 8-day averages) prior to blood pressure measurement (prenatal visit date), based on maternal ZIP code, to evaluate associations between short-term exposures and blood pressure patterns during pregnancy (i.e., longitudinally measured blood pressure patterns). There are 109 ZIP codes in Allegheny County, with a mean area of 16.8 km² and an average of 129 grids in each ZIP code.

2.3. Statistical analysis

To examine associations between trimester-specific air pollution exposures and systolic and diastolic blood pressure changes between the first 20 weeks of gestation and late pregnancy, we performed multiple linear regression with robust variance estimators to account for non-independence of women living within the same ZIP code area. Our estimates of the coefficients are the same as the estimates based on ordinary least square regression with slightly different standard errors, since the robust variance estimators take into account non-independence of maternal residences within ZIP codes. We calculated systolic and diastolic blood pressure changes between the first 20 weeks of gestation and late pregnancy for each woman, subtracting the average of the respective blood pressure measurements in the first 20 weeks of gestation from the average of the 2 measurements taken during the last prenatal care visits. Among 1684 women, 6% had only one systolic or diastolic blood pressure measurement available before 20 weeks of gestation. We coded blood pressure measurements as missing (< 1% of measurements) for measurements outside a reasonable range; i.e., systolic blood pressure below 40 mmHg or above 250 mmHg, and diastolic blood pressure below 40 mmHg or above 180 mmHg.

To examine whether short-term air pollution exposures contributed to changes in blood pressure patterns during pregnancy, we fitted linear mixed-effects models, using maximum likelihood estimation with random intercepts and a spherical correlation structure (range=60

day, nugget effect=0.8) to account for correlations between visits at different intervals. Air pollution exposures (including trimester averages and lag days concentrations) were evaluated as continuous measures and reported as increases per interquartile range (IQR).

We controlled for variables based upon previous published literature (Bell et al., 2007; Ritz et al., 2007; van den Hooven et al., 2011) and visualization, using causal diagram methods, as well as the change in estimate criteria for pollutants by more than 10% (Mickey and Greenland, 1989). Thus, in linear regression models, we controlled for maternal age (years), race (Caucasian, African-American), pre-pregnancy body mass index (kg/m^2), parity (first birth, second or subsequent birth), number of cigarettes smoked during pregnancy, multivitamin or prenatal vitamin use (yes/no), ambient temperature (mean ambient temperature during pregnancy), season (spring, summer, fall, winter), and year of entering the study (for PM_{10} and other pollutants, spanning 1997–2001; for $\text{PM}_{2.5}$, 1999–2001). In linear mixed-effects models, we also controlled for gestational weeks at visit (days) and ambient temperature at each lag day(s) but not multivitamin or prenatal vitamin use, since it did not meet the change in estimate criteria when we included the variable in the model. Other potential confounders, including marital status, alcohol intake during pregnancy, maternal education, household income, required public assistance (yes/no), and gestational weeks at delivery, were not included. These factors did not change the estimates for pollutants by more than 10% when included in preliminary analyses (Mickey and Greenland, 1989).

Previous studies reported different blood pressure patterns for smokers and non-smokers during pregnancy (Bakker et al., 2010; Matkin et al., 1999). In addition, women who develop gestational hypertension and preeclampsia may also exhibit different blood pressure patterns. Thus, we conducted sensitivity analyses restricted only to women without pregnancy-induced hypertension (preeclampsia and gestational hypertension) and to non-smokers. Moreover, race may modify associations between air pollution and blood pressure changes. We investigated effect modification by race (mainly African-American and Caucasian), using interaction terms in our models and stratified analyses.

We relied on any blood pressure measurements taken during the first 20 weeks of gestation and the last two measurements of blood pressure taken during prenatal care visits to calculate blood pressure changes. For women who delivered preterm (i.e., before 37 gestational weeks) or who had different prenatal visit patterns (i.e., different intervals between visits and different numbers of visits), we averaged blood pressure measurements from slightly different periods for each woman (i.e., average blood pressure measurements from earlier gestational weeks for women who delivered preterm rather than average measurements for women who delivered at term). We also performed sensitivity analyses in which we calculated the blood pressure changes based only on measurements taken between 15 and 20 weeks and measurements taken between 30 and 36 weeks of gestation.

3. Results

The mean maternal age of our study population was 24.9 years (standard deviation (SD) = 5.9) at enrollment. Mean pre-pregnancy body mass index was 25.4 kg/m^2 (Table 1). The majority of our study participants was Caucasian (63%), did not smoke during pregnancy (68%), and took multivitamins or prenatal vitamins (86%). Each woman made an average of 11 visits (range 3 to 16). The 1684 women contributed a total of 18,909 and 18,873 measurements of systolic and diastolic blood pressures, respectively, during pregnancy. The mean gestational age was 13.8 weeks (SD=1.8 weeks; range 6 to 20) for blood pressures taken during the first 20 weeks of gestation and 36.7 weeks (SD=2.7 weeks; range 21–42) for blood pressures taken in the late third trimester. Average systolic and diastolic blood

pressures increased with gestational age. The average systolic and diastolic blood pressures in the first 20 weeks of gestation were 112.5 mmHg (SD = 8.3) and 68.4 mmHg (SD=6.1), respectively, while the average systolic and diastolic blood pressures increased to 117.2 mmHg (SD=10.1) and 72.6 mmHg (SD = 7.7) late in the third trimester. Among our study participants, 32 (2%) developed preeclampsia and 110 (7%) received a diagnosis of gestational hypertension.

Table 2 summarizes means and correlations of pollutant concentrations in the first trimester. Pollutant means and correlations were very similar for other trimesters. Average first-trimester PM₁₀, PM_{2.5}, and O₃ concentrations were strongly positively correlated with each other but negatively correlated with CO, SO₂, and NO₂.

3.1. Trimester ambient air pollution and blood pressure changes between the first 20 weeks of gestation and late pregnancy

An IQR increase in PM₁₀ was associated with a 1.18 mmHg increase in average systolic blood pressure (95% CI=0.10 to 2.26) and a 0.48 mmHg increase in average diastolic blood pressure (95% CI= -0.35 to 1.30) between the first 20 weeks of gestation and late pregnancy in adjusted single-pollutant models for the entire study population (Table 3). We found weaker associations between first-trimester PM_{2.5} exposure and changes in both systolic and diastolic blood pressure between the first 20 weeks of gestation and late pregnancy and the 95% CI did not exclude the null value. First trimester O₃ exposure was associated with changes in both systolic and diastolic blood pressures between the first 20 weeks of gestation and late pregnancy. An IQR increase in O₃ was associated with 1.47 mmHg (95% CI= -0.10 to 3.04) and 0.74 mmHg (95% CI= -0.48 to 1.95) increases in systolic and diastolic blood pressures, respectively, between the first 20 weeks of gestation and late pregnancy.

When we restricted our analyses to non-smokers, effect estimates were larger for PM₁₀, PM_{2.5}, and O₃. Examined increases in diastolic and systolic blood pressure per IQR increase of PM₁₀ in the first trimester among nonsmokers, adjusted single-pollutant models suggested a 1.88 mmHg (95% CI=0.84 to 2.93) increase in systolic blood pressure and a 0.63 mmHg (95% CI= -0.50 to 1.76) increase in diastolic blood pressure between the first 20 weeks of gestation and late pregnancy (Table 3). We also observed a 1.84 mmHg (95% CI=1.05 to 4.63) and a 1.13 mmHg (95% CI= -0.46 to 2.71) increase in systolic and diastolic blood pressures, respectively, per IQR increase in O₃. Association were much weaker for second and third trimester air pollution exposures to PM₁₀, PM_{2.5}, and O₃ and blood pressure changes between the first 20 weeks of gestation and late pregnancy (see Supplemental Materials. Tables S2 and S3). All 95% confidence intervals included the null values except the estimate for third trimester O₃ exposure and systolic blood pressure change for all women. We observed 0.46 mmHg (95% CI= -1.01 to 1.93) and 0.37 mmHg (95% CI= -0.52 to 1.26) increases in systolic blood pressures for PM₁₀ exposure (per IQR increase) during the second and third trimesters, respectively, in adjusted single-pollutant models for non-smokers. For CO, SO₂ and NO₂, associations were null for the entire population and nonsmokers only (results not shown).

Generally, effect estimates for PM₁₀, PM_{2.5}, O₃ and blood pressure changes between the first 20 weeks of gestation and late pregnancy changed only slightly when we excluded women with preeclampsia and gestational hypertension disorders in adjusted single-pollutant models (see Supplemental Materials. Table S4). Sensitivity analyses examining associations only for women with blood pressure measurements during the periods of 15 to 20 and 30 to 36 gestational weeks produced smaller estimates for both PM₁₀ and PM_{2.5} (see Supplemental Materials, Table S5); i.e., per IQR increase in first trimester PM₁₀, the change in systolic blood pressure between the first 20 weeks of gestation and late-pregnancy for

nonsmokers was 1.15 mmHg (95% CI= −0.07 to 2.37) in an adjusted single-pollutant model. When we stratified our results by race, first-trimester PM₁₀ and ozone exposures affected both diastolic and systolic blood pressure changes in both races. For example, first trimester PM₁₀ exposure (per IQR increase) was associated with a 1.13 mmHg (95% CI= −0.26 to 2.52) and a 1.11 mmHg (95% CI= −1.24 to 3.46) increase in systolic blood pressure in women of Caucasian and Africa-America race, respectively (results not shown).

3.2. Short-term ambient air pollution and longitudinally measured blood pressure patterns during pregnancy

We only observed a slight rise in systolic and diastolic blood pressures during pregnancy with 8-day average O₃ exposure. For example, an IQR increase in 8-day average O₃ was associated with a 0.41 mmHg increase in systolic blood pressure (95% CI=0.01 to 0.80) and a 0.30 mmHg increase in diastolic blood pressure (95% CI= −0.01 to 0.61) during pregnancy (see Supplemental Materials, Table S6). However, none of the other short-term air pollution exposure measures (lag0 to lag7 days prior to blood pressure measurement) were associated with changes in systolic or diastolic blood pressure patterns during pregnancy.

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4. Discussion

We identified associations between first-trimester exposure to PM₁₀ and O₃ air pollution and increases in mean systolic and diastolic blood pressures between the first 20 weeks of gestation and late pregnancy in our cohort of pregnant women. Associations between particulate and O₃ air pollution exposures and mean blood pressure changes between the first 20 weeks of gestation and late pregnancy were stronger when we restricted our analyses to nonsmokers. Our study is among the first to assess the relation between air pollution exposure and blood pressure changes in pregnant women. This relationship provides new insights into how first-trimester exposure to air pollution may adversely affect birth outcomes.

A growing number of experimental observational and epidemiological studies have examined possible links between ambient air pollution and blood pressure changes in healthy individuals, the elderly, and people with cardiovascular diseases (Auchincloss et al., 2008; Brook and Rajagopalan, 2009; Harrabi et al., 2006; Ibal-Mulli et al., 2004; Sergio Chiarelli et al., 2011; Urch et al., 2005; Zanobetti et al., 2004). However, only one study examined associations between air pollution exposure and blood pressure changes in pregnant women (van den Hooven et al., 2011). The mechanisms by which air pollution might affect blood pressure changes over time in pregnancy are likely different and more complex than those in nonpregnant populations. In aging populations, changes in blood pressure are most commonly attributed to arterial vascular degeneration. In pregnant women, however, changes in blood pressure result from systemic adaptation necessary to accommodate the needs and presence of the developing fetus. During normal pregnancy, maternal blood volume begins to increase in early pregnancy, and by 32 weeks of gestation, blood volume is increased by approximately 25–50% (Torgersen and Curran, 2006). These

blood volume increases are accompanied by decreases in systemic vascular resistance. The lowest systemic vascular resistance occurs in the first and second trimesters, but increases again during the third trimester until delivery. This adaptation leads to lower systolic and diastolic blood pressure in early pregnancy and a gradual blood pressure increase during the late second trimester and throughout the third (Blackburn, 2003).

Our central hypothesis was that air pollution exposure during early pregnancy is critical for adverse pregnancy outcomes or complications due to the importance of that period for vascular remodeling of the maternal vessels supplying the placenta. When this process is disturbed, it has been implicated in several adverse pregnancy outcomes, including hypertensive pregnancy disorder, preeclampsia, and preterm birth. However, since we had access to longitudinal blood pressure data for these women, we also examined whether short-term air pollution exposures affected blood pressure in pregnant women. Our data did not suggest such associations for short-term air pollution exposures and changes in blood pressure patterns during pregnancy.

A recent Dutch study examined the associations of air pollution exposures with blood pressure in each trimester of pregnancy (van den Hooven et al., 2011). Relying on one blood pressure measurement in each trimester, they reported associations for higher PM₁₀ exposures in the second and third trimesters only, and with elevated systolic blood pressures during the same trimesters (van den Hooven et al., 2011). Additionally, higher NO₂ exposure was related to elevated systolic blood pressure in all three trimesters. These results cannot easily be compared to our findings. The outcome of interest in our study was defined as blood pressure changes between the first 20 weeks of gestation and late pregnancy, while the Dutch study examined the associations of trimester average air pollution exposures with blood pressure measurements in each trimester. Furthermore, the Dutch exposure assessment relied on spatiotemporal dispersion modeling that accounts for traffic point sources, including NO₂ emissions from vehicles. Detailed assessment of spatial variations due to traffic sources could not be achieved in our study of Allegheny County.

In a sensitivity analysis restricting blood pressure measurements to those taken 15 to 20 and 30 to 36 gestational weeks, we observed weaker associations between blood pressure changes and first-trimester particulate air pollution exposures. This may be due to the fact that most women we excluded delivered preterm or developed gestational hypertension. Excluding women with higher blood pressure changes between the first 20 weeks of gestation and late pregnancy in our analysis may have attenuated associations.

Studies on air pollution and adverse birth outcomes have reported consistent results for particulate air pollution and preterm birth (Ritz et al., 2007; Sagiv et al., 2005; Shah and Balkhair, 2010). Recently, a larger hospital-based study in California examined the association between traffic-related air pollution during pregnancy and preeclampsia, and reported odds ratios of 1.33 (95% CI=1.18 to 1.49) and 1.42 (95% CI=1.26 to 1.59) for preeclampsia in the highest exposure quartiles for NO_x and PM_{2.5} (Wu et al., 2009). Another study in western Washington state found no association between PM_{2.5} and preeclampsia, but reported a weak association between CO exposure during the first 7 calendar months of pregnancy (per 0.1 ppm) and preeclampsia (OR=1.07, 95% CI=1.02 to 1.13) (Rudra et al., 2011). It has been hypothesized that particulate air pollution may induce blood pressure changes that result in preterm birth (Slama et al., 2008); pregnancy-related hypertension is one of the key signs of preeclampsia. However, the sample size of our cohort (with 142 preterm births and 32 cases of preeclampsia) precluded us from determining whether blood pressure changes mediate the associations between air pollution and these adverse outcomes. Nevertheless, our novel findings that PM₁₀ and O₃ air pollution are associated with mean increases in blood pressure between the first 20 weeks of gestation and

late pregnancy provide new insights into possible pathways linking air pollution and pregnancy outcomes.

Pregnancy-associated hypertension has been associated with increased risks of preterm birth, low birth weight, small for gestational age, still birth, and neonatal mortality (Ray et al., 2001; Xiong and Fraser, 2004). In contrast, women with preeclampsia delivering after 37 weeks of gestation delivered a higher proportion of large for gestational age infants (Xiong and Fraser, 2004). Thus, the impact of pregnancy-associated hypertension upon fetal growth is multifactorial and complex. Zhang et al. (2007) reported that even in normotensive women, a rise in systolic and/or diastolic blood pressure from early pregnancy (average blood pressure between 12 and 19 weeks of gestation) to mid-third trimester (average blood pressure between 30 and 34 weeks of gestation) is associated with spontaneous preterm birth. The risk of preterm birth was greater with a greater increase in blood pressure. They also reported that women who had late spontaneous preterm birth (defined as delivery between 34 and 36 weeks of gestation) experienced an average rise of 3.6 mmHg (95% CI=2.5 to 4.8) and 3.1 mmHg (95% CI=1.7 to 4.4) in systolic and diastolic blood pressure, respectively, than women with term births (Zhang et al., 2007). In our study, an IQR increase in PM₁₀ and O₃ exposure in the first trimester was associated with an average increase in systolic blood pressure of 1.9 mmHg (95% CI=0.84 to 2.93) and 1 mmHg (95% CI = 1.05 to 4.63), respectively, in nonsmokers. Although these increments are smaller than those reported by Zhang et al. (2007), it is possible that air pollution could be related to preterm delivery through such increases in blood pressure.

We did not find associations between mean blood pressure changes between the first 20 weeks of gestation and late pregnancy and gaseous combustion-related air pollutants; i.e., CO, NO₂, and SO₂, which previous studies linked to adverse birth outcomes (Bell et al., 2007; Ritz et al., 2007). Our null findings for an association between these pollutants and blood pressure are most likely due to our inability to sufficiently capture the spatial distribution of these pollutants due to the small number of monitoring stations measuring CO and NO₂ (2 and 3 monitoring stations, respectively) in Allegheny County. For pollutants that are highly spatially heterogeneous, such as CO, a small number of monitoring stations does not fully represent local sources adequately, due to poor spatial resolution. Furthermore, while we observed a positive association of PM_{2.5} with mean blood pressure changes, the estimated effect size was much smaller than for PM₁₀; fewer years of monitoring for fine particles resulted in a smaller sample size, limiting our analyses of fine particles.

Trimester-specific air pollution exposures have been evaluated in a number of air pollution and birth outcomes studies, and the most consistent evidence points to the importance of first and third trimester exposures for preterm and low birth weight outcomes (Bell et al., 2007; Leem et al., 2006; Ritz et al., 2007; Shah and Balkhair, 2010). Clinical studies have reported that first-trimester growth restriction (determined by crown-to-rump length) is significantly related to increased risks of preterm birth, small for gestational age, and low birth weight (Bukowski et al., 2007; Mook-Kanamori et al., 2010; Smith et al., 1998). Furthermore, it is in the first half of pregnancy that vascular remodeling of maternal vessels supplying the intervillous space is completed. Failures in these adaptations have been associated with intrauterine growth restriction, preeclampsia, and preterm birth. Our data suggest that first-trimester particulate and O₃ air pollution exposures are important for mean blood pressure increases between the first 20 weeks of gestation and late pregnancy.

Our study has several limitations. First, blood pressure measurements may have been subject to factors that increase variability of blood pressure in the short term, such as anxiety and caffeine consumption at the time of a prenatal visit. However, the early blood pressure

measurements we used represent an average of at least two measurements of blood pressure taken during the first 20 weeks of gestation and one measurement at each of two visits late in the third trimester. While even more readings of blood pressure would have been preferable to reduce random variability, this was not feasible to attain in our study, and averaging over two measurements reduced the variability of blood pressure to some extent. Second, unlike trial-based conditions with more constrained measurement procedures (e.g., measuring blood pressure multiple times at each visit and ensuring that the blood pressure cuff is always worn on the same arm, etc.), our blood pressure data were necessarily based upon routinely collected clinical blood pressure readings taken by nursing staff at multiple visits during pregnancy. This may have increased measurement errors. However, all nursing staff involved was instructed to apply standard procedures (i.e., seating patients during readings and placing the cuff at the level of the subject's heart). These instructions, if followed by staff, would have limited measurement errors. Third, when performing kriging interpolation for estimating PM_{2.5} and PM₁₀ concentrations, we relied on data collected during different routine air monitoring cycles (i.e., every day, every 3rd or 6th day), which might have contributed to measurement errors. Unfortunately, very few PM₁₀ and PM_{2.5} monitoring stations in Allegheny County collected data every day. If we had restricted our exposure measures to those stations, we would not have captured the spatial variability of particles when performing kriging. In addition, we lacked maternal residential history during pregnancy and had to rely on residential information at birth to assess air pollution exposure, resulting in further exposure measurement error. However, because participants in this longitudinal study received their prenatal care in the same hospital they delivered in, we believe that our assumption is reasonable that most women in our study either did not move or moved only within the same neighborhood (or ZIP code) during pregnancy, as has been suggested by Chen et al. (2010).

5. Conclusions

In summary, first-trimester exposures to PM₁₀ and ozone air pollution during pregnancy were positively associated with mean systolic and diastolic blood pressure changes between the first 20 weeks of gestation and late pregnancy. These associations were stronger when we restricted our analyses to nonsmokers. Our results suggest that blood pressure increases between the first 20 weeks of gestation and late pregnancy may play a role in mediating reported associations between air pollution and adverse birth outcomes through remodeling of vessels that supply the placenta, which leads to an increase in maternal blood pressure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PM ₁₀	particles of less than 10 µm diameter
PM _{2.5}	particles of less than 2.5 µm diameter
O ₃	ozone

CO	carbon monoxide
NO ₂	nitrogen dioxide
SO ₂	sulfur dioxide
IQR	interquartile range
SD	standard deviation

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Fig. 1.
The distribution of air monitoring stations in Allegheny County.

Table 1Demographics and major risk factors in the study population ($N=1684$).

Continuous measures	Mean	Standard deviation
Pre-pregnancy body mass index (kg/m ²)	25.4	6.4
Maternal age (years)	24.9	5.9
Average systolic blood pressure (mmHg) in the first 20 weeks of gestation ^a	112.5 (range = 70–155)	8.3
Average diastolic blood pressure (mmHg) in the first 20 weeks of gestation ^b	68.4 (range = 40–94)	6.1
Average systolic blood pressure (mmHg) in the last two blood pressure measurements	117.2 (range = 79–170)	10.1
Average diastolic blood pressure (mmHg) in the last two blood pressure measurements	72.6(range = 50–130)	7.7
Categorical measures	N	%
Maternal race/ethnicity		
Caucasian	1040	63
African-American	610	37
Parity		
First birth	1033	61
Second or subsequent birth	651	39
Smoking status during pregnancy		
Yes	527	32
No	1104	68
Multivitamin or prenatal vitamins taken		
Yes	1440	86
No	143	8
Missing	101	6
Year entering the study		
1997	197	12
1998	299	18
1999	371	22
2000	498	29
2001	319	19
Season entering the study		
Spring (March-May)	523	31
Summer (June-August)	428	25
Fall (September-November)	373	22
Winter (December-February)	360	22
Preeclampsia		
Yes	32	2
No	1652	98
Gestational hypertension		
Yes	110	7
No	1574	93

Missing observations for maternal race other than Caucasian and African-American ($N=34$); and maternal smoking status during pregnancy ($N=53$).

^a 104 women had only one systolic blood pressure measurement available; 1580 women contributed a total of 5640 measurements in the first 20 weeks of gestation.

^b 108 women had only one diastolic blood pressure measurement available; 1576 women contributed a total of 5621 measurements in the first 20 weeks of gestation.

Table 2

Descriptive statistics of first-trimester air pollution exposures.

Pollutants	Mean ± Standard deviation	IQR	Percentile					Pearson correlation						
			Minimum	25th	50th	75th	95th	Maximum	PM ₁₀	PM _{2.5}	O ₃	NO ₂	SO ₂	CO
PM ₁₀ (μg/m ³)	26.1 ± 4.8	7.3	13.8	22.4	25.4	29.6	34.7	40.0	1					
PM _{2.5} (μg/m ³) ^a	16.5 ± 2.7	3.8	10.8	14.3	16.2	18.1	21.6	24.7	0.9	1				
O ₃ (ppb)	22.7 ± 8.6	15.3	6.3	14.8	22.9	30.1	35.6	42.7	0.7	0.5	1			
NO ₂ (ppb)	18.7 ± 2.9	4.0	9.0	16.7	18.8	20.7	23.3	26.1	-0.3	-0.5	-0.5	1		
SO ₂ (ppb)	8.6 ± 2.4	3.6	3.3	6.7	8.1	10.3	12.8	17.5	-0.3	-0.3	-0.6	0.3	1	
CO (ppm)	0.5 ± 0.2	0.3	0.1	0.3	0.4	0.6	0.8	1.1	-0.1	-0.2	-0.4	0.7	0.3	1

^aFor years of 1999, 2000, and 2001.

Table 3

Increase in average blood pressure (in mmHg)^a between the first 20 weeks of gestation and late pregnancy per iqr increase in first-trimester air pollution exposure.

	<i>N</i>	<u>Change in blood pressure (95% CI)</u>	
		Crude	Adjusted ^a
<i>For the entire population</i>			
PM₁₀ (µg/m³)			
Systolic blood pressure	1684	1.09 (0.38 to 1.81)	1.18 (0.10 to 2.26)
Diastolic blood pressure	1684	0.47 (−0.20 to 1.14)	0.48 (−0.35 to 1.30)
PM_{2.5} (µg/m³)			
Systolic blood pressure	1128	0.12 (−0.71 to 0.94)	0.40 (−0.66 to 1.46)
Diastolic blood pressure	1128	0.23 (−0.42 to 0.87)	0.38 (−0.41 to 1.18)
O₃ (ppb)			
Systolic blood pressure	1684	1.32 (0.57 to 2.08)	1.47 (−0.10 to 3.04)
Diastolic blood pressure	1684	0.75 (−0.05 to 1.54)	0.74 (−0.48 to 1.95)
<i>For non-smokers</i>			
PM₁₀ (µg/m³)			
Systolic blood pressure	1104	1.13 (0.33 to 1.94)	1.88 (0.84 to 2.93)
Diastolic blood pressure	1104	0.41 (−0.37 to 1.18)	0.63 (−0.50 to 1.76)
PM_{2.5} (µg/m³)			
Systolic blood pressure	726	0.17 (−0.83 to 1.17)	0.84 (−0.33 to 2.00)
Diastolic blood pressure	726	0.33 (−0.37 to 1.02)	0.60 (−0.27 to 1.47)
O₃ (ppb)			
Systolic blood pressure	1104	1.40 (0.50 to 2.30)	1.84 (1.05 to 4.63)
Diastolic blood pressure	1104	0.65 (−0.29 to 1.59)	1.13 (−0.46 to 2.71)

^a All models were adjusted for maternal age, race, parity, number of cigarettes smoked during pregnancy (for the entire population only), multivitamin or prenatal vitamin use during pregnancy, maternal pre-pregnancy body mass index, temperature, and season and year of enrollment (1997 to 2001 for PM₁₀ and O₃; and 1999 to 2001 for PM_{2.5}).