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Prenatal Air Pollution Exposure and Newborn Blood Pressure

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Abstract

Background: Air pollution exposure has been associated with increased blood pressure in adults.

Objective: We examined associations of antenatal exposure to ambient air pollution with newborn systolic blood pressure (SBP).

Methods: We studied 1,131 mother-infant pairs in a Boston-area pre-birth cohort. We calculated average exposures by trimester and during the 2 to 90 days before birth for temporally-resolved particulate matter (PM)_{2.5}, black carbon (BC), NO_x, NO₂, O₃ and carbon monoxide (CO) measured at stationary monitoring sites, and for spatiotemporally-resolved estimates of PM_{2.5} and BC at the residence level. We measured SBP at a mean age of 30±18 hours with an automated device. We used mixed effects models to examine associations between air pollutant exposures and SBP, taking into account measurement circumstances; child's birth weight; mother's age, race/ethnicity, socio-economic position, 3rd trimester BP; and time trend. Estimates represent differences in SBP associated with an interquartile (IQR) increase in each pollutant.

Results: Higher mean PM_{2.5} and BC exposures during the third trimester were associated with higher SBP (e.g., 1.0 mmHg; 95% CI: 0.1, 1.8 for a 0.32-μg/m³ increase in mean 90-day residential BC). In contrast, O₃ was negatively associated with SBP (e.g., -2.3 mmHg; 95% CI: -4.4, -0.2 for a 13.5 ppb increase during the 90 days before birth).

Conclusions: Exposures to PM_{2.5} and BC in late pregnancy were positively associated with newborn SBP, while O₃ was negatively associated with SBP. Longitudinal follow-up will enable us to assess the implications of these findings for health during later childhood and adulthood.

Introduction

During the prenatal period, a critical period for cardiovascular growth and development, fetuses may be especially vulnerable to adverse health effects of ambient air pollution (Selevan et al. 2000). Earlier studies have reported associations of greater prenatal exposure to air pollution to low birth weight, preterm birth, (Bonzini et al. 2010; Bosetti et al. 2010; Ghosh et al. 2007; Glinianaia et al. 2004; Maisonet et al. 2004; Shah and Balkhair 2011; Sram et al. 2005; Stillerman et al. 2008) and higher maternal blood pressure (BP) in pregnancy (van den Hooven et al. 2011). Effects of prenatal air pollution on neonatal BP has not been explored previously, but there is evidence that infant BP is influenced by prenatal maternal conditions including hypertension, maternal drug use (Kent et al 2009), and by infant's weight, gestational age, and postnatal age (Gillman et al. 2004; Huxley et al. 2000; Kent et al. 2009; Morrison et al. 2013; Simonetti et al. 2011). In adults, air pollution has been positively associated with BP (as reviewed in Brook 2005), although inverse associations between BP and the pollutants PM and NO_x have also been reported (Hampel et al. 2011, Sorensen et al. 2012). Some studies have reported an association between air pollution and higher blood pressure in healthy children (Sughis et al. 2012, Bilenko et al. 2013). Despite the abundant research interest in the early origins of vascular dysfunction, we know of no published study that has assessed the association between prenatal exposure to ambient air pollution and offspring BP.

This study investigates associations of prenatal exposures to air pollution (PM_{2.5}, black carbon (BC), NO_x, NO₂, O₃, and CO) with blood pressure in newborns. Although prior studies have generally used particulate matter (PM) as a proxy for air pollution exposure (Brook and Rajagopalan, 2009), we also considered BC, which is a traffic-related component of PM that has

been associated with blood pressure in adults (Mordukhovich et al. 2009). We hypothesized that PM_{2.5}, BC, NO_x or NO₂ exposure during pregnancy would be associated with higher newborn BP. We had no prior hypothesis regarding the direction of the association between O₃ and newborn BP, given the conflicting results reported in adults, including the findings from our research group of lower BP with increased O₃ among adults with diabetes in Boston (Hoffmann et al. 2012). The latter shows that the direction of the association may be different in vulnerable subgroups, such as newborns. In addition, while ambient monitors have been used in prior cohort studies to examine effects of pollution exposure, more emphasis is now shifting to spatio-temporal models that capture geographic variations in exposure within a metropolitan area. We have incorporated this for PM_{2.5} and BC.

Methods

Study design and participants

Study subjects were participants in Project Viva, a prospective pre-birth observational cohort study of the influences of antenatal and perinatal factors on maternal and child health. We recruited women who were attending their initial prenatal visit at one of 8 urban and suburban obstetrical offices of Harvard Vanguard Medical Associations, a multi-specialty group practice located in eastern Massachusetts, between April 1999 and July 2002. Details of recruitment and retention procedures are available elsewhere (Gillman et al. 2004). The human subjects committees of participating institutes approved the study protocols and all mothers provided written informed consent. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.

The cohort started with 2,128 live births. We performed in-person visits during the inpatient hospital stay with mothers only on weekdays (n=1,714, 81%), and we measured BP of their newborn (n=1,131, 66%). Reasons for not obtaining a BP measurement were parents not giving consent for measurements (n=328), infant not available when staff was present (n=104), infant transferred to neonatal intensive care unit (n=78), measurements could not be performed (infant too fussy)(n=32), and other reasons (n=41).

Measurements

Participant characteristics

Maternal age (years) was ascertained at enrollment. Maternal third trimester BP (mmHg) obtained from the medical record was calculated as the average BP between 28 and 32 weeks of gestation. Maternal pre-pregnancy weight and height (which we used to calculate BMI) and serial urine and blood pressure measurements (which we used to identify gestational hypertension or pre-eclampsia), were derived from the medical record. Mother's self-reported race/ethnicity was categorized as Black, Hispanic, White or other. Maternal smoking and physical activity were also self-reported. We obtained birth weight (kg) and date of birth from the hospital record. We included socio-economic status on an individual level estimated by maternal education at enrollment (college graduate vs. less) and at the neighborhood level as median household income derived from the Census 2000.

Outcome

We measured newborn BP with a Dinamap (Critikon, Inc) Pro 100 (or, before February 21, 2001, model 8100) automated oscillometric recorder (GE Medical Services, Tampa, FL) according to a standardized protocol. For each of 5 measurements taken 1 minute apart, we also

recorded conditions during the measurement: infant position (in bassinet or held), extremity used (left or right arm), cuff size, and infant state (quiet sleep, active sleep, quiet awake, crying). We obtained 5 readings on 1,092 infants, 4 readings on 15 infants, 3 readings on 7 infants, 2 readings on 7 infants, and 1 reading on 10 infants, for a total of 5,565 readings on the 1,131 participants. We used systolic BP rather than diastolic BP as our primary outcome, because of the validity of its measurement with the oscillometric device, and superior prediction of long-term BP (Gillman and Cook 1995).

Temporally-resolved exposure measures

Ambient concentrations of fine particle mass (with aerodynamic diameter less than 2.5 μm , $\text{PM}_{2.5}$) and black carbon (BC), were measured hourly at a central monitoring site (Harvard Supersite) in Boston, MA. We measured $\text{PM}_{2.5}$ concentrations with a Tapered Element Oscillation Microbalance (Model 1400A, Rupprecht and Pastashnick, East Greenbush, NY), and BC concentrations using an Aethalometer (Magee Scientific Co., Model AE-16, Berkeley, CA). Air sampling, processing of samples, analysis, and reporting were conducted according to standard operating procedures (Kang et al. 2010). We calculated hourly ambient concentrations of the sum of nitrogen oxides ($\text{NO}_x = \text{NO}_2 + \text{NO}$), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) by averaging data from the Massachusetts Department of Environmental Protection's Greater Boston monitoring sites (N=4 for CO and O_3 ; N=5 for NO_2 and NO_x); thus these estimates represent a city wide exposure. Most of the nitrogen oxides emitted by traffic are in the form of NO; however, part of NO is oxidized to NO_2 by O_3 . Therefore, we consider NO_x as a more robust metric of nitrogen oxide exposures related to traffic, though NO_2 is more often used as a marker in air pollution studies. Weather data were collected from the National Weather

Service Station at Logan Airport (East Boston, MA). Missing hourly data for PM_{2.5} and BC (but not other pollution or weather parameters) were imputed. This imputation procedure used long term trend; seasonality (sine and cosine terms); season (1=May-Sept, 0=otherwise); hour of the day; day of the week; weather (barometric pressure, relative humidity, mean temperature, horizontal visibility, wind direction, and wind speed); gasses: CO, NO₂, SO₂; ozone during summer months; and interactions with season, wind, and hour of the day. In total, 2% of the 24-hour PM_{2.5} and BC estimates were imputed.

All the pollutants were first summarized in 24-hour (9am-9am) intervals. For calculating the trimester specific exposures, we calculated gestational age at birth from the last menstrual period or from the second trimester ultrasound if the two estimates differed by >10 days (N=200, 9%). Trimester 1 ended at last menstrual period + 93 days, trimester 2 at last menstrual period + 187 days and trimester 3 at the day before birth. We also calculated different time windows of exposure to air pollution (“moving averages”) from 2 to 7, 14, 30, 60, and 90-days before birth for a more specific evaluation of air pollution exposures close to the time of birth. The moving averages excluded the day of the blood pressure measurement. For each central site exposure period of interest, for each participant, we required that participants live within 40 km of the Harvard Supersite and that exposure data be available for at least 75% of the time in the specific averaging period; otherwise, the exposure was set to missing.

Spatially- and temporally-resolved estimated PM_{2.5} and BC exposures

Mothers reported their home address at enrollment and updated it at each subsequent study visit, including at birth. We geocoded addresses using ESRI ArcGIS[®] software StreetMap data.

Estimated spatially- and temporally-resolved PM_{2.5} exposure data were generated by previously described PM_{2.5} prediction models validated for the New England region (Kloog et al. 2012). In brief, we used mixed effects models with random slopes and intercepts for day to calibrate satellite Aerosol Optical Depth (AOD) data at a resolution of a 10x10 km spatial grid (2000–2008) with monitored ground PM_{2.5} measurements. We then used a generalized additive mixed model with spatial smoothing to estimate PM_{2.5} in location-day pairs with missing AOD satellite data (due to snow, clouds, etc.), using regional measured PM_{2.5}, AOD values in neighboring cells, and land use variables. "Out-of-sample" ten-fold cross-validation was used to quantify the accuracy of our predictions. That is, 10% of the days were held out of the analysis that generated the prediction, and the accuracy tested against those held out measurements. This was repeated 10 times. For days with available AOD data we found high "out-of-sample" R² (mean "out-of-sample" R²=0.87). For days without AOD values, our model performance was also excellent (mean "out-of-sample" R²=0.85). A regression of the held out data against the predicted had a slope of 1, indicating no bias. To estimate daily spatially and temporally-resolved PM_{2.5} exposure, each residence (for the period when the participant lived there) was linked to the 10x10 km grid in which it was located. Exposure by trimester and for each averaging period was calculated by averaging daily PM_{2.5} concentrations as described above. Because PM_{2.5} was modeled for 2000-2008, data were missing for newborns born between April-December 1999.

We predicted individual-level estimates of residential BC concentrations from a validated spatiotemporal land-use regression model. Details of the model and its validation have been published earlier (Gryparis et al. 2007; Zanobetti et al 2013). In short, daily concentrations at the Boston central-site monitor were used as a predictor to reflect average concentration levels for a given day, serving as a direct estimate of the daily time effect. Out-of-sample cross-validation at

32 monitoring sites showed an average correlation of 0.73 between predicted and observed daily BC levels. Data from 148 other stationary air monitors were used to fit the model and estimate the effect of each covariate in the land-use regression model. Covariates in the BC prediction model included measures of land use for each address (cumulative traffic density within 100 m, population density, per cent urbanization), location (latitude and longitude), daily meteorological factors (apparent temperature, wind speed and height of the planetary boundary layer) and temporal factors (day of week and day of season). Separate models were fit for the warm and cold season. Interaction terms between the temporal meteorological predictors and land-use variables allowed for space–time interactions. Regression splines allowed main effect terms to non-linearly predict exposure levels, and thin-plate splines modeled the residual spatial variability additional spatial variability unaccounted for by the spatial predictors. Daily BC predictions outside of the observed range of the monitored exposure measurements were excluded. To assess the validity of the model, we checked different specifications of the hyperparameters. The results were reasonably robust to even large changes in the specification of the hyperparameters.

Statistical analyses

To assess associations between air pollutants and newborn systolic BP, we used mixed effects models that incorporated each of the up to 5 BP measurements from each infant as repeated outcome measures (Laird and Ware 1982). Some advantages of this modeling approach, compared with using the average of available measures for each child as the outcome, are that persons with more measurements and less variability among those measurements receive more weight than those with fewer measurements and/or more variability (Fitzmaurice 2011).

We modeled each environmental exposure separately. In all multivariable models, we adjusted for order of measurement and infant state during the measurement. We also adjusted for maternal age, maternal third trimester BP, infant's postnatal age (in hours) and birth weight, because these variables were predictive of newborn BP in an earlier report (Gillman et al. 2004). We adjusted for mother's race/ethnicity (categorical: black, Hispanic, other, white), and for mother's educational level (categorical: college degree vs. less), and median neighborhood income (continuous) as indicators of socio-economic position. Using penalized splines in R version 2.10.0 (R Development Core Team, 2009), the model included a variable representing date to take into account seasonality and time trend. Furthermore, we included outdoor temperature (continuous) on the day of the blood pressure measurement. Other weather conditions did not change the estimates of blood pressure (data not shown), and were therefore not included in the model. We visually checked continuous variables for departure from linearity with the outcome with penalized splines, which was not the case for any variable (data not shown). The estimates were scaled to the interquartile range (25th to 75th percentile), and reported with their 95% confidence intervals (CI). Each estimate gives the difference in BP in mmHg for each interquartile increase in the pollutant.

We performed a series of sensitivity analyses. First, we considered multi-pollutant models, one with PM_{2.5} and O₃ together in the same model, and another with O₃ and NO_x together. Second, mother's blood pressure, infant birth weight, and gestational age could be mediators in the association between trimester-specific exposure to air pollution and newborn blood pressure. Therefore, we also ran a model excluding these potential intermediates. Third, the association of air pollution with BP may differ according to level of specific characteristics, because of differential vulnerability of subgroups to the effect of air pollution on blood pressure. Therefore,

using interaction terms, we evaluated gender (boy vs. girl), socio-economic status (both on a neighborhood (median income on a continuous scale) and individual level (college graduate vs. less)), race/ethnicity (Black, Hispanic, other vs. White), gestational age (weeks); and for O₃ season as potential effect modifiers (warm season: May-September, cold season: October-April). We considered effect modification present if the p-value of the interaction term was <0.05. Fourth, for the central monitor exposures we restricted the sample to mothers that lived within 10 km of the Harvard Supersite. Fifth, we restricted the models for the spatiotemporal variables to those children who had information on the temporal variables. Sixth, we repeated the analyses with diastolic BP. Last, we considered additional lifestyle and maternal comorbidities (i.e. maternal physical activity, obesity, parity, preeclampsia, hypertension, and cesarean section) as confounding factors by adding these to the multivariable models and checking the change in estimate for blood pressure.

Statistical analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA) and R version 2.10.0. A p-value of <0.05 was considered statistically significant.

Results

Table 1 shows the characteristics of the mother-infant pairs in the study, and Supplemental Material, Table S1 shows the association of these characteristics with third trimester air pollution exposures. The children included in this study were all born at 33-42 weeks, although only 4% were born before 37 weeks of gestation. Mean blood pressure of children born preterm (72.3 mmHg±9.7) and children born term (72.5 mmHg±8.9) was similar. Mean blood pressure varied according to infant's state (quiet sleep: 70.5 mmHg±7.9; active sleep 72.1 mmHg±9.2; quiet awake: 74.3 mmHg±9.3; active awake: 77.3 mmHg±10.3). Compared with the 997 mothers of

infants with no BP measurement at birth, the 1,131 participants included in this analysis had higher educational level (67.0% versus 62.0% completed more than a college degree), had a higher proportion of white (68.7% versus 64.0%), and their children had a higher birth weight (3.52 versus 3.39 kg) and gestational age (39.7 versus 39.1 weeks). Participants included in the study did not substantially differ with respect to income, smoking status, maternal age or maternal third trimester BP compared with those excluded (data not shown) or the whole study population. A comparison of characteristics between the study population and the analysis sample is presented in Supplemental Material, Table S2. We present the distributions of air pollutant concentrations for the 2-, 30-, and 90-day moving averages in Supplemental Material, Table S3, and the correlation between 2- and 90-day moving averages in Supplemental Material, Tables S4 and S5. Correlations were high for $PM_{2.5}$, but more moderate for BC, especially with increasing number of days averaged. Interquartile range was lower in magnitude with higher number of days averaged.

In multivariate analyses, newborn SBP was 1.4 mmHg (95% CI: 0.3, 2.5) higher in association with an IQR increase in temporally-resolved BC averaged over the third trimester (Table 2). In contrast, SBP was 2.5 mmHg (95% CI: -4.5, -0.4) lower in association with an IQR increase in third trimester O_3 .

Second trimester temporally-resolved $PM_{2.5}$ and BC were not associated with newborn SBP. Higher second trimester averaged concentrations of the gaseous pollutants NO_x , and CO were negatively associated with changes in blood pressure. Higher second trimester averaged concentration of the secondary gaseous pollutant O_3 was positively association with changes in SBP.

There were no statistical associations between exposure to any air pollutant in the first trimester and newborn SBP. A key result of this study is our finding of associations of neonatal BP with spatio-temporally resolved as well as temporally resolved air pollution. The association of SBP with spatiotemporally-resolved third trimester BC was consistent with that for temporally-resolved BC (1.0 mmHg higher; 95% CI: 0.2, 1.8) for an IQR increase. For PM_{2.5} both temporally and spatio-temporally resolved exposures were not associated with SBP.

For BC and PM_{2.5}, cumulative 2 to 90 day exposure was positively associated with SBP, and suggested possible effects of short-term exposures, as well as effects of more long-term exposures (Figure 1). Associations for temporally resolved and spatio-temporally resolved BC and PM_{2.5} were similar, although associations with spatio-temporally resolved PM_{2.5} seemed to decrease for longer term exposures. For the gases, the predominant associations were related to long-term 30- to 90-day averages (Figure 2), in particular for O₃ and NO_x, where O₃ was negatively associated with SBP and NO_x was positively associated with SBP.

We performed a series of sensitivity analyses. First, we considered two-pollutant models for 60-day moving averages that included temporally resolved BC and O₃ or NO_x and O₃. The correlation between the 60-day moving averages of BC and O₃ was -0.17. In the multi-pollutant model the associations for BC and O₃ with newborn SBP were attenuated when including them both in the model: BC from 1.2 mmHg (95% CI: 0.2, 2.1) to 0.7 mmHg (95% CI: -0.3, 1.6), and estimates for O₃ attenuated from -3.3 mmHg (95% CI: -5.3, -1.3) to -2.8 mmHg (95% CI: -4.9, -0.8). The correlation between the 60-day moving averages of NO_x and O₃ was -0.9. In the multi-pollutant model the association for NO_x with newborn SBP was attenuated when including both NO_x and O₃ in the model: NO_x from 2.1 mmHg (95% CI: 0.2, 3.9) to -0.7 mmHg (95% CI: -3.4,

2.1), but the estimate for O₃ increased from -3.3 mmHg (95% CI: -5.3, -1.3) to -3.9 mmHg (95% CI: -5.8, -1.9). In a two-pollutant model with PM_{2.5} and O₃, the estimates were fairly similar as the estimates of the one pollutant model (data not shown). To assess the robustness of the short term averages, we have also ran a 2-pollutant model including short-term BC/PM_{2.5} and O₃; estimates of BC, PM_{2.5} and O₃ were fairly similar as the estimates of the one pollutant model (data not shown).

Excluding mother's blood pressure and birth weight from the model did not materially change the estimated associations, suggesting that these factors did not mediate the relationship (data not shown).

Effect modification models resulted in interaction terms for child's gender, socio-economic status, race/ethnicity, gestational age/preterm birth, and season (tested for O₃) that were mostly associated with p-values >0.10 (data not shown), so we did not stratify the results.. Restricting the sample to mothers who lived within 10 km (2776/5565 observations) of the monitoring produced similar estimates, and restricting the spatiotemporal models to participants who also had data for the temporal models (5140/5565) did not change the estimates (data not shown).

Last, repeating the analyses with diastolic BP were similar in relative magnitude and direction, but seemed weaker overall (Supplemental Material, Table S6 and Figures S1 and S2).

In general, adjusting for maternal physical activity, obesity, parity, preeclampsia, hypertension, and cesarean section did not substantially influence associations between newborn SBP and air pollutants (data not shown).

Discussion

In this study of prenatal air pollution and newborn BP, we found that higher short-term and longer-term trimester-specific concentrations of PM_{2.5} and BC were associated with higher newborn BP, whereas higher concentrations of NO₂, NO_x, and O₃ were associated with lower and higher newborn BP (depending on the pregnancy period). Associations were mainly seen in the 2nd and 3rd trimester, and for PM_{2.5} and BC for both shorter, and in particular for BC, longer-term cumulative exposure. For gaseous pollution, BP changes were associated with longer-term exposures.

Blood pressure is a function of cardiac output and peripheral vascular resistance, each of which can be influenced by a number of factors. Epidemiological and experimental studies in adults suggest that underlying mechanisms for short-term air pollution effects on increased blood pressure relate to autonomic imbalance, and systemic oxidative/inflammatory responses promoting vascular endothelial dysfunction (Brook 2005). A growing literature supported by animal models suggests that longer term exposures to particle pollution in adults can lead to atherosclerosis and vascular remodeling (Pope et al. 2004; Sun et al. 2005; Soares et al. 2009).

These short and long term vascular responses could be applicable to the fetus as well: at least one study has found adverse effects of antenatal air pollution (PM_{2.5}, CO, NO₂, SO₂) on placental vascular structure in a rodent model (Veras et al. 2008). Adjustment for the potential mediators such as maternal blood pressure or birth weight did not alter associations, suggesting that air pollution may have influenced cardiac output and structure directly through increasing placental vascular or fetal vascular resistance and cardiac output. However, experimental studies in

animals of air pollution in pregnancy and BP in offspring are lacking and human interventions investigating this issue may be difficult to perform.

In an earlier study, we reported opposing associations of particle pollutants and O₃ with BP in an adult population with diabetes after adjustment for season and ambient temperature (Hoffmann et al. 2012). We found that exposure to particle pollutants was associated with higher BP, while exposure to O₃ was associated with lower BP in the 3rd trimester, but with higher BP in the 2nd trimester. In addition, exposure to CO and NO_x in the 2nd trimester was associated with lower BP. An earlier study reported an inverse association between nitrogen oxides and BP in adults (Sørensen et al 2012). Thus, particle pollutants and gaseous pollutants may have different mechanisms underlying the air pollution – newborn BP association. A fall in cardiac output has been shown in mice exposed to O₃ (Lee and Pisarri 2001) but how this phenomenon might work *in utero* is unknown. Alternatively, O₃ was strongly inversely correlated with NO₂ (r_{90 days average} = -0.69) and NO_x (r_{90 days average} = -0.92) in our study, which is consistent with its chemical properties: NO_x is a primary vehicular pollutant that quenches O₃. In addition, ground-level O₃ is higher with higher temperature and low wind speed. While the association of O₃ with lower BP may be spurious due to its negative correlation with NO_x and other pollutants (Brook et al. 2009), the strong negative correlations make it difficult to disentangle effects. In two-pollutant models, O₃ was robust to adjustment for BC and NO₂, while the estimates for BC and NO₂ were attenuated.

The consistent findings of short-term PM associations, and short and longer-term (30-to-90 day and trimester-specific) BC associations with BP suggest that these associations were not confounded by season or other unmeasured exposures that season may represent. With the

stationary-site measured gases, we only find long-term associations with BP. Because of this, despite our adjustment with penalized splines for season and for year-by-season trends, we cannot rule out the possibility that whether the trimester-specific or 30-to-90 day average gas (NO_x or O_3) associations with BP may be partly confounded by unmeasured factors related to these 30 to 90 day periods. This is, of course, a consideration in all studies that use trimester-specific or 90 –day averaged temporally but not spatially-resolved pollution, as time periods shorter than 365 days overlap with season. Future modeling of spatio-temporally resolved NO_x in our study will help us further disentangle season from pollution associations.

This study has many strengths including careful measures of newborn BP and information on a number of antenatal predictors and potential confounders. Nevertheless, some limitations exist. The precision of exposure estimates may have been reduced by using central site measures for many exposures of interest. However, this was not reflected in the estimates as the third trimester BC associations with BP were less strong for the spatiotemporal estimates of BC than for the temporal measures of BC. It is possible that regional BC may better reflect exposure than residence-specific BC, because participants may not be at home during the day. In contrast with BC, third trimester spatiotemporal $\text{PM}_{2.5}$ estimates had larger, more precise associations with BP than did central site measures of PM, even though the satellite-based estimates of $\text{PM}_{2.5}$ was based on a 10 km, not a residence-specific spatial resolution. A limitation of the present study is the spatial resolution of 10X10 km, and the missings for the spatiotemporally estimates of $\text{PM}_{2.5}$. However, the missings are not likely to be associated with the exposure and/or outcome variable and therefore probably only reduce precision. Although we have adjusted for season, some seasonal components may still be mixed with the effects of the 90-day and trimester-specific estimates of air pollutant. Included and excluded participants differed according to maternal race

and education. This could have led to selection bias if the association between air pollution and blood pressure differed in those who were not in the study. Although this is unlikely, we cannot completely rule out the possibility. Finally, our study consisted of healthy neonates, and therefore the results cannot be generalized to less healthy infants, including children born preterm.

Circulatory changes in the first hours and days of life are profound; some of the cardiovascular measures at birth may represent transient responses and others may have long-term implications. Neonatal blood pressure may have a different meaning than blood pressure measured later in infancy, childhood or adulthood. From infancy onwards, children tend to maintain their blood pressure ranking, meaning that infant with a relatively high blood pressure are more likely to have a high blood pressure in adulthood(Chen and Wang 2008). The literature on the implication of neonatal BP for later cardiovascular disease or risk of hypertension is sparse (Levine et al. 1978; Schachter et al. 1979; de Swiet et al. 1980; Higgins et al. 1980; Zinner et al. 1985). To our knowledge there is no follow-up study that assessed the association between neonatal BP and later cardiovascular health.

Conclusion

Our study contributes unique insight into prenatal pollution exposures and neonatal BP. In summary, we found that 3rd trimester antenatal exposures to BC, and to a lesser extent PM_{2.5}, were associated with higher newborn BP , whereas concentrations of O₃ in the 3rd trimester were associated with lower BP. Future follow-up will indicate whether these associations persist into later childhood.

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Table 1. Characteristics of 1,131 mother-infant pairs with neonatal blood pressure measurements in Project Viva.

Characteristics	N (%) or Mean \pm SD
Maternal characteristics	
Maternal age	32.0 \pm 5.3
Maternal education	
College graduate	752 (67.0)
Mother's race/ethnicity	
Black	193 (17.2)
Hispanic	70 (6.2)
White	771 (68.7)
Other	89 (7.9)
Median income in neighborhood ^a	58,604 \pm 24,833
Maternal smoking during pregnancy	
Never	778 (69.2)
Former	213 (19.0)
Smoker	133 (11.8)
Maternal third trimester systolic blood pressure (mmHg) ^b	111.1 \pm 8.1
Gestational age (weeks)	39.7 \pm 1.4
Preterm birth (<37 weeks)	
Yes	47 (4.2)
No	1084 (95.8)
Child characteristics	
Birth weight (kg)	3.52 \pm 0.50
Birth weight for gestational age z -score	0.20 \pm 0.95
Newborn blood pressure (mmHg)	72.5 \pm 9.0
Infant state at blood pressure measurement	
Quiet sleep	551 (48.7)
Active sleep	131 (11.6)
Quiet awake	351 (31.8)
Active awake	98 (8.7)

^aCensus data for address at birth available for 1,125 families. ^bAvailable for 1,126 mothers.

Table 2. Association between interquartile range of trimester specific estimates of air pollution and systolic blood pressure (mmHg) in newborns (single-pollutant model)

Exposure	1 st Trimester	2 nd Trimester	3 rd Trimester
Spatiotemporally resolved PM_{2.5}^a			
N	765	845	970
IQR (μg/m ³)	2.29	1.97	2.24
β (95% CI)	-0.3 (-1.3, 0.7)	0.4 (-0.4, 1.2)	0.3 (-0.6, 1.2)
Temporally resolved PM_{2.5}			
N	1,032	1,031	1,030
IQR (μg/m ³)	2.35	1.77	2.05
β (95% CI)	0.1 (-0.9, 1.2)	0.1 (-0.7, 1.0)	0.5 (-0.4, 1.5)
Spatiotemporally resolved BC^b			
N	1,099	1,099	1,102
IQR (μg/m ³)	0.36	0.33	0.33
β (95% CI)	0.00 (-0.8, 0.8)	0.3 (-0.5, 1.0)	1.0 (0.2, 1.8)
Temporally resolved BC			
N	1,032	1,031	1,030
IQR (μg/m ³)	0.15	0.16	0.18
β (95% CI)	-0.9 (-1.7, 0.0)	0.3 (-1.1, 1.6)	1.4 (0.3, 2.5)
NO₂			
N	1,032	1,031	1,030
IQR (ppm)	2.63	2.96	3.16
β (95% CI)	0.3 (-0.8, 1.5)	-0.5 (-1.9, 0.8)	-0.5 (-1.8, 0.7)
NO_x			
N	1,032	1,031	1,030
IQR (ppm)	16.7	17.8	18.2
β (95% CI)	0.3 (-0.8, 1.4)	-1.6 (-2.9, -0.2)	0.6 (-1.2, 2.5)
O₃			
N	1,032	1,031	1,030
IQR (ppm)	13.0	12.8	13.6
β (95% CI)	1.2 (-1.0, 3.5)	1.7 (0.3, 3.0)	-2.5 (-4.5, -0.4)
CO			
N	1,032	1,031	1,030
IQR (ppb)	295.3	269.4	218.1
β (95% CI)	1.9 (-0.1, 3.9)	-2.4 (-3.8, -1.0)	0.1 (-1.5, 1.7)

Estimates are adjusted for neighborhood median income; mother's age, third trimester blood pressure, educational level, and race/ethnicity; child birth weight; infant's age at BP measurement, BP measurement conditions; and time trend.

^aPM = Particulate matter. ^bBC = Black carbon.

Figure Legends

Figure 1. Association of spatiotemporally resolved PM_{2.5} exposure, temporally resolved PM_{2.5}, spatiotemporally resolved BC; and temporally resolved BC during different time windows before birth ("moving averages") with blood pressure in newborns. Estimates represent mean difference in systolic blood pressure (95% confidence interval) for an IQR in exposure and are adjusted for neighborhood median income; mother's age, third trimester blood pressure, educational level, and race/ethnicity; child birth weight; infant's age at BP measurement, BP measurement conditions; and time trend.

Figure 2. Association of NO₂, NO_x, CO, and O₃ exposure during different time windows before birth ("moving averages") with blood pressure in newborns. Estimates represent mean difference in systolic blood pressure (95% confidence interval) for an IQR in exposure and are adjusted for neighborhood median income; mother's age, third trimester blood pressure, educational level, and race/ethnicity; child birth weight; BP measurement conditions; and seasonality.

Figure 1.

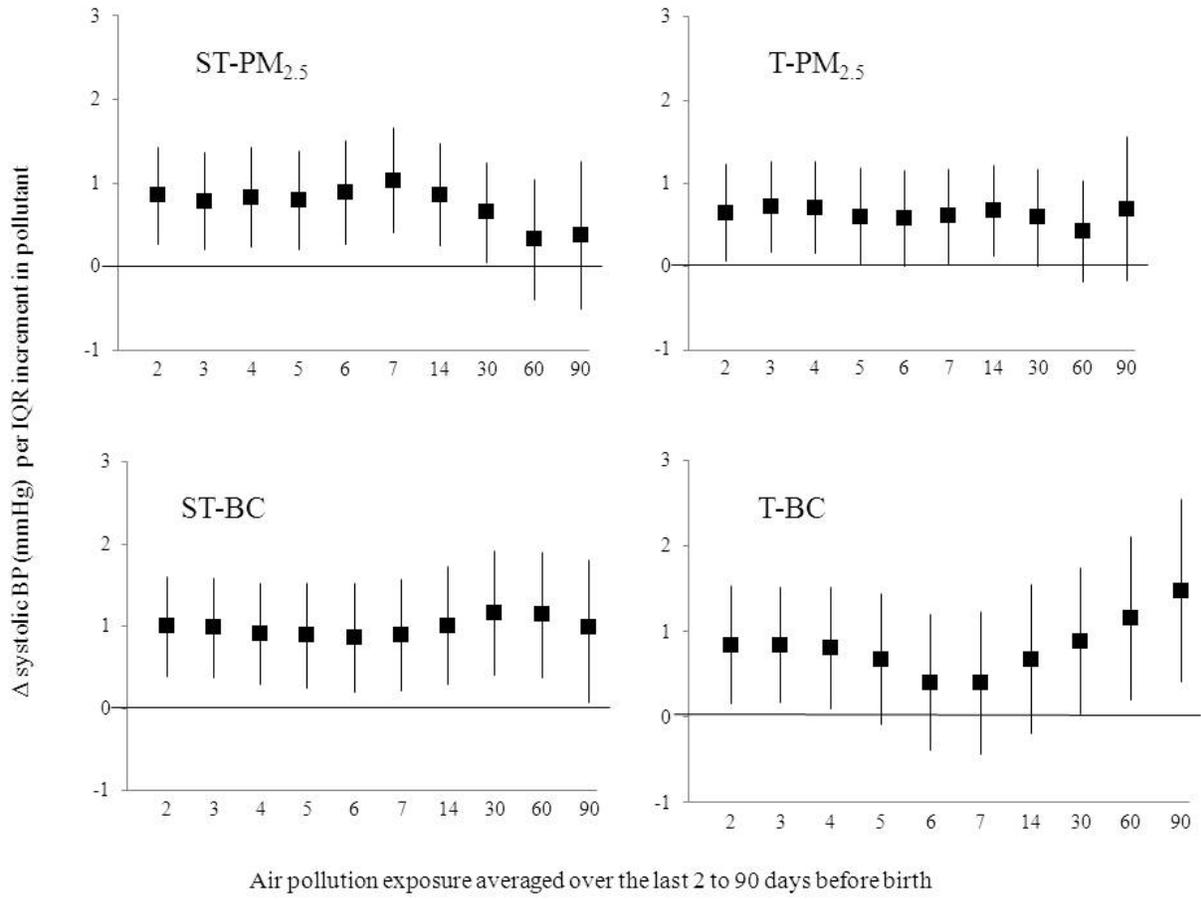


Figure 2.

