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Prenatal Air Pollution Exposure and Ultrasound Measures of Fetal Growth in Los Angeles, California

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Abstract

Background—Few previous studies examined the impact of prenatal air pollution exposures on fetal development based on ultrasound measures during pregnancy.

Methods—In a prospective birth cohort of more than 500 women followed during 1993-1996 in Los Angeles, California, we examined how air pollution impacts fetal growth during pregnancy. Exposure to traffic related air pollution was estimated using CALINE4 air dispersion modeling for nitrogen oxides (NO_x) and a land use regression (LUR) model for nitrogen monoxide (NO), nitrogen dioxide (NO_2) and NO_x. Exposures to carbon monoxide (CO), NO_2, ozone (O_3) and particles <10 μm in aerodynamic diameter (PM_{10}) were estimated using government monitoring data. We employed a linear mixed effects model to estimate changes in fetal size at approximately 19, 29 and 37 weeks gestation based on ultrasound.

Results—Exposure to traffic-derived air pollution during 29 to 37 weeks was negatively associated with biparietal diameter at 37 weeks gestation. For each interquartile range (IQR) increase in LUR-based estimates of NO, NO_2 and NO_x, or freeway CALINE4 NO_x we estimated a

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reduction in biparietal diameter of 0.2-0.3 mm. For women residing within 5 km of a monitoring station, we estimated biparietal diameter reductions of 0.9-1.0 mm per IQR increase in CO and NO_2. Effect estimates were robust to adjustment for a number of potential confounders. We did not observe consistent patterns for other growth endpoints we examined.

Conclusions—Prenatal exposure to traffic-derived pollution was negatively associated with fetal head size measured as biparietal diameter in late pregnancy.

Keywords

ambient air pollution; fetal growth; pregnancy; traffic-related air pollution; ultrasound measurements

Introduction

Epidemiologic studies have associated prenatal air pollution exposure with various measures of intrauterine growth restriction, including small for gestational age, term low birth weight, and reductions in birth weight, length and head circumference (Shah and Balkhair 2011; Woodruff et al. 2009). Most studies used ambient concentrations from government monitoring stations to assess exposure. European and Canadian studies focusing specifically on air pollution from motor vehicles, reported more consistent positive associations for these outcomes and exposures based on land use regression (LUR) or dispersion models than simpler proximity to roadway measures (Aguilera et al. 2009; Ballester et al. 2010; Estarlich et al, 2011; Brauer et al. 2008; Gehring et al. 2011a; Gehring et al. 2011b; Genereux et al. 2008; Malmqvist et al. 2011; Slama et al. 2007; van den Hooven et al. 2012b; Wilhelm and Ritz 2005). Ambient and personal measures of polycyclic aromatic hydrocarbons (PAHs) – fuel combustion by-products – have also been associated with reduced fetal growth (Choi et al. 2008; Dejmek et al. 2000). PAHs can be carried into the body by ultrafine particles (<0.1 μm in aerodynamic diameter), and may disturb fetal development through adverse changes in placental transport or through oxidative stress pathways (Jedrychowski et al. 2010; Sram et al. 1999).

The relatively short nine month period of fetal development provides unique opportunities to study exposures acting during narrow susceptibility windows. However, there is a lack of toxicological information to help guide selection of relevant exposure periods for most environmental toxins and fetal growth end-points. Currently there is no consensus on pregnancy periods most susceptible to air pollution impacts, although associations have been reported somewhat more consistently for first and third trimester averages (Woodruff et al. 2009). Exposures during early pregnancy may result in disruption of placental formation and function leading to growth retardation throughout gestation (Dejmek et al. 2000) while exposures during later pregnancy may interfere with the fastest period of fetal body mass accumulation (Kline and Susser 1989). Furthermore, inflammation and oxidative stress in the early of pregnancy or toward the end of pregnancy are also related to the onset of parturition. We have previously reported air pollution exposure to be associated with increased C-reactive protein concentrations (>8 μg/ml) in early pregnancy (Lee et al. 2011) and a Dutch cohort study recently confirmed these observations (van den Hooven et al. 2012a).

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Five previous European and Australian studies measured fetal growth via ultrasound to examine air pollution impacts (Aguilera et al. 2010; Hansen et al. 2008; Slama et al. 2009; van den Hooven et al. 2012b, Iñiguez et al, 2012). Here, we present the first U.S. results in a prospective birth cohort study conducted 1993-1996 in the heavily polluted region of Los Angeles, California. We used government monitoring data to assess prenatal exposures to several criteria air pollutants (carbon monoxide, CO; NO_2; ozone, O_3; PM_{10}), and also estimated prenatal exposures to nitrogen oxides as markers of traffic-related air pollutants using the CALINE4 air dispersion model (Benson 1989) and a LUR model we developed for the LA basin (Su et al. 2009).

Methods

Study Population

The Behavior in Pregnancy Study conducted at Cedars-Sinai Medical Center followed 688 ethnically and socioeconomically diverse women prospectively to assess the impact of chronic stress on preterm birth and low birth weight from 1993 to 1996 (Hobel et al. 1999). Detailed demographic data and information on maternal behaviors and medical conditions were collected three times at gestational ages: 18 to 20 weeks (mean=19.1), 28 to 30 weeks (mean=28.8), and 35 to 37 weeks (mean=36.7). Gestational age was estimated from self-reported date of last menstrual period. For about one quarter of participants, a first-trimester dating ultrasound was available and those for whom the two gestational age measures differed by more than 10 days, the date determined from the first-trimester ultrasound estimate was used as the actual gestational age. For all participants, the estimated gestational age was corroborated by ultrasound estimates at each follow-up visit. At each visit, real-time ultrasound was conducted using an ATL, HDI 3000 ultrasound machine (Philips Medical Systems, Best, the Netherlands). Measurements of the following parameters were obtained by 5 sonographers trained and supervised by an author (CH): femur length, abdominal circumference, head circumference and biparietal diameter. From among 688 pregnant women who completed a baseline screening interview, 639 gave birth to a live infant, and 578 completed one or more study visits. Eligible pregnant women were those aged 18 years or older, English- or Spanish-speaking, and less than 20 weeks pregnant with a single gestation. We also excluded women whose pregnancy ended in stillbirths (n=2), or infants with birth weights <500 grams (n=5) or gestational age >308 days (n=1), leaving 566 women and 17 women reporting illegal drug use during pregnancy (marijuana, cocaine, heroin or speed). Of those remaining, 478 (84%) completed three ultrasound visits, 66 (12%) two and 22 (4%) one visit.

Air Pollution Exposure Assessment

Air pollution exposures were based on participants' residential addresses reported at baseline and mapped using three methods: 406 (72%) were geocoded to the parcel level using the TeleAtlas Address Point database, 117 (21%) were geocoded using address interpolation via the TeleAtlas EZ Locate geocoding service, and 38 (7%) were mapped using Google Earth (equivalent to highest quality match using EZ Locate). Three addresses could only be located to a ZIP code centroid and were assigned regional air quality but not

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traffic exposures. Addresses for two subjects could not be mapped resulting in missing air pollution assignments.

Regional air quality exposure assignments—Prenatal exposures for the criteria pollutants CO, NO_2, PM_{10}, and O_3 were estimated using measurement data from the U.S. EPA's Air Quality System (http://www.epa.gov/ttn/airs/airsaqs/) and the University of Southern California's Children's Health Study conducted in 1992-1996 (Peters et al. 2004). NO_2 and O_3 data from the Children's Health Study versus the Air Quality System were used when both were available for a station because the Children's Health Study data were subjected to greater quality assurance (Alcorn and Lurmann 2004). However, Air Quality System Federal Reference Method (FRM) PM_{10} data were used instead of Children's Health Study non-FRM data when both existed for a station because the U.S. National Ambient Air Quality Standard for PM_{10} is defined in terms of FRM measured data. Data on particles <2.5 μm in aerodynamic diameter ($PM_{2.5}$) levels were unavailable for this time period from either source.

The following averages were first generated for each day if at least 75% of required hourly readings were available (see also Supplemental Table 1): 8-hour daily maximum averages for CO (ppm), 12-hour daytime (6am-6pm) averages for NO_2 (ppb), 8-hour daytime (10am-6pm) averages for O_3 (ppb) and 24-hour averages for PM_{10} (μg/m^3). The daily averages were then averaged for each woman over the following three pregnancy periods: estimated date of conception to first ultrasound date, approximately 0-19 weeks gestation (period 1); first to second ultrasound date, 19-29 weeks gestation (period 2); and second to third ultrasound date, 29-37 weeks gestation (period 3). Gaseous pollutant exposures were generated if there were valid daily averages for ≥75% of each pregnancy period. For PM_{10}, this criterion was lowered to ≥12.5% since most 24-hour measures were only available every six days.

Average pregnancy period exposures were estimated at each residence location based on inverse distance-squared weighting of values from up to the four closest monitoring stations within 50 km (31.1 mi) for NO_2, O_3 and PM_{10} and 25 km (15.5 mi) for CO. However, whenever one or more stations were located within 5 km (3.1 mi) of a residence, only these stations were used for interpolation. For consistency, interpolations for all three periods of pregnancy were based on data from the same stations. Because large offshore - onshore pollutant gradients have been shown to exist along the southern California coast (Main et al. 1991), the interpolations were carried out with pseudo-stations located ~30 km offshore and assigned the following concentrations based on long-term measurements at a clean coastal location (Lompoc, CA): 0.3 ppm CO, 4 ppb NO_2, 29 ppb O_3, and 15 μg/m^3 PM_{10}. For CO and NO_2, 17% and 18% of exposure estimates were based on stations within 5 km of residences, respectively. For O_3 and PM_{10}, 19% and 10% of exposure estimates were based on stations within 5 km of residences, and 81% and 89% within 5-25 km of residences, respectively.

CALINE4 nitrogen oxides (NO_x) exposure estimates—We used the CALINE4 line source dispersion model (Chen et al. 2009; Benson 1989) which accounts for traffic emissions, roadway characteristics and meteorological conditions, to estimate pregnancy

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period exposures to local, traffic-derived NO_x, including roadways within 5 km of subjects' residences. This approach has proven useful in studies of traffic and health effects in southern California (e.g. Gauderman et al. 2007). Traffic count data from Tele Atlas/ Geographic Data Technology (GDT) (www.teleatlas.com) were assigned to streets as explained in Supplemental Material.

Hourly surface wind speeds and directions were acquired from 20 routine, ambient air quality stations in the study region for the 1992-1996 study time period (http://www.epa.gov/ttn/airs/airsaqs/). Due to lack of adequate information for 1992-1993, estimates were based on average hourly wind direction and speed values for the period 1994-1996. Thus, the modeling reflects average, within-year seasonal fluctuations in wind direction and speed, but not year-to-year variation in these factors across 1992-1996. We assigned subgroups of residences to 14 meteorological stations with sufficiently complete hourly data (>75%) during 1994-1996 using Thiessen polygons and terrain data.

Vehicle fleet average emission factors were based on the California Air Resource Board's EMFAC2007 (version 2.3) model. Summer and winter average emission factors for vehicles in Los Angeles County in 1993, 1994, 1995, and 1996 were calculated using California Air Resource Board recommended default parameters. The emission factors for 65, 50, 35, and 30 mph were used for travel on freeways, state highways, arterials, and collectors, respectively. Diurnal and weekday/weekend volume variation profiles were based on average conditions observed at weigh-in-motion sensor locations in Southern California (Coe et al. 2004).

Land Use Regression (LUR) exposures—We extracted nitrogen monoxide (NO), NO_2, and NO_x concentration estimates at residential locations from land use regression (LUR) model surfaces we developed for the LA Basin (see Su et al. 2009). The LUR surfaces were based on two-week average Ogawa NO_2 and NO_x measures we collected in September 2006 and February 2007 at 181 locations (196 samplers in total) simultaneously throughout LA County. Final regression models explained 81%, 86% and 85%, respectively, of the variance in measured NO, NO_2 and NO_x concentrations. Cross-validation analyses suggested high prediction accuracy in the range of 87-91%. The LUR models most closely approximate annual average concentrations, and thus provide spatial but not temporal contrasts.

Statistical Methods

Fetal growth data was collected longitudinally for up to three time points per pregnancy. All models were fit using the Mixed procedure in SAS 9.2 (SAS Institute, Cary NC) using restricted maximum likelihood (REML) estimation. Missing data in the outcomes is handled automatically in a maximum likelihood framework. In particular, maximum likelihood assumes missing at random which is weaker than the missing completely at random assumption that could have been required (43 observations had at least one or more missing predictors except for pollution data; two subjects whose addresses could not be mapped, thus did not have pollution data, were omitted from the analysis).

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Times of observation were restricted to a two week window that was plus or minus one week around each desired gestational age visit time of 19, 28 and 37 weeks. We plotted data in profile plots (Weiss 2005, chapter 2) and after fitting models we plotted residual plots. Residual plots identified five subjects with later ultrasound dates and much lower fetal measurements suggesting errors in estimated conception dates. After excluding these five outliers, residual plots indicated good model fit; also, omitting unusual points (outliers) did not change our conclusions. Within each window, fetal size appeared linearly related to gestational age. Across visits, we considered a linear time trend for fetal growth but a quadratic time effect was significant for all outcomes. Thus, across visits, growth was non-linearly related to gestational age. There are several choices for parameterizing this model and after much consideration we parameterized the model in terms of the total growth from conception to the average time of the current visit. A linear adjustment was fit to the data to adjust for visit times that were early or late compared to the average visit time. Different linear adjustments were used for each visit time and each outcome.

Define $\underline{Y}_{ij}$ as the observation for subject i at visit j for $j=1, 2,$ or 3 and observed at time t_{ij}. Let $\overset{G}{t}_j$ be the average visit time for visit j and let ε_{ij} be the residual for subject i's j^{th} visit. Then the model can be written as

$$Y_{i1}=a_{1i}+a_2*(t_{i1}-\overset{G}{t}_1)+\varepsilon_{i1}, \quad (1)$$

$$Y_{i2}=b_{1i}+b_2*(t_{i2}-\overset{G}{t}_2)+\varepsilon_{i2}, \quad (2)$$

$$Y_{i3}=c_{1i}+c_2*(t_{i3}-\overset{G}{t}_3)+\varepsilon_{i3}. \quad (3)$$

Parameters a_2, b_2, and c_2 are unknown slopes that adjust for an early or late visit date compared to the average date for that visit. The unknown parameters a_{1i} are the fetal growth from conception to the average visit time at visit 1, adjusted for covariates for subject i over the period from conception to visit 1. Similarly b_{1i} is the growth from conception to the average time for visit 2 adjusted for covariates and c_{1i} is the growth from conception to the average time for visit 3 adjusted for covariates. If parameters a_{1i}, b_{1i}, and c_{1i} had not been adjusted for covariates, the subscript i could be omitted. Covariates are discussed shortly. The model for the residuals is

$$\begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \varepsilon_{i3} \end{bmatrix} \sim N_3\left(0_3, \sum\right), \quad (4)$$

where Σ is an unstructured 3×3 covariance matrix with 3 unknown variance parameters and 3 unknown covariance parameters. The unstructured (UN) covariance model (4) is more general than the random intercept (RI) model commonly used for repeated measures data and the UN model fit much better than the RI model. Similarly the UN model is more

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general than and fit better than the random intercept and slope model frequently used for growth data.

Our null hypotheses are that the given pollutant measured in period j has no effect on growth in period j. We evaluated both per unit and interquartile range (IQR) increases in air pollution exposure metrics, the latter allowing us to compare effect estimates across pollutants within a given pregnancy period.

Based on our previous studies (Ritz et al. 2007; Wilhelm and Ritz 2005) and using directed acyclical graph (DAGs) methods, the following variables were considered confounders and were included as covariates adjusting parameters a_{1i}, b_{1i}, and c_{1i} : maternal age at delivery (categorized as <20, 20-24, 25-29, 30-34, >=35), race/ethnicity (white, black, Hispanic/Asian/Other), education (less than high school grad, high school grad, some college), and previous parity (zero or more than zero). We also present results from a model additionally adjusting for: sex of the infant, mother's marital status (married, other), whether the mother smoked in the period before each ultrasound visit, maternal pre-pregnancy height, maternal pre-pregnancy weight, pregnancy weight gain (calculated based on weight measured at each ultrasound visit), payment source for prenatal care (government, private (HMO or other), self-pay), maternal infections in period before each visit, presentation (breech versus vertex or transverse), and sonographer. Time-fixed covariates only have a single value at all periods during the pregnancy (maternal age, race, education, parity, sex, marital status, pre-pregnancy weight, payment), other covariates are time-varying covariates and have values that may differ from one period to the next. Time-fixed covariates were treated as having time-fixed effects except sex which was treated as having different effects for each period. Time-varying covariates were treated as having time-varying effects, meaning different coefficients for their effects in each period. Time-varying effects that are adjustments to time period 1 are also included as adjustments to time period 2 as growth during time period 2 would have started from a smaller or larger point depending on the adjustments to period 1. Similarly time-varying adjustments from period 1 and 2 are included as adjustments to period 3. We conducted stratified analyses for ever-smoking during pregnancy, infection during pregnancy, obesity (pre-pregnancy BMI > 30) and living within 5 km of a monitoring station.

Results

Demographic characteristics for the 566 mother infant pairs included in our prospective cohort are reported in Table 1. CALINE4 exposures were strongly correlated across pregnancy periods, but only moderately correlated with the LUR exposure estimates, and weakly correlated with monitoring-based exposure estimates (Supplemental Table 2). LUR based exposures (NO, NO_2 and NO_x) were also strongly correlated with each other, but moderately correlated with measures based on monitoring data. Overall, the correlations indicate that the three methods (CALINE4, LUR, monitor-based) capture different spatial and temporal aspects of air pollution exposure, but high correlation among some of the pollutant measures across periods do not allow us to distinguish between pollutant effects in a period and the effects of a prior period's pollution on that period.

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Traffic-related air pollution, as assessed by LUR and CALINE4 modeling and by monitoring-based measures of CO and NO_2, was negatively associated with biparietal diameter growth during the first and third pregnancy periods, but estimates were most consistent across exposure models for the third pregnancy period. For each interquartile range (IQR) increase in LUR-based NO, NO_2 and NO_x exposures, we estimated a reduction in biparietal diameter of 0.22-0.31 mm in the third period (fully adjusted models: β= -0.27, 95% CI=-0.58, 0.04; β= -0.22, 95% CI=-0.54, 0.10; β= -0.31, 95% CI=-0.65, 0.003) (Table 2 and Supplemental Table 3). Similarly, for each IQR increase in CALINE4-estimated log-transformed NO_x from freeways, we estimated a 0.22 mm reduction in biparietal diameter (fully adjusted model β= -0.22, 95% CI=-0.47, 0.04) in period 3. These effect estimates were robust to adjustment for potentially confounding variables Point estimates were similar or slightly greater when excluding women who smoked at any point during pregnancy, or obese women, or women who reported infections during the period prior to exam (Table 3). For women residing within 5 km of an air monitoring station, we estimated biparietal diameter reductions of 0.91 and 1.0 mm per IQR increase in CO and NO_2 during the third pregnancy period, and again estimates did not change markedly with adjustment (Table 2), or when limiting this analysis to non-smokers, non-obese, or infection-free women (Table 3).

We did not observe consistent patterns of associations for the other pollutants ($PM_{10,}$ Ozone) or for the three growth endpoints evaluated. While the LUR measures of NO, NO_2 and NO_x in the first and third pregnancy periods were negatively associated with head circumference, the 95% CIs spanned the null value for all point estimates and were especially wide for association measures from the monitoring-based estimates for CO and NO_2 restricted to women living within a 5km radius of a station (supplemental table 4). We estimated a ~0.4 mm reduction in femur length at the third ultrasound visit per IQR increase (12.2 $\mu g/m^3$) in average PM_{10} exposure during the third pregnancy period (supplemental table 5). However, this association appeared to be strongly influenced by smoking (β= -0.70, 95% CI= -1.56, 0.15 in smokers *versus* β= -0.24, 95% CI=-0.61, 0.13 in non-smokers) or obesity (β= -0.77, 95% CI=-1.63, 0.08 in obese *versus* β= -0.17, 95% CI=-0.54, 0.21 in non-obese women).

Discussion

We estimated 0.2 to 1 mm reductions in biparietal diameter at approximately 37 weeks pregnancy for interquartile range increases in exposure to traffic-derived pollutants over pregnancy weeks 29-37, controlling for exposures in prior pregnancy periods. Point estimates were robust to adjustment for a number of confounders and similar when limiting analyses to non-smokers or non-obese women. Associations were observed for mainly localized traffic exposures, represented by LUR and CALINE4 estimates for NO, NO_2 and NO_x, as well as traffic exposures based on CO and NO_2 from government monitoring stations near homes that also captured temporal-variability.

Four previous studies outside the U.S. examined associations between air pollution exposure and fetal growth during pregnancy, but results thus far are not consistent with regard to impacts on head growth. A French study presented the strongest findings, reporting negative

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associations between traffic-related air pollution and both biparietal diameter and head circumference throughout pregnancy (Slama et al. 2009). Biparietal diameter was reduced by 0.4mm during the first trimester and by 0.6mm in the second and third trimester per natural log-increase in benzene from personal measurements taken during the 27th week of gestation, while head circumference was reduced by 1.5 mm in the second and 1.9 mm in the third trimester and at birth. Although benzene exposure in this study was based on a single, one-week measurement which assumes temporal stability, exposure misclassification is potentially lowest in this study since personal monitoring was used. The remaining studies, similar to ours, employed measures or models of outdoor exposures at homes. The largest study to date followed 7,772 pregnant women living in the Netherlands, and reported 0.12 to 0.18 mm reductions in head circumference in the third trimester per 1 μg/m^3 increase in average exposure to PM_{10} and NO_2 estimated at home addresses using temporally-adjusted air dispersion models (biparietal diameter was not evaluated) (van den Hooven et al. 2012b). A Spanish study reported that exposure to NO_2 and aromatic hydrocarbons (benzene, toluene, ethyl benzene and xylenes (BTEX)) during weeks 1-12 of gestation from temporally-adjusted LUR models reduced biparietal diameter during weeks 20-32 of gestation (-2.8, 95% CI=-6.01, 0.53 and -4.8, 95% CI=-9.12, -0.45 mean percent change in standard deviation scores for biparietal diameter growth per IQR increase in NO_2 and BTEX, respectively) (Aguilera et al. 2010). An Australian study relying on routine ultrasound measurements taken between 13–26 weeks of gestation (Hansen et al. 2008) reported a 1.02-mm reductions of head circumference associated with PM_{10} during gestational days 91–120, and a 0.68 mm reduction in biparietal diameter associated with SO_2 during gestational days 0–30, but PM_{10} includes industrial emissions and wind-blown dust in addition to traffic. Also, monitoring-based NO_2 exposures were not associated with head circumference or biparietal diameter in mid-pregnancy in this study.

Our inconclusive or null findings for measures other than biparietal diameter may be partially driven by exposure misclassification in addition to error in ultrasound measurements for other outcomes.

We observed negative associations between the first and third pregnancy period LUR exposures and head circumference, but estimates did not reach conventional statistical significance. In this study, the head circumference was assessed by a machine determined ellipse which was adjusted by the sonographer to fit image limits of the skull (i.e., an ellipse was generated by the ultrasound system, guided by limit points set by the sonographer) whereas biparietal diameter was always manually determined. When restricting analyses to measures from a single sonographer (CH, n=444, results not shown), negative associations between head circumference and LUR measures of NO, NO_2 and NO_x strengthened for the first pregnancy period (e.g. β= -1.44, 95% CI=-2.71, -0.16 for each IQR increase in NO_x). Differences in ultrasound measurement methods could also explain inconsistencies in findings across studies, however, differences in populations in terms of other risk factors such as race/ethnicity, smoking and body mass index, contributions from different emission sources, exposure model formulation, covariates included in models, timing of measurements, and magnitude of exposure misclassification are other possible explanations. Future studies should also evaluate consistency of ultrasound measures across sonographers and ultrasound instruments and obtain size measures in each trimester of pregnancy.

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Sonography related error in fetal size measurements may also at least partially explain our lack of findings for femur length and abdominal circumference. Nevertheless, we estimated 0.1-0.4 mm reductions in femur length in the first and third period of gestation per 10 ppb increase in LUR NO_x and per 10 μg/m^3 increase in ambient PM_{10}, and the latter estimate was similar in magnitude to that reported by Hansen et al. (2008), but 95% CIs for all estimates, except for PM_{10} at the end of pregnancy, spanned the null value. Also, this result appeared isolated to women who smoked, were obese, or reported infections during pregnancy. Unlike Hansen et al. (2008), we did not observe consistent associations between abdominal circumference and any of our air pollution exposure metrics.

Based on animal and epidemiologic data, and focusing mainly on the effects of particulate matter and associated metals and PAHs a number of pathways have been proposed by which exposure to traffic-related air pollution may affect fetal growth, including systemic oxidative stress and related DNA damage, pulmonary and placental inflammation, blood coagulation, endocrine disruption, and altered endothelial function and hemodynamic responses (Kannan et al. 2006). We saw somewhat stronger impacts on femur length due to air pollution from PM_{10} in women reporting infections in pregnancy, results that might suggest inflammatory pathways as an avenue for future research concerning the impacts of air pollution on fetal growth.

An extensive body of literature provides evidence that the brain, particularly regions associated with learning and memory, is a developmental target for the constituents of cigarette smoke (Mukhopadhyay et al. 2010). Biological mechanisms have mostly been explored for nicotine but not combustion-related toxics present in air pollution. There is little information on whether and how prenatal air pollution exposure and subsequent subtle alternations in head growth may impact cognitive development in childhood. Perera et al. (2006) reported prenatal exposure to PAHs to impact mental development and increase the risk of cognitive developmental delay at three years of age; further follow-up indicated associations with lower IQ at five years of age (Perera et al. 2009). Since associations between prenatal PAH exposures and measures of cognition remained after adjustment for birth weight and head circumference, effects of PAHs on mental development however did not seem to be mediated by changes in head size at birth in this study.

Negative associations between CALINE4 estimates and biparietal diameter at 37 weeks of pregnancy in our study were driven by NO_x from freeways versus other roadways within 5,000m. Similarly, freeways and truck routes were important predictors of NO, NO_2 and NO_x in our LUR models (Su et al. 2009). For example, freeway vehicle density within 11,000 m explained 47% of the model variance for NO_x. Also, compared to all other variables explored, distance to truck routes correlated most strongly with NO, NO_2 and NO_x measures (correlation coefficient = 0.57–0.67), and explained 44.2% of the model variance for NO_2. Freeways may be particularly important exposure sources due to diesel vehicles, including heavy-duty trucks, which emit more particulate matter on a fleet averaged, gram-per-vehicle mile mass basis than gasoline vehicles (Zhu et al. 2002). Ultrafine particle and NO concentrations on freeways are greater than those on non-freeway roadways in LA and increase with number of diesel trucks (Westerdahl et al. 2005).

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CALINE4 NO_x exposure estimates were highly correlated across pregnancy periods, reflecting the greater importance of spatial versus temporal variability in pollutant concentrations within 5,000m of roadway sources. The LUR estimates most closely reflect annual average exposures (Su et al. 2009) and thus provide only spatial comparisons. Nonetheless, we also observed associations between monitor-based estimates of CO and NO_2 exposures for women living within 5km of stations, suggesting that both spatially and temporally driven variability in traffic pollution may be important for fetal growth.

Our LUR spatial pollution surfaces were developed more than a decade after the fetal growth measures were obtained in this pregnancy cohort and we assumed that on average the spatial relations between high and low traffic pollution areas remained stable. If this assumption is wrong, we expect non-differential misclassification of these exposures. Since we had to rely solely on addresses at recruitment early in pregnancy to generate pollution measures, for women who moved this would have caused additional exposure misclassification mostly for the finer spatial scale LUR and CALINE4 exposures later in pregnancy and might explain why we find associations in the first pregnancy period i.e. the period which was not affected by misclassification due to moving. Also, we did not have enough information on time-activity to account for higher or lower personal exposures for women at work and away from their residences during pregnancy introducing additional potential for exposure misclassification. If women however did not move and stayed at home more often towards the very end of their pregnancies, as has previously been observed (Nethery et al. 2009), this would reduce exposure misclassification due to time-activity in the third period and possibly explain at least partially why we find stronger associations in the last pregnancy period. Because the first measurement in this study occurred at approximately 19 weeks gestation, unlike Slama et al. (2009), Aguilera et al. (2010), and van den Hooven et al. (2012b), we were unable to assess air pollution impacts on fetal growth in the first trimester. However, we were able to assess change in size from mid to the end of pregnancy (i.e. from weeks 19 to 38), when most of the constitutional variation in growth occurs (Hindmarsh et al. 2002), unlike the prior three studies where the last measures were taken at earlier gestational ages (~30-33 weeks). Racially and ethnically diverse women were intentionally selected into our study cohort, thus, this cohort was not representative of all pregnant women residing in LA County during the study time period. Rather it had a higher percentage of African Americans (42% compared to 9%), and a lower percentage of Hispanics (31% compared to 61%) compared to LA County births in 1995. Studies in New York City indicate that African Americans may be particularly susceptible to air pollution impacts on fetal growth, especially for PAHs (Choi et al. 2008). The sample size was not large enough for us to examine differences across race/ethnicity, but our results may largely reflect the influence of this possibly high-risk group. Although we adjusted for active smoking in each pregnancy period, we were unable to adjust for passive smoke exposure, a potential source of residual confounding. We evaluated a large number of models for this study, but the consistent pattern of associations we observed across the LUR, CALINE4 and monitoring-based exposures for CO and NO_2 and the robustness of effect estimates to adjustment for a range of important confounders support the conclusion that the observed associations with biparietal diameter are not solely due to chance.

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A major strength of this study was the efficient use of existing prospective data that is logistically difficult and expensive to collect in order to examine air pollution impacts on fetal growth during pregnancy. The study provided us with information on many covariates including active maternal smoking and maternal height and pre-pregnancy weight and weight gain during pregnancy to adjust for as time-dependent and independent measures. Use of multiple exposure approaches (CALINE4, LUR and ambient monitors) provided information on the importance of local and some regional air pollution and our results were consistent across the traffic-related measures.

Conclusions

Based on a prospective cohort study conducted in the mid-1990s in Los Angeles, California, we estimated reductions in biparietal diameter with increased exposure to traffic-related pollutants in late pregnancy. Our results call for additional studies in U.S. urban areas to examine air pollution impacts on fetal growth endpoints employing ultrasound measures, especially those documenting head growth, and for studying air pollution impacts on neurodevelopment in children. Future investigations may want to take advantage of multiple exposure assessment approaches to explore the importance of air pollution sources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The study has been approved by the UCLA Institutional Review Board for Human Subjects

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Highlights

- We collected multiple ultrasound measures in a prospective pregnancy cohort
- We modeled traffic-related air pollution with dispersion/land-use regression models
- Ambient government air monitors provided us with measures for CO and NO2
- Fetal biparietal diameter decreased with different traffic pollution measures
- Head size but no other fetal growth measures were affected by air pollution

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Table 1

Maternal and infant characteristics of the Behavior in Pregnancy Study prospective cohort (n=566)

	N (%)
Maternal age (years)	
<20	32 (6)
20-24	147 (26)
25-29	178 (31)
30-34	152 (27)
≥35	57 (10)
Maternal race/ethnicity	
White, non-Hispanic	124 (22)
Hispanic	173 (31)
African American	238 (42)
Asian	24 (4)
Other	7 (1)
Maternal education (years)	
<12	92 (16)
12	189 (33)
>12	285 (50)
Marital status	
Single, separated, divorced or widowed	276 (49)
Married	290(51)
Parity	
Nulliparous	220 (39)
Multiparous	346 (61)
Source of care payment	
Government assisted insurance[a]	263 (47)
Private insurance (HMO or Other)	303 (53)
Infant's sex	
Male	287 (51)
Female	279 (49)
Maternal smoking	
First pregnancy period	
Yes	102 (18)
No	463 (82)
Missing	1
Second pregnancy period	
Yes	30 (5)
No	536 (95)
Third pregnancy period	
Yes	24 (4)
No	542 (96)

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	N (%)
Maternal infections	
First pregnancy period	
Yes	222 (39)
No	343 (61)
Missing	1
Second pregnancy period	
Yes	108 (19)
No	458 (81)
Third pregnancy period	
Yes	91 (16)
No	475 (84)
Presentation	
First ultrasound	
Breech	206 (36)
Vertex/transverse/other (n=2)	360 (64)
Second ultrasound	
Breech	95 (17)
Vertex/transverse/other (n=4)	448 (79)
Missing	23 (4)
Third ultrasound	
Breech	10 (2)
Vertex/transverse/other (n=2)	468 (83)
Missing	88 (16)
	Mean (SD)[range]
Bi-parietal diameter (mm) (n=566)	
First ultrasound	44.1 [34.0-54.9]
Second ultrasound	73.3 [62.6-87.0]
Third ultrasound	89.4 [80.8-102.7]
Maternal height (m) (n=560)	1.63 (0.07)
Maternal pre-pregnancy weight (kg) (n=565)	67.4 (17.6)
Maternal pregnancy weight gain (kg)	
First pregnancy period (n=565)	11.9 (11.1)
Second pregnancy period (n=543)	10.7 (6.3)
Third pregnancy period (n=477)	8.8 (5.6)
Gestational age (weeks) (n=566)	
First ultrasound	19.1 [16.9-23.9]
Second ultrasound	28.8 [25.3-33.7]
Third ultrasound	36.7 [34.1-40.7]
Birth	39.1 (2.3)

[a] Includes 6 women reporting self-pay

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Table 2

Regression estimates (beta, 95% CI) for air pollution (per IQR increase) and growth in biparietal diameter (mm) in each pregnancy period

Exposure	IQR	Crude[a]	Model 1[b]	Model 2[c]
CALINE4 NO_x – freeways [e]				
		528, 1481 [d]	528, 1481 [d]	501, 1392 [d]
Period 1	1.4	0.04 (-0.18, 0.26)	0.08 (-0.14, 0.31)	0.03 (-0.18, 0.25)
Period 2	1.4	0.04 (-0.18, 0.26)	0.04 (-0.18, 0.26)	0.07 (-0.16, 0.29)
Period 3	1.4	-0.20 (-0.45, 0.06)	-0.19 (-0.45, 0.06)	-0.22 (-0.47, 0.04)
LUR NO_x				
		534, 1495 [d]	534, 1495 [d]	501, 1392 [d]
Period 1	12.5	-0.23 (-0.52, 0.05)	-0.11 (-0.44, 0.20)	-0.23 (-0.54, 0.08)
Period 2	12.5	0.09(-0.20, 0.38)	0.09 (-0.20, 0.38)	0.16 (-0.14, 0.46)
Period 3	12.5	-0.25 (-0.58, 0.08)	-0.25 (-0.58, 0.08)	-0.31 (-0.65, 0.003)
Monitor-based CO [f]				
		97, 259 [d]	97, 259 [d]	93, 248 [d]
Period 1	1.1	-0.40 (-0.90, 0.11)	-0.35 (-0.90, 0.19)	-0.40 (-1.00, 0.20)
Period 2	1.2	0.21 (-0.32, 0.73)	0.23 (-0.30, 0.76)	0.30(-0.23, 0.81)
Period 3	1.2	-0.79 (-1.43, -0.15)	-0.78 (-1.43, -0.14)	-0.91 (-1.56, -0.26)
Monitor-based NO2 [f]				
		102, 274 [d]	101, 274 [d]	98, 260 [d]
Period 1	11.9	-0.50 (-1.11, 0.09)	-0.40 (-1.01, 0.21)	-0.49 (-1.16, 0.17)
Period 2	13.3	0.48 (-0.10, 1.06)	0.51(-0.08, 1.10)	0.59 (0.003, 1.18)
Period 3	13.9	-0.92 (-1.58, -0.27)	-0.93 (-1.58, -0.28)	-1.00 (-1.66, -0.34)

[a] Adjusted for pregnancy period and (mean time at measurement × pregnancy period)

[b] Adjusted for [a] plus maternal age, race/ethnicity (Hispanic, Asian and other races combined), education level, and parity.

[c] Adjusted for [b] plus prenatal care payment, marital status, maternal smoking before each ultrasound visit (yes/no), maternal infections before each ultrasound visit (yes/no), maternal height, maternal pre-pregnancy weight, weight gain in each pregnancy period, presentation (breech vs. vertex/transverse), and sonographer.

[d] Number of subjects/observations in analysis.

[e] IQR for natural log-scaled values.

[f] Restricted to only those women residing within 5km of monitoring stations.

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Table 3

Regression estimates (beta, 95% CI) for traffic related air pollution (per IQR increase) and growth in biparietal diameter (mm) in the third pregnancy period (29-37 weeks gestation) for subgroups[a]

	Non-smoking women	Non-obese women	Women who reported no infections
Exposure			
CALINE4 NO_x – freeways [b]	-0.14	-0.27	-0.27
	(-0.42, 0.14)	(-0.55, 0.02)	(-0.67, 0.12)
	(417, 1170)[c]	(405, 1119)[c]	(231, 628)[c]
LUR NO_x	-0.32	-0.35	-0.31
	(-0.69, 0.04)	(-0.74, 0.05)	(-0.88, 0.26)
	(416, 1167)[c]	(405, 1119)[c]	(229, 622)[c]
Ambient CO[d]	-0.72	-0.96	-1.02
	(-1.37, -0.08)	(-1.70, -0.21)	(-1.86, -0.17)
	(81, 215)[c]	(75, 197)[c]	(40, 101)[c]
Ambient NO_2[d]	-0.80	-1.37	-0.88
	(-1.46, -0.14)	(-2.11, -0.63)	(-1.99, 0.22)
	(85, 225)[c]	(79, 206)[c]	(43, 109)[c]

[a] Adjusted for same variables as model 2 in table 2.

[b] IQR for natural log-scaled values.

[c] Number of subjects/observations in analysis.

[d] Restricted to women residing 5km of monitoring stations.