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Differences in Birth Weight Associated with the 2008 Beijing Olympic Air Pollution Reduction: Results from a Natural Experiment

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Running title: Olympic air pollution reductions and birth weight

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Abstract

Background: Previous studies have reported decreased birth weight associated with increased air pollutant concentrations during pregnancy. However, it is not clear when during pregnancy increases in air pollution are associated with the largest differences in birth weight.

Objectives: Using the natural experiment of air pollution declines during the 2008 Beijing Olympics, we evaluated whether having specific months of pregnancy (i.e. 1st…8th) during the 2008 Olympic period was associated with larger birth weights, compared with pregnancies during the same dates in 2007 or 2009.

Methods: Using n=83,672 term births to mothers residing in 4 urban districts of Beijing, we estimated the difference in birth weight associated with having individual months of pregnancy during the 2008 Olympics (8/8/08–9/24/08) compared to the same dates in 2007/2009. We also estimated the difference in birth weight associated with interquartile range (IQR) increases in mean ambient particulate matter <2.5 µm in aerodynamic diameter ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO) concentrations during each pregnancy month.

Results: Babies with their 8th month of pregnancy during the 2008 Olympics were, on average, 23g larger (95% CI: 5g, 40g) than babies having their 8th month in 2007 or 2009. IQR increases in $PM_{2.5}$ (19.8 $\mu g/m^3$), CO (0.3 ppm), SO_2 (1.8 ppb), and NO_2 (13.6 ppb) concentrations during the 8^{th} month of pregnancy were associated with 18g (-32g, -3g), 17g (95% CI: -28g, -6g), 23g (95% CI: -36g, -10g), and 34g (95% CI: -70g, 3g) decreases in birth weight, respectively. We did not see significant associations for months 1-7.

Conclusions: Short-term decreases in air pollution late in pregnancy in Beijing during the 2008 Summer Olympics, a normally heavily polluted city, were associated with higher birth weight.

Introduction

Previous studies have examined the association between exposure to air pollution at various times during pregnancy (e.g. 1^{st}, 2^{nd}, or 3^{rd} trimester, whole pregnancy) and birth weight, but have reported inconsistent findings due in part to differences in study design (time series, cohort study), study data sources (birth certificates versus hospital discharge data), exposure error related to pollution data (from central site monitors, land use regression estimates, etc.), and potential residual confounding by subject characteristics (Woodruff et al. 2009). In a meta-analysis of 14 studies, increased particulate matter <10 μm in aerodynamic diameter (PM_{10}) and PM <2.5 μm ($PM_{2.5}$) concentrations across the entire pregnancy were associated with increases in the risk of low birth weight (<2500g) and decreases in birth weight among term births (≥37 weeks gestation) (Dadvand et al. 2013). However, because these studies have not identified specific gestational age windows (e.g. early or late pregnancy) during which exposure to air pollution is consistently associated with low birth weight, understanding potential mechanisms of any pollutant effect on fetal growth has been difficult (Woodruff et al. 2009).

Within natural experiments, where an industrial employee strike, legislative mandate, or large scale sporting event resulted in decreased pollutant concentrations or changes in the air pollution composition over a city or region, investigators have reported reductions in respiratory outcomes (Friedman et al. 2001; Heinrich et al. 2000; Lee et al. 2007; Pope 1989, 1991), total and/or cause specific mortality rates (Clancy et al. 2002; Hedley et al. 2002; Pope et al. 2007), and increases in life expectancy (Tonne et al. 2008). Using data from the closure of a large steel mill in the Utah Valley for 13 months, (Pope 1989, 1991), when PM_{10} concentrations were reduced by ~43% (from 90 $\mu g/m^3$ to 51 $\mu g/m^3$)(Pope 1989), we previously reported that mothers who were already pregnant at the time of mill closure were less likely to deliver prematurely than mothers pregnant before or after the closure. Further, the strongest associations were observed for pregnancies in which the 2nd trimester occurred during the mill closure (RR=0.86; 95% CI =0.75, 0.98). However, we did not find a significant reduction in birth weight for babies born during the steel mill closure (Parker et al, 2008). Although this study took advantage of a natural experiment to examine changes in preterm birth and fetal growth, the duration of the reduction in air pollution was relatively long (~13 months), thus making investigation into the gestational age specific windows of pregnancy (e.g. 1st month or last month) when reduced air pollution might result in an improved pregnancy outcomes, difficult.

Beijing is one of the most polluted cities in the world, with annual mean concentrations of $PM_{2.5}$ exceeding 100 μg/m^3 (Zhang et al. 2010) and daily mean concentrations of $PM_{2.5}$ at times exceeding 200 μg/m^3 (Xu and Zhang 2004), with several studies documenting even higher levels on 'haze days' compared to 'non-haze' days (Sun et al. 2013; Tao et al. 2014; Zhao et al. 2013). Sources contributing to Beijing's air pollution are complex, but include local emissions from motor vehicles, residential/commercial/industrial combustion devices, and fugitive emissions, as well as long-range transport of regional pollutants and secondary formation (Wang et al 2010; Zhou et al 2010). Thus, as a condition for hosting the 2008 Olympic Games, the Chinese government agreed to temporarily and substantially improve air quality in Beijing for the Olympics and subsequent Paralympics (August 8 to September 24, 2008). These actions included implementing heightened vehicular emissions standards, restricting use of vehicles by license plate number, relocating and closing industrial facilities in Beijing and the surrounding province, and stopping construction activities (Zhang et al. 2013). We previously reported that concentrations of several pollutants ($PM_{2.5}$, nitrogen dioxide [NO_2], carbon monoxide [CO], sulfur dioxide [SO_2], sulfate, elemental carbon, organic carbon) monitored between June and

October of 2008 decreased during this Olympics/Paralympics period by 18% to 59% from Pre-Olympic levels (Rich et al. 2012; Zhang et al. 2013). In fact, daily concentrations of PM_{10}, NO_2, and SO_2 all gradually decreased in the weeks preceding the Olympics and also increased gradually in the weeks following the Olympics. Although these were general trends, large day-to-day variations in pollutant levels were observed during each of the pre-, during-, and post-Olympic periods, largely due to variations in meteorological conditions (Zhang et al, 2013).

Using birth records from mothers residing in Beijing during their pregnancy, we hypothesized that term pregnancies (i.e. 37-41 weeks gestational age) with at least one month of pregnancy during the Olympic/Paralympic period would have higher birth weights than pregnancies with those same gestational months during August 8-September 24, 2007 or August 8-September 24, 2009 (Hypothesis #1). Further, using our air pollution data from June 2 to October 30, 2008, we hypothesized that increased air pollution concentrations would be associated with decreased birth weights among term births, among pregnancies with at least one month of pregnancy (months 1-8) occurring between June 2 and October 30, 2008 (Hypothesis #2). Our first goal was to evaluate whether short periods of pregnancy during the time of lowered overall air pollution levels would be associated with increased birth weight. Our second goal evaluated whether there were specific air pollutants that were associated with these birth weight changes.

Methods

Study population and birth data. Records of Beijing births are created and maintained by the Beijing Obstetrics and Gynecology Hospital. Using this birth registry, we included all singleton live births of infants who were 28 completed weeks of gestation or greater occurring between January 1, 2007 and December 31, 2010 to mothers who resided in 1 of 4 adjacent Beijing districts (Xicheng, Haidan, Fengtai, and Chaoyang) at the time of birth (N=140,298). Gestational age was calculated as the number of complete weeks since the end of the last menstrual period. For each birth/pregnancy, we also obtained the following variables: birth weight (g), maternal age at birth (years), gestational week of 1st medical check-up during pregnancy, maternal occupation, maternal education level, pregnancy complications (gestational hypertension, pre-eclampsia, eclampsia, fetal macrosomia, fetal distress, placental abruption, threatened preterm labor, polydramnios, oligohydramnios, and premature rupture of the membranes), and whether the pregnancy resulted in a live birth or still born. Gestational hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or both, on two or more occasions at least four hours apart in normotensive women after 20 weeks gestation. Preeclampsia was defined as new-onset hypertension, in addition to new-onset proteinuria, or in the absence of proteinuria, new-onset end-organ dysfunction after 20 weeks gestation (e.g. thromobocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms). Eclampsia was defined as preeclampsia with grand mal seizures. Fetal macrosomia was defined as a birth weight >4,000 grams regardless of gestational age. Fetal distress was defined as the presence of signs or symptoms that the fetus was not well, including decreased movement felt by the mother, meconium in the amniotic fluid, a non-reassuring fetal heart rate pattern, or fetal acidosis. Placental abruption was defined as premature separation of a normally implanted placenta from the uterus after 20 weeks gestation. Threatened preterm labor was defined as documented uterine contractions without evidence of cervical change. Preterm labor was defined as documented uterine contractions associated with evidence of cervical change, with the delivery ended before 37 weeks gestation. Polyhydramnios was defined as excess amniotic fluid volume (i.e. AFV≥8cm or AFI≥25cm), whereas, oligohydramnios was defined as amniotic fluid volume less than expected for gestational age (AFV≤2cm or AFI≤5cm). Premature rupture of membranes was defined as rupture of the amniotic sac before labor began.

We then excluded births with weights more or less than 5 standard deviations above or below the mean (N=73), and those with a gestational age at birth of >41weeks (N=1575), so as to avoid errors in gestational age and birth weight. We did not have data on the infants' gender or mode of delivery (vaginal or Caesarian). After deleting 5,809 births with dates of last menstrual periods before June 19, 2006 and after March 31, 2010 to avoid fixed cohort bias (since we were studying both preterm birth and birth weight effects of air pollution)(Barnett 2011), we then excluded all preterm deliveries (N=4,937 with <37 weeks gestational age), leaving n=127,904 term births (37-41 weeks gestational age) available for analysis. This study was approved by the Research Subjects Review Board at the University of Rochester Medical Center and the Ethics Review Committee of Peking University Health Sciences Center in Beijing, China.

Air pollution and weather. First, we obtained daily PM_{10}, NO_2, and SO_2 concentrations averaged across the air pollution monitoring stations located in the same 4 Beijing districts (1258 km^2) in which our study subjects lived from August 8 to September 24 in 2007, 2008, and 2009. We then used these daily Beijing-average concentrations to describe the differences in mean pollutant concentrations observed in 2007, 2009, and 2008 during the Olympics for descriptive purposes only (Hypothesis #1).

Second, we used our previously collected air pollution and weather measurements, which included $PM_{2.5}$ and CO, (Rich et al. 2012; Zhang et al. 2013) in our Hypothesis #2 statistical analyses. Briefly, we measured hourly concentrations of fine particles ($PM_{2.5}$) using a tapered element oscillating microbalance (TEOM) from June 2, 2008 to October 30, 2008. We also measured gaseous pollutants (SO_2, NO_2, CO) during these same times using monitors that were calibrated and maintained following manufacturer's protocols (Ecotech Ltd., Australia). We measured ambient temperature and relative humidity (RH) at the same site. All the samplers and monitors were collocated on the roof top of a seven-story building in the center of the Peking University 1st Hospital campus, located in central Beijing. The 1st hospital pollutant concentrations were well correlated with the Beijing average pollutant concentrations (NO_2: r=0.84; SO_2: r=0.65; PM_{10} vs. $PM_{2.5}$ r=0.85). These pollutant and weather data were used in our statistical analyses for Hypothesis #2 described below.

Statistical analyses. Hypothesis 1: First, using the date of birth and gestational age included in the dataset, we calculated the beginning and end of each month of pregnancy. We then included only those pregnancies ending in a term birth with at least 24 days of pregnancy in a given month (i.e. either 1st, 2nd, 3rd…..8th month) occurring in the 47 days between August 8th and September 24th in 2007, 2008, or 2009. This definition ensures that any subject has at most one month of pregnancy in the Olympic period in our analysis. For simplicity of presentation, we defined the 1st month of pregnancy to begin with the 1st day after LMP. No attempt was made to correct for the date of conception. Using these n=71,803 births, we calculated descriptive statistics for subject characteristics by year. In preparation for model fitting, using all 71,803 term births, we fit a semiparametric additive model (Hastie and Tibshirani 1990) in which birth weight was modeled as a smooth function of maternal age, adjusting for indicator variables for the Olympics (i.e. 2008 vs. 2007/2009), residential district, gestational week, and maternal education level (bachelor's degree, some college or technical school, high school or less). We used both 2007 and 2009 as controls to control for confounding by time trends in birth weight and air pollution across these years. Using generalized cross validation (using the mgcv package in R) we determined that 4 degrees of freedom for the smooth on maternal age was reasonable.

Next, we fit eight separate semiparametric additive models, one for each month of pregnancy (month 1-8 only), in which birth weight was modeled as a smooth function of maternal age with 4 degrees of freedom. We then re-ran these analyses including the covariates described above. The smooth function was estimated by a smoothing spline, using the gam package in R. We used results from these models to estimate the difference in birth weight among term births (with 95% confidence interval) associated with having a specified month of pregnancy during the 2008 Olympic period, compared to having that same month of pregnancy during the same dates in 2007 or 2009.

Hypothesis 2: Starting from the n=127,904 births, we included only term births with at least one month of pregnancy (months 1-8) occurring between June 2 and October 30, 2008 (time period for which we measured the air pollutants described above), leaving n=32,506 births (83,672 observations: subjects could have multiple months of pregnancy in this time period) available for analysis. We calculated descriptive statistics for air pollutant concentrations, weather conditions, and subject characteristics for these births. We then calculated mean pollutant concentrations, temperature, and relative humidity for each gestational month for all months where at least 75% of the measured values were not missing. Again using semiparametric additive models, we regressed birth weight on the mean $PM_{2.5}$ concentration in the 1st month of pregnancy for each study subject. We also included indicator variables for gestational age (complete weeks) at delivery, residential district, maternal education (bachelor's degree, some college or technical school, high school or less), linear terms for the mean temperature and relative humidity levels during the same 1st month of pregnancy, and a smooth term for maternal age (smoothing spline with 4 degrees of freedom). We repeated this same model to estimate the difference in birth weight associated with the mean 1st month SO_2, NO_2, and CO concentration. We then repeated these analyses for the 2nd, 3rd … 8th month mean pollutant concentrations in the same manner.

Sensitivity analyses. To examine if our findings were limited to pregnancies with one or more pregnancy complications (i.e. less healthy individuals), we restricted our analyses to those without a pregnancy-related hypertensive disorder (i.e. without gestational hypertension, pre-eclampsia, or eclampsia) and then again to those without a fetal placental condition (i.e. without fetal macrosomia, fetal distress, placental abruption, threatened preterm labor, polydramnios, oligohydramnios, and premature rupture of the membranes). We did not have data on pre-existing hypertension. We than re-ran the same set of models described above. Next, for each year separately, we generated Q-Q plots of residuals from our Hypothesis #1: 8th month model described above. In these plots, residuals were sorted, and the sorted values were plotted against the expected sorted birth weight values from a normal distribution with the same mean and variance. If the model residuals have an exact normal distribution, the points would fall on the diagonal 1:1 line. We were interested in deviations from normality in the extreme values (e.g. the upper and lower tails). If deviations from normality at the upper or lower tails differed for 2008 as compared to 2007 or 2009, this would suggest differences in birth weight associated with the 2008 Olympic period were restricted to either small or large for gestational age babies. Last, we examined whether our findings were limited to pregnant women residing in only one Beijing district or only to women who were college graduates (i.e. presumably of higher socioeconomic status). We estimated the difference in birth weight associated with having a specific month of pregnancy during the 2008 Olympic period compared to the same calendar dates in 2007 or

2009, for pregnant women living in each district separately, by adding interaction terms (Fengtai*2008; Haidan*2008; Chaoyang*2008) to these models. Similarly, we estimated these same birth weight differences for women with a bachelor's degree or more, some technical school, or high school or less, separately adding interaction terms to the models (TechSchool*2008; HighSchool*2008). We used SAS version 9.32 (©SAS Institute, Inc. Cary, NC) to construct all datasets and conduct descriptive analyses, and R (version 2.15.1; R Foundation for Statistical Computing, Vienna, Austria) to perform all semiparametric additive model analyses.

Results

Hypothesis #1. Characteristics of the study subjects included in the Hypothesis #1 analyses (n= 70,787) are shown in Table 1. Across the three years (2007-2009), the distributions of maternal age, gestational age at delivery, residential district, frequency of pregnancy complications, and birth weight are similar. However, maternal education level increases slightly across the three years (percentage of mothers with bachelor's degree increases from 50.8% in 2007 to 60.6% in 2009). Daily PM_{10}, NO_2, and SO_2 concentrations were substantially lower in 2008 during the Olympics than during the same dates in 2007 or 2009 (Figure 1).

In unadjusted analyses, having the 2^{nd} month or the 8^{th} month during the 2008 Beijing Olympics, compared to the same dates in 2007 or 2009, were associated with significant 21g decrease (95% CI:-40, -2) and a 22g increase (95% CI: 5, 40) in birth weight, respectively (Table 2). After adjusting for several covariates, pregnancies for which the 2^{nd} month of gestation occurred during the 2008 Olympic period had a small, non-significantly decreased birth weight (-16 g; 95% CI: -345g, 2g) compared to pregnancies for which the 2^{nd} month of gestation occurred during the same dates in 2007 or 2009. However, pregnancies having a month of gestation other than the 2nd month during the 2008 Olympics, instead of the same dates in 2007 or 2009, were generally associated with small increases in birth weight, with the largest being a significant 23g increase (95% CI: 5g, 40g) in birth weight among those pregnancies with the 8th month during the 2008 Olympic games (Table 2).

We next evaluated whether our 8th month finding was limited to pregnancies with 1 or more complications (i.e. either a pregnancy-related hypertensive disorder or a fetal placental condition), or to small or large birth weight babies. When excluding the 2.0% (n=189) of pregnancies with a pregnancy-related hypertensive disorder and then the 12.9% (n=1204) of pregnancies with a fetal placental condition, having the 8th month of pregnancy during the 2008 Olympic period, instead of the same dates in 2007 or 2009, was still associated with significant 24 g (95% CI:7g, 42g) and 22 g (95% CI: 4g, 37g) increases in birth weight, respectively. Further, Q-Q plots revealed similar patterns of residuals in the upper and lower ends of the birth weight distribution across all three years (Figure 2). Thus, our reported increase in birth weight for pregnancies with their 8th month of pregnancy during the Olympic period (23g), compared to the same dates in 2007 or 2009 described above, does not appear to be driven by differences in the low or high end of the birth weight distribution. We observed increases in birth weight associated with having the 8th month of pregnancy during the 2008 Olympic period, compared to the same dates in 2007 and 2009, among pregnant women living in Xicheng (20g; 95% CI: -46g, 86g), Haidan (41g; 95% CI:10g, 71g), and Chaoyang (32g; 95% CI:4g, 59g) districts, but not in Fengtai (-18g; 95% CI: -57g, 19g). Last, we observed increases in birth weight associated with having the 8th month of pregnancy during the 2008 Olympic period, compared to the same dates in 2007 and 2009, for all maternal education levels (Bachelor's degree or more: 29g, 95% CI: 5, 52; Technical School: 22g, 95% CI: -9, 52; High School or less: 5g; 95% CI:-40, 50), although the largest difference was observed among those with a Bachelor's degree or more.

Hypothesis #2. Moving average monthly pollutant concentrations and weather characteristics for the period of analysis (June 2 to October 30, 2008) are shown in Table 3. Study subjects' gestational month mean $PM_{2.5}$ concentrations were highly correlated with both their SO_2 (r=0.86) and CO mean concentrations (r=0.71), but slightly negatively correlated with NO_2 concentrations (r=-0.25)(Table 4). Monthly mean NO_2 concentrations were highly inversely correlated with both temperature (r = -0.96) and relative humidity means (r = -0.70). Monthly mean $PM_{2.5}$ concentrations were moderately correlated with temperature (r=0.41), but monthly mean SO_2 and CO concentrations were not (r's≤ 0.10). Monthly mean $PM_{2.5}$, SO_2, and CO concentrations were only weakly correlated with monthly mean relative humidity levels (r's≤0.28).

IQR increases in $PM_{2.5}$, SO_2, and CO concentration in the 8th month of pregnancy were associated with significant decreases in birth weight, after adjustment for gestational age at delivery, residential district, maternal education, and mean temperature and relative humidity in the same month ($PM_{2.5}$: -18g, 95% CI: -32g, -3g; SO_2: -23g, 95% CI:-36g, -10g; CO: -17g, 95% CI: -28g, -6g; Supplemental Material, Table S1 and Figure 3). Each IQR increase in the mean NO_2 concentration in the 8th month was associated with a similarly sized, albeit non-significant, decreased birth weight (-34g; 95% CI: -72g, 3g). IQR increases in other monthly mean pollutant concentrations were generally associated with smaller decreases in birth weight, with some being essentially null (e.g. -1g to 2g). None were statistically significant (Supplemental Material, Table S1 and Figure 3). Although not statistically significant, each 13.6 ppb increase in NO_2 concentration during the 6th month was associated with a 22g increase in birth weight (95% CI: -

17, 60). However, 6th month and 8th month pollutant concentrations were inversely correlated ($PM_{2.5}$; r = -0.71 ; NO_2: r = -0.95 ; SO_2: r = -0.88; CO: r = -0.70), likely due to one being during the Olympic period and its lower air pollutant concentrations.

Discussion

We took advantage of the natural experiment that occurred during the 2008 Beijing Summer Olympics, where the Chinese government successfully reduced and restricted air pollution emissions in Beijing and the surrounding province resulting in 20-60% reductions in most pollutants (Rich et al. 2012; Zhang et al. 2013). We examined whether babies born to mothers residing in Beijing during this time had babies with larger birth weights, and whether certain air pollutant concentration reductions were associated with this response. We found that if the 8th month of pregnancy was during the 2008 Olympics, the mean birth weight among infants born at term was 23g larger than those pregnancies with their 8th month during the same dates in 2007 or 2009. This association was independent of maternal age and education, residential district in Beijing, gestational age, and pregnancy-related hypertensive and fetal/placental pregnancy complications. Further, this difference was not limited to women living in just one Beijing district, and was seen in women of all education levels, although the increase in birth weight was largest among women with a Bachelor's degree or more. Similarly, using air pollution measurements made in the center of Beijing from a longer time period, interquartile range increases in $PM_{2.5}$ (19.8 $\mu g/m^3$), SO_2 (1.8 ppb), NO_2 (13.6 ppb), and CO (0.3 ppm) concentrations during the 8th month of pregnancy were associated with 18g (95% CI: -32, 3), -23g (95% CI: -36, -10), -34g (95% CI: -72, 3), and -17g (95% CI: -28, -6) decreases in birth weight among term births, respectively. We found no such evidence of consistent associations across our hypothesis #1 and #2 analyses for pollution exposure during months 1 to 7. These complimentary analyses provide evidence that decreases in ambient air pollution levels during the 2008 Summer Olympics and Paralympics, during the 8^{th} month of pregnancy, had a beneficial impact on pregnancies, specifically on birth weight.

These findings are consistent with Wang et al (1997), who reported 10% (95% CI = 5%, 14%) and 11% (95% CI = 6%, 16%) increases in the risk of low birth weight associated with 100 $\mu g/m^3$ increases in total suspended particulate and SO_2 concentrations across the entire pregnancy, respectively, among pregnant women living in some of the same Beijing districts as those in our analysis (Wang et al. 1997). In a meta-analysis of 14 existing studies done around the world, both increased PM_{10} and $PM_{2.5}$ concentrations during the entire pregnancy were associated with an increased risk of low birth weight, with a 10 $\mu g/m^3$ increase in PM_{10} concentration associated with a 8.9g (95% CI: -13.2, -4.6) decrease in birth weight (Dadvand et al. 2013). Our findings, rescaled to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ during the 8th month of pregnancy (-9g; 95% CI = -32, -3) for comparison, are also consistent with another meta-analyses (some of the same studies), which reported that 20 $\mu g/m^3$ increases in mean PM_{10} concentration and 10 $\mu g/m^3$ increases in mean $PM_{2.5}$ concentrations during the entire pregnancy, were associated with -16.8g (95% CI = -20.2, -13.3) and -23.4g (95% CI = -45.5, -1.4) decreases in birth weight, respectively (Stieb et al, 2012). Our findings, although for only the 8^{th} month of pregnancy and not the entire pregnancy, are consistent with these meta-analyses.

Our finding of greater birth weight associated with lower air pollution levels during the natural experiment of the Beijing Olympics is consistent with recent work by Fleischer et al (2014), who reported that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations in the last month of pregnancy was associated with a significant 7% increase (95% CI = 1%, 14%) in the risk of a low birth weight baby among term births in China (Fleischer et al. 2014). Similarly, our findings are consistent with Pedersen et al (2013) who reported that each 5 μg/m^3 increase in $PM_{2.5}$ concentration, and each 10 μg/m^3 increase in PM_{10} concentration during pregnancy were associated with increased risks of low birth weight at term (PM_{10}: OR=1.18, 95% CI = 1.06, 1.33; $PM_{2.5}$: OR = 1.16, 95% CI = 1.00, 1.35). However, our findings are inconsistent with those of Parker et al. (2008) who reported no beneficial increase in birth weight associated with a Utah Valley steel mill employee strike from August 1986 to September 1987 (Parker et al. 2008). In studies examining individual trimesters during pregnancy, our findings are consistent with those reporting birth weight associations with increased air pollutant concentrations in the 3rd trimester, but not those reporting associations with 1st and 2nd trimester pollutant exposures (Woodruff et al. 2009).

Potential mechanistic explanations. Our finding of increased birth weight associated with decreased pollutant concentrations in the 8th month of pregnancy, may suggest potential mechanisms acting during that time of pregnancy, including those mechanisms that affect maternal, placental, or fetal health. Maternal factors associated with poorer fetal growth include maternal hypertension and cardiopulmonary disease. Though exposure to air pollution in pregnancy has been associated with an increased risk of hypertensive disorders later in pregnancy (Hampel et al. 2011; van den Hooven et al. 2011; Wu et al. 2009), we found similar estimates of birth weight differences associated with having the 8th month of pregnancy during the 2008 Olympics compared to the same dates in 2007 or 2009, for pregnancies with and without hypertensive complications or with and without fetal/placental complications. This suggests that late pregnancy pollutant effects on fetal growth may not be mediated primarily by these complications.

Evidence from observational studies suggests that exposure to PM may affect the human placenta during pregnancy. van den Hooven et al reported that increased ambient PM_{10} and NO_2 concentrations during pregnancy were associated with higher levels of soluble fms-like tyrosine kinase and lower levels of placental growth factor (anti-angiogenic effects), as well as an increased risk of placental notching during the 3rd trimester (abnormality on ultrasound; marker of blood flow resistance)(van den Hooven et al. 2012b). Janssen et al reported that increased PM_{10} concentrations during the last month of pregnancy were associated with decreased placental mitochondrial DNA content, which have been associated with increased oxidative stress and inflammation (Janssen et al. 2012). Increased maternal C-reactive protein levels have also been associated with increased pollutants concentrations during pregnancy (van den Hooven et al. 2012a). Exposure to air pollution during the 7 days before delivery was associated with lower IL-10 (an anti-inflammatory cytokine) measured in cord blood, and during the three months leading up to delivery with higher levels of the inflammatory mediator IL-1beta also measured in cord blood (Latzin et al. 2011). Further, in a panel of healthy young men and non-pregnant women living in Beijing before, during, and after the 2008 Summer Olympics, we reported large decreases (-13% to -34%) in markers of oxidative stress, inflammation, and thrombosis during the Olympics when air pollutant concentrations were decreased substantially (-135 to -60%) compared to pre-Olympic levels (Gong et al. 2013; Rich et al. 2012; Zhang et al. 2013). However, whether PM exposure leading to changes in mitochondrial DNA content, inflammation, and oxidative stress in the last month of pregnancy affects placental function and then fetal growth has not yet been studied.

Strengths and limitations. Our study had several strengths including the use of a natural experiment design with its better control of confounding than purely observational designs

(Dominici and Mittleman 2012), large sample size, and available air pollutant monitoring data. For the first time, we were able to demonstrate in complimentary analyses in the same study that a gestational month (8^{th} month) when pollutant concentrations were decreased was associated with increased birth weight, and increased pollutant concentrations during the same 8^{th} gestational month was associated with decreased birth weight. Isolation of such a short duration time window during pregnancy (i.e. 47 days) where air pollutant concentrations changed substantially and then returned to background levels, to study whether that was associated with a measurable difference in birth weight, has not been possible in previous epidemiologic studies. Previous studies have generally been limited to studying whether trimester specific mean pollutant concentrations were associated with markers of reduced fetal growth (Dadvand et al. 2013; Rich et al. 2009; Woodruff et al. 2009).

However, there are several limitations that should be considered when making inference from these results. First, for our air pollution analyses, we used ambient $PM_{2.5}$, NO_2, SO_2, and CO concentrations, measured at one central site monitoring location, to represent each pregnancy's gestational monthly air pollution exposure, regardless of how close the pregnant woman lived, worked, or was near the monitoring site, resulting in exposure error. However, on average, this error is likely a combination of Berkson and classical error (Bateson et al. 2007; Zeger et al. 2000), with any classical error likely resulting in a bias towards the null and underestimates of effect.

Second, although we measured multiple particle ions and species, gases, polycyclic aromatic hydrocarbons, and elemental composition of particles in our previous study (Rich et al. 2012; Zhang et al. 2013), we did not measure these pollutants every day during the study period, resulting in limited variability in monthly mean concentrations in many of them (e.g. benzo(a)pyrene, total PAHs, etc.)(Zhang et al. 2013). Further, given the drastic pollutant concentration decrease at the beginning of the Olympic period and the increase after the Olympics (Rich et al. 2012; Zhang et al. 2013), these pollutants were all highly correlated during the study period, making assessments of health effects associated with individual pollutants and/or pollutant sources difficult.

This estimated increase in birth weight associated with having the 8th month of pregnancy during the 2008 Olympic period, compared to the same dates in 2007 and 2009, could be due to residual confounding by socioeconomic status. If women of lower socioeconomic status (e.g. lower level of maternal education), who are also at higher risk of adverse pregnancy outcomes (e.g. low birth weight, preterm birth) moved out of the study area during the 2008 Olympics, than this could explain the estimated increase in birth weight associated with the 2008 Olympics. However, we do not feel this was the case, as women in 2008 had a larger proportion with a bachelor's degree (54.7%) than women in 2007 (50.8%). Residual confounding by other factors such as maternal stress and noise associated with living near the Olympic venues or Olympic traffic could also affect the estimated birth weight difference.

We did not have data on several potential confounders including parity, pre-pregnancy body mass index, smoking, attendance at pre-natal care visits, and race/ethnicity. However, China's Family Planning Policy (also known as the One-Child Policy) enacted in 1979, restricted the number of children married couples in Beijing could have during the study period to one, with exceptions for those living in rural areas, ethnic minorities, and for couples where each partner had no siblings. Therefore, one can assume almost all of the pregnancies included in this study are the first child for each pregnant woman. Second, smoking rates in women living in Chinese cities are generally low. A recent letter reported that in 2010, an estimated 28.1% of adults in China (52.9% of men and 2.4% of women) were current smokers, and that the prevalence was significantly higher among rural residents than urban inhabitants (Li et al, 2011), such as those in our study. We did not have data on 2nd hand smoke exposure of women in our study. However, our hypothesis #1 analyses, a temporal analysis comparing the birth weight of pregnancies in 2008 to pregnancies in 2007 and 2009, are unlikely to be confounded by this unless there are substantial differences in 2nd hand smoke exposure for pregnant women in 2008 versus 2007 and 2009. Third, in Beijing during the study period there was little variability in race/ethnicity with the vast majority being Han Chinese. Last, gestational age was defined using the date of the last day of the last menstrual period, rather than an ultrasound during pregnancy, resulting in some error. Therefore, this could result in residual confounding by gestational age in our analyses.

This 47 day reduction in ambient air pollutant concentrations during the Beijing Olympics and Paralympics may be too short of a time period for beneficial reproductive health effects to be observed if this air pollution reduction occurred early in pregnancy. For example, for pregnancies with their 1st, 2nd, or 3rd months of pregnancy during the Olympics, it is possible that any beneficial fetal growth effect of an Olympic air pollution reduction during these times was then masked by adverse fetal growth effects of air pollution increases in months 4 to 9 when air pollution returned to the normally elevated levels after the Olympics. Our estimate of a 23g bigger baby associated with having the 8th month of pregnancy during the Olympic period is a small increase relative to the median birth weight in our study population (<1%). However, this size increase in birth weight may have been larger if the air pollutant concentration reductions lasted for several months or lasted the entire pregnancy.

We did not have residential addresses during pregnancy, only the residential district at the time of delivery. However, air pollution reductions were observed across Beijing, and as long as subjects remained in Beijing, the substantially lower air pollutant concentrations in the summer of 2008 compared to 2007 and 2009 would be comparable proxies for subjects' ambient air pollution exposures during these time periods. Since we did not have district specific air pollutant measurements, we could also not assess whether pollutant/birth weight associations were different for each district.

Last, China's Family Planning Policy which restricted the number of children married couples in Beijing could have during the study period to one, with few exceptions. This likely resulted in healthier pregnancies in this Beijing study population compared to the U.S. population (e.g. less pregnancy complications, fewer preterm births, less small for gestational age babies, etc.), as evidence by the lower preterm birth rate in Beijing in 2008 (3.3%) compared to the United States in 2008 (12.3%)(Are preterm births on the decline in the United States? Recent data from the national vital statistics system, [Martin et al. 2010]) and 2012 (11.5%)(Preliminary data for 2012, [Hamilton et al. 2013]). Therefore, this may limit the generalizability of our findings to generally healthy pregnancies.

In summary, reductions in late pregnancy ambient air pollution exposures were associated with increased birth weights among pregnant women living in Beijing during the 2008 Summer Olympics. However, the associations of birth weight with $PM_{2.5}$, SO_2, and CO concentrations we report should not be interpreted as those pollutants being the individual pollutants associated with any health effects. Rather, the entire air pollutant mixture or specific components correlated with $PM_{2.5}$, SO_2, NO_2, and CO concentrations in Beijing during this time may be responsible for these estimated improvements in birth weight late in pregnancy. Further work should replicate this finding, examine potential mechanistic explanations, and study health effects of specific pollutant mixtures (e.g. traffic pollution, secondary organic aerosols, etc.).

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Table 1. Study subject characteristics by year. N (%) or mean ± SD unless otherwise indicated.

Characteristic	**Control Period 2007 N=21,227**	**Olympic Period 2008 N=23,361**	**Control Period 2009 N=26,201**
Maternal Age			
<24	771 (3.6)	918 (3.9)	874 (3.3)
24-26	4140 (19.5)	3857 (16.5)	3560 (13.6)
27-29	7436 (35.0)	8211 (35.1)	9684 (37.0)
30-32	5186 (24.4)	6207 (26.6)	7456 (28.5)
33-35	2535 (11.9)	2752 (11.8)	2906 (11.1)
>35	1159 (5.5)	1416 (6.1)	1721 (6.6)
Mean ± SD	29.2± 3.6	29.3 ± 3.6	29.5 ± 3.6
Maternal Education			
Bachelor	10,793 (50.8)	12,768 (54.7)	15,886 (60.6)
Some College or Technical School	3250 (15.3)	3501 (15.0)	3305 (12.6)
High school or less	7184 (33.8)	7092 (30.4)	7010 (26.8)
Residential District			
Chaoyang	7971 (38)	9399 (40)	11,111 (42)
Fentai	4732 (22)	4959 (21)	5651 (22)
Haidian	6852 (32)	7537 (32)	7845 (30)
Xicheng	1672 (8)	1466 (6)	1594 (6)
Pregnancy Complications			
PREGNANCY-RELATED HYPERTENSIVE DISORDERS	156 (0.7)	236 (1.0)	291 (1.1)
Gestational Hypertension	93 (0.4)	143 (0.6)	188 (0.7)
Preeclampsia	59 (0.3)	88 (0.4)	101 (0.5)
Eclampsia	4 (0.0)	5 (0.0)	2 (0.0)
FETAL-PLACENTAL CONDITIONS	2458 (11.6)	2736 (11.7)	3129 (11.9)
Fetal Macrosomia	1413 (6.7)	1533 (6.6)	1772 (6.8)
Fetal Distress	511 (2.4)	613 (2.6)	648 (2.5)
Placental Abruption	13 (0.1)	24 (0.1)	28 (0.1)
Threatened Preterm Labor	30 (0.1)	15 (0.1)	16 (0.1)
Polyhydramnios	22 (0.1)	20 (0.1)	42 (0.2)
Oligohydramnios	215 (1.0)	221 (0.9)	294 (1.1)
Premature Rupture of Membranes	400 (1.9)	457 (2.0)	527 (2.0)
Gestational Age			
37	1313 (6)	1598 (7)	1660 (6)
38	4247 (20)	4921 (21)	5327 (20)

Characteristic	**Control Period 2007 N=21,227**	**Olympic Period 2008 N=23,361**	**Control Period 2009 N=26,201**
39	6838 (32)	7553 (32)	8478 (32)
40	6141 (29)	6560 (28)	7543 (29)
41	2688 (13)	2729 (12)	3193 (12)
Mean ± SD	39.3 ± 1.1	39.2 ± 1.1	39.2 ± 1.1
Birth weight			
Mean ± SD	3417g±414g	3414g±419g	3415g±410g
Minimum	1290g	1500g	930g
5th percentile	2770g	2750g	2760g
10th percentile	2900g	2900g	2900g
25th percentile	3145g	3130g	3150g
50th percentile	3400g	3400g	3400g
75th percentile	3690g	3685g	3680g
90th percentile	3950g	3950g	3950g
95th percentile	4100g	4120g	4100g
Maximum	5250g	5800g	5860g

Table 2. Difference in birth weight associated with a month of pregnancy during 2008 (August 8 – September 24, 2008), compared to same dates in 2007 or 2009.

		UNADJUSTED ANALSYES		ADJUSTED ANALYSES	
Month of pregnancy[a]	**N**	**Difference in birth weight (g) (95% Confidence Interval)**	**p-value**	**Difference in birth weight (g) (95% Confidence Interval)[b]**	**p-value**
1	8,969	2 (-16, 20)	0.81	4 (-13, 21)	0.62
2	8,305	-21 (-40, -2)	0.03	-16 (-35, 2)	0.08
3	8,191	-11 (-31, 9)	0.29	4 (-15, 24)	0.68
4	8,864	-14 (-32, 4)	0.13	-4 (-22, 14)	0.64
5	9,065	2 (-16, 20)	0.86	3 (-15, 21)	0.74
6	9,294	0 (-17, 18)	0.96	5 (-12, 22)	0.57
7	9,808	0 (-17, 17)	0.99	5 (-12, 22)	0.54
8	9,307	22 (5, 40)	0.01	23 (5, 40)	0.01

[a]We defined the 1st month of pregnancy to begin with the 1st day after the last menstrual period (LMP). [b]All models included indicator variables for gestational age (complete weeks) at delivery, residential district, maternal education (bachelor's degree, some college or technical school, high school or less), and a smooth term for maternal age (smoothing spline with 4 degrees of freedom).

Table 3. Descriptive statistics of mean ambient air pollutant concentrations and weather characteristics in Beijing, China, at 1st Hospital.

Pollutant/Weather Characteristic	N	Mean	Standard Deviation	Minimum	5th %tile	25th %tile	50th %tile	75th %tile	95th %tile	Maximum
Monthly Averages[a]										
Temperature (°C)	11,770	24.9	3.8	16.8	17.4	22.1	25.9	27.8	29.1	29.6
Relative Humidity (%)	11,770	62.4	5.0	47.7	52.1	61.1	63.3	64.9	68.3	69.8
$PM_{2.5}$ ($\mu g/m^3$)	10,771	61.3	11.1	43.7	46.4	51.5	59.8	71.3	77. 8	85.1
Sulfur dioxide (ppb)	8,961	5.9	1.2	3.7	4.0	5.1	5.7	6. 9	7.5	8.2
Nitrogen dioxide (ppb)	11,770	24.3	8.5	12.6	13.0	16. 6	24.0	30.2	39.4	41. 6
Carbon monoxide (ppm)	11,770	0.8	0.2	0. 6	0.6	0.6	0.7	0.9	1.1	1.3

NOTE: June 2, 2008 to October 30, 2008; n=11,770 possible subjects with monthly averages; ppb=parts per billion; Ppm=parts per million.

[a]Monthly averages used in 8th month analyses of Hypothesis #2.

Table 4. Pearson correlation coefficients for study subject's 8th month mean pollutant concentrations and weather parameters.

Variable	Temperature	Relative Humidity	$PM_{2.5}$	Sulfur Dioxide	Nitrogen Dioxide	Carbon Monoxide
Temperature	---					
Relative Humidity	0.85	---				
$PM_{2.5}$	0.41	0.28	---			
Sulfur dioxide	0.10	0.15	0.86	---		
Nitrogen dioxide	-0.96	-0.70	-0.25	0.13	---	
Carbon monoxide	0.02	0.23	0.71	0.89	0.20	---

Figure Legend

Figure 1. Distributions of daily mean PM_{10}, NO_2, and SO_2 concentrations across Beijing from August 8 to September 24, 2007, 2008, and 2009.Boxes extend from the 25th to the 75th percentile, horizontal bars represent the median, whiskers indicate the 5th and 95th percentiles, squares indicate the mean, and outliers are represented as circles.

Figure 2. Plots of sorted birth weight residuals for births with the 8^{th} month of pregnancy from August 8 to September 24 versus sorted expected values from a normal distribution with the same mean and variance (Q-Q plots) in: a. 2007, b. 2008, or c. 2009

Figure 3. Change in birth weight (g; and 95% confidence interval), among term births, associated with each interquartile range increase in mean pollutant concentration during a specified month of pregnancy (June 2, 2008 to October 30, 2008). All models included indicator variables for gestational age (complete weeks) at delivery, residential district, maternal education (bachelor's degree, some college or technical school, high school or less), linear terms for the mean temperature and relative humidity levels during the 8th month of pregnancy, and a smooth term for maternal age (smoothing spline with 4 degrees of freedom).

Figure 1.

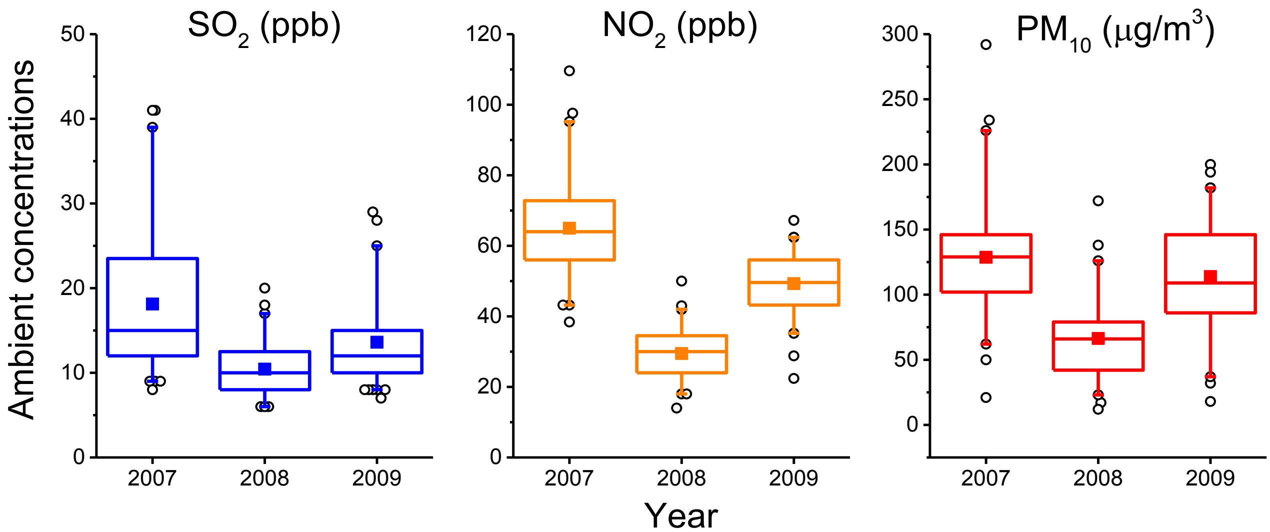
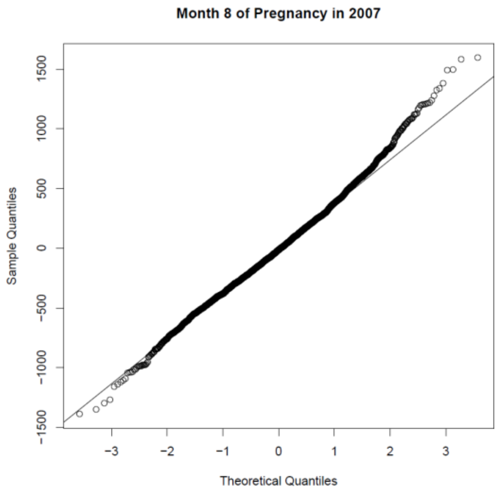
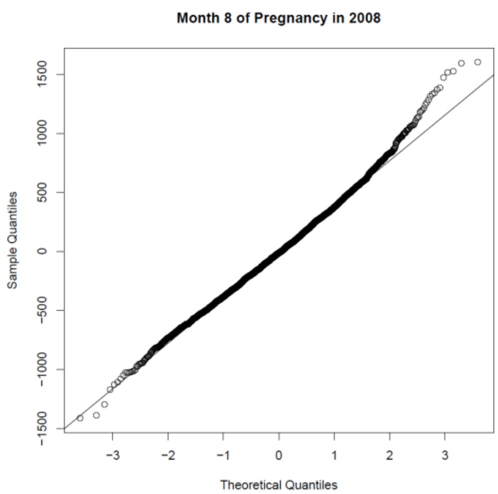

SO_2 (ppb)
NO_2 (ppb)
PM_{10} (μg/m^3)
Ambient concentrations
Year
2007
2008
2009
0
10
20
30
40
50
0
20
40
60
80
100
120
0
50
100
150
200
250
300

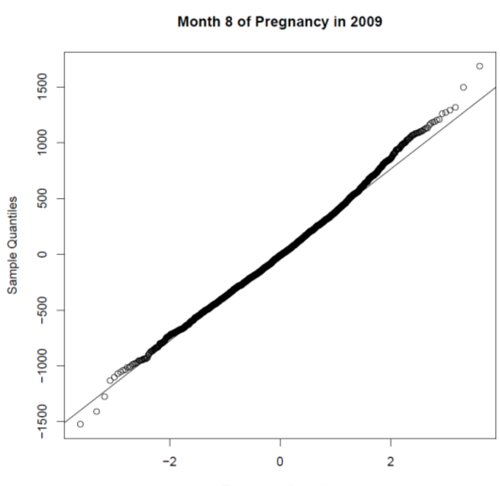
Figure 2.



a. 2007

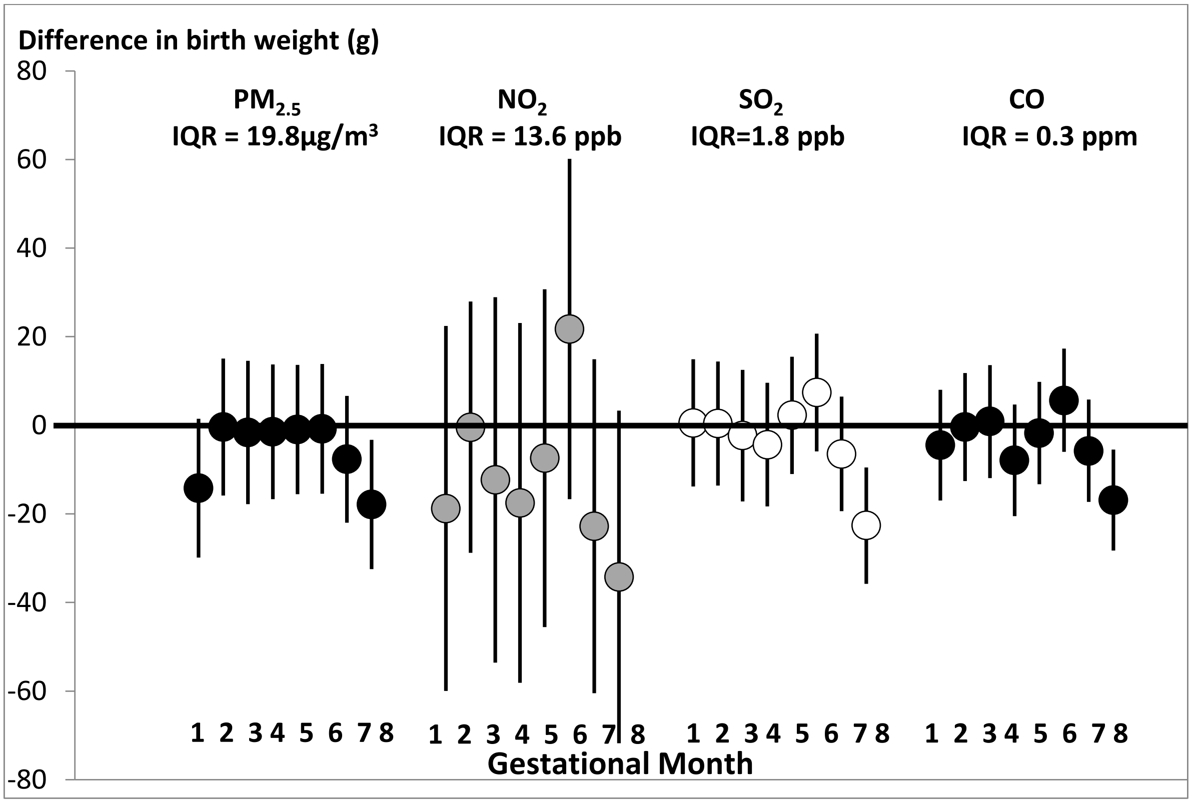


b. 2008



c. 2009

Figure 3.


Difference in birth weight (g)
80
60
40
20
0
-20
-40
-60
-80
PM2.5
IQR = 19.8µg/m3
NO2
IQR = 13.6 ppb
SO2
IQR=1.8 ppb
CO
IQR = 0.3 ppm
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
Gestational Month