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The Role Of Folate In The Association Between Perinatal Air Pollution Exposure And Birth Outcomes In Lanzhou, China

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Abstract

Background: China's rapid economic and industrial development over the past few decades has been accompanied by tremendous increases in air pollutant emissions and come at a serious cost to the environment and public health. Recent research has revealed an increased risk of adverse birth outcomes associated with perinatal air pollution exposure. Although the mechanisms by which air pollutants contribute to adverse birth outcomes have not yet been established, folate intake has been shown to counteract several of the hypothesized biological pathways.

Hypothesis: Dietary folate intake and folic acid supplementation modify the association between perinatal air pollution exposure (PM_{10}, NO_2, SO_2) and risk of preterm birth and low birth weight.

Methods: A hospital-based cohort study in Lanzhou, China was conducted between 2010-2012. Demographic information and dietary intake during pregnancy were collected during an in-person interview near the time of delivery, and pregnancy outcomes and complications were abstracted from medical records. All 8,969 participants' air pollutant exposures throughout pregnancy were calculated utilizing daily PM_{10}, NO_2, and SO_2 levels from local air monitoring stations and inverse-distance weighting based on both residential and work addresses. Unconditional logistic regression modeling was used to examine the association between perinatal air pollution exposure and adverse birth outcomes and the role of folate as a potential effect modifier.

Results: Mothers exposed to PM_{10} and SO_2 levels above the Chinese NAAQS were at a higher unadjusted risk of adverse birth outcomes than mothers with exposure levels under the standards. Both folate supplementation and high dietary folate intake during pregnancy were significantly protective against both preterm birth and low birth weight without adjustment. Compared to women with air pollutant exposures below the China NAAQS who took folic acid supplements, mothers who did not supplement and had average PM_{10} and SO_2 exposures during pregnancy above the NAAQS were at the highest risk of preterm birth and low birth weight. Women who supplemented with folic acid and were exposed to pollution above the NAAQS had the next highest observed risk, followed by women whose exposures were below the NAAQS but did not supplement.

Similar results were observed for dietary folate intake. Mothers with low dietary folate intake and average PM_{10} and SO_2 exposures above the China NAAQS were at the highest risk of both preterm birth and low birth weight, followed by mothers over the NAAQS with high dietary folate intake, and mothers under the NAAQS with low dietary folate intake. These trends were not observed for NO_2. There was no significant interaction between folic acid supplementation or dietary folate intake and any of the air pollutant exposure variables in any of the models.

Conclusion: Our findings support the hypothesis that perinatal exposure to PM_{10} and SO_2 increases the risk of low birth weight and preterm birth. The highest observed risks of adverse birth outcomes were among women highly exposed to PM_{10} and SO_2 with low dietary folate intake and who did not take folic acid supplements. These findings have important public health implications, as birth outcomes like birth weight and gestational age may be indicative of health outcomes later in life, and are relevant for future air pollution policies and standards as well as maternal nutrition recommendations.

Introduction

China has undergone rapid economic and industrial development over the past few decades, but this economic growth has been accompanied by tremendous increases in air pollutant emissions and come at a serious cost to the environment and public health (Chan & Yao, 2008; Matus, 2012). Energy consumption in China has increased annually at a rate as high as 10% and is the leading source of anthropogenic air pollution emissions (Wang & Hao, 2012). China's coal-dominated energy structure combined with increased urbanization and traffic emissions have produced some of the heaviest air pollution in the world (Chan & Yao, 2008; Wang & Hao, 2012). It is estimated that 3.7 million premature deaths worldwide are caused by ambient air pollution (WHO, 2014a), which is why the World Health Organization has declared air pollution as the world's largest environmental health risk (WHO, 2016). Western Pacific countries, and China in

particular, bear a disproportionately high burden with 1.67 million air pollution-related deaths annually (GBD, 2010; WHO, 2014b).

Anthropogenic emissions consist of many types of air pollutants, including particulate matter, nitrogen dioxide, and sulfur dioxide, all of which pose potential health risks to humans. Particulate matter easily passes from the lungs to the blood and is not readily phagocytized because of its size (Ritz, 2007). Once particulates enter circulation they induce oxidative inflammation of the lungs, placenta, and other organs (Liu, 2003; Kannan, 2006) and can lead to altered trophoblast formation and incorrect vascularization of the placenta (Roberts, 1991). Nitrogen dioxide (NO_2) has also been found to induce inflammation of the airways, reduce lung function, and repress the body's natural antioxidant defense systems (Tabacova, 1998; WHO, 2014a). As with other air pollutants, sulfur dioxide (SO_2) has been found to transfer easily into the bloodstream and lead to impaired lung function, inflammation, and developmental toxicity (Balchum, 1960; WHO, 2014a; Singh, 1988).

Although previous research has produced strong evidence linking air pollution exposure to cardiovascular disease, respiratory illness, and cancer (Anderson, 2012; Kan, 2012; Matus, 2012; Hoek, 2013; WHO, 2014a; WHO, 2014b; Wu, 2014; Fajersztajn, 2013), recent evidence has revealed an increased risk of adverse birth outcomes (Shah, 2011). Increased risk of low birth weight has been associated with elevated exposures to particulate matter, sulfur dioxide, and nitrogen dioxide during pregnancy. (Xu, 1995; Ha, 2001; Lee, 2003; Gouvenia, 2004; Huynh, 2006; Bell 2007; Wang & Pinkerton, 2007; Morello-Frosch, 2010; Seo, 2010; Dadvand, 2013). Studies have also linked exposure to these air pollutants with increased risk of preterm birth (Xu, 1995; Bobak, 2000; Liu, 2003; Wilhelm & Ritz 2003; Sagiv, 2005; Kannan, 2006; Ritz, 2007). Although the biological pathways through which these effects occur are not yet clear impaired

DNA methylation, oxidative stress, systemic inflammation, blood coagulation, impaired endothelial function, and hemodynamic responses have all been cited as potential mechanisms for these associations (Kannan, 2006; Breton, 2012).

Because maternal nutrition also plays a key role in the same hypothesized pathways between air pollution exposure and adverse birth outcomes, exploring nutrient intake as an effect modifier may be one way to approach this issue (Dejmek, 1999; Hennig, 2005; Šrám, 2005b; Kannan, 2006; WHO, 2006). To our knowledge, no previous studies on perinatal air pollution exposure and birth outcomes have examined effect modification by nutrition. Dietary nutrients and other bioactive compounds are believed to have the capacity to either magnify or buffer the toxic effects associated with other environmental pollutants (Hennig, 2005; Kannan, 2006). Folate is well-recognized for reducing the risk of neural tube defects, heart defects, and craniofacial malformations, which is why many countries recommend folic acid supplementation during the periconceptional period (Czeizel & Dudas, 1992; Locksmith & Duff, 1998; Berry, 1999; Loffredo, 2001; Wald, 2001; Prescott, 2002; WHO, 2006; Blom, 2009). Additionally, folate deficiency is associated with increased risk of preterm birth (Baumslag, 1970), and periconceptional folic acid supplementation has been shown to reduce the risk of low birth weight, preterm birth, and small for gestational age (Baumslag, 1970; Christian, 2003; Steegers-Theunissen, 2009; Timmermans, 2009).

Although the mechanisms by which air pollutants contribute to adverse birth outcomes have not yet been established, folate intake has been shown to counteract several of the hypothesized biological pathways (Kannan, 2006). For instance, folate displays antioxidant properties that may reduce the impact of air pollution-induced oxidative stress (Kannan, 2006). Folate is an essential nutrient for DNA methylation and greatly influences DNA stability, repair,

and gene expression process, which may in turn modify alterations in oxidative stress caused by maternal air pollution exposure (Kannan, 2006; Timmermans, 2009). Deficiencies in methylation-related nutrients also result in elevated homocysteine, which can influence vascular coagulation, another proposed pathway between air pollution and birth outcomes (McCully, 1993; Kannan, 2006). Although less extensively studied, maternal air pollution exposure is hypothesized to trigger endothelial dysfunction (Otsuka, 2001), a condition which folic acid intake has been shown to improve (Cuevas, 2004).

We conducted a birth cohort study in Lanzhou, China to further investigate the impact of perinatal air pollution exposure on maternal and child health in a high air pollution setting. Lanzhou is situated in a valley basin in northwest China, and as a result of its geography and booming petrochemical, metallurgical, and mechanical industries has become one of the most heavily polluted cities in China (Tao, 2014; Zhang, 2014). We analyzed data from the Lanzhou birth cohort study to investigate the association between perinatal air pollution exposure and adverse birth outcomes and the role of folate as a potential effect modifier.

Methods

Study Population

The Lanzhou birth cohort study was conducted at the Gansu Provincial Maternity and Child Care Hospital, the largest maternity and child care hospital in Lanzhou, China. Pregnant women who came to the hospital from 2010-2012 for delivery with gestational age ≥20 weeks, no history of mental illness, and at least 18 years of age were eligible for enrollment. All eligible women were notified of the study upon arrival at the hospital for delivery. Of the 14,535 pregnant women who came to the hospital for delivery, 176 were deemed ineligible for the study (13 had mental

illness, 39 were under 18 years of age, and 124 gave birth < 20 gestational weeks). Of the 14,359 eligible mothers, 3,721 refused to participate and 105 failed to complete an in-person interview. 10,542 women completed the in-person interview after providing written consent. The interview consisted of a standardized and structured questionnaire that collected information on demographic factors, reproductive and medical history, smoking, alcohol and tea consumption, occupational and residential history, physical activity, work environment, and dietary and supplement intake. The majority of women (84%) were interviewed within three days of delivery, while others were interviewed up to 2 days before delivery. Birth outcomes and complications were abstracted from hospital medical records. All study procedures were approved by the Human Investigation Committees at the Gansu Provincial Maternity and Child Care Hospital and Yale University.

Birth Outcomes

Gestational age at delivery was calculated by number of complete weeks since the first day of the last menstrual period. Preterm birth was defined as delivery <37 of gestation and term births were defined as delivery at 37 or more gestational weeks (WHO, 2015). Low birth weight was defined as <2500 g, regardless of gestational age (WHO, 2006).

Folate and Folic Acid Intake

Dietary information was collected via a semi-quantitative food frequency questionnaire (FFQ). Estimates of daily dietary folate intake were calculated from the frequency of consumption and portion sizes of food items using the Chinese Standard Tables of Food Consumption (INHF). Information on folic acid supplement use, duration, and frequency was collected for the first trimester (1-13 weeks), second trimester (14-27 weeks), and third trimester (>27 weeks). The use

of both folic acid supplement alone and folic acid-containing multivitamins were documented for each trimester. Non-users were defined as those who never took folic acid supplements or folic acid-containing multivitamins during the time period of interest.

Exposure Assessment

The Gansu Provincial Environmental Monitoring Central Station provided 24-hour average concentrations for particulate matter <10μm (PM_{10}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) through an automated data reporting system from four monitoring stations in Lanzhou. The 24-hour air pollution averages were measured from April 1, 2009 to December 31, 2012 at two stations, and from January 1, 2011 to December 31, 2012 for the other two stations. The monitors are located in the southern part of the city near the metropolitan center. The distance from the participants' residential and work addresses to the nearest monitoring station ranged from 0.1 to 88.5 km (mean: 5.0 km, median: 3.3 km); however, 90% of participants lived within 5.5 km of a monitoring station.

Each participant's residential and work address was collected, including move-in and move-out dates. We used the earth online sharing website provided by Google (www.earthol.com) to obtain the geographic coordinates of each subject's home and work address. Participants whose residence(s) during pregnancy was outside of Lanzhou were excluded from the analysis (n = 1,344) due to lack of air monitoring data. Daily air pollutant concentrations for PM_{10}, NO_2, and SO_2 were calculated using 1) the nearest monitor, 2) all four monitors with the inverse-distance weighting approach, and 3) the two monitors in operation throughout the full study period (April 2009 to December 2012) and inverse distance weighting.

We factored in exposure time at home and at work to calculate the overall exposure level during pregnancy. Because regular working hours are typically 8 h/day, we used a time-weighted approach to calculate daily levels on weekdays for each subject, and weekend exposures were based solely on home addresses. Residential mobility was also factored into calculations using time-weighted averaging to account for relocation during the pregnancy. Daily exposures were averaged for each trimester and throughout the entire pregnancy. Exposures to each air pollutant were analyzed both as a continuous variable and as a binary variable for meeting or exceeding the China National Ambient Air Quality Standard (NAAQS). The China NAAQS Grade II standards were 150 $\mu g/m^3$for PM_{10}, 60 $\mu g/m^3$ for SO_2, and 40 $\mu g/m^3$ for NO_2.

Statistical Analysis

The final sample size was 8,969 mother-baby pairs after excluding multiple births (n=323) and still births (n=53). Univariate-analyses were conducted to examine the distribution of selected characteristics between preterm/term births and low birth weight/normal birth weight births. *P* values were obtained using the χ^2 test for categorical variables and Student's *t* test for continuous variables.

Unconditional logistic regression models were used to estimate the odds ratios and 95% confidence intervals for the association between the average maternal PM_{10}, NO_2, and SO_2 exposure during pregnancy (continuous variable) and risk of preterm birth and low birth weight. Each outcome was analyzed individually, and each air pollutant was analyzed both individually and while controlling for the other two pollutants. A second unconditional logistic regression analysis was conducted using categorical exposure variables. Women were assigned to one of four groups designated by a dichotomous air pollutant variable (above/below China NAAQS) and

binary dietary folate or folic acid supplementation variable. Three indicator variables were created (below NAAQS, low folate/no supplementation; above NAAQS, high folate/supplementation; above NAAQS, low folate/no supplementation) and compared to the reference group (below NAAQS, high folate/supplementation). Dietary folate and folic acid supplementation were analyzed separately, though each model controlled for the other folate variable. Dietary folate intake was assigned as above or below the study population median. Folic acid supplementation was defined as ever or never supplemented during pregnancy.

All logistic regression models adjusted for potential confounding variables, including maternal age, maternal education (< college, ≥ college), family monthly income per capita (<2000 yuan, 2000-5000 yuan, >5000 yuan), maternal employment during pregnancy (yes/no), pre-pregnancy BMI (≤18.5, 18.5-25, ≥25), active smoking during pregnancy (yes/no), passive smoking during pregnancy (yes/no), parity (primiparous/multiparous), preeclampsia (yes/no), gestational diabetes (yes/no), and cooking fuel (gas or electric, biomass or coal, none, other). All of the same potential confounders were included in the analyses to maintain consistency between the preterm and low birth weight analyses. Each air pollutant was analyzed both individually and while controlling for the other two pollutants in the model. All analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Basic Characteristics

Of the 8,969 live singleton births included in the study, 677 (7.5%) were preterm, 8292 were term, 453 (5.1%) were low birth weight, and 8483 were normal birth weight (33 missing birth weight data).

Women who delivered preterm babies were more likely to have a lower education level, lower family income, and be unemployed during pregnancy (Table 1). Compared to women with term births, women with preterm births were more frequently multiparous, overweight, preeclamptic, or diabetic. Women with preterm babies were also more likely to use biomass, coal, or other cooking fuels and less likely to use gas or electric compared to mothers with term births. No significant differences between preterm and term mothers were observed in regards to maternal age, active smoking during pregnancy, and passive smoking during pregnancy.

Compared to mothers with normal weight babies, mothers who delivered low birth weight babies were less educated, had lower monthly family income, and were less likely to be employed during pregnancy (Table 1). Mothers with low birth weight babies were more likely to be multiparous, preeclamptic, and in the overweight BMI range. Although there was no significant difference in active smoking between the two groups, mothers with low birth weight babies were more likely to be exposed to passive smoking than mothers with normal birth weight babies. Low birth weight mothers were also less likely to use gas or electric and more likely to use biomass, coal, or other cooking fuels compared to mothers with normal weight births. There was no significant difference in maternal age, active smoking during pregnancy, or prevalence of gestational diabetes between low weight births and normal weight births.

Main Effects of Air Pollutants and Folate/Folic Acid

The mean concentrations of exposure during pregnancy to PM_{10}, SO_2, and NO_2 for all 8,969 mothers were 142.09 $\mu g/m^3$, 48.91 $\mu g/m^3$, and 43.28 $\mu g/m^3$, respectively (Table 2). Given the study location, it is not surprising that the mean exposures to PM_{10} and SO_2 were relatively high and close to the exposure standards. The mean NO_2 exposure was above the NAAQS of 40

μg/m^3, indicating that the majority of mothers were highly exposed. This skewed sample may have impacted subsequent findings.

Without adjusting for confounders, mothers exposed to PM_{10} levels above the Chinese NAAQS of 150 μg/m^3 were at a higher risk of both preterm birth (OR: 1.344, 95% CI: 1.1433, 1.5805) and low birth weight (OR: 1.2483, 95% CI: 1.0256, 1.5194) than mothers with exposure levels under the standard (Table 2). Similarly, mothers with an average SO_2 exposure during pregnancy above the 60 μg/m^3 standard were at a higher risk of preterm birth (OR: 1.2739, 95% CI: 1.0635, 1.5260) and low birth weight (OR: 1.1924, 95% CI: 0.9566, 1.4862). 66.77% and 74.23% of mothers with preterm births and term births were exposed to NO_2 levels over the NAAQS, respectively. Similarly, 65.12% of mothers of low birth weight babies and 74.28% of mothers with normal birth weight babies had mean pregnancy exposures over 40 μg/m^3. This produced an OR of 0.6975 (95% CI: 0.5900, 0.8245) for the risk of preterm birth and 0.6466 (95% CI: 0.5298, 0.7891) for low birth weight (Table 2).

Of the 8,969 mothers in the study, 7,177 (80.02%) used folate supplements at one point during their pregnancy (Table 3). The median folate intake was 765.264 micrograms, and this cutoff was used to stratify the study population into “high dietary folate intake” and “low dietary folate intake” groups. Both folate supplementation and high dietary folate intake during pregnancy were significantly protective against both preterm birth and low birth weight (Table 3).

Categorical Analyses

When categorized into four groups by pollutant exposure and folic acid supplementation, apparent trends emerged with increasing risk group (Table 4). Compared to the below PM_{10} NAAQS and folate supplementation reference group, mothers below the NAAQS exposure who

did not supplement during pregnancy had 1.156 (95% CI: 0.898, 1.487) times the odds of preterm birth after adjusting for basic characteristics and other air pollutant exposures. The OR for women above the PM_{10} NAAQS who took folic acid supplements during pregnancy was 1.588 (95% CI: 1.278, 1.972), and the highest observed risk was for women who were exposed to PM_{10} above the NAAQS who did not take folic acid supplements (OR: 1.652, 95% CI: 1.201, 2.273). A similar trend examining the relationship between SO_2, folic acid supplementation, and risk of preterm birth was observed after adjusting for basic characteristics and PM_{10} and NO_2 exposure (Table 4), with women exposed to SO_2 above the NAAQS who did not supplement experiencing the highest risk (OR: 1.876, 95% CI: 1.335, 2.637), followed by women above the SO_2 NAAQS limit who did supplement (OR: 1.417, 95% CI: 1.110, 1.808) and women below the SO_2 NAAQS limit who did not supplement (OR: 1.014, 95% CI: 0.799, 1.285) (Table 4). The same trend was not observed for NO_2 (Table 4). Mothers whose exposure levels were under the NO_2 NAAQS and did not supplement had an OR of 0.931 (95% CI: 0.644, 1.347). Mothers exposed to NO_2 levels over the NAAQS who supplemented with folic acid had an OR of 0.646 (95% CI: 0.524, 0.797) and who did not supplement was 0.733 (95% CI: 0.559, 0.960). The interactions between folic acid supplementation and the PM_{10}, NO_2, and SO_2 exposure variables were not significant (Table 4).

Similar trends were observed when examining air pollutant exposure, folic acid supplementation, and risk of low birth weight after adjusting for potential confounders (Table 4). Women who were exposed to PM_{10} above the NAAQS who did not take folic acid supplements were at the highest risk of low birth weight after adjusting for basic characteristics and other pollutants (OR: 1.703, 95% CI: 1.172, 2.474). The OR was lower for women above the PM_{10} standard who did supplement (OR: 1.380, 95% CI: 1.052, 1.810) and lowest for mothers below the PM_{10} standard who did not supplement (OR: 1.245, 95% CI: 0.928, 1.670). Compared to

women exposed to SO_2 below the NAAQS who supplemented with folic acid, mothers below the standard who did not supplement had 1.1089 (95% CI: 0.841, 1.461) times the odds of low birth weight, and mothers above the SO_2 NAAQS who did and did not take folic acid supplements had 1.218 (95% CI: 0.895, 1.659) times and 1.946 (95% CI: 1.308, 2.895) times the odds of low birth weight, respectively (Table 4). This trend was not observed for NO_2 exposure and folic acid supplementation (Table 4). Compared to the reference group, mothers with NO_2 exposures under the NAAQS with low dietary folate had 1.222 (95% CI: 0.909, 1.642) times the odds of preterm birth. Mothers exposed to pollutant levels over the NO_2 NAAQS with high dietary folate and low dietary folate intake had OR of 0.678 (95% CI: 0.503, 0.914) and 0.817 (95% CI: 0.615, 1.084), respectively. The interactions between folic acid supplementation and all three exposure variables were not significant (Table 4).

The categorical analyses conducted for dietary folate intake produced similar increasing trends by risk profile (Table 5). Compared to the reference group consisting of mothers with PM_{10} exposure under 150 $\mu g/m^3$ with high dietary folate intake, mothers with PM_{10} exposure under the standard with low dietary folate intake had 1.221 (95% CI: 0.990, 1.506) times the odds of preterm birth. The OR was higher for mothers over the PM_{10} NAAQS who had high dietary folate intake (OR: 1.652, 95% CI: 1.261, 2.163) and low dietary folate intake (OR: 1.792, 95% CI: 1.380, 2.327). A similar pattern was observed with SO_2 exposure, dietary folate, and preterm birth (Table 5). The OR for under SO_2 NAAQS and low dietary folate, above SO_2 NAAQS and high dietary folate, and above SO_2 NAAQS and low dietary folate were 1.293 (95% CI: 1.063, 1.572), 1.698 (95% CI: 1.297, 2.223), and 1.700 (95% CI: 1.233, 2.344), respectively. This trend of increasing risk was not observed with NO_2 (Table 5). The interactions between dietary folate intake and the PM_{10}, NO_2, and SO_2 exposure variables were not significant (Table 5).

The risk of low birth weight showed similar trends in relation to air pollutant exposure and dietary folate intake (Table 5). Compared to the reference group, mothers with exposure under the PM_{10} NAAQS with low dietary folate intake during pregnancy had 1.059 (95% CI: 0.825, 1.359) times the odds of low birth weight. For mothers over the PM_{10} NAAQS of 150 $\mu g/m^3$, those with low dietary folate intake had the highest risk of low birth weight (OR: 1.460, 95% CI: 1.064, 2.003), followed by those with high dietary folate intake (OR: 1.375, 95% CI: 0.992, 1.906). A similar trend was observed in relation to SO_2 exposure (Table 5). Mothers above the NAAQS of 60 $\mu g/m^3$ with low dietary folate intake had the highest observed risk (OR: 1.520, 95% CI: 1.040, 2.221), followed by mothers above the NAAQS with high dietary folate intake (OR: 1.326, 95% CI: 0.951, 1.850). Mothers with exposure under 60 $\mu g/m^3$ with low dietary folate intake had the lowest risk compared to the reference group (OR: 1.073, 95% CI: 0.851, 1.354). Similar trends were not observed for NO_2 (Table 5). None of the interactions between dietary folate and the individual exposure variables were significant (Table 5).

Continuous Analyses

Mean maternal exposure to air pollutants during pregnancy was also evaluated as a continuous variable. After stratifying the analysis by folic acid supplementation status during pregnancy, there was no significantly increased risk of preterm birth or low birth weight associated with any of the continuous air pollution variables (Table 6). Similarly, the analyses stratified by dietary folate intake did not find that any of the continuous air pollutant variables posed a significantly increased risk of preterm birth or low birth weight (Table 7).

Discussion

Our study results support the hypothesis that there is an increased risk of preterm birth and low birth weight associated with maternal exposure to PM_{10} and SO_2 during pregnancy. Although the interaction between air pollutants and folate intake/folic acid supplementation were not significant, the risk of adverse birth outcomes appears to be greater amongst those with low dietary folate intake and who do not take folic acid supplements.

Preterm birth and low birth weight can both be induced through several biological mechanisms, and it is currently hypothesized that exposure to air pollutants during pregnancy can induce adverse perinatal outcomes through oxidative stress, systemic inflammation, blood coagulation, impaired endothelial function, or hemodynamic responses (Kannan, 2006). The Normative Aging Study found that subjects with defects in the methyl-nutrient pathway or with lower methyl-nutrient intake have higher susceptibility to cardiovascular outcomes associated with air pollution (Baccarelli, 2008), suggesting that DNA methylation may be a major mechanism through which air pollution exerts its adverse effects. Perera et al. (1999) found higher levels of DNA adducts in infants compared with their mothers, suggesting increased fetal susceptibility to DNA damage from air pollutant exposure. Additionally, DNA adducts were found to be positively associated with an increased risk of numerous birth outcomes (Perera, 1999). In particular, exposure to particulate matter has been shown to impair DNA methylation in children (Breton, 2012), while SO_2 inhalation has produced DNA damage in animal studies (Meng, 2005).

During this critical period of rapid growth, developing organs are extremely sensitive to the availability of nutrients and can undergo permanent adaptations as a result of low availability of critical nutrients (Timmermans, 2009). We chose to examine folate as a potential effect modifier in the relationship between perinatal air pollution exposure and birth outcomes because of its

critical role in homocysteine metabolism (Timmermans, 2009). This pathway plays a critical role in protein, lipid, and DNA synthesis, and folate deficiency has been shown to cause expression of chromosome fragile sites, chromosome breaks, excessive uracil in DNA, micronucleus formation, and DNA hypomethylation (Šrám, 2005b; Timmermans, 2009). The synthesis of methionine and its derivative *S*-adenosyl-methionine require methyl groups from folate (Timmermans, 2009). *S*-adenosyl-methionine is one of the most important methyl donors for DNA methylation (Hibbard, 1964; Czeizel & Dudas, 1992; Steegers-Theunissen, 1992; Hernandez-Diaz, 2000), which is why it is biologically plausible that folate may modify the association between air pollution and birth outcomes. Additionally, periconceptional folic acid supplementation has been found to increase methylation of the IGF2 gene in the child, which may affect growth, development, and health outcomes later in life (Steegers-Theunissen, 2009).

Although there were no observed significant interactions between folic acid supplementation or dietary folate with air pollutant exposure, there was an apparent trend in relation to dietary folate intake/folic acid supplementation and air pollutant exposure. Mothers exposed to levels of PM_{10} and SO_2 above the China NAAQS were at a higher risk of both preterm birth and low birth weight than those below the standard, and this risk was highest amongst women who did not take folic acid supplements or had low dietary folate intake (Table 4 and Table 5). Although folate intake did not significantly modify the association, there appears to be a lower risk of adverse birth outcomes associated with air pollution exposure amongst mothers who had higher dietary folate and supplemented with folic acid.

This study also contributes to existing evidence suggesting that perinatal exposure to PM_{10} and SO_2 increases the risk of preterm birth and low birth weight. Without adjustment, mothers exposed to PM_{10} and SO_2 above their respective China NAAQS were at an increased risk of both

preterm birth and low birth weight compared to mothers with exposures below the standards (Table 2). After adjusting for demographic characteristics and other air pollutants, there was still an increased risk of preterm birth and low birth weight amongst mothers with PM_{10} and SO_2 exposure levels over the NAAQS (Table 4 and Table 5). These findings contribute to the existing literature investigating perinatal air pollution exposure and birth outcomes.

Several studies have assessed the effects of air pollutants on birth weight. Lee et al. (2003) found a slightly increased risk of low birth weight associated with interquartile range increases of both PM_{10} (OR: 1.06, 95% CI: 1.01, 1.10) and SO_2 (OR: 1.14, 95% CI: 1.04, 1.24). However, the risk of low birth weight in this study was not significant with increasing interquartile range for NO_2 (Lee, 2003). Bobak and Leon (1999) observed a significant increase in low birth weight risk (OR: 1.10, 95% CI: 1.02, 1.17) associated with a 50 $\mu g/m^3$ increase in SO_2. A study conducted in Vancouver, Canada found a significant association between exposure to SO_2 during the first month of pregnancy and risk of low birth weight (OR: 1.11, 95% CI: 1.01, 1.22 for 5 ppb increase) (Liu, 2003). Seo et al. (2010) found an increased risk of low birth weight per PM_{10} increments (difference between maximum and minimum concentrations) throughout the pregnancy in two study cities, but failed to reach significance in the other five study locations. Two studies have found an increased risk of low birth weight associated with an interquartile range increases in NO_2 concentration during the first trimester (Ha, 2001) and throughout the entire pregnancy (Bell, 2007).

Many studies have also examined risk of preterm birth associated with perinatal air pollution exposure. A prospective cohort study in Beijing found an increased risk of preterm birth for each ln $\mu g/m^3$ increase in SO_2 (OR: 1.21, 95% CI: 1.01, 1.46) and for each 100 $\mu g/m^3$ in total suspended particulates (OR: 1.10, 95% CI: 1.01, 1.20) (Xu, 1995). Two studies examined the

association between SO_2 exposure in the weeks before birth and found significantly higher risk of preterm birth (Liu, 2003; Sagiv, 2005). Bobak (2000) also found a significant risk of preterm birth per 50 $\mu g/m^3$ increase in mean SO_2 concentrations across all three trimesters. Ritz et al. (2000) reported a 20% increase (OR: 1.20, 95% CI: 1.09, 1.33) in preterm birth per 50 $\mu g/m^3$ increase in average PM_{10} levels during the 6 weeks prior to birth. However, this prospective cohort study in Southern California failed to find consistent effects associated with NO_2 exposure during any pregnancy period (Ritz, 2000). A population-based study conducted in Lithuania reported an OR of 1.67 (95% CI: 1.28, 2.18) per 10 $\mu g/m^3$ increase in NO_2 exposure during the first trimester, but failed to find any significant associations in the second and third trimesters (Maroziene & Grazuleviciene, 2002).

Several studies have reported no significant associations between SO_2 exposure during pregnancy and risk of low birth weight (Alderman, 1987; Ha, 2001; Maisonet, 2001; Gouveia, 2004; Sagiv, 2005; Salam, 2005; Bell, 2007; Morello-Frosch, 2010) and preterm birth (Landgren, 1996). Similarly, non-significant associations between PM_{10} exposure and risk of preterm birth (Sagiv, 2005) and low birth weight (Maisonet, 2001; Chen, 2002; Lin, 2004; Bell, 2007; Madsen, 2010; Morello-Frosch, 2010) have been observed. Our study failed to find an increased risk of both preterm birth and low birth weight associated with NO_2 exposure above the NAAQS, which is consistent with many previous studies that have failed to find significant associations (Bobak, 2000; Liu, 2003; Gouveia, 2004; Lin, 2004; Salam, 2005; Madsen, 2010). As previously mentioned, the majority of mothers in this Lanzhou birth cohort were exposed to NO_2 levels above the China NAAQS. Future studies investigating the relationship between NO_2 exposure and birth outcomes may benefit from a greater distribution in exposure values, as this may have skewed our findings. Additionally, further investigation into the composition of NO_x pollutants in the Lanzhou

valley may be warranted. A previous study on the concentrations of NO, NO_2, and NO_x in Lanzhou revealed that NO concentrations have greater seasonal variability than NO_2 (Ta, 2004). Only NO_2 levels were measured and evaluated in the present study, so it is unclear how much NO and NO_x mothers were exposed to and how these exposures impacted birth outcomes. Research on the effect of NO and NO_x concentrations on birth outcomes, as well as further research on NO_2 in Lanzhou, may help to elucidate the mechanisms behind our unique NO_2 findings. Additionally, the importance of average NO_2 exposures compared to peak exposures during critical windows during pregnancy warrants further study. In a recent review of air pollution and birth outcomes, four of the studies included found a significantly increased risk of adverse birth outcomes, including preterm birth, low birth weight, and small for gestational age, associated with the first month or first trimester of pregnancy (Shah, 2011). Because this study utilized mothers' average exposures throughout pregnancy, the effect of peak exposures during critical time periods may have been overlooked.

This study also contributed to the literature proposing that folic acid supplements and folate may protect against preterm birth and low birth weight (Table 3). Compared to mothers who did not take folic acid supplements or had low dietary folate intake, mothers with higher folate during pregnancy had a lower risk of adverse birth outcomes when exposed to PM_{10} and SO_2 above the China NAAQS (Table 4 and Table 5). Previous studies have yielded similar results. A prospective birth cohort study in the Netherlands found a positive association between folic acid supplementation and fetal growth (Timmermans, 2009). Folic acid supplementation prior to conception was associated with 68 g higher birth weight (95% CI: 37.2, 99.0) compared to no folic acid supplementation (Timmermans, 2009). Mothers who started supplementing with folic acid after conception also experienced a reduced risk of low birth weight compared to mothers who did

not supplement (OR: 0.61; 95% CI: 0.40, 0.94), though the risk was lower in mothers who started supplementation preconceptionally (OR: 0.43, 95% CI: 0.28, 0.69) (Timmermans, 2009).

To our knowledge, this is the first study examining the contrasting effects of perinatal air pollution exposure and folate intake during pregnancy on risk of adverse birth outcomes. A previous study by Šrám et al. (2005b) investigated the effect of maternal folate intake on intrauterine growth restriction (IUGR) in smoking and non-smoking mothers. The results indicated that the highest tertile of maternal folic acid significantly reduced the risk of IUGR in the gestational age over 32 weeks (OR = 0.44, 95% CI: 0.20, 0.95) and over 36 weeks (OR = 0.38, 95% CI: 0.17, 0.89). However, the effect of folic acid was even more pronounced in smoking mothers, with OR of 0.24 (95% CI: 0.06, 0.90) and 0.14 (95% CI: 0.03, 0.68) in gestational ages over 32 weeks and over 36 weeks, respectively (Šrám, 2005b). Because folate intake was more protective against IUGR in smoking mothers, further studies investigating the effect of folate intake on pregnancy outcomes in relation to other environmental exposures is warranted.

Strengths and limitations of the study should be considered when interpreting results. The study cohort had a large sample size (n = 8,969) which allowed for greater statistical power. A major strength of the exposure assessment methodology was the use of both residential and occupational addresses, as well as residential mobility, to minimize exposure misclassification. Rural areas within Lanzhou city limits did not have air monitoring stations, but over 90% of women in the study lived within 5.5 km of a monitor. Sensitivity analyses using data from different exposure assessment approaches (e.g. nearest monitors, inverse-distance weighting using two or four monitors, using data for mothers within 5.5 km or 12.9 km of a monitor) produced consistent exposure results. Because we could not account for differences between indoor and outdoor exposures, using this method may not represent the actual individual exposure level. Regardless,

this is the most commonly used method in air pollution epidemiology and was the most feasible method for estimating exposures for a cohort of this size.

Detailed information on both folic acid supplementation and dietary folate intake were collected using FFQs, which allowed for an examination of the effects of both routes of folate intake individually. This particular study population is unique in that periconceptional supplementation with folic acid is not yet universal, thus providing the opportunity to conduct a prospective study without the ethical issues that would be associated with a randomized control trial. All air pollution exposure and folate intake and supplementation data were compiled across all three trimesters, which improved upon previous study designs that relied upon single measurements. The detailed questionnaire also included information on many other potential confounding factors, including both active and passive smoking, cooking fuels, and demographic information, which were all controlled for in the analysis. Although the questionnaire collected information on many important confounding factors, there is always the possibility of residual confounding. Birth outcomes and pregnancy complications were abstracted from medical records, thus minimizing the potential for outcome misclassification. However, the FFQ was administered through an in-person interview at delivery, which may have led to potential recall bias. Additionally, this birth cohort was hospital-based, which may affect generalizability. However, the Gansu Provincial Maternity and Child Care Hospital is the largest maternity and child hospital in Lanzhou, and for this reason it may be reasonable to assume that most women receiving perinatal care in Lanzhou would have been captured.

In conclusion, our study supports the hypothesis that perinatal exposure to PM_{10} and SO_2 increases the risk of low birth weight and preterm birth, and the risk is even higher amongst women with low dietary folate intake and who do not take folic acid supplements. However, we were

unable to find the same trends with NO_2. These findings have important public health implications and are relevant for future air pollution policies and standards as well as maternal nutrition recommendations. Given that this is the first study investigating the effect of maternal folate intake on pregnancy outcomes related to environmental exposures, additional studies are warranted.

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Table 1. Basic Characteristics

Characteristics (Preterm)	Cases (677)	%	Controls (8292)	%	p-value
Maternal Age	28.8 (5.2)		28.6 (4.1)		0.35
Highest Education Level					<0.0001
<College	340	51.44	2844	34.9	
≥ College	321	47.42	5305	65.1	
Family Monthly Income					<0.0001
<2000	205	33.06	1674	22.35	
2000-5000	358	57.74	4941	65.96	
> 5000	57	9.19	876	11.69	
Employment during Pregnancy					<0.0001
No	368	54.36	3786	45.66	
Yes	309	45.64	4506	54.34	
Pre-Pregnancy BMI					0.003
≤ 18.5	133	20.27	1708	21.19	
18.5-25	459	69.97	5842	72.47	
≥ 25	64	9.76	511	6.34	
Active Smoking During Pregnancy					0.881
No	671	99.11	8223	99.17	
Yes	6	0.89	69	0.83	
Passive Smoking During Pregnancy					0.069
No	534	78.88	6775	81.71	
Yes	143	21.12	1517	18.29	
Parity					<0.0001
Primiparous	452	66.77	6282	75.76	
Multiparous	225	33.23	2010	24.24	
Preeclampsia					<0.0001
No	583	86.12	8020	96.72	
Yes	94	13.88	272	3.28	
Gestational Diabetes					0.031
No	664	98.08	8207	98.97	
Yes	13	1.92	85	1.03	
Cooking Fuel					<0.0001
None	4	0.62	105	1.31	
Gas or electric	550	85.27	7237	90.61	
Biomass or coal	37	5.74	184	2.3	
Other	54	8.37	461	5.77	

Characteristics (LBW)	Cases (453)	%	Controls (8483)	%	p-value
Maternal Age	28.6 (5.2)		28.6 (4.1)		0.816
Highest Education Level					<0.0001
<College	247	56.14	2927	35.11	
≥ College	193	43.86	5410	64.89	
Family Monthly Income					<0.0001
<2000	139	34.84	1735	22.59	
2000-5000	227	56.89	5051	65.76	
> 5000	33	8.27	895	11.65	
Employment during Pregnancy					<0.0001
No	251	55.41	3885	45.8	
Yes	202	44.59	4598	54.2	
Pre-Pregnancy BMI					0.045
≤ 18.5	102	23.34	1734	21.02	
18.5-25	296	67.73	5981	72.51	
≥ 25	39	8.92	533	6.46	
Active Smoking During Pregnancy					0.917
No	449	99.12	8412	99.16	
Yes	4	0.88	71	0.84	
Passive Smoking During Pregnancy					0.034
No	352	77.7	6928	81.67	
Yes	101	22.3	1555	18.33	
Parity					<0.001
Primiparous	297	65.56	6411	75.57	
Multiparous	156	34.44	2072	24.43	
Preeclampsia					<0.0001
No	371	81.9	8200	96.66	
Yes	82	18.1	283	3.34	
Gestational Diabetes					0.066
No	452	99.78	8386	98.86	
Yes	1	0.22	97	1.14	
Cooking Fuel					<0.0001
None	5	1.17	104	1.27	
Gas or electric	352	82.63	7407	90.62	
Biomass or coal	27	6.34	193	2.36	
Other	42	9.86	470	5.75	

Table 2. Main Effects of Pollutants

All Participants	Mean (ug/m3)	SD			
PM10	142.09	17.56			
SO2	48.91	13.15			
NO2	43.28	5.96			
Preterm	Cases	%	Controls	%	OR (95%CI)
PM10					1.34 (1.14, 1.58)
<150 ug/m3	419	61.89	5687	68.58	
≥150 ug/m3	258	38.11	2605	31.42	
NO2					0.70 (0.59, 0.82)
<40 ug/m3	225	33.23	2137	25.77	
≥40 ug/m3	452	66.77	6155	74.23	
SO2					1.27 (1.06, 1.53)
<60 ug/m3	504	74.45	6532	78.77	
≥60 ug/m3	173	25.55	1760	21.23	
LBW	Cases	%	Controls	%	OR (95%CI)
PM10					1.25 (1.03, 1.52)
<150 ug/m3	287	63.36	5797	68.34	
≥150 ug/m3	166	36.64	2686	31.66	
NO2					0.65 (0.53, 0.79)
<40 ug/m3	158	34.88	2182	25.72	
≥40 ug/m3	295	65.12	6301	74.28	
SO2					1.19 (0.96, 1.49)
<60 ug/m3	342	75.5	6668	78.6	
≥60 ug/m3	111	24.5	1815	21.4	

Table 3. Main Effects of Folate and Folic Acid

All Participants	N	%	Mean (SD)	Median	
Dietary Folate (μg)			882.588 (1377.98)	765.26422	
Ever Supplemented	7177	80.02			
Preterm	Cases	%	Controls	%	OR (95%CI)
Dietary Folate*					0.76 (0.65, 0.89)
Low	381	56.28	4104	49.49	
High	296	43.72	4188	50.51	
Folic Acid Supplement					0.73 (0.60, 0.87)
Ever	507	74.89	6670	80.44	
Never	170	25.11	1622	19.56	
LBW	Cases	%	Controls	%	OR (95%CI)
Dietary Folate*					0.82 (0.68, 0.99)
Low	248	54.75	4218	49.72	
High	205	45.25	4265	50.28	
Folic Acid Supplement					0.61 (0.49, 0.75)
Ever	324	71.52	6825	80.46	
Never	129	28.48	1658	19.54	

*Dietary folate was defined as less than or equal to the median (Low) and greater than the median folate intake (High)

Table 4. Categorized Analysis of Air Pollutants and Folic Acid Supplementation

PM10	Folic Acid Supplement	Preterm Cases (#)	Controls (#)	PM10 Only OR (95%CI)	All Pollutants OR (95%CI)
<150 ug/m3	Yes	320	4691	1	1
<150 ug/m3	No	99	996	1.10 (0.86, 1.42)	1.16 (0.90, 1.49)
≥150 ug/m3	Yes	187	1979	1.31 (1.08, 1.58)	1.59 (1.28, 1.97)
≥150 ug/m3	No	71	626	1.24 (0.92, 1.65)	1.65 (1.20, 2.27)
p for interaction=				0.44	0.59
NO2	Folic Acid Supplement	Preterm Cases (#)	Controls (#)	NO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<40 ug/m3	Yes	181	1790	1	1
<40 ug/m3	No	44	347	0.92 (0.64, 1.33)	0.93 (0.64, 1.35)
≥40 ug/m3	Yes	326	4880	0.68 (0.56, 0.83)	0.65 (0.52, 0.80)
≥40 ug/m3	No	126	1275	0.78 (0.60, 1.00)	0.73 (0.56, 0.96)
p for interaction=				0.30	0.36
SO2	Folic Acid Supplement	Preterm Cases (#)	Controls (#)	SO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<60 ug/m3	Yes	389	5302	1	1
<60 ug/m3	No	115	1230	0.96 (0.76, 1.21)	1.01 (0.80, 1.29)
≥60 ug/m3	Yes	118	1368	1.20 (0.96, 1.51)	1.42 (1.11, 1.81)
≥60 ug/m3	No	55	392	1.51 (1.09, 2.07)	1.88 (1.34, 2.64)
p for interaction=				0.21	0.21

PM10	Folic Acid Supplement	LBW Cases (#)	Controls (#)	PM10 Only OR (95%CI)	All Pollutants OR (95%CI)
<150 ug/m3	Yes	212	4781	1	1
<150 ug/m3	No	75	1016	1.18 (0.88, 1.57)	1.25 (0.93, 1.67)
≥150 ug/m3	Yes	112	2044	1.12 (0.88, 1.43)	1.38 (1.05, 1.81)
≥150 ug/m3	No	54	642	1.25 (0.89, 1.75)	1.70 (1.17, 2.47)
p for interaction=				0.80	0.97
NO2	Folic Acid Supplement	LBW Cases (#)	Controls (#)	NO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<40 ug/m3	Yes	124	1828	1	1
<40 ug/m3	No	34	354	1.01 (0.66, 1.54)	1.02 (0.67, 1.56)
≥40 ug/m3	Yes	200	4997	0.61 (0.48, 0.77)	0.58 (0.45, 0.75)
≥40 ug/m3	No	95	1304	0.78 (0.58, 1.05)	0.74 (0.54, 1.01)
p for interaction=				0.32	0.37
SO2	Folic Acid Supplement	LBW Cases (#)	Controls (#)	SO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<60 ug/m3	Yes	255	5414	1	1
<60 ug/m3	No	87	1254	1.04 (0.79, 1.36)	1.11 (0.84, 1.46)
≥60 ug/m3	Yes	69	1411	1.02 (0.77, 1.36)	1.22 (0.90, 1.66)
≥60 ug/m3	No	42	404	1.54 (1.06, 2.22)	1.95 (1.31, 2.90)
p for interaction=				0.13	0.14

Table 5. Categorized Analysis of Air Pollutants and Dietary Folate

PM10	Dietary Folate	Preterm Cases (#)	Controls (#)	PM10 Only OR (95%CI)	All Pollutants OR (95%CI)
<150 ug/m3	High	166	2709	1	1
<150 ug/m3	Low	253	2978	1.27 (1.03, 1.56)	1.22 (0.99, 1.51)
≥150 ug/m3	High	130	1479	1.28 (1.01, 1.64)	1.65 (1.26, 2.16)
≥150 ug/m3	Low	128	1126	1.57 (1.22, 2.01)	1.79 (1.38, 2.33)
p for interaction=				0.81	0.49
NO2	Dietary Folate	Preterm Cases (#)	Controls (#)	NO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<40 ug/m3	High	82	949	1	1
<40 ug/m3	Low	143	1188	1.24 (0.92, 1.66)	1.22 (0.91, 1.64)
≥40 ug/m3	High	214	3239	0.73 (0.56, 0.97)	0.68 (0.50, 0.91)
≥40 ug/m3	Low	238	2916	0.86 (0.65, 1.13)	0.82 (0.62, 1.08)
p for interaction=				0.77	0.94
SO2	Dietary Folate	Preterm Cases (#)	Controls (#)	SO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<60 ug/m3	High	186	3016	1	1
<60 ug/m3	Low	318	3516	1.34 (1.11, 1.63)	1.29 (1.06, 1.57)
≥60 ug/m3	High	110	1172	1.42 (1.10, 1.83)	1.70 (1.30, 2.22)
≥60 ug/m3	Low	63	588	1.54 (1.13, 2.10)	1.70 (1.23, 2.34)
p for interaction=				0.28	0.20

PM10	Dietary Folate	LBW Cases (#)	Controls (#)	PM10 Only OR (95%CI)	All Pollutants OR (95%CI)
<150 ug/m3	High	122	2743	1	1
<150 ug/m3	Low	165	3054	1.10 (0.86, 1.41)	1.06 (0.83, 1.36)
≥150 ug/m3	High	83	1522	1.06 (0.79, 1.42)	1.38 (0.99, 1.91)
≥150 ug/m3	Low	83	1164	1.27 (0.94, 1.72)	1.46 (1.06, 2.00)
p for interaction=				0.67	0.99
NO2	Dietary Folate	LBW Cases (#)	Controls (#)	NO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<40 ug/m3	High	64	957	1	1
<40 ug/m3	Low	94	1225	0.99 (0.71, 1.40)	0.98 (0.70, 1.39)
≥40 ug/m3	High	141	3308	0.60 (0.43, 0.82)	0.54 (0.38, 0.77)
≥40 ug/m3	Low	154	2993	0.68 (0.49, 0.93)	0.64 (0.46, 0.89)
p for interaction=				0.53	0.42
SO2	Dietary Folate	LBW Cases (#)	Controls (#)	SO2 Only OR (95%CI)	All Pollutants OR (95%CI)
<60 ug/m3	High	139	3052	1	1
<60 ug/m3	Low	203	3616	1.12 (0.89, 1.41)	1.07 (0.85, 1.35)
≥60 ug/m3	High	66	1213	1.09 (0.80, 1.49)	1.33 (0.95, 1.85)
≥60 ug/m3	Low	45	602	1.38 (0.96, 1.98)	1.52 (1.04, 2.22)
p for interaction=				0.61	0.79

Table 6. Air Pollution as a continuous variable. ORs (CIs) for birth outcome per 10 ug/m3 increase in mean concentration of each air pollutant

Preterm Birth				
	Supplementation During Pregnancy		No Supplementation During Pregnancy	
Pollutant	OR (Single Pollutant)	OR (All Pollutants)	OR (Single Pollutant)	OR (All Pollutants)
PM10	0.98 (0.93, 1.03)	1.03 (0.95, 1.10)	1.04 (0.95, 1.13)	1.05 (0.93, 1.19)
NO2	0.75 (0.64, 0.89)	0.69 (0.56, 0.85)	0.87 (0.66, 1.13)	0.62 (0.43, 0.90)
SO2	0.96 (0.90, 1.04)	1.04 (0.94, 1.15)	1.08 (0.95, 1.22)	1.18 (0.99, 1.41)
Low Birth Weight				
	Supplementation During Pregnancy		No Supplementation During Pregnancy	
Pollutant	OR (Single Pollutant)	OR (All Pollutants)	OR (Single Pollutant)	OR (All Pollutants)
PM10	0.97 (0.91, 1.04)	1.05 (0.95, 1.14)	1.03 (0.93, 1.14)	1.07 (0.93, 1.23)
NO2	0.69 (0.56, 0.85)	0.61 (0.47, 0.79)	0.81 (0.60, 1.10)	0.58 (0.39, 0.88)
SO2	0.95 (0.87, 1.04)	1.04 (0.92, 1.17)	1.06 (0.91, 1.22)	1.17 (0.96, 1.43)

Table 7. Air Pollution as a continuous variable. ORs (CIs) for birth outcome per 10 ug/m3 increase in mean concentration of each air pollutant

Preterm Birth				
	High Folate During Pregnancy		Low Folate During Pregnancy	
Pollutant	OR (Single Pollutant)	OR (All Pollutants)	OR (Single Pollutant)	OR (All Pollutants)
PM10	1.04 (0.97, 1.11)	1.06 (0.97, 1.16)	0.96 (0.90, 1.02)	1.01 (0.93, 1.10)
NO2	0.93 (0.77, 1.14)	0.74 (0.56, 0.98)	0.68 (0.56, 0.83)	0.63 (0.50, 0.81)
SO2	1.05 (0.96, 1.15)	1.10 (0.97, 1.24)	0.95 (0.87, 1.04)	1.04 (0.93, 1.18)
Low Birth Weight				
	High Folate During Pregnancy		Low Folate During Pregnancy	
Pollutant	OR (Single Pollutant)	OR (All Pollutants)	OR (Single Pollutant)	OR (All Pollutants)
PM10	1.01 (0.93, 1.10)	1.08 (0.97, 1.21)	0.98 (0.91, 1.06)	1.03 (0.92, 1.15)
NO2	0.78 (0.62, 0.98)	0.60 (0.44, 0.83)	0.73 (0.57, 0.93)	0.65 (0.48, 0.88)
SO2	0.99 (0.89, 1.11)	1.09 (0.94, 1.27)	0.98 (0.88, 1.09)	1.05 (0.91, 1.22)

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