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Impact of the 2008 Beijing Olympics on the Risk of Pregnancy Complications

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ABSTRACT

Taking advantage of the natural experiment of the 2008 Beijing Olympics (8/8 to 9/24), when air pollution levels decreased by 13%-60%, we assessed whether having ≥ 1 pregnancy month during the Olympics was associated with decreased risks of hypertensive disorders (HD) and/or fetal-placental conditions (FPC). We included singleton births to mothers with ≥ 1 pregnancy month in 2008 or 2009 (n=56,155). Using generalized additive models, we estimated the risk of HD and FPC associated with 1) the 2008 Olympics compared with the same dates in 2009, and 2) increased mean ambient PM_{10}, NO_2 and SO_2 concentrations during each trimester. However, we found no association between HD or FPC and having any trimester during the 2008 Olympic period. This may, in part, be due to a small number of pregnancy complications in this population.

Key words: 2008 Beijing Olympics, air pollution reduction, pregnancy complications, hypertensive disorders, placental conditions

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INTRODUCTION

Ambient air pollution has been implicated in the development of adverse birth outcomes such as low birth weight, preterm birth, and intrauterine growth restriction. [1-6] However, air pollution mediated preterm birth and fetal growth restriction may share underlying biological mechanisms with pregnancy complications.[7-12] Previous studies have reported increased risks of individual pregnancy complications (e.g., gestational hypertension, preeclampsia, and eclampsia) associated with increased ambient air pollution during pregnancy.[13-20] However, the few studies that have examined associations between ambient air pollution and complications categorized as hypertensive disorders of pregnancy have generated inconsistent results.[21-23] Inconsistencies may be due to differences in outcome definition (e.g. inclusion of all hypertensive disorders of pregnancy versus assessment of individual complications; inclusion of only early or late onset pre-eclampsia versus inclusion of all pre-eclampsia), differences in time windows during pregnancy assessed (e.g. individual trimesters versus entire pregnancy), exposure assessment methods (e.g. proximity models; land use regression models; or dispersion models), and residual confounding by characteristics such as pre-pregnancy body mass index, maternal smoking status, environmental tobacco smoke exposure, and season. [19] However, use of a “natural experiment” where ambient air pollutant concentrations were reduced city wide for a short period of time, allowed an assessment of whether the pollution/complication associations seen in these previous studies could be replicated. Further, natural experiments should offer better control of confounding by long-term time trends, one of the major threats to internal validity in observational studies.[24]

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In order to host the 2008 Olympic Games, the Chinese government implemented numerous air pollution emission controls to substantially improve air quality in Beijing for the Olympic and Paralympic Games.[25, 26] Taking advantage of this natural experiment, we previously reported that those pregnancies of women residing in 4 urban districts of Beijing, with their 8th month of pregnancy during this 47 day Olympic period, had on average 23g heavier babies at birth, compared to Beijing residents with their 8th month of pregnancy during the same dates in 2007 or 2009 (Rich et al. Submitted to Environmental Health Perspectives). Using the same air pollutant and birth registry data, we assessed whether pregnancies during the 2008 Olympic Games had a reduced risk of several pregnancy complications. We hypothesized that having at least one month of pregnancy during the 2008 Olympics (August 8 to September 24) would be associated with a decreased relative odds of hypertensive disorders and fetal-placental conditions, compared to having that same month from August 8 to September 24, 2009.

MATERIALS AND METHODS

Study population. Our study population has been described previously (Rich et al. Submitted). Briefly, birth registry data was obtained from the Beijing Maternal and Child Health (MCH) Center for all registered births to women delivering in Beijing from January 1, 2007 to December 31, 2009. We retained all singleton births to mothers who resided in 1 of 4 adjacent Beijing districts (Fengtai, Haidian, Chaoyang, and Xicheng) at the time of delivery, with a gestational age of 28-42 weeks and a birth weight greater than 500 grams (n=132,841). We then further restricted the sample to include only those that had at least one month of pregnancy during the Olympic time period (August 8-September 24) in 2008 and 2009 (n=56,392). To

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avoid potential bias arising from outcome misclassification, we did not use data from 2007 since it was entered manually as opposed to electronically as in 2008 and 2009, and therefore may not be as complete with regard to pregnancy complications. From the birth registry, we also retained maternal characteristics such as age at birth, educational level, and district of maternal residence, gestational age at first clinic visit, and diagnoses of pregnancy complications as recorded in the registry (i.e. these were not self-reported). We further excluded women with missing values for gestational age at first clinic visit (n=237), leaving 56,155 births available for our analyses described below. Women excluded were similar in characteristics (maternal age mean ± standard deviation = 29.1 ± 3.7; 45% had bachelor's degree; 37% lived in Chaoyang) to those included in the study. We did not have data on infant gender, maternal height, pre-pregnancy weight, maternal smoking status, environmental tobacco smoke exposure, date of diagnosis, residential address, or parity.

Outcome definitions. A maximum of three complications were recorded for each birth in the registry. We defined 'hypertensive disorders' as a diagnosis of gestational hypertension, preeclampsia, or eclampsia. 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. thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms). Eclampsia was defined as preeclampsia with grand mal seizures.

Fetal-placental conditions consisted of a diagnosis of fetal macrosomia, fetal distress, placental abruption, threatened preterm labor, polyhydramnios, oligohydramnios, or premature rupture of membranes. Fetal macrosomia was defined as a birth weight >4,000 grams regardless of gestational age. Fetal distress was defined as presence of signs or symptoms that the fetus was not well, including any of 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. Threatened preterm labor was defined as documented uterine contractions without evidence of cervical change. Polyhydramnios was defined as excess amniotic fluid volume (i.e. AFV $\geq$ 8 cm), whereas, oligohydramnios was defined as AFV less than expected for gestational age (i.e. $\leq$ 2 cm). Premature rupture of membranes was defined as rupture of the amniotic sac before labor began.

Olympic time period definition. As in our birth weight analysis (Rich et al. submitted), the exposure period was defined as the dates of the 2008 Beijing Olympics and Paralympics (August 8 to September 24, 2008). The unexposed period was defined as the same dates in 2009 (August 8 to September 24, 2009). We used all births with at least one month of pregnancy during August 8 to September 24 in 2008 or 2009. Since the sample size for each month was generally small (e.g., 1st month=6,590 births, but n=62 hypertensive disorders), all pregnancies with their 1st, 2nd, or 3rd month during the Olympic time period were defined as the 'first trimester,' pregnancies with their 4th, 5th, or 6th month during the same time period as 'second trimester,' and pregnancies with their 7th, 8th, or 9th month defined as 'third trimester.'

Air pollution. We retrieved average daily PM_{10}, NO_2, and SO_2 concentrations for the study period (June 19, 2008 to March 12, 2009), from eight government-run monitoring stations located within the four study districts (i.e. for each day we have PM_{10}, NO_2, and SO_2 concentrations averaged across the 8 monitors). There were no missing daily PM_{10}, NO_2, or SO_2 concentrations during the study period. We then assigned a monthly average PM_{10}, NO_2, and SO_2 concentration to each gestational month (i.e. 1st, 2nd 3rd ….9th) of each pregnancy. Next, we calculated 1st trimester mean PM_{10}, NO_2, and SO_2 concentrations by averaging the 1st, 2nd, and 3rd month PM_{10}, NO_2, and SO_2 concentrations. We repeated this for months 4-6, and months 7-9 to generate second trimester and third trimester-mean PM_{10}, NO_2, and SO_2 concentrations, respectively.

Statistical Analysis: We fit a generalized additive model to estimate the relative odds of hypertensive disorder and fetal-placental conditions associated with having parts of the first, second, or third trimester of pregnancy during the 2008 Olympics (August 8-September 24) compared to the same dates in 2009. Specifically, the logit probability of a 'hypertensive disorder' (1=Yes, 0=No) was modelled as a function of Olympic time period (1=2008, 0=2009), adjusting for a smooth function of maternal age, a smooth function of gestational age at first clinic visit, and indicator variables for maternal education (bachelor's degree, some college or technical school, and high school or less), and district of maternal residence (Xicheng, Chaoyang, Fengtai, Haidian) as covariates. The smooth functions allow the shape of the relationships to be determined by the data. Using generalized cross validation (using the Mixed GAM Computation Vehicle [MGCV] package in R (R Foundation for Statistical Computing, www.r-project.org,version 2.15.1), we determined the appropriate smoothing parameters for maternal age and gestational age at first clinic visit. The MGCV package suggested that a linear term for maternal age and 3 degrees of freedom for gestational age at first clinic visit was reasonable. We fit a similar model to assess the relative odds of a 'fetal-placental condition,' including the same covariates modelled in the same way. From each model, we report the odds ratio associated with the Olympic time period and its 95% confidence interval.

Next, we used a generalized additive model to estimate the relative odds of a 'hypertensive disorder' associated with each interquartile range increase in PM_{10} concentration during each trimester of pregnancy. We again adjusted for maternal age (linear term), gestational age at first clinic visit (smooth term with 3 degrees of freedom), and indicator variables for maternal education (bachelor's degree, some college or technical school, and high school or less), district of maternal residence (Xicheng, Chaoyang, Fengtai, Haidian), in addition to relative humidity, and temperature. Again, the MGCV package was used to select the appropriate smoothing parameters for relative humidity and temperature. Based upon these results, relative humidity and temperature were kept as linear terms.

Similarly, we re-ran this model to estimate the relative odds of a 'hypertensive disorder' associated with each IQR increase in NO_2 and SO_2 concentrations during each trimester of pregnancy, adjusting for the same covariates modelled in the same way. We also fit similar models to estimate the relative odds of a 'fetal-placental condition' associated with each IQR increase in NO_2, SO_2, and PM_{10} concentrations during the first, second, and third trimesters of pregnancy, adjusting for the same covariates modelled in the same way . 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 other statistical analyses.

RESULTS

The characteristics of study subjects with a portion of their pregnancy from August 8 to September 24, 2008 and from August 8 to September 24, 2009 are shown in Table 1. The distributions of maternal age, district of maternal residence, and gestational age at first clinic visit were similar in 2008 and 2009. However, the proportion of mothers with a bachelor's degree increased from 54% in 2008 to 59% in 2009 (Table 1). There were also similar proportions of subjects/pregnancies experiencing a hypertensive disorder in 2008 (n=286; 1.1% of all pregnancies) and 2009 (n=347; 1.2% of all pregnancies), and a fetal-placental condition in 2008 (n=3,088; 11.7% of all pregnancies) and 2009 (n=3,486; 11.7% of all pregnancies) (Table 1).

The distributions of mean pollutant concentrations of our study subjects with part of their first trimester during the Olympic time period (August 8 to September 24 in 2008 and 2009) are shown in Table 2. Monthly PM_{10}, NO_2, and SO_2 concentrations for study subjects were generally lower in 2008 (median PM_{10} = 87 μg/m^3; median NO_2 = 73 μg/m^3; median SO_2 = 31 μg/m^3) than in 2009 (median PM_{10} = 111 μg/m^3; median NO_2 = 90 μg/m^3; median SO_2 = 34 μg/m^3).The correlation coefficients between these mean monthly pollutant concentrations, relative humidity, and temperature during the first trimester of pregnancy are presented in Table 3. PM_{10} was moderately correlated with SO_2 (r=0.39) and NO_2 (r=0.41), while SO_2 and NO_2 were highly correlated (r=0.76). Due in part to the lower 2008 Olympic pollutant concentrations occurring in the middle of the summer, all three pollutants were inversely correlated with both temperature (r = -0.34 to -0.95) and relative humidity (r = -0.43 to -0.80)(Table 3).

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In unadjusted analyses, having the 1st, 2nd, or 3rd trimester of pregnancy during the Olympic time period was not significantly ($p<0.05$) associated with a decreased odds of a hypertensive disorder of pregnancy (Table 4). In models that adjusted for maternal education, district of maternal residence, maternal age, and gestational age at first clinic visit, the estimates of the relative odds of a hypertensive disorder associated with having part of the pregnancy during the 1st trimester (OR=1.10; 95%CI= 0.84, 1.44), 2nd trimester (OR=0.87; 95% CI= 0.68, 1.11), and 3rd trimester (OR=0.77; 95% CI=0.57, 1.06) were similar to the unadjusted models. We also found no association between having the 1st, 2nd, or 3rd trimester of pregnancy during the 2008 Olympics, compared to having that trimester during the same dates in 2009, and the odds of a fetal-placental condition in either unadjusted and adjusted analyses (Table 4).

We also did not observe a significantly increased odds of a hypertensive disorder associated with IQR increases in PM_{10}, SO_2, or NO_2 concentrations during the 1st, 2nd, or 3rd trimesters (Table 5). Inconsistent with our *a priori* hypothesis, each 8 $\mu g/m^3$ increase in mean SO_2 concentration during the 3rd trimester was associated with significant decrease in the odds of a hypertensive disorder (OR=0.71; 95% CI=0.53, 0.97). We also did not observe significantly increased relative odds of fetal placental conditions associated with IQR increases in PM_{10}, SO_2, or NO_2 concentrations during the 1st, 2nd, or 3rd trimesters. (Table 5).

DISCUSSION

Taking advantage of the natural experiment in Beijing during the 2008 Summer Olympics, where air pollutant concentrations were reduced by 13% to 60%, [25, 26] we examined whether pregnancies with at least one month during the 2008 Olympics had a lower odds of hypertensive disorders or fetal-placental conditions. We found no clear evidence of a decreased risk of either hypertensive disorders or fetal-placental conditions associated with having the part of the 1st, 2nd, or 3rd trimester of pregnancy during the 2008 Beijing Olympics compared to the same dates in 2009. Further, increases in PM_{10}, NO_2, and SO_2 concentrations during the 1st, 2nd, or 3rd trimester were not associated with an increased odds of either complication, after adjustment for maternal education, district of maternal residence, maternal age, and gestational age at first clinic visit.

Other studies done in the United States, Netherlands, and Spain also found no association between hypertensive complications of pregnancy and increases in trimester-specific PM_{10}, NO_2 concentrations [17, 22] and whole pregnancy NO_2 concentrations.[21, 27] However, others have reported increased risks of hypertensive disorders associated with IQR increases in mean PM_{10} concentrations during the entire pregnancy[28] (IQR =3.92 μg/m^3; OR=1.07; 95%CI=1.04, 1.11), NO_2 concentrations during the first trimester[23] (IQR=5.39 ppb; OR=1.14; 95%CI=1.01,1.29), NO_2 concentrations in the third trimester[16] (IQR=5.63 ppb; OR=1.30; 95%CI=1.07,1.58), and NO_x concentrations over the entire pregnancy[14] (IQR=5.65 ppb; OR=1.11; 95%CI=1.06, 1.16). Xu et al, also reported an increased risk of hypertensive disorders associated with each IQR increase in mean SO_2 concentrations during the first trimester (IQR=3.73 ppb; OR=1.14; 95%CI=1.05, 1.23) and the entire pregnancy (IQR=2.55 ppb; OR=1.13; 95%CI=1.01, 1.25).[23] Recently, Pedersen et al. conducted a meta-analysis of 17 epidemiological studies in eight different countries (USA, Netherlands, Iran, Japan, Canada, Spain, Sweden, and Australia) that examined the association between exposure to ambient air pollution and pregnancy-induced hypertensive disorders. Pedersen et al. reported a 23% increase (95% CI=4%, 42%) in the risk of hypertensive disorders associated with each 10 μg/m^3 increase in NO_2 concentration during the entire pregnancy.[19] Hu et al. also conducted a meta-analysis of 10 epidemiological studies that investigated the association between hypertensive disorders of pregnancy and criteria air pollutants in six different countries (USA, Netherlands, Canada, Spain, Sweden, and Australia). Hu et al reported a 16% (95% CI=3%, 30%) increase in the risk of hypertensive disorders associated with each 10 μg/m^3 increase in NO_2 concentration during the entire pregnancy. [20] To our knowledge, our study is the first to evaluate the association between ambient air pollution concentrations and complications categorized as fetal-placental conditions. However, Dadvand et al, observed that preterm premature rupture of membranes, a component of our definition of fetal-placental conditions, was associated with IQR increases in NO_2 exposure during the third trimester (IQR= 17.8 μg/m^3; OR=1.47; 95%CI=1.03, 2.11) and the entire pregnancy (IQR=15.6 μg/m^3; OR=1.42; 95%CI=1.01, 2.01). [27]

Although our study has several strengths including the use of a natural experiment study design, there are a few limitations that should be considered when making inference. First, mean trimester pollutant concentrations were based on measurements from the closest monitoring site, regardless of individual daily mobility or various behavior patterns, resulting in exposure error. This exposure error is likely to be a combination of Berkson and classical error, with the classical error resulting in a bias towards the null. [29, 30]

Second, our findings may be due, in part, to residual confounding by temporal trends since we did not include 2007 pregnancy complications in our analyses. These 2007 data were entered manually, while the 2008 and 2009 were available in electronic format. Thus, the number of complications in 2007 was substantially lower in comparison to 2008 and 2009 suggesting the possibility of missing data.

Third, we did not have data on smoking or secondhand smoke exposure of each pregnant woman in the study, and thus our findings, may, in part, be due to residual confounding by smoking exposure. However, smoking rates of Chinese women living in Chinese cities are generally low. A recent 2010 report estimated that 28.1% of adults in China (52.9% of men and 2.4% of women) were current smokers, with the prevalence significantly higher among rural residents than urban inhabitants, [31] such as those in our study. We did not have data on secondhand smoke exposure of women in our study. However, our comparison of complications in 2008 and 2009 is unlikely to be confounded by this unless there are substantial differences in secondhand smoke exposure for pregnant women in 2008 versus 2009.

Fourth, our ability to detect a significantly increased risk of hypertensive disorders of pregnancy may have been limited by a small number of these pregnancy complications in 2008 (n=286 hypertensive disorders; 1.1% of N=26,451 births) and 2009 (n=347 hypertensive disorders; 1.2% of N=29,704 births). This may, in part, be due to 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, etc.), as evidence by the lower preterm birth rate in Beijing in 2008 (3.3%) compared to the United States in 2008 (12.3%)[32] and 2012 (11.5%).[33] Some complications may also have been missed since prenatal care providers were only able to list a maximum of three per birth record.

Fifth, similar to previous studies, [16, 21-23, 28] we did not have data on the date of pregnancy complication diagnosis. Therefore, we may have included some subjects where the mean 3rd trimester pollutant concentration was after onset of the pregnancy complication.

In summary, we did not find a significantly decreased risk of hypertensive disorders or fetal-placental conditions associated with having the part of the 1st, 2nd, or 3rd trimester of pregnancy during the 2008 Beijing Olympics compared to the same dates in 2009 as hypothesized. Further, we did not see evidence of an increased risk of these complications associated with increased PM_{10}, NO_2, or SO_2 concentrations.

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REFERENCES

1. Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. Environmental Health Perspectives. 2003; 111:207.

2. Šrám RJ, Binková B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: a review of the literature. Environmental health perspectives. 2005:375-82.

3. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. American Journal of Epidemiology. 2007; 166:1045-52.

4. Rich DQ, Demissie K, Lu S-E, Kamat L, Wartenberg D, Rhoads GG. Ambient air pollutant concentrations during pregnancy and the risk of fetal growth restriction. Journal of epidemiology and community health. 2009; 63:488-96.

5. Bonzini M, Carugno M, Grillo P, Mensi C, Bertazzi P, Pesatori AC. Impact of ambient air pollution on birth outcomes: systematic review of the current evidences. La Medicina del lavoro. 2009; 101:341-63.

6. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environmental health perspectives. 2013; 121:267-373.

7. Naeye R. Placenta Previa Predisposing Factors and Effects on the Fetus and Surviving Infants. Obstetrics & Gynecology. 1978; 52:521-5.

8. Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. Obstetrics & Gynecology. 1980; 55:701-4.

9. Kannan S, Misra DP, Dvonch JT, Krishnakumar A. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential. Ciencia & saude coletiva. 2007; 12:1591-602.

10. Goswami D, Tannetta D, Magee L, Fuchisawa A, Redman C, Sargent I, et al. Excess syncytiotrophoblast microparticle shedding is a feature of early-onset pre-eclampsia, but not normotensive intrauterine growth restriction. Placenta. 2006; 27:56-61.

11. Crispi F, Domínguez C, Llurba E, Martín-Gallán P, Cabero L, Gratacós E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. American journal of obstetrics and gynecology. 2006; 195:201-7.

12. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, et al. Meeting report: atmospheric pollution and human reproduction. Environmental Health Perspectives. 2008; 116:791-8.

13. Woodruff TJ, Morello-Frosch R, Jesdale B. Air pollution and preeclampsia among pregnant women in California, 1996–2004. Epidemiology. 2008; 19:S310.

14. Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ Health Perspect. 2009; 117:1773-9.

15. Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA. Research| Children's Health. Environmental health perspectives. 2011; 119:887.

16. Pereira G, Haggar F, Shand AW, Bower C, Cook A, Nassar N. Association between pre-eclampsia and locally derived traffic-related air pollution: a retrospective cohort study. Journal of epidemiology and community health. 2012.

17. Lee P-C, Roberts JM, Catov JM, Talbott EO, Ritz B. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Maternal and child health journal. 2013; 17:545-55.

18. Rudra C, Williams M. A prospective study of periconceptional ambient air pollutant exposures and preeclampsia risk. Epidemiology. 2006; 17:S104-S5.

19. Pedersen M, Stayner L, Slama R, Sørensen M, Figueras F, Nieuwenhuijsen MJ, et al. Ambient Air Pollution and Pregnancy-Induced Hypertensive Disorders A Systematic Review and Meta-Analysis. Hypertension. 2014:HYPERTENSIONAHA. 114.03545.

20. Hu H, Ha S, Roth J, Kearney G, Talbott EO, Xu X. Ambient air pollution and hypertensive disorders of pregnancy: A systematic review and meta-analysis. Atmospheric Environment. 2014; 97:336-45.

21. van den Hooven EH, de Kluizenaar Y, Pierik FH, Hofman A, van Ratingen SW, Zandveld PY, et al. Air Pollution, Blood Pressure, and the Risk of Hypertensive Complications During Pregnancy The Generation R Study. Hypertension. 2011; 57:406-12.

22. Mobasher Z, Salam MT, Goodwin TM, Lurmann F, Ingles SA, Wilson ML. Associations between ambient air pollution and Hypertensive Disorders of Pregnancy. Environmental research. 2013; 123:9-16.

23. Xu X, Hu H, Ha S, Roth J. Ambient air pollution and hypertensive disorder of pregnancy. Journal of epidemiology and community health. 2014; 68:13-20.

24. Dominici F, Mittleman MA. China's air quality dilemma: reconciling economic growth with environmental protection. JAMA. 2012; 307:2100-2.

25. Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, et al. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA. 2012; 307:2068-78.

26. Zhang J, Zhu T, Kipen H, Wang G, Huang W, Rich D, et al. Cardiorespiratory biomarker responses in healthy young adults to drastic air quality changes surrounding the 2008 Beijing Olympics. Research report (Health Effects Institute). 2013:5-174.

27. Dadvand P, Figueras F, Basagaña X, Beelen R, Martinez D, Cirach M, et al. Ambient air pollution and preeclampsia: a spatiotemporal analysis. Environmental health perspectives. 2013; 121:1365.

28. Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. Paediatric and perinatal epidemiology. 2012; 26:91-100.

29. Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environmental health perspectives. 2000; 108:419.

30. Bateson TF, Coull BA, Hubbell B, Ito K, Jerrett M, Lumley T, et al. Panel discussion review: session three—issues involved in interpretation of epidemiologic analyses—statistical modeling. Journal of Exposure Science and Environmental Epidemiology. 2007; 17:S90-S6.

31. Li Q, Hsia J, Yang G. Prevalence of smoking in China in 2010. New England Journal of Medicine. 2011; 364:2469-70.

 ACCEPTED MANUSCRIPT

32. Martin JA, Osterman M, Sutton PD. Are preterm births on the decline in the United States? Recent data from the National Vital Statistics System. NCHS data brief. 2010:1-8. Available: http://www.cdc.gov/nchs/data/databriefs/db39.pdf [accessed April 9, 2014].

33. Hamilton BE MJ, Ventura SJ. 2013. Preliminary data for 2012. Available: http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_03.pdf [accessed April 9, 2014].

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Table 1. Demographic Characteristics of Study Population by Exposure Period (n=56,155)

	2008 N = 26,451	**2009 N = 29,704**
	N (%)	**N (%)**
Maternal age (years, mean ± SD)	29.4 ± 3.6	29.5 ± 3.6
Maternal education		
High school diploma or less	4, 275 (16)	4, 080 (14)
Some college or technical school	7, 939 (30)	7, 958 (27)
Bachelor's degree	14, 237 (54)	17, 666 (59)
District of maternal residence		
Chaoyang district	10,491 (40)	12,568 (42)
Fengtai district	5,753 (22)	6,465 (22)
Haidian district	8,540 (32)	8,896 (30)
Xicheng district	1,667 (6)	1,775 (6)
Gestational age at first clinic visit (weeks, mean ± SD)	7.3 ± 3.6	7.1 ± 2.7
Pregnancy complications		
Hypertensive disorders	286 (1.1)	347 (1.2)
Gestational hypertension	166 (0.6)	218 (0.7)
Preeclampsia	113 (0.4)	126 (0.4)

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Eclampsia	7 (0.0)	3 (0.0)
Fetal-placental conditions	3,088 (11.7)	3,486 (11.7)
Fetal macrosomia	1,620 (6.1)	1,868 (6.3)
Fetal distress	565 (2.1)	570 (1.9)
Placental abruption	23 (0.1)	26 (0.1)
Threatened preterm labor	181(0.7)	231 (0.8)
Polyhydramnios	17 (0.1)	30 (0.1)
Oligohydramnios	226 (0.9)	261 (0.9)
Premature rupture of membranes	456 (1.7)	500 (1.7)

Table 2. Distribution of mean monthly (gestational month) air pollutant concentrations for pregnancies with part of 1st trimester during 2008 Beijing Olympics and same calendar dates in 2009.

Pollutant	Year	N	Mean	Standard deviation	Minimum	25th	50th	75th	Maximum	p-value*
PM_{10} (μg/m^3)	2008	8,257	88	6	81	83	87	93	102	<0.001
PM_{10}(μg/m^3)	2009	10,121	114	6	107	110	111	118	129	
NO_2 (μg/m^3)	2008	8,257	75	17	56	58	73	92	105	<0.001
NO_2 (μg/m^3)	2009	10,121	94	9	83	85	90	105	115	
SO_2 (μg/m^3)	2008	8,257	37	10	26	29	31	42	68	<0.001
SO_2 (μg/m^3)	2009	10,121	39	10	31	31	34	45	68	

*testing differences in mean pollutant concentrations between 2008 and 2009

Table 3. Pearson correlation coefficients for mean pollutant concentrations, relative humidity, and temperature during 1st trimester of pregnancy for 2008 and 2009 (n=56,155)

	PM_{10}	SO_2	NO_2	Relative Humidity	Temperature
PM_{10}	1	--	--	--	--
SO_2	0.39	1	--	--	--
NO_2	0.41	0.76	1	--	--
Relative Humidity	-0.43	-0.8	-0.69	1	--
Temperature	-0.34	-0.95	-0.84	0.79	1

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Table 4. Relative odds of pregnancy complications associated with the 2008 Olympic time period compared to the same dates in 2009, by trimester

	Trimester	N (births)	n (complications)	UNADJUSTED ANALYSES OR (95% CI)	ADJUSTED ANALYSES[a] OR (95% CI)
Hypertensive Disorders	1	18,278	217	1.13 (0.86-1.47)	1.10 (0.84-1.44)
	2	20,027	265	0.89 (0.70-1.13)	0.87 (0.68-1.11)
	3	17,850	167	0.79 (0.58-1.08)	0.77 (0.57-1.06)
Fetal-placental conditions	1	18,278	2,308	0.96 (0.88-1.05)	0.96 (0.88-1.05)
	2	20,027	2,552	0.99 (0.91-1.07)	0.99 (0.91-1.07)
	3	17,850	2,146	1.02 (0.93-1.12)	1.02 (0.93-1.12)

[a]Adjusted for maternal education, district of maternal residence, maternal age, and gestational age at first clinic visit

Table 5. Relative odds of pregnancy complications associated with interquartile range increases in trimester-specific mean pollutant concentrations

Pollutant	Trimester	Interquartile Range	N (births)	n (complications)	UNADJUSTED ANALYES OR (95% CI)	ADJUSTED ANALYSES[a] OR (95% CI)
Hypertensive Disorders						
PM_{10} (μg/m^3)	1	10	18,278	217	0.96 (0.87-1.05)	1.03 (0.91-1.16)
	2	10	20,027	265	1.03 (0.95-1.12)	1.04 (0.93-1.15)
	3	10	17,850	167	1.06 (0.97-1.16)	1.02 (0.92-1.13)
NO_2 (μg/m^3)	1	34	18,278	217	0.69 (0.52-0.90)	1.03 (0.53-1.99)
	2	26	20,027	265	1.09 (0.90-1.31)	1.29 (0.80-2.07)
	3	32	17,850	167	1.49 (1.10-2.01)	1.24 (0.67-2.31)
SO_2	1	13	18,278	217	0.81 (0.67-	1.18 (0.74-

(μg/m³)					0.98)	1.90)
	2	8	20,027	265	1.01 (0.92-1.11)	0.89 (0.69-1.14)
	3	8	17,850	167	1.09 (0.97-1.24)	0.71 (0.53-0.97)
Fetal-placental conditions						
PM_{10} (μg/m³)	1	10	18,278	2,308	1.02 (0.99-1.05)	1.03 (0.99-1.07)
	2	10	20,027	2,552	1.00 (0.97-1.03)	1.00 (0.96-1.04)
	3	10	17,850	2,146	0.99 (0.97-1.02)	1.01 (0.98-1.04)
NO_2 (μg/m³)	1	34	18,278	2,308	1.03 (0.94-1.12)	1.14 (0.91-1.41)
	2	26	20,027	2,552	1.02 (0.96-1.09)	0.98 (0.83-1.15)
	3	32	17,850	2,146	0.92 (0.85-1.01)	0.96 (0.80-1.15)
SO_2 (μg/m³)	1	13	18,278	2,308	1.00 (0.95-1.06)	1.00 (0.86-1.16)
	2	8	20,027	2,552	1.01 (0.98-	0.97 (0.89-

					1.04)	1.06)
	3	8	17,850	2,146	0.99 (0.95-1.03)	1.09 (1.00-1.20)

[a]Adjusted for maternal education, district of maternal residence, maternal age, gestational age at first clinic visit, relative humidity, and temperature