January 2013

Ambient Air Pollutant Pm10 And The Risk Of Preterm Birth In Lanzhou, China

Nan Zhao
Yale University, sixsunzh@gmail.edu

Ambient air pollutant PM_{10} and the risk of preterm birth in Lanzhou, China

By

Nan Zhao

A Thesis Presented to

The Faculty of the Department of Epidemiology and Public Health

Yale University

In Candidacy for the Degree of

Master of Public Health

2013

Permission to Copy

Permission for photocopying, microfilming, or computer electronic scanning of “Ambient air pollutant PM_{10} and the risk of preterm birth in Lanzhou, China” for the purpose of individual scholarly consultation of reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

____Nan Zhao_______________
Signature of Author

____29/4/2013_______________
Date

ABSTRACT

Background: Early studies have inconsistently linked ambient air pollutant PM_{10} exposure during pregnancy to the risk of preterm birth. However, majority of early studies were based on registry data which could result in misclassification of exposure due to the lack of detailed home and work addresses, as well as failed to collect information on potential confounders. China has the world's most polluted cities and suffers the second largest burden of preterm births. Very few studies, however, have been conducted in China to investigate the association between PM_{10} exposure and preterm birth. Building upon a birth cohort study conducted in Lanzhou, China, we investigated the hypothesis that high level exposure to PM_{10} during pregnancy increases the risk of preterm birth.

Methods: A total of 2,902 singleton live births without birth defects delivered at the Gansu Provincial Maternity and Child Care Hospital in 2009-2011 were included in the study. Air pollutant data of 24-hour average particulate matter with an aerodynamic diameter less than 10 um (PM_{10}) was collected from four monitoring stations. Individual exposure levels of PM_{10} were assigned based on home and work addresses to air monitoring stations using inverse-distance weighting approach. Unconditional logistic regression model was used to calculate the Odds Ratio (OR) and 95% confidence interval (CI) to determine the association between preterm birth and PM_{10} exposure. We also explored the association after adjustment for the co-linearity by using Principal Component Analysis. Potential confounding factors such as maternal age, hypertension during pregnancy, season of conception, cesarean section, parity, active and passive smoking, and folic acid intake before pregnancy were included in the final model.

Results: Using the China National Ambient Air Quality Standards (NAAQS) Grade II level (0.15mg/m3), which is equivalent to the U.S. NAAQS level, as the reference, higher daily average concentration of PM_{10} during entire pregnancy was associated with an increased risk of preterm based on home address only (OR=2.15, 95%CI: 1.47-3.16). Similar association was also observed for the first trimester. Using the weighted concentration based on both home and work addresses, similar patterns were observed for the entire pregnancy (OR=1.96, 95%CI: 1.33-2.90) and the first trimester (OR=2.08, 95% CI: 1.22-3.52). Percentage of the days with daily average concentration of PM_{10} exceeding the standard was positively associated with the risk of preterm birth during the first trimester.

Conclusions: This study suggests that the ambient air pollutant PM_{10} has positive correlation with the preterm birth in Lanzhou, China.

Keywords: Preterm birth, PM_{10}, China, Lanzhou, Birth cohort

TABLE OF CONTENTS

1. Introduction

1.1 Preterm Birth

Preterm birth is defined as delivery prior to 37 completed weeks or 259 days of gestation (Beck, Wojdyla et al. 2010). It is classified into three conditions: medically indicated (iatrogenic) preterm birth, preterm premature rupture of membranes (PPROM) or elective preterm deliveries, and spontaneous (idiopathic) preterm birth, which account for about 25% (18.7-35.2%), 25% (7.1–51.2%), and 50% (23.2–64.1%), respectively. The majority of multiple pregnancies are delivered preterm, among those about 50% due to medical indications (Moutquin 2003). Approximately 10% of preterm births are multiple births.

Preterm birth has been considered as a leading cause of neonatal morbidity and mortality (Mathews and MacDorman 2006), has long-term adverse consequences for health (Huddy, Johnson et al. 2001). It has also been linked to adult chronic diseases including cardiovascular diseases, diabetes, and cancer etc. (Falah, McElroy et al. 2013). Recent studies found that incidence rates of preterm births have increased worldwide since 1990 (WHO). The causes of this increase are poorly understood. In general, the rates of preterm birth in developed countries ranges from 5% to 9%, while the rates in developing countries are over 15% (Goldenberg, Culhane et al. 2008).The preterm birth rate increased from 7.5% in 1990 with a total preterm of 2 million in the 65 countries to 8.6% in 2010 with a total of 2.2 million preterm births worldwide. In United States, the preterm birth rate has increased from 9.4% to 12% of all birth over the last 2 decades (Moore 2002). China has suffered the second largest number of preterm in the world (WHO).

A number of risk factors have been suggested to be associated with the risk of preterm birth, including ethnicity, nutrition, body mass index (BMI), marital status (Raatikainen, Heiskanen et al. 2005), genetic make-up (Winkvist, Mogren et al. 1998), subfertility (Pinborg 2012), maternal age at the lower and upper years, which are 18 years old (Goldenberg, Culhane et al. 2008) and 35 years old (Martius, Steck et al. 1998), maternal height and weight (Dohme), infection (Moutquin 2003), alcohol consumption, cigarette smoking (Shiono PH 1995), multiple birth (Gardner, Goldenberg et al. 1995), high blood pressure (Goldenberg RL 1998), preeclampsia (Banhidy, Acs et al. 2007), diabetes (Rosenberg, Garbers et al. 2005), asthma, thyroid disease, heart disease, polyhydramnios or oligohydramnios (Goldenberg RL 1998), anxiety and depression (Dole, Savitz et al. 2003), birth defects (Dolan, Gross et al. 2007), infections during pregnancy (Goldenberg, Hauth et al. 2000), problem with the uterus or cervix, etc. However, these factors cannot explain all preterm births. Recent evidence suggests that the environmental factors may play a role in preterm births, such as ambient air pollution (Ritz B 2000, Sagiv, Mendola et al. 2005, Wilhelm and Ritz 2005, Jiang, Zhang et al. 2007, Kim, Ha et al. 2007, Brauer, Lencar et al. 2008, Darrow, Klein et al. 2009, Suh, Kim et al. 2009, Zhao, Liang et al. 2011, van den Hooven, Pierik et al. 2012).

1.2 Air Pollution and Preterm Birth

Studies have suggested that ambient air pollutants are associated with the risk of preterm births as reviewed by Ritz et al. For example, the average CO over 6 weeks before birth and over the first month of pregnancy can cause the risk of preterm birth increased by about 12% and 4%, respectively (Ritz B 2000); an increases of 10mg/m^3 of 8-week average SO_2,NO_2 and O_3 corresponded to 11.89%, 5.43%, and 4.63% increase in the risk of preterm birth (Jiang, Zhang et al. 2007); and daily preterm birth rates were associated with average NO_2 concentrations in the preceding 6 weeks and with average $PM_{2.5}$ sulfate and $PM_{2.5}$ water-soluble metal concentration in the preceding week (Darrow, Klein et al. 2009). China Xu's results showed that there was a significant dose-dependent association between gestational age and sulfur dioxide and total suspended particulate concentrations. They found that each 100-micrograms/m^3 increase in total suspended particulates corresponded to 10% increase in the risk of preterm birth (Xu, Ding et al. 1995).

1.3 PM_{10} and Preterm Birth

Maternal exposure to ambient air pollutant PM_{10} during pregnancy has been suggested to be associated with the risk of preterm birth. To the best of our knowledge, eleven published epidemiological studies investigated the association between ambient PM_{10} exposure during pregnancy and risk of preterm birth. The results, however, have been inconsistent.

A majority of the studies are based on registry or administrative database (Ritz B 2000, Sagiv, Mendola et al. 2005, Wilhelm and Ritz 2005, Hansen, Neller et al. 2006, Jiang, Zhang et al. 2007, Brauer, Lencar et al. 2008, Darrow, Klein et al. 2009, Suh, Kim et al. 2009, Zhao, Liang et al. 2011).

Ritz and colleagues reported a 20% increase in preterm birth per 50μg/m^3 increase in ambient PM_{10} levels averaged over 6 weeks before birth and a 16% increase when averaged over the first month of pregnancy in a study consisted of 106,483 subjects in Southern California (Ritz B 2000). After adjustment of other risk factors, they found smaller or no effects for PM_{10}. Further, they also explored PM_{10} effects by season of birth or conception and the cesarean section, the results showed significant association between PM_{10} exposure and preterm only in winter and spring, and increases in risk of premature delivery with increasing PM_{10} during the first month of pregnancy, but no effect observed before birth.

Then Wilhelm and Ritz conducted another study based on the birth certificates, which were provided by the California Department of Health Services, performed a ZIP-code-level analysis in which they selected all births during 1994-2000 (Wilhelm and Ritz 2005). The result of this study confirmed their previous observation for the period 1989-1993 (Ritz B 2000). They calculated the distance from each home to the nearest air monitoring station. For PM_{10} exposure, there were 6 stations. They did not observe the risk increase for PM_{10} exposure and preterm birth for first trimester and 6 weeks before delivery based on the ZIP-code-level analyses. Yet women in the highest exposure quartile and residing within 1 mi of a station had a 17% increased risk during early pregnancy (PM_{10}>51.2μg/m^3). And results for first month average concentration were similar to those found for first-trimester concentration.

A study collecting all live singleton births whose mothers resided in four Pennsylvania counties between January 1, 1997 and December 31, 2001 (n=187,997) also observed increased risk for preterm delivery with exposure to average PM_{10} in the 6 weeks before birth (Sagiv, Mendola et al. 2005). In addition, they examined lags up to 7 days before the birth and found an acute effect of exposure to PM_{10} two days and five days before birth, and a marginal significant result was found.

A retrospective cohort of 476,489 births between 1994 and 2004 in 5 central counties of metropolitan Atlanta investigating aggregated daily counts of preterm birth in relation to ambient levels of six air pollutants (Darrow, Klein et al. 2009). Darrow et al observed daily preterm birth rates were associated with $PM_{2.5}$ sulfate and $PM_{2.5}$ water-soluble metal concentration in preceding week, but no observed association of preterm birth with PM_{10}.

Hansen et al. conducted a study in Australia from 2000 to 2003 with 28,200 participates (Hansen, Neller et al. 2006). They reported a relationship between PM_{10} and preterm births observed in the first trimester and the last trimester, which corresponding 15% and 4% increases, respectively.

A cohort study identified 70,249 singleton births from 1999 to 2002 using administrative data with complete covariate data and maternal residential history in Vacouver, British Columbia, Canada (Brauer, Lencar et al. 2008). They evaluated the impacts of the traffic-related air pollutant on birth outcomes, and found that, for risk of very preterm birth (<30 weeks), elevated ORs for a larger number of pollutants including PM_{10}.

A study based on the Korea National Statistical office for 374,167 subjects who were delivered between 1998 and 2000 in Seoul, South Korea found that effect of PM_{10} exposure prior to the 37 weeks of gestational period was stronger on the risk of premature birth than that posterior to the 37 weeks of gestational weeks (Suh, Kim et al. 2009). And this trend was consistent for each trimester; however, the hazard ratios for preterm birth related to PM_{10} exposure in the first and third trimester were slightly higher than those of the second trimester.

A cohort consisting of 7,772 of mothers and singleton live births in the Netherlands was conducted to investigate the relationship between the air pollution exposure including PM_{10} during pregnancy and adverse birth outcomes (van den Hooven, Pierik et al. 2012). The individual exposure to PM_{10} was assessed at the home address using a combination of continuous monitoring data and dispersion modeling techniques, and both the spatial and temporal variation in the air pollution were taken into account. They observed the exposures in the third and fourth quartiles were positively associated with preterm birth, compared with mothers in the lowest quartile of PM_{10} exposure level. After including both PM_{10} and NO_2 in the models, association for PM_{10} exposure with preterm birth became stronger.

There were only two studies conducted in China and based on registry data as well. Zhao et al found that an increase of 100ug/m^3 of air pollutants corresponded to relative risk (RRs) of 1.0688 (95%:1.0074-1.1301) in exploring the correlation between air pollution and preterm birth in Guangzhou city by using Generalized Addictive Model (GAM) extended Poisson regression model in 2007 with 142,312 subjects. After adjusting co-linearity and exploring the association at their strongest cumulative effects, both suggested similar increase results (Zhao, Liang et al. 2011).

Another study obtaining the data from the live birth database maintained by Shanghai Municipal Center of Disease Control and Prevention in China observed an increase of 10 microg/m^3 of 8-week average PM_{10} corresponding to 4.42%(95%CI:0.35%,8.91%) increase of preterm birth (Jiang, Zhang et al. 2007).

Only two studies, to date, were not based on the registry or administrative database. One of them was a hospital-based birth cohort study conducted in Seoul between 2001 and 2004 (Kim, Ha et al. 2007), another was a prospective cohort study conducted in Netherlands between 2001 and 2005 (van den Hooven, Pierik et al. 2012). Kim et al observed a marginal relationship of 5% increase in the risk of preterm birth with per 10ug/m^3 of PM_{10} concentration increase during the third trimester, no significant association was observed during the first and second trimesters. Van den Hooven et al reported that the third and fourth quartiles of PM_{10} exposure corresponded to 40% and 32% increase respectively in the risk of preterm birth. After adjusted for NO_2, this association became even stronger.

Limitations should be considered when interpreting the results of these studies. First, potential exposure misclassification is the major concern. Individual exposure to air pollution in majority of the studies was based on residential address only without considering the subjects' work addresses. Some of the studies did not even consider the spatial variation of the exposure. For example, air pollution level was based on city levels which only take time variation into consideration. Second, Because of using registry database, potential confounding factors, such as smoking, socioeconomic status, nutrition, maternal complication during pregnancy, prenatal care, and delivery methods, etc. were not collected and therefore were not controlled in the studies. Third, many studies failed to consider time windows of exposure which might have different impact on the risk of preterm. Finally, due to inconsistent approaches of exposure assessment used in different studies and large variation of exposure levels in different population, it is quite challenge to make comparison of the results from different studies.

In light of the unclear association between PM_{10} and preterm birth, paucity of the literature regarding the relationship, as well as the limitation suffered from early studies, we conducted a birth cohort study in Lanzhou, China with detailed information on both home and work addresses, as well as potential confounders to examine ambient PM_{10} exposure during pregnancy and risk of preterm birth. China has the world's most pollutant cities and suffers the second largest burden of preterm births. Very few studies, however, have been conducted in China to elucidate the association between air pollution and adverse birth outcomes.

2. Methods

2.1 Study population

A birth cohort study was conducted between February 2010 and December 2011 at the Gansu Provincial Maternity and Child Care Hospital (GPMCCH), the largest maternity and child care hospital in Lanzhou, China. The eligible population was composed of 4,359 pregnant women who came to the hospital for delivery during the study period with gestational age greater than 22 weeks. A total of 3,670 women participated in the study. After exclusion of women who delivered stillbirths (n=15), multiple birth (n=127), and birth with congenital defects (n=113), 3,432 pregnant women had a normal singleton live birth. Because the study was focusing on ambient air pollution and risk of preterm, study population who resided in the areas that were not covered by air monitoring stations were excluded from the analysis, which yielded a sample size of 2,902.

2.2 Date Collection

All study procedures were approved by the Human Investigation Committees at the GPMCCH and Yale University. Eligible women were informed upon their arrival at the hospital for delivery. After obtaining their written consent forms, an in-person interview was conducted at the hospital either before or after delivery using a standardized and structured questionnaire by trained study interviewers. The questionnaire covers information on demographics, reproductive and medical history, smoking, alcohol and tea consumption, physical activity, occupational and residential history, and dietary intakes. Information on birth outcomes and maternal complications were abstracted from the medical records.

2.3 Exposure Assessment

Lanzhou is the largest city and capital of the Gansu Province, and is located in northern China with a population about 3.5 million (Figure 1). Lanzhou has relatively highest burden of the air pollution levels in China and in the world (Zheng, Wang et al. 2013), since it is a heavy industry city with industrial development as the pillar of its urban development. It has a number of industries includes petrochemicals, oil refinery, textile mills, etc.

We estimated prenatal exposure to ambient air pollution using government ambient air monitoring data. The China's EPA office located in Lanzhou collects the 24-hr average concentration for air pollutants through an automated data reporting system. The 24-hour average particulate matter with an aerodynamic diameter less than or equal to 10μm (PM_{10}) from the four stations in Lanzhou for the period between April 1, 2009 and December 31, 2012 for two of the stations (Huanghebei and Xigu), and between January 1, 2011 and December 31, 2012 for another two stations (Xizhan and Tieluju) were collected. The longitude and latitude coordinates of 4 monitoring stations are used to calculate the distance between stations, which are Xigu: 103°37′53″, 36°6′11″; Huanghebei: 103°50′29″, 36°4′21″; Xizhan: 103°42′42″, 36°4′32″; and Tieluju: 103°49′51″, 36°2′47″ (see figure 2).

We used the earth online sharing website provided by Google (www.earhol.com) to obtain longitude and latitude coordinates of each subject's home and work addresses. We assigned everyday PM_{10} concentration data from four monitoring stations to each home or work address using the inverse-distance weighting approach, the formula as followed:

$$W(a) = \frac{\frac{A+B+C+D}{A}}{\frac{A+B+C+D}{A} + \frac{A+B+C+D}{B} + \frac{A+B+C+D}{C} + \frac{A+B+C+D}{D}}$$

where W(a) represents the weight of one address when considering the data from monitoring station "a"; A represents the distance from the address to monitoring station "a"; B represents the distance from the address to monitoring station "b"; C represents the distance from the address to monitoring station "c"; D represents the distance from the address to monitoring station "d". Then, the PM_{10} level for this address is: $C = W(a) \times C(a) + W(b) \times C(b) + W(c) \times C(c) + W(d) \times C(d)$

For each subject exposure level, we used two different approaches. First, we only based on the home address, which means that the subject's daily exposure level of PM_{10} is the daily concentration of PM_{10} of his home address. Second, we considered both home and work address. According to subject's time of work is around 8 hours per day, and they spent the rest of the time at home, we used average weighted approach to calculate the daily concentration of exposure levels, which means that, for each subject, the daily concentration based on home address corresponds to two thirds of total daily exposure level, and the concentration based on work address corresponds to one third of total daily exposure level.

2.4 Statistical Analysis

We used two different approaches to set up reference groups. The first one is to directly divide concentrations of exposure into tertiles and use the first tertile as reference exposure level. For the second approach, the China National Ambient Air Quality Standards (NAAQS) Grade II level ($0.15 mg/m^3$ or $150 \mu g/m^3$), which is equivalent to the U.S. NAAQS level, was used as the reference, and then the rest of exposure data of PM_{10} were divided into two categories based on medium level. In addition to analysis of this relationship by daily average concentration of PM_{10} exposure level, we also explored the association by examining the percentage of the days with daily average concentration of PM_{10} exceeding the standard. All these associations were also examined by exposure windows (by entire pregnancy and by trimesters).

Preterm birth was defined as delivery before 37 completed weeks of gestation (Beck, Wojdyla et al. 2010). Controls were defined as births delivered 37 completed weeks or more of gestation with birth weight equal to or larger than 2,500g. Univariate-analysis (χ^2 test) was conducted to examine the distributions of selected characteristics between the cases and controls. Unconditional logistic regression model was used to calculate the odds ratios (OR) and 95% confident intervals (CI).

The Principal Component Analysis was used to adjust the co-linearity within trimesters and between trimesters and season of conception. Because we found there were high correlations between the first and the last trimesters, and between trimesters and season of conception. Then we transformed the point estimates β calculated by the principal components back to the ORs of the original PM_{10} exposure levels for each trimester and season of conception. Meanwhile, we calculated the 95% CI for them as well.

The potential confounding factors, such as maternal age, ethnicity, education levels, family monthly income, alcohol consumption, active and passive smoking status during pregnancy, folic acid use before conception, season of conception, history of pregnancy affected by preterm, parity, history of childbirth, and hypertension during pregnancy, were included into the final model. We also explored the potential effect modification between ambient air pollutants and these variables in the risk of preterm birth.

All analyses were performed using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

3. Results

3.1 Distribution of Selected Characteristics of the Study Population

The distribution of demographic and maternal characteristics of the subjects was presented in Table 1. A total of 183 subjects were preterm births (cases) and 2719 subjects were term babies (controls). Women who had preterm deliveries were younger (p=0.0272), less educated (p=0.0170), less likely to take folic acid before conception (p=0.0281), and more likely to be multiparous (p=0.0318) than the women who had term deliveries. There were no differences in race, family income, and active and passive smoking between the preterm and control groups (p>0.05). Women who delivered preterm birth were slightly more likely to consume alcohol (p=0.0497). Women who had preterm deliveries were more likely to having conception during heating season (p=0.0004), to have history of pregnancy affected by preterm

($p<0.0001$), to have cesarean delivery ($p=0.0002$), and to suffering hypertension during pregnancy ($p<0.0001$).

3.2 Associations between Preterm Birth and PM_{10} based on Home Address only

Table 2 showed the results based on tertiles of the daily average concentration of PM_{10} exposure levels. Compared to the lowest tertile of the exposure level of PM_{10} during entire pregnancy, the second tertile was negatively associated with the risk of preterm birth (OR=0.63, 95%CI: 0.41, 0.97), the third tertile was not significantly associated with the risk of preterm (OR=1.35, 95%CI: 0.92, 1.98). We also did not find significant association for each 100μg/m^3 PM_{10} increase (OR=1.92, 95%CI: 0.82, 4.49). Then we analyzed the data by trimesters. For the first trimester, for each 100μg/m^3 increase in PM_{10} exposure level, there was no change in the risk of preterm birth (OR=1.29, 95%CI: 0.77, 2.15). Compared to the lowest tertile, the second tertile was associated with 76% increased risk (OR=1.76, 95%CI: 1.09, 2.08), while the third tertile was not significantly associated with the risk of preterm birth (OR=1.57, 95%CI: 0.92, 2.68). For the second trimester, each 100μg/m^3 increase in PM_{10} exposure level corresponded to no significant association with the risk of preterm birth (OR=0.86, 95%CI: 0.59, 1.26). Compared to the lowest tertile, the second tertile and the third tertile were not associated with the risk of preterm (OR=0.75, 95%CI: 0.44, 1.29; OR=0.94, 95%CI: 0.67, 1.32; respectively). For the third trimester, for each 100μg/m^3 increase in PM_{10} exposure level, there was also no association observed (OR=0.79, 95% CI: 0.47, 1.33), and the second and third tertiles were not associated with the risk of preterm (OR=0.55, 95% CI: 0.28, 1.04; OR=1.00, 95% CI: 0.59, 1.67)

Table 3 showed the results using China's NAAQS Grade II (0.15mg/m^3) as the reference level. Compared to the China NAAQS level, the highest level (>165.4μg/m^3) was associated with the risk of preterm birth (OR=2.15, 95% CI: 1.47, 3.16). After stratify by trimesters, for the first trimester, the second exposure level (150-165.3μg/m^3) was also associated with the risk preterm birth (OR=2.10, 95% CI: 1.25, 3.51), while the highest level was not significantly associated with the risk of preterm (OR=1.37, 95% CI: 0.84, 2.22). For the second trimester, both the second (150-165.3μg/m^3) and the third/highest (>165.4μg/m^3) exposure levels were not significant associated with the risk of preterm birth (OR=0.78, 95% CI: 0.48, 1.28; OR=1.04, 95% CI: 0.73, 1.48; respectively). Similar patterns were showed for the third trimester.

Table 4 showed the results when explored the association by examining the percentage of the days with daily average concentration of PM_{10} exceeding the standard. For entire pregnancy period, for each one percent increase in percentage of days exceeding the standard, there was 2% increase in the risk of preterm birth. When analyzed by tertiles, no significant associations were found for both the second tertile and the third tertile as compared to the first tertile. For the first trimester, each one percent increase in percentage of exceeding days corresponded only 1% increase in the risk of preterm birth, and there were significant associations between the higher tertiles of percentage of exceeding days and the risk of preterm birth (OR=1.68, 95% CI: 1.03, 2.75 for second tertile; OR=1.63, 95% CI: 1.16, 2.30 for third tertile). For the second trimester, for each one percent increase in PM_{10} exposure level, there was no significant association with the risk of preterm birth. For the third trimester, each one percent increase in percentage of exceeding days corresponded to 3% decrease in the risk of preterm. When analyzed by tertiles, no significant association observed in higher exposure levels for the second and the third trimesters.

3.3Associations between Preterm Birth and PM_{10} using Weighted Concentrations based on Home and Work Addresses

Table 5 showed the results based on tertiles of the daily average concentration of PM_{10} exposure levels. Compared to the lowest tertile of the exposure level of PM_{10} during entire pregnancy, either the second or third tertiles were not significantly associated with the risk of preterm (OR=0.79, 95%CI: 0.52, 1.21 for the second tertile; OR=1.43, 95%CI: 0.97, 2.11 for the third tertile). We also did not find significant association for each 100μg/m^3 PM_{10} increase (OR=2.16, 95%CI: 0.91, 5.15). Then we stratified by trimesters. For each trimester, there is no increase or decrease in risk of preterm for each 100 μg/m^{3}increase in PM_{10} exposure level (OR=1.19, 95% CI: 0.68, 2.08 for the first trimester; OR=1.10, 95% CI: 0.71, 1.71 for the second trimester; OR=1.12, 95% CI: 0.62, 2.04 for the third trimester). Compared to the lowest tertile, the second and the third tertiles were not significantly associated with the risk of preterm birth for each trimester.

Table 6 showed the results using China's NAAQS Grade II (0.15mg/m^3) as the reference level. Compared to the China NAAQS level, the highest level (>165.4μg/m^3) was associated with the risk of preterm birth (OR=1.96, 95% CI: 1.33, 2.90). After analyzed the data by trimesters, for the first trimester, the second exposure level (150-165.3μg/m^3) was strongly associated with the risk preterm birth (OR=2.08, 95% CI: 1.22, 3.52). While, the highest level was not associated with the risk of preterm (OR=1.53, 95% CI: 0.93, 2.51). For the second and the third trimesters, both the second (150-165.3μg/m^3) and the third/highest (>165.4μg/m^3) exposure levels were not significant associated with the risk of preterm birth (OR=0.91, 95% CI: 0.57, 1.47; OR=1.05, 95% CI: 0.74, 1.49, respectively, for the second trimester; OR=1.07, 95% CI: 0.59, 1.95; OR=1.12, 95% CI: 0.67, 1.83, respectively, for the third trimester).

Table 7 showed the results when explored the association by examining the percentage of the days with daily average concentration of PM_{10} exceeding the standard. For entire pregnancy period, for each one percent increase in percentage of exceeding days, there was 2% increase in the risk of preterm birth. While, there was no significant association found for both the second tertile and third tertile. For the first trimester, each one percent increase in percentage of exceeding days, there was 1% increase in the risk of preterm birth, and there were significant associations between the higher tertiles of percentage of exceeding days and the risk of preterm birth (OR=1.64, 95% CI=1.00, 2.68 for second tertile; OR=1.63, 95% CI=1.16, 2.29 for third tertile). For the second trimester, for each one percent increase in percentage of exceeding days, there was no change in the risk of preterm birth. For the third trimester, each one percent increase in percentage of exceeding days corresponded to 3% decrease in the risk of preterm. No significant associations observed in higher levels of percentage of exceeding days of the second and the third trimesters, compared to the lowest level.

3.4 Associations between Preterm Birth and PM_{10} after Adjustment for Co-linearity by using Principal Component Analysis

Table 8 showed the results when explored the association by using Principal Component Analysis to adjust for co-linearity. According to the results based on the home address only, for the first trimester, we found significant association for each 100μg/m^3 PM_{10} increase (OR=1.11, 95%CI: 1.03, 1.20), while, for the second trimester, there was no association for each 100μg/m^3 PM_{10} increase in the risk of preterm birth (OR=0.96, 95%CI: 0.84, 1.10), for the third trimester, for each 100μg/m^3 PM_{10} increase, there was 11% decrease in the risk of preterm birth (OR=0.89, 95%CI: 0.83, 0.95). Similar patterns found based on the weighted average concentration of home and work addresses (OR=1.12, 95%CI: 1.03, 1.21 for the first trimester; OR=0.96, 95%CI: 0.84, 1.10 for the second trimester; OR=0.89, 95%CI:

0.83, 0.95). Meanwhile, there was also positive association between the season of conception and the risk of preterm birth (OR=1.12, 95%CI: 1.05, 1.20).

4. Discussion

Our study suggests that maternal higher level exposure to PM_{10} is positively associated with an increased risk of preterm birth and the risk varies by trimesters. Specifically, we found that higher daily average concentration of PM_{10} during entire pregnancy was associated with an increased risk of preterm birth. The higher percentage of the days with daily average concentration of PM_{10} exceeding the standard was positively associated with the risk of preterm birth. For each 100$\mu g/m^3$ increase in PM_{10} exposure, we observed an increased risk of preterm birth. Similar patterns were also observed when analyzing the association using percentage of days of average concentration exceeding the China NAAQS standard.

Our point estimates showed greater magnitude compared to those reported in the previous literatures. Van den Hooven et al reported that there were associations observed in third quartile and the fourth quartile (OR=1.40, 95% CI: 1.03, 1.89; OR=1.32, 95% CI: 0.96, 1.79) (van den Hooven, Pierik et al. 2012). While, we observed a stronger association, for example, there were greater magnitude effects of the highest exposure level (>165.4$\mu g/m^3$) on the risk of preterm birth during entire pregnancy period (OR=2.15, 95% CI: 1.47, 3.16). It is possible that our study population experienced much higher levels of PM_{10} compared to other study populations, such as the mean levels of PM_{10} exposure of all four stations in our study population is ranged from 127.26μg/m^3 to 159.81μg/m^3, while others the mean level of PM_{10} exposure ranged from 13μg/m^3 to 90μg/m^3 (Ritz B 2000, Sagiv, Mendola et al. 2005, Wilhelm and Ritz 2005, Hansen, Neller et al. 2006, Kim, Ha et al. 2007, Brauer, Lencar et al. 2008, Darrow, Klein et al. 2009, Suh, Kim et al. 2009, Zhao, Liang et al. 2011, van den Hooven, Pierik et al. 2012).

Many studies including ours suggest that the risk due to air pollution is greater for exposures experienced in the first trimester. For instance, Hansen et al observed associations between the PM_{10} exposure and the risk of preterm birth during the first trimester (OR=1.15, 95% CI=1.06-1.25) was greater than it during the last trimester (OR=1.04, 95% CI=0.92-1.16) (Hansen, Neller et al. 2006). In our study, no matter using the home address only or both home and work addresses to calculate the daily concentration, significantly increased risk of preterm birth associated with higher level of PM_{10} was observed for the first trimester, but not for the second and the third trimesters. Because the first and the third trimesters were highly negatively correlated with each other, a negative association between the PM_{10} exposure and the risk of preterm birth was observed for the third trimester. To take co-linearity into consideration, we also analyzed the data using Principal Component Analysis, which provided the same conclusion that there was a positive association between PM_{10} and risk of preterm for the first trimester, a negative association for the third trimester, and no association for the second trimester.

4.1 Mechanism

It is biologically plausible that high level exposure to PM_{10} increases the risk of preterm birth. Peter et al reported that in women the OR for plasma viscosity above the 95th percentile of the distribution (1.38 mPa s) was 3.6 (95% CI 1.6-8.1) comparing measurements during the air pollution episode with non-episode measurements after adjustment for cardiovascular risk factors and meteorological variables, and this results indicated that exposure to air pollutant PM_{10} induces altered blood rheology due to inflammatory processes in the lung which lead to an acute-phase reaction(Peters, Doring et al. 1997). The hypothesis that a suboptimal haemodilution is a risk factor for an unfavorable course of pregnancy, and are in agreement with the pathophysiologic mechanism proposed by Huisman: a higher viscosity of the placenta(Huisman, Zwart et al. 2013). And inflammation was associated with inadequate placental perfusion (Zondervan, Oosting et al. 1987, Knottnerus, Delgado et al. 1990, Sagiv, Mendola et al. 2005).

Another possible mechanism regarding the impact of air pollutants on preterm birth is maternal infection in long-term process during pregnancy(Sagiv, Mendola et al. 2005). Higher particulate matter during pregnancy is associated with higher natural killer cell fractions in newborns and, in maternal blood, a lower percentage of T-cells, a lower percentage of CD3+ CD4+ cells, and a reduced CD4+: CD8+ cell ratio (Hertz-Picciotto, Dostal et al. 2002). Thus, exposure to specific air pollutants might have adverse impact on immune function then result in maternal infection (Gardner 1984). Moreover, Minkoff H et al. hypothesized that the presence of various vaginal pathogens in early pregnancy was associated with the subsequent development of premature rupture of membranes or preterm labor (Minkoff, Grunebaum et al. 1984). Also, they conclude that subtle changes in the immune system promote vaginal phthogens associated with bacterial vaginosis, a risk factor for preterm birth, could lead to changes among vaginal flora. Therefore they suggested that microbiologic screening in early pregnancy may provide the earlier evidence in the assessment of the risk of preterm birth in pregnant women. Also McDonald et al. stated that women carry G. vaginalis or U. urealytium during the midtrimester had about a two-fold risk of preterm delivery, while women positive for U. urealyticum had more than a three-fold risk of pretermprelabour rupture of membranes (McDonald, O'Loughlin et al. 1992). Other studies also suggest the association between maternal infections and preterm birth, like pneumonia, pyelonephritis, as well as urinary infections (Benedetti, Valle et al. 1982, Fan, Pastorek et al. 1987, Romero and Mazor 1988).

Some studies suggest that most of the significant results which indicating the associations between the urban ambient air pollutants including PM_{10} and preterm birth seems to be observed in early pregnancy or late pregnancy, or both. The biological pathway for this event is still unknown, it may also include disturbances of the pituitary-adrenocortico-placental system or uterine blood flow, and/or maternal infections and/or premature rupture of membranes stated as before (Wilhelm and Ritz 2005).

4.2 Strengths in our study

Thus far, almost all the studies that investigated the relationship between air pollutants and preterm birth were based on registry or administrative database (Ritz B 2000, Sagiv, Mendola et al. 2005, Wilhelm and Ritz 2005, Hansen, Neller et al. 2006, Jiang, Zhang et al. 2007, Brauer, Lencar et al. 2008, Darrow, Klein et al. 2009, Suh, Kim et al. 2009, Zhao, Liang et al. 2011). Therefore, all these studies were lack of individual exposure data and potential confounders such as active and passive smoking, alcohol consumption, medication use, supplemental use, history of pregnancy affected by preterm, and hypertension information during pregnancy, etc.

Compared to previous studies, our study used in-person interview and collected detailed information on both home and work addresses, which allowed us to calculate daily exposure concentration level through inverse-distance weighting approach. As a previous study stated that this road distance measures are straightforward, precise, directly relevant to land use policy, and easy to assess and apply in areas without high monitor density (Brauer, Lencar et al. 2008). In addition, we collected potential confounding factors, such as maternal age, hypertension during pregnancy, season of conception, cesarean section, parity, active and passive smoking, and folic acid intake before pregnancy, which allowed us to control the potential confounding factors in the model.

Another strength of our study is that we explored the association between PM_{10} exposure and the risk of preterm birth through two approaches of concentration estimates (based on home address only and based on the weighted concentration of home and work addresses). In comparison of these two results from using those two approaches, we found that the associations examined based on home address only were similar to those based on the average weighted concentration of both home and work addresses. It is because the distributions of PM_{10} concentrations of four air monitoring stations (Figure 3) showed minimal spatial variations. As such, daily average concentration of PM_{10} for each participant would be similar no matter using home address only or both home and work addresses.

We also explored the association between the PM_{10} exposure and the risk of preterm birth by using Principal Component Analysis in order to adjustment for co-linearity, which was only used in one previous study related to examining the PM_{10} exposure and the risk of preterm birth (Zhao, Liang et al. 2011). The observed associations were strengthened after using Principal Component analysis.

4.3 Limitations of our study

One of the concerns about our study is that the air pollutant PM_{10} was estimated using the data from stationary outdoor monitors, which may not represent the actual individual exposure level, compared to measurement of personal air monitoring instrument. However, as early studies, the personal air monitoring instrument was infeasible for large population-based studies.

The number of cases (183) and controls (2719) may be another limitation of our study, because of small sample size would result in lower statistical power to detect the significant results. However, the distribution of locations of our subjects showed sufficient coverage of Lanzhou area. Our study subjects were recruited from the Gansu Provincial Maternity and Child Care Hospital, which is a well-known in Lanzhou. And the pregnant women's age distribution was similar to the women age distribution of census data. The ability of representative would not be problematic.

Though the measurement of inverse-distance weighting approach used both the home and work addresses of participants, we also did not consider the moving status of the subject during the pregnancy period. However, based on the information we collected , study subjects in our study who moved during pregnancy accounted for only a small portion of the entire study population (less than 8%) and moving distances of these study subjects were short and within the city. As such the potential exposure misclassification due to the lack of consideration of moving during pregnancy is likely minimal.

4.4 Conclusion

We comprehensively examined the association between ambient air pollutant PM_{10} and the risk of preterm birth In Lanzhou, China. The study found that higher level of PM_{10} exposure was significantly associated with the risk of preterm, particularly the high level of PM_{10} during the first trimester. The observed associations were strengthened after controlling the co-linearity by using Principal Component Analysis. The results provide supportive evidence that ambient air pollutant PM_{10} plays an important role in preterm birth. This finding has important public health significance, and also provides important scientific evidence to policy makers to make effort to reduce the air pollution levels in China.

5. Appendix

5.1 Tables

Table 1. Distributions of selected characteristics between cases and controls

		Cases (n=183)			Controls (n=2719)		P value
		N	%		N	%	
Maternal age (years)							
	<25	25	13.7		236	8.7	
	25-35	141	77.0		2295	84.4	0.0272
	>35	17	9.3		188	6.9	
Race							
	Han	173	94.5		2619	96.3	0.2205
	Others	10	5.5		100	3.7	
Highest education level							
	High schoo	95	51.9		1177	43.3	
	College or	84	45.9		1503	55.3	0.0170
	missing	4	2.2		39	1.4	
Family monthly income (RMB)							
	<3,000	85	46.4		1206	44.4	
	≥3,000	90	49.2		1320	48.5	0.8321
	missing	8	4.4		193	7.1	
Alcohol drinking							
	No	181	98.9		2704	99.4	
	Yes	2	1.1		7	0.3	0.0497
	missing	0	0.0		8	0.3	
Smoking (Active and passive)							
	No	143	78.1		2120	78.0	
	Yes	38	20.8		573	21.1	0.9282
	missing	2	1.1		26	1.0	
Folic acid use before conception							
	No	130	71.0		1712	63.0	0.0281
	Yes	53	29.0		1007	37.0	
Season of conception							
	Heating se	83	45.4		886	32.6	0.0004
	non-heatin	100	54.6		1833	67.4	
History of pregnancy affected by preterm							
	No	82	44.8		1078	39.6	<0.0001
	Yes	5	2.7		1	0.0	
	missing	96	52.5		1640	60.3	
Parity							
	Primiparou	95	51.9		1636	60.2	0.0318
	Multiparou	87	47.5		1079	39.7	
	missing	1	0.5		4	0.1	
C-section							
	No	90	49.2		1758	64.7	0.0002
	Yes	87	47.5		951	35.0	
	missing	6	3.3		10	0.4	
Hypertension during pregnancy							
	No	166	90.7		2661	97.9	<0.0001
	Yes	17	9.3		58	2.1	

Table 2. Associations between air pollutant PM_{10} and risk of preterm based on home address

	Cases	Controls	OR (95%CI)
Daily average concentration of PM_{10}(ug/m3)			
During pregnancy			
<=133.8	71	897	1.0
133.9-155.7	38	925	0.63(0.41-0.97)
>155.8	74	897	1.35(0.92-1.98)
per 100 ug/m^3			1.92(0.82-4.49)
During the first trimester			
<=133.8	63	1229	1.0
133.9-155.7	27	323	1.76(1.09-2.08)
>155.8	93	1167	1.57(0.92-2.68)
per 100 ug/m^3			1.29(0.77-2.15)
During the second trimester			
<=133.8	75	1015	1.0
133.9-155.7	19	355	0.75(0.44-1.29)
>155.8	89	1349	0.94(0.67-1.32)
per 100 ug/m^3			0.86(0.59-1.26)
During the third trimester			
<=133.8	103	1241	1.0
133.9-155.7	13	349	0.55(0.28-1.04)
>155.8	67	1129	1.00(0.59-1.67)
per 100 ug/m^3			0.79(0.47-1.33)

Entire pregnancy: adjustment for maternal age, hypertension during pregnancy, season of conception, C-section, parity, smoking during pregnancy, and folic acid

Trimesters: adjustment for maternal age, hypertension during pregnancy, C-section, parity, smoking during pregnancy, and folic acid

Table 3. Associations between air pollutant PM_{10} and risk of preterm based on home address

	Cases	Controls	OR(95%CI)
Daily average concentration of PM_{10}(ug/m^3)			
During pregnancy			
<=150 (China NAAQS)	98	1638	1.0
150-165.3	30	541	1.14(0.74-1.76)
>165.4	55	540	2.15(1.47-3.16)
During the first trimester			
<=150 (China NAAQS)	79	1459	1.0
150-165.3	39	372	2.10(1.25-3.51)
>165.4	65	888	1.37(0.84-2.22)
During the second trimester			
<=150 (China NAAQS)	90	1260	1.0
150-165.3	24	453	0.78(0.48-1.28)
>165.4	69	1006	1.04(0.73-1.48)
During the third trimester			
<=150 (China NAAQS)	112	1475	1.0
150-165.3	22	353	1.03(0.57-1.87)
>165.4	49	891	0.97(0.60-1.59)

Entire pregnancy: adjustment for maternal age, hypertension during pregnancy, season of conception, C-section, parity, smoking during pregnancy, and folic acid

Trimesters: adjustment for maternal age, hypertension during pregnancy, C-section, parity, smoking during pregnancy, and folic acid

Table 4. Associations between air pollutant PM_{10} and risk of preterm based on home address

	Cases	Controls	OR(95%CI)
Percentage of days of average concentration of PM_{10}(ug/m^3) in which exceeding the China NAAQS standard			
During entire pergnancy			
<=28.5	70	907	1.0
28.6-39.8	40	909	0.68(0.45-1.03)
>39.8	73	903	1.40(0.95-2.06)
per 1 percent			1.02(1.00-1.03)
During the first trimester			
<=28.5	62	1224	1.0
28.6-39.8	25	304	1.68(1.03-2.75)
>39.8	96	1191	1.63(1.16-2.30)
per 1 percent			1.01(1.00-1.02)
During the second trimester			
<=28.5	83	1031	1.0
28.6-39.8	16	344	0.60(0.35-1.05)
>39.8	84	1344	0.75(0.54-1.04)
per 1 percent			1.00(0.99-1.00)
During the third trimester			
<=28.5	44	940	1.0
28.6-39.8	75	906	1.10(0.72-1.68)
>39.8	64	901	0.21(0.13-0.32)
per 1 percent			0.97(0.96-0.97)

Entire pregnancy: adjustment for maternal age, hypertension during pregnancy, season of conception, C-section, parity, smoking during pregnancy, and folic acid

Trimesters: adjustment for maternal age, hypertension during pregnancy, C-section, parity, smoking during pregnancy, and folic acid

Table 5. Associations between air pollutant PM_{10} and risk of preterm based on average weigted concentration of home and work addresses

	Cases	Controls	OR(95%CI)
Daily average concentration of PM_{10}(ug/m^3)			
During entire pregnancy			
<=133,8	67	897	1.0
133.9-154.7	43	925	0.79(0.52-1.21)
>154.8	73	897	1.43(0.97-2.11)
per 100 ug/m^3			2.16(0.91-5.15)
During the first trimester			
<=133,8	64	1237	1.0
133.9-154.7	21	306	1.33(0.72-2.47)
>154.8	98	1176	1.41(0.77-2.59)
per 100 ug/m^3			1.19(0.68-2.08)
During the second trimester			
<=133,8	76	1019	1.0
133.9-154.7	18	353	0.68(0.39-1.19)
>154.8	89	1347	1.17(0.81-1.71)
per 100 ug/m^3			1.10(0.71-1.71)
During the third trimester			
<=133,8	105	1253	1.0
133.9-154.7	10	320	0.58(0.27-1.22)
>154.8	68	1146	1.38(0.75-2.53)
per 100 ug/m^3			1.12(0.62-2.04)

Entire pregnancy: adjustment for maternal age, hypertension during pregnancy, season of conception, C-section, parity, smoking during pregnancy, and folic acid

Trimesters: adjustment for maternal age, hypertension during pregnancy, C-section, parity, smoking during pregnancy, and folic acid

Table 6. Associations between air pollutant PM_{10} and risk of preterm based on average weigted concentration of home and work addresses

	Cases	Controls	OR(95%CI)
Daily average concentration of PM_{10}(ug/m^3)			
During pregnancy			
<=150 (China NAAQS)	101	1673	1.0
150-165.3	33	523	1.21(0.79-1.85)
>165.4	49	523	1.96(1.33-2.90)
During the first trimester			
<=150 (China NAAQS)	79	1457	1.0
150-165.3	37	380	2.08(1.22-3.52)
>165.4	67	882	1.53(0.93-2.51)
During the second trimester			
<=150 (China NAAQS)	87	1259	1.0
150-165.3	26	446	0.91(0.57-1.47)
>165.4	70	1014	1.05(0.74-1.49)
During the third trimester			
<=150 (China NAAQS)	112	1475	1.0
150-165.3	21	366	1.07(0.59-1.95)
>165.4	50	878	1.12(0.67-1.83)

Entire pregnancy: adjustment for maternal age, hypertension during pregnancy, season of conception, C-section, parity, smoking during pregnancy, and folic acid

Trimesters: adjustment for maternal age, hypertension during pregnancy, C-section, parity, smoking during pregnancy, and folic acid

Table 7. Associations between air pollutant PM_{10} and risk of preterm based on average weigted concentration of home and work addresses

	Cases	Controls	OR(95%CI)
Percentage of days of average concentration of PM_{10}(ug/m^3) in which exceeding the China NAAQS standard			
<=28.5	67	904	1.0
28.6-39.4	45	921	0.80(0.53-1.21)
>39.5	71	894	1.44(0.97-2.14)
per 1 percent			1.02(1.00-1.04)
During the first trimester			
<=28.5	62	1221	1.0
28.6-39.4	25	310	1.64(1.00-2.68)
>39.5	96	1188	1.63(1.16-2.29)
per 1 percent			1.01(1.00-1.02)
During the second trimester			
<=28.5	81	1027	1.0
28.6-39.4	18	343	0.71(0.41-1.20)
>39.5	84	1349	0.76(0.54-1.06)
per 1 percent			1.00(0.99-1.00)
During the third trimester			
<=28.5	128	1268	1.0
28.6-39.4	29	290	1.00(0.65-1.54)
>39.5	26	1161	0.22(0.14-0.34)
per 1 percent			0.97(0.96-0.97)

Entire pregnancy: adjustment for maternal age, hypertension during pregnancy, season of conception, C-section, parity, smoking during pregnancy, and folic acid

Trimesters: adjustment for maternal age, hypertension during pregnancy, C-section, parity, smoking during pregnancy, and folic acid

Table 8. Associations between air pollutant PM_{10} and risk of preterm by using Principle Compnent Analysis

	OR[a](95%CI)	OR[b](95%CI)
Daily average concentration of PM_{10} (per 100ug/m^3)		
During the first trimester	1.11(1.03-1.2)	1.12(1.03-1.21)
During the second trimester	0.96(0.84-1.10)	0.96(0.84-1.10)
During the third timester	0.89(0.83-0.95)	0.89(0.83-0.95)
Season of conception	1.12(1.05-1.20)	1.12(1.05-1.20)

[a] home address only

[b] home and work addresses

5.1 Figures

Figure1: Geographic information of Lanzhou, China

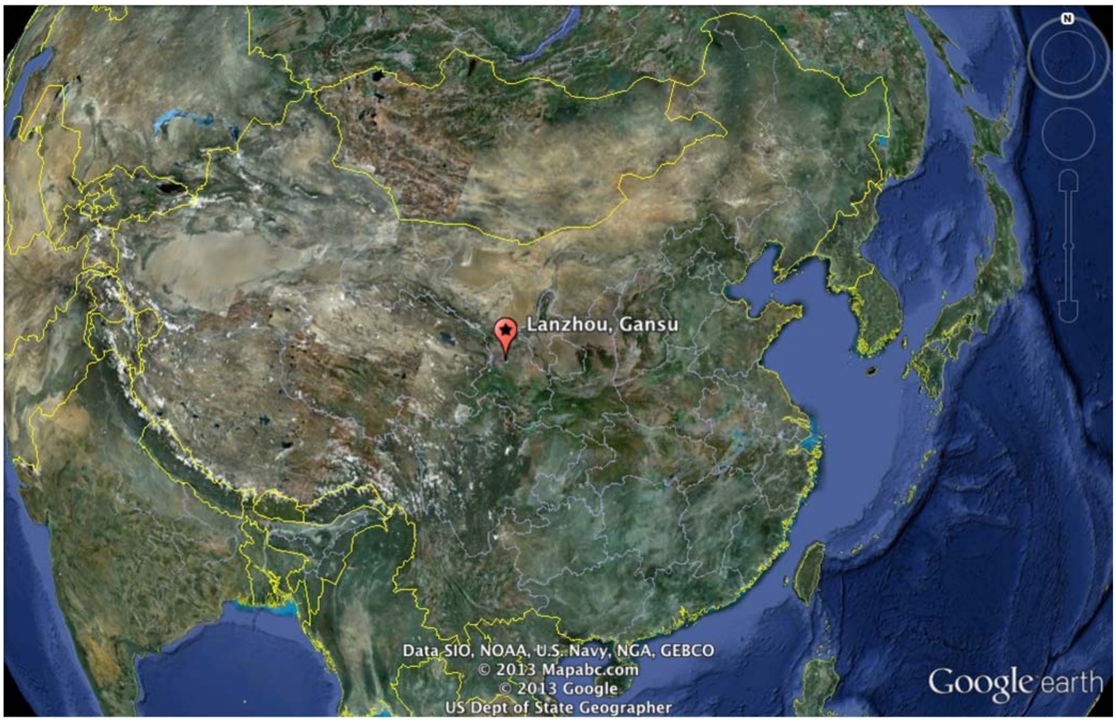
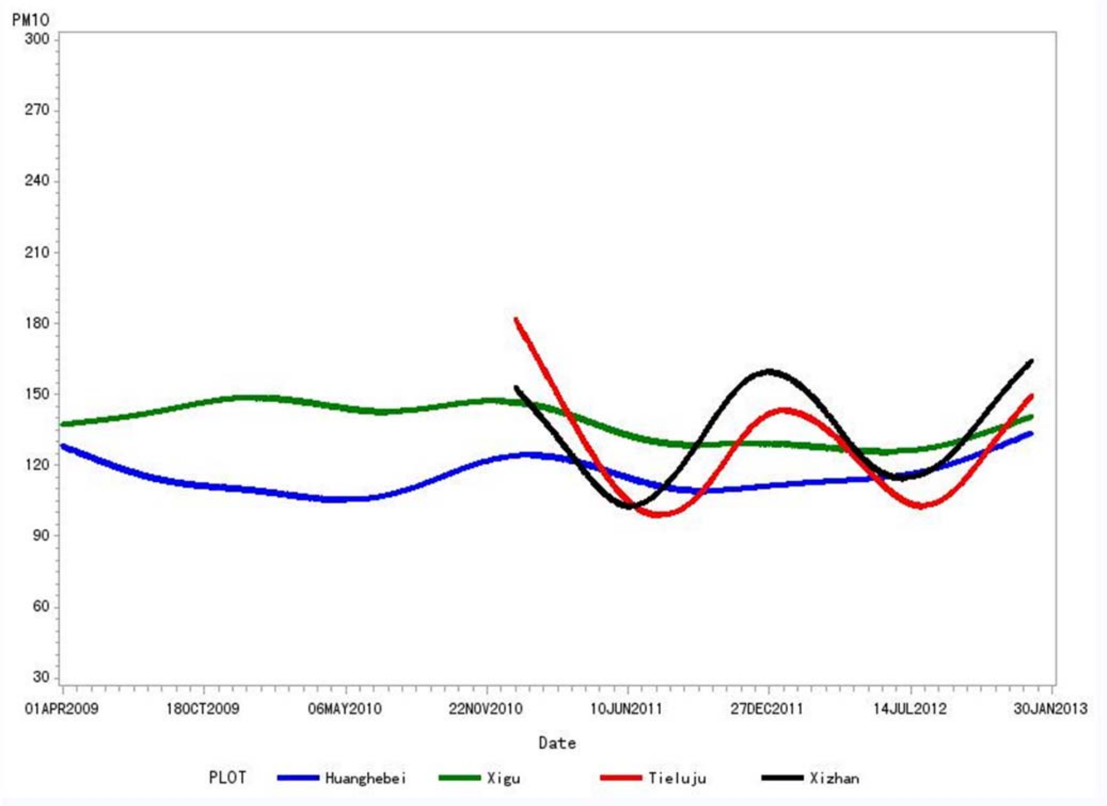


Figure2: Locations of four air monitoring stations in Lanzhou, China

Figure 3: Distribution of PM_{10} Concentrations (μg/m^3)



6. Acknowledgements

There are many people that I want to express my gratitude for helping me finish this thesis and accomplish my two-year study at Yale. First, I really appreciate all the guidance and encouragement from my academic and thesis advisor, Dr. Yawei Zhang. I would also like to thank my second reader, Dr. Tongzhang Zheng, who helped me with the understanding of the environmental epidemiological background of my thesis. I am thankful to all the professors at Department of Environmental Health Science and Yale School of Public Health. Last, I would like to thank my family and friends for their support and help during these years.

7. References

Banhidy, F., N. Acs, E. H. Puho and A. E. Czeizel (2007). "Pregnancy complications and birth outcomes of pregnant women with urinary tract infections and related drug treatments." Scand J Infect Dis **39**(5): 390-397.

Beck, S., D. Wojdyla, L. Say, A. P. Betran, M. Merialdi, J. H. Requejo, C. Rubens, R. Menon and P. F. Van Look (2010). "The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity." Bull World Health Organ **88**(1): 31-38.

Benedetti, T. J., R. Valle and W. J. Ledger (1982). "Antepartum pneumonia in pregnancy." Am J Obstet Gynecol **144**(4): 413-417.

Brauer, M., C. Lencar, L. Tamburic, M. Koehoorn, P. Demers and C. Karr (2008). "A cohort study of traffic-related air pollution impacts on birth outcomes." Environ Health Perspect **116**(5): 680-686.

Darrow, L. A., M. Klein, W. D. Flanders, L. A. Waller, A. Correa, M. Marcus, J. A. Mulholland, A. G. Russell and P. E. Tolbert (2009). "Ambient air pollution and preterm birth: a time-series analysis." Epidemiology **20**(5): 689-698.

Dohme, M. S. "Risk factors present before pregnancy." Merck Manual Home Edition.

Dolan, S. M., S. J. Gross, I. R. Merkatz, V. Faber, L. M. Sullivan, F. D. Malone, T. F. Porter, D. A. Nyberg, C. H. Comstock, G. D. Hankins, K. Eddleman, L. Dugoff, S. D. Craigo, I. Timor-Tritsch, S. R. Carr, H. M. Wolfe, D. W. Bianchi and M. E. D'Alton (2007). "The contribution of birth defects to preterm birth and low birth weight." Obstet Gynecol **110**(2 Pt 1): 318-324.

Dole, N., D. A. Savitz, I. Hertz-Picciotto, A. M. Siega-Riz, M. J. McMahon and P. Buekens (2003). "Maternal stress and preterm birth." Am J Epidemiol **157**(1): 14-24.

Falah, N., J. McElroy, V. Snegovskikh, C. J. Lockwood, E. Norwitz, J. C. Murray, E. Kuczynski, R. Menon, K. Teramo, L. J. Muglia and T. Morgan (2013). "Investigation of genetic risk factors for chronic adult diseases for association with preterm birth." Hum Genet **132**(1): 57-67.

Fan, Y. D., J. G. Pastorek, 2nd, J. M. Miller, Jr. and J. Mulvey (1987). "Acute pyelonephritis in pregnancy." Am J Perinatol **4**(4): 324-326.

Gardner, D. E. (1984). "Oxidant-induced enhanced sensitivity to infection in animal models and their extrapolations to man." J Toxicol Environ Health **13**(2-3): 423-439.

Gardner, M. O., R. L. Goldenberg, S. P. Cliver, J. M. Tucker, K. G. Nelson and R. L. Copper (1995). "The origin and outcome of preterm twin pregnancies." Obstet Gynecol **85**(4): 553-557.

Goldenberg, R. L., J. F. Culhane, J. D. Iams and R. Romero (2008). "Epidemiology and causes of preterm birth." Lancet **371**(9606): 75-84.

Goldenberg, R. L., J. C. Hauth and W. W. Andrews (2000). "Intrauterine infection and preterm delivery." N Engl J Med **342**(20): 1500-1507.

Goldenberg RL, I. J., Mercer BM, et al. (1998). "The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network." American Journal of Public Health **88**(2): 233-238.

Hansen, C., A. Neller, G. Williams and R. Simpson (2006). "Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia." BJOG **113**(8): 935-941.

Hertz-Picciotto, I., M. Dostal, J. Dejmek, S. G. Selevan, G. Wegienka, A. Gomez-Caminero and R. J. Sram (2002). "Air pollution and distributions of lymphocyte immunophenotypes in cord and maternal blood at delivery." Epidemiology **13**(2): 172-183.

Huddy, C. L., A. Johnson and P. L. Hope (2001). "Educational and behavioural problems in babies of 32-35 weeks gestation." Arch Dis Child Fetal Neonatal Ed **85**(1): F23-28.

Huisman, C. M., J. J. Zwart, J. W. Roos-Hesselink, J. J. Duvekot and J. van Roosmalen (2013). "Incidence and predictors of maternal cardiovascular mortality and severe morbidity in The Netherlands: a prospective cohort study." PLoS One **8**(2): e56494.

Jiang, L. L., Y. H. Zhang, G. X. Song, G. H. Chen, B. H. Chen, N. Q. Zhao and H. D. Kan (2007). "A time series analysis of outdoor air pollution and preterm birth in Shanghai, China." Biomed Environ Sci **20**(5): 426-431.

Kim, O. J., E. H. Ha, B. M. Kim, J. H. Seo, H. S. Park, W. J. Jung, B. E. Lee, Y. J. Suh, Y. J. Kim, J. T. Lee, H. Kim and Y. C. Hong (2007). "PM10 and pregnancy outcomes: a hospital-based cohort study of pregnant women in Seoul." J Occup Environ Med **49**(12): 1394-1402.

Knottnerus, J. A., L. R. Delgado, P. G. Knipschild, G. G. Essed and F. Smits (1990).

"Haematologic parameters and pregnancy outcome. A prospective cohort study in the third trimester." J Clin Epidemiol **43**(5): 461-466.

Martius, J. A., T. Steck, M. K. Oehler and K. H. Wulf (1998). "Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks): univariate and multivariate analysis of 106 345 singleton births from the 1994 statewide perinatal survey of Bavaria." Eur J Obstet Gynecol Reprod Biol **80**(2): 183-189.

Mathews, T. J. and M. F. MacDorman (2006). "Infant mortality statistics from the 2003 period linked birth/infant death data set." Natl Vital Stat Rep **54**(16): 1-29.

McDonald, H. M., J. A. O'Loughlin, P. Jolley, R. Vigneswaran and P. J. McDonald (1992). "Prenatal microbiological risk factors associated with preterm birth." Br J Obstet Gynaecol **99**(3): 190-196.

Minkoff, H., A. N. Grunebaum, R. H. Schwarz, J. Feldman, M. Cummings, W. Crombleholme, L. Clark, G. Pringle and W. M. McCormack (1984). "Risk factors for prematurity and premature rupture of membranes: a prospective study of the vaginal flora in pregnancy." Am J Obstet Gynecol **150**(8): 965-972.

Moore, M. L. (2002). "Preterm birth: a continuing challenge." J Perinat Educ **11**(4): 37-40.

Moutquin, J. M. (2003). "Classification and heterogeneity of preterm birth." BJOG **110 Suppl 20**: 30-33.

Peters, A., A. Doring, H. E. Wichmann and W. Koenig (1997). "Increased plasma viscosity during an air pollution episode: a link to mortality?" Lancet **349**(9065): 1582-1587.

Pinborg, A. W., U. B.; Romundstad, L. B.; Loft, A.; Aittomaki, K.; Soderstrom-Anttila, V.; Nygren, K. G.; Hazekamp, J. et al. (2012). "Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis." Human Reproduction Update **19**(2): 87-104.

Raatikainen, K., N. Heiskanen and S. Heinonen (2005). "Marriage still protects pregnancy." BJOG **112**(10): 1411-1416.

Ritz B, Y. F., Chapa G, Fruin S (2000). "Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993." Epidemiology **11**(5): 502-511.

Romero, R. and M. Mazor (1988). "Infection and preterm labor." Clin Obstet Gynecol **31**(3): 553-584.

Rosenberg, T. J., S. Garbers, H. Lipkind and M. A. Chiasson (2005). "Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups." Am J Public Health **95**(9): 1545-1551.

Sagiv, S. K., P. Mendola, D. Loomis, A. H. Herring, L. M. Neas, D. A. Savitz and C. Poole (2005). "A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997-2001." Environ Health Perspect **113**(5): 602-606.

Shiono PH, K. M., Nugent RP, Cotch MF, Wilkins DG, Rollins DE, Carey CJ, Behrman RE (1995). "Fetus-Placenta-Newborn: the Impact of Cocaine and Marijuana Use on Low Birth Weight and Preterm Birth: a Multicenter Study." American Journal of Obstetrics & Gynecology **172**(1 Pt 1): 19-27.

Suh, Y. J., H. Kim, J. H. Seo, H. Park, Y. J. Kim, Y. C. Hong and E. H. Ha (2009). "Different effects of PM10 exposure on preterm birth by gestational period estimated from time-dependent survival analyses." Int Arch Occup Environ Health **82**(5): 613-621.

van den Hooven, E. H., F. H. Pierik, Y. de Kluizenaar, S. P. Willemsen, A. Hofman, S. W. van Ratingen, P. Y. Zandveld, J. P. Mackenbach, E. A. Steegers, H. M. Miedema and V. W. Jaddoe (2012). "Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: a prospective cohort study." Environ Health Perspect **120**(1): 150-156.

WHO "http://www.who.int/bulletin/volumes/88/1/08-062554/en/."

WHO "http://www.who.int/mediacentre/factsheets/fs363/en/."

Wilhelm, M. and B. Ritz (2005). "Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA." Environ Health Perspect **113**(9): 1212-1221.

Winkvist, A., I. Mogren and U. Hogberg (1998). "Familial patterns in birth characteristics: impact on individual and population risks." Int J Epidemiol **27**(2): 248-254.

Xu, X., H. Ding and X. Wang (1995). "Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study." Arch Environ Health **50**(6): 407-415.

Zhao, Q., Z. Liang, S. Tao, J. Zhu and Y. Du (2011). "Effects of air pollution on neonatal prematurity in Guangzhou of China: a time-series study." Environ Health **10**: 2.

Zheng, S., M. Wang, S. Wang, Y. Tao and K. Shang (2013). "Short-term effects of gaseous pollutants and particulate matter on daily hospital admissions for cardio-cerebrovascular disease in Lanzhou: evidence from a heavily polluted city in China." Int J Environ Res Public Health **10**(2): 462-477.

Zondervan, H. A., J. Oosting, M. R. Hardeman, M. E. Smorenberg-Schoorl and P. E. Treffers (1987). "The influence of maternal whole blood viscosity on fetal growth." Eur J Obstet Gynecol Reprod Biol **25**(3): 187-194.