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The Effect Of Spatiotemporally-Dependent Air Pollution Exposure On Birthweight In The Lanzhou Birth Cohort

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Abstract

Introduction: Low birthweight serves as a proxy risk factor for a number of conditions later in development. Of China's urban centers, Lanzhou has long been considered one of the worst-affected cities by air pollution.

Objectives: This study uses spatial heterogeneity in air pollution exposure across addresses in Lanzhou and temporal heterogeneity resulting from the differential timing of pregnancy in the Lanzhou Birth Cohort to investigate the association between PM_{10} exposure and birthweight.

Methods: The study population consisted of 4,865 mother-child pairs from the Gansu Provincial Maternity and Child Care Hospital. Participants completed an epidemiological questionnaire and patient data were collected from hospital records. Environmental data from four monitoring stations were provided by the Gansu Provincial Environmental Monitoring Central Station. Linear regressions were used to model the relationship between mean PM10 exposure during the whole pregnancy and birthweight.

Results: The lowest PM_{10} exposure quartiles had a mean birthweight of 3396 g, compared to a mean birthweight of 3373 g for the highest PM_{10} exposure quartiles. A 10 $\mu g/m^3$ increase in mean PM_{10} exposure during the 2^{nd} trimester was associated with an 8 g (sd 2 g) decrease in birthweight (P=0.0002) and the same increase during the 3^{rd} trimester was associated with a 4 g (sd 1 g) decrease in birthweight (P=0.0019). Mean PM_{10} exposure during the whole pregnancy was not found to have significant interactions with income, maternal BMI, newborn sex, or dietary factors.

Conclusion: PM_{10} exposure, especially during the 2^{nd} and 3^{rd} trimesters, may be associated with decreased birthweight. Though Lanzhou long topped lists of cities most affected by air pollution in China, the local government launched a major initiative in 2012 to significantly reduce air pollution presenting opportunities for natural experiments to understand the burden of air pollution. The findings of this study may serve as a reference for comparison of future results.

Introduction

Air pollution

Air pollution is a serious and growing environmental problem for China as it undergoes economic, demographic, and epidemiological transitions, and also poses a significant challenge to the health of hundreds of millions of Chinese citizens[29]. In general, exposure to particulate matter (PM) has been found in epidemiological and clinical studies to be a risk factor for respiratory conditions such as asthma[48] and cardiovascular conditions from hypertension to ischemic stroke to myocardial infarction via direct toxicity as well as indirect injury due to systemic inflammation and oxidative stress[12].

Air quality in Lanzhou

Of China's urban centers, Lanzhou has long been considered one of the worst-affected cities by air pollution due to its topography, climate, and economic structure[44]. Lanzhou is a city of 3 million and the capital of Gansu Province in Northwest China. Situated along the Yellow River, It lies in a valley, where temperature inversions frequently prevent the dissipation of pollution from dust, secondary aerosols, car exhaust, industrial activities, and the burning of coal for heating in winter[39]. Among adults in Beijing and in Lanzhou, air pollutants have been associated with hospital admissions for respiratory and cardiovascular diseases[11,57], with particularly strong effects among women, the elderly[44], and potentially the unborn.

Birth outcomes

An extensive literature has linked maternal exposure to air pollution to fetal outcomes such as low birthweight (LBW)[15,27,33], preterm birth (PTB), intrauterine growth restriction (IUGR) and small for gestational age, as well as all-cause post-neonatal mortality[24] and both cardiovascular and respiratory outcomes[5,22]. Birthweight is an important indicator of proper prenatal growth, and LBW serves as a proxy risk factor for a number of conditions later in development. Many factors are well-established predictors of LBW and IUGR, including maternal and paternal anthropometrics (ex. height, weight, BMI), race, socioeconomic factors (ex. profession, income, diet), behavioral factors (ex. stress, hours worked, active and passive smoking)[17,32,41].

Literature review: natural experiments, cohort studies, and effect modification

One paper examining the 2008 Beijing Olympics, a period during which major steps were taken to temporarily curb air pollution, found that the natural experiment led to small but significant increases in the birthweights of infants who were in their 8th month of gestation during the Olympics[40], though another attributed the increases to NO_2 concentration in the 3rd trimester, with null findings for PM_{10}[19].

A large cohort study across 12 European countries found that even low concentrations of ambient air pollution were associated with increased risk of term LBW[37] and another large study in Belgium found that the effect of particulate air pollution on fetal growth was actually stronger at lower concentrations[50]; studies in areas with high air

pollution are relatively uncommon. Specifically, PM_{10} has repeatedly been found to be associated with reduced birthweight on the order of 10 g per 10 ug/m^3 increase in PM_{10}[10,25,40], as well as elevated risk of LBW[8,38] and/or PTB[2]. A previous study in the Lanzhou birth cohort, in an area of high pollutant concentrations, found an association between exposure to ambient air pollution and PTB[58].

Other studies in Canada and England also found evidence of effect modification, whereby PM exposure had a stronger negative effect on birthweight among the socioeconomically disadvantaged[43] and in mothers who smoked, consumed alcohol, or used drugs, suggesting that certain populations are especially vulnerable to the effects of air pollution[14]. In other settings, modification by SES exhibited a more complex, context-specific pattern[43].

However, the specific nature of the relationship between exposure to air pollution and birthweight is not yet clear, due to complicated mixes of pollutants and exposures, long latencies and the difficulty of studying biological mechanisms, and the heterogeneity of exposed populations as well as study methodologies.

Objectives

Using baseline data from the Lanzhou Birth Cohort, we investigated the impact of air pollution, and in particular PM_{10}, on birthweights of infants born in Lanzhou, China, and also considered the effects during different windows of exposure. Given the frequency of co-exposure to air pollution and new nutritional patterns in a rapidly urbanizing society[29], we also looked at potential interactions between air pollution and dietary patterns as well as socioeconomic status. Specifically, this study uses spatial heterogeneity in air pollution exposure across addresses in Lanzhou and temporal heterogeneity resulting from the differential timing of pregnancy to investigate the association between PM_{10} exposure and birthweight.

Material and Methods

Study Population

The study population consisted of 10,542 mother-child pairs where the child was born to the mother, aged 18 or older with no history of mental illness, from January 2010 to December 2012 at the Gansu Provincial Maternity and Child Care Hospital in Lanzhou, the largest maternity hospital in Gansu, in the People's Republic of China. These pairs represented 73.4% of eligible participants. The study design was reviewed by the Human Investigation Committees at the Hospital and at Yale University. Participants provided written consent, and completed a questionnaire with an interviewer in the three days before or after delivery regarding medical and reproductive history, lifestyle factors, and basic demographic details. Patient data including maternal and fetal reproductive outcomes were collected from hospital records. Additional details on the Lanzhou birth cohort can be found in previous publications[58].

Observations with missing or incomplete environmental data (due to missing addresses, for example) were dropped. Similarly, individuals with missing or inconsistent data on birthweight, gestational time, or the covariates identified for analysis (including dietary data) were not excluded. Finally, mothers who experienced preterm delivery

were not considered, consistent with the practices of many other studies investigating birthweight, as a different set of factors, previously identified in the Lanzhou birth cohort[58], may mediate PTB as compared to LBW at term. Ultimately, data from 4865 mother-child pairs were used for the analyses. The exclusion of individuals with incomplete data did not generally change the observable characteristics of the study population, and was not expected to have changed the results of the study (data not shown).

Air Pollution Data

Environmental data were provided by the Gansu Provincial Environmental Monitoring Central Station, which collected daily average concentrations of PM_{10}, NO_2, and SO_2 from four monitoring stations concentrated in the urban center of Lanzhou from April 2009 to December 2012. These included SO_2, NO_2, and daily temperature and PM_{10} records. Home and work addresses from the questionnaire were geocoded. PM_{10}, Daily NO_2, and SO_2 exposures were estimated for each pregnant woman and for each day of her pregnancy by using the inverse distance-weighting method on the basis of the distances from her home and work addresses to the four stations, taking into account changes in residence and employment. The home address was weighted at 16 hours and the work address at 8 hours on weekdays, but only exposures associated with the home address were considered on weekends. Exposures were averaged over the duration of the pregnancy and, for PM_{10}, also over trimesters (days 1-90, 91-180, 181+) and months (1-30, 31-60, 61-90, etc.) for the consideration of critical exposure windows. These continuous variables for exposure were also transformed into quartiles for stratified analysis. All pollution variables were scaled so that a one unit change corresponded to a 10 $\mu g/m^3$ increase or decrease.

Birth Outcome Data

Continuous birthweight at term delivery was the primary outcome for analyses in this study. As such, preterm births, defined as delivery at <37 weeks of gestation, were excluded from the analysis. Low birthweight was defined as a birthweight of <2500 g.

Covariates

The outcome was continuous birthweight, while the explanatory variable of interest was PM_{10}, measured at different timescales during the pregnancy. Covariates included socioeconomic status indicators (educational attainment, household income), newborn's sex, maternal conditions (gestational diabetes, gestational hypertension, preeclampsia, vaginal bleeding), maternal and paternal BMI, maternal age, and age at menarche (see Table 1). Placenta and umbilical cord conditions were considered fetal conditions, and were not included. Potential covariates with very little variation in this cohort, such as smoking, rare in Chinese women, were also excluded.

Dietary Data

Self-reported dietary data on 33 food items from the food frequency section of the questionnaire were reduced to four factors using principal component analysis (PCA). As the actual frequencies of consumption and quantities

consumed per sitting were not sufficiently complete, simple binary variables representing whether or not an individual consumed each food item were used.

Statistical Analysis

Summary statistics including frequencies and means were calculated for all variables in the total population, and also among LBW and normal birthweight infants. Given the low incidence of LBW (<2500 g) following the exclusion of preterm births, birthweight was treated as a continuous outcome rather than a binary one in later analyses. For the descriptive analysis, mean PM_{10} exposure during the whole pregnancy and during each trimester were stratified to look for associations between exposure quartile and continuous birthweight. Subsequently, unadjusted and adjusted linear regressions were used to model the relationship between mean PM_{10} exposure during the whole pregnancy and birthweight. Full multivariate (adjusted) regression models were reduced using backward selection and a P-value of 0.05. In the consideration of exposure windows, uncorrelated trimesters or uncorrelated months were substituted for PM_{10} exposure during the whole pregnancy in the previously identified models adjusting for confounders. Lastly, four dietary factors created using PCA were added to the model, along with interaction terms, to look for dietary impacts on birthweight as well as potential effect modification. All analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Spatial and temporal heterogeneity of different air pollutants

PM_{10} and SO_2 levels at each of the four stations were highly seasonal (autocorrelated), peaking in winter and reaching minimums in summer, and thus also highly correlated with one another (Figure 1). The fold increase between seasons was especially notable for SO_2. Seasonality was less clear for NO_2. There was not a clear qualitative damping of PM_{10}, SO_2, or NO_2 concentrations suggesting long-term improvement in air quality over the timeframe of the study.

During the whole pregnancy, SO_2 was highly correlated with NO_2 ($r=0.61619$, $P<0.0001$). PM_{10} was more weakly correlated with both SO_2 ($r=0.49325$, $P<0.0001$) and NO_2 (0.34965, $P<0.0001$). During each trimester, PM_{10} was more highly correlated with SO_2 ($r=0.82643$, 0.77298, 0.81718; $P<0.0001$) than with NO_2 ($r=0.57128$, 0.55381, 0.73755; $P<0.0001$); SO_2 and NO_2 were also correlated during each trimester ($r=0.63915$, 0.69255, 0.75560; $P<0.0001$). (Figure 2)

PM_{10} was also more closely associated with NO_2 during certain months of pregnancy. As there is no reason that PM_{10} should be more highly correlated with NO_2 during a particular trimester if the trimesters are equally likely to include any given three months of the year, this suggests possible bias or seasonality in the timing of pregnancy in the sample population.

In addition to temporal trends, there were also spatial differences in pollutant concentrations. Among the four stations, Xigu had the highest mean concentration of SO_2 while Huanghebei had the highest variance; for PM_{10}, Xigu had the highest mean concentration and the highest variance; spatial differences in NO_2 were not apparent (data not shown). Means and variances were not calculated or compared by years or seasons.

See Figure 1 for additional information. Trend lines and moving averages were not added, but a more specific treatment will be given to time-series analysis of environmental monitoring data in the future.

Characteristics of the study population

Slightly higher numbers of study participants became pregnant during the summer and autumn months of June-October than during the winter and spring months of November-May (Figure 1). As this is a reflection as much of study recruitment as of seasonal trends in pregnancy, future studies should adjust for this differential timing of the start of pregnancy.

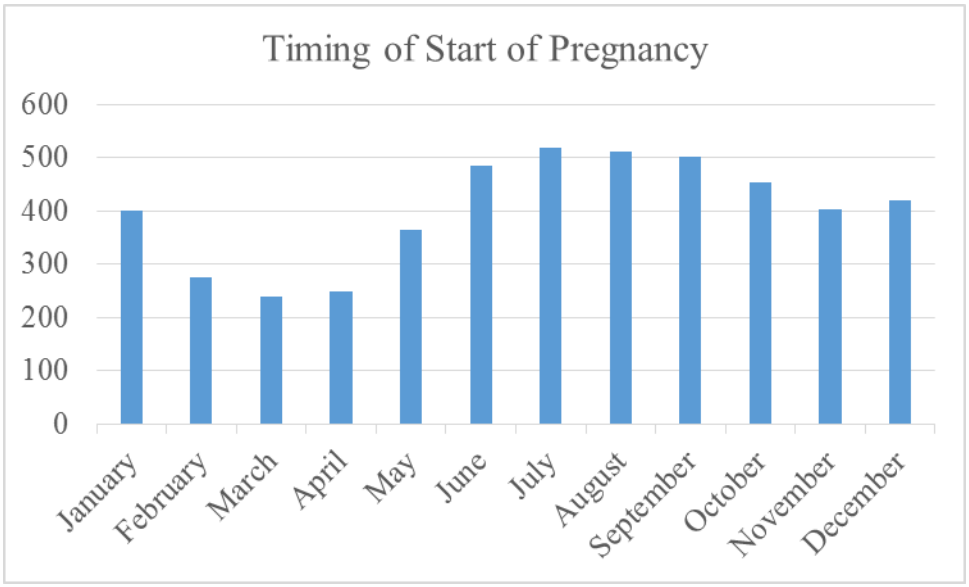

Figure 2. Timing of start of pregnancy by month, between 2009 and 2012, among study participants (n=4820).

83% of mothers received at least a high school education, and 50% of mothers lived in households with income of at least 3000 RMB (approximately $500 USD) per month. For comparison, the national GDP per capita was roughly 3800 RMB per month. 53% of infants born during the study period were male, and 47% female, close to the national male/female sex ratio of roughly 1.15 at birth. 1% of mothers had gestational diabetes, and another 1% had gestational hypertension, while 2% experienced preeclampsia, and 12% experienced some form of vaginal bleeding. The mean maternal and paternal BMIs were 20.6 (sd 2.6) and 24.0 (sd 3.1), respectively. The average mother was 29 years old, and experienced menarche at age 14. Women consumed 1456 calories per day during the year before pregnancy, and roughly 1700-1800 calories daily during pregnancy.

On average, women were exposed to 140.2 $\mu g/m^3$ (IQR 130.0-149.4) of PM_{10} during their whole pregnancies. For reference, the U.S. National Ambient Air Quality Standard for PM_{10} is 150 $\mu g/m^3$, not to be exceeded more than once per year. Additionally, they were exposed to 43.8 ppb and 50.2 ppb of NO_2 and SO_2, respectively, during their whole pregnancies, for which the relevant U.S. standards are 100 ppb and 75 ppb. Table 1 presents these descriptive statistics, also stratified by low and normal birthweight.

Table 1. Characteristics of the study population.

	Total (%), N=4865	Low Birthweight (%), N=54	Normal Birthweight (%), N=4811
Education			
No formal education	0.72	0.00	0.73
Elementary school	2.16	3.70	2.14
Middle school	13.67	25.93	13.53
High school	16.88	25.93	16.77
Community college	23.70	18.52	23.76
College	34.61	18.52	34.80
Graduate school	8.26	7.41	8.27
Household Income			
<1000	4.91	9.26	4.86
1000-1999	16.32	18.52	16.30
2000-2999	28.78	40.74	28.64
3000-3999	23.95	14.81	24.05
4000-4999	13.50	11.11	13.53
5000+	12.54	5.56	12.62
Newborn Sex			
Male	52.64	57.41	52.59
Female	47.36	42.59	47.41
Gestational Diabetes	1.11	0.00	1.12
Gestational Hypertension	1.11	5.56	1.06
Preeclampsia	1.93	5.56	1.89
Vaginal Bleeding			
None	87.75	83.33	87.80
Mild	11.53	14.81	11.49
Severe	0.72	1.85	0.71
	Total, Mean (SD)	**Low Birthweight, Mean (SD)**	**Normal Birthweight, Mean (SD)**
Maternal BMI	20.60 (2.63)	20.29 (2.95)	20.61 (2.63)
Paternal BMI	23.99 (3.10)	23.59 (3.38)	23.99 (3.09)
Maternal Age	28.61 (4.02)	28.15 (4.60)	28.62 (4.01)
Menarche Age	13.75 (1.50)	13.93 (1.34)	13.75 (1.50)
Calories Per Day			
Year Before Pregnancy	1455.65 (482.86)	1449.14 (440.42)	1455.73 (483.36)
1st Trimester	1682.48 (504.24)	1597.76 (440.88)	1683.43 (504.87)
2nd Trimester	1783.50 (551.18)	1700.89 (486.00)	1784.42 (551.85)
3rd Trimester	1792.26 (558.76)	1686.94 (475.82)	1793.44 (559.55)
Average NO_2			
Whole Pregnancy	0.0438 (0.0055)	0.0440 (0.0057)	0.0438 (0.0055)
1st Trimester	0.0446 (0.0094)	0.0426 (0.0096)	0.0446 (0.0094)
2nd Trimester	0.0447 (0.0101)	0.0452 (0.0107)	0.0447 (0.0101)
3rd Trimester	0.0421 (0.0123)	0.0443 (0.0130)	0.0420 (0.0123)
Average SO_2			
Whole Pregnancy	0.0502 (0.0130)	0.0515 (0.0147)	0.0502 (0.0130)
1st Trimester	0.0526 (0.0278)	0.0506 (0.0310)	0.0527 (0.0277)
2nd Trimester	0.0532 (0.0290)	0.0516 (0.0255)	0.0533 (0.0291)
3rd Trimester	0.0449 (0.0289)	0.0528 (0.0326)	0.0448 (0.0288)

Average PM_{10}			
Whole Pregnancy	0.1402 (0.0139)	0.1432 (0.0146)	0.1402 (0.0138)
1st Trimester	0.1342 (0.0379)	0.1326 (0.0410)	0.1343 (0.0379)
2nd Trimester	0.1434 (0.0339)	0.1474 (0.0300)	0.1434 (0.0339)
3rd Trimester	0.1429 (0.0417)	0.1497 (0.0420)	0.1428 (0.0417)

The mean birthweight for term infants was 3382 g (sd 410 g), closely consistent with the findings of other studies. 54 (1.11%) of 4865 terms infants had clinical LBW.

Birthweight by Air Pollutant Exposure Quartiles

Based on stratified analysis, higher quartiles of PM_{10} exposure during the whole pregnancy or during the 3rd trimester appeared to be associated with generally lower birthweight (Table 2). For both the whole pregnancy and the 3rd trimester, the lowest PM_{10} exposure quartiles had a mean birthweight of 3396 g, compared to a mean birthweight of 3373 g for the highest PM_{10} exposure quartiles. The same trend was observed for the 2nd trimester, but the opposite trend was observed for the 1st trimester, with an association between higher quartiles of PM_{10} exposure and higher birthweight. The mirroring of the trends suggested that the 3rd trimester might be the critical exposure window.

However, effect sizes were small and may not have been statistically significant. Nonetheless, the effects of air pollution during the 2nd and 3rd trimesters were candidates to explain the overall effect of PM_{10} exposure during pregnancy on birthweight. The effects of NO_2 and SO_2 exposure were less clear from stratified analysis, though an association between higher quartile of SO_2 exposure during the 1st trimester and generally higher birthweight was noted.

Table 2. Birthweight by air pollutant exposure quartiles.

		Whole Pregnancy	**1st Trimester**	**2nd Trimester**	**3rd Trimester**
PM_{10} Exposure Level	1st Quartile (Lowest)	3396 (394)	3365 (412)	3387 (398)	3396 (415)
	2nd Quartile	3383 (407)	3380 (411)	3396 (422)	3389 (401)
	3rd Quartile	3375 (417)	3382 (394)	3380 (396)	3370 (408)
	4th Quartile (Highest)	3373 (423)	3400 (424)	3364 (425)	3373 (417)
SO_2 Exposure Level	1st Quartile (Lowest)	3361 (409)	3364 (416)	3366 (407)	3379 (407)
	2nd Quartile	3400 (409)	3379 (417)	3397 (416)	3394 (397)
	3rd Quartile	3375 (401)	3381 (393)	3389 (411)	3377 (421)
	4th Quartile (Highest)	3391 (421)	3405 (413)	3376 (407)	3378 (416)
NO_2 Exposure Level	1st Quartile (Lowest)	3377 (412)	3374 (414)	3352 (408)	3379 (407)
	2nd Quartile	3371 (403)	3401 (408)	3415 (411)	3380 (409)
	3rd Quartile	3408 (415)	3363 (413)	3373 (402)	3390 (404)
	4th Quartile (Highest)	3372 (411)	3383 (405)	3389 (417)	3378 (421)

*All sample sizes between 1211 and 1219.

Linear Regression Models

Education, household income, newborn sex, gestational diabetes, vaginal bleeding, maternal and paternal BMI, maternal age, calories during the 2nd trimester, and PM_{10} exposure during the 3rd trimester were each associated with birthweight in simple (unadjusted) regression models. Higher SO_2 exposure during the 1st trimester was once again found to be associated with higher birthweight. The full model including mean exposures and daily caloric intake during the whole pregnancy and all covariates identified preeclampsia but not maternal age in addition to the aforementioned predictors as being significantly and independently associated with birthweight; the results of the reduced model were consistent with the full model. Pollutant exposures and caloric intake by trimester were not included in the full and reduced models to prevent multicollinearity.

As expected, female infants were 109 g (sd 12 g) smaller than their male counterparts, and gestational diabetes significantly increased birthweight by 176 g (sd 55 g) while preeclampsia significantly decreased birthweight by 119 g (sd 42 g). A 10 $\mu g/m^3$ increase in mean PM_{10} exposure during the whole pregnancy had a more modest but still significant effect, being associated with a 13 g (sd 5 g) decrease in birthweight. Meanwhile, a 10 $\mu g/m^3$ increase in mean SO_2 exposure during the whole pregnancy was associated with a 15 g (sd 5 g) increase in birthweight. (Table 3) Variance inflation factors were also checked for all models to confirm the absence of multicollinearity.

Table 3. Linear regression models.

	Simple		Full*		Reduced*	
	Beta (SE)	**P**	**Beta (SE)**	**P**	**Beta (SE)**	**P**
Education	12.92 (4.51)	0.0042	8.61 (4.90)	0.0791		
Household Income	13.43 (4.29)	0.0017	10.51 (4.59)	0.0222	13.89 (4.22)	0.0010
Newborn's Sex (Female)	-110.84 (11.67)	<0.0001	-109.41 (11.50)	<0.0001	-109.21 (11.50)	<0.0001
Gestational Diabetes	229.33 (56.05)	<0.0001	175.76 (55.10)	0.0014	176.26 (54.97)	0.0014
Gestational Hypertension	54.61 (56.14)	0.3307	26.14 (54.80)	0.6333		
Preeclampsia	-78.22 (42.72)	0.0671	-118.39 (42.15)	0.0050	-118.82 (42.04)	0.0047
Vaginal Bleeding	-35.66 (16.48)	0.0305	-46.35 (16.38)	0.0047	-42.47 (16.17)	0.0087
Maternal BMI	22.48 (2.21)	<0.0001	21.99 (2.26)	<0.0001	22.12 (2.21)	<0.0001
Paternal BMI	9.32 (1.90)	<0.0001	6.68 (1.87)	0.0004	7.24 (1.86)	0.0001
Maternal Age	6.05 (1.46)	<0.0001	2.13 (1.48)	0.1494		
Menarche Age	-3.25 (3.93)	0.4089	2.45 (3.91)	0.5301		
Calories Per Day (per 100cal)						
Year Before Pregnancy	1.92 (1.22)	0.1147	1.18 (1.20)	0.3281		
1st Trimester	2.20 (1.17)	0.0588				
2nd Trimester	2.13 (1.07)	0.0457				
3rd Trimester	2.06 (1.05)	0.0508				
Average NO_2 (per 10 units)						
Whole Pregnancy	4.96 (10.73)	0.6442	14.87 (13.60)	0.2742		
1st Trimester	2.56 (6.25)	0.6827				
2nd Trimester	5.43 (5.83)	0.3512				
3rd Trimester	-1.94 (4.78)	0.6851				
Average SO_2 (per 10 units)						
Whole Pregnancy	5.46 (4.53)	0.2273	10.76 (6.07)	0.0762	15.28 (5.16)	0.0028

1st Trimester	4.88 (2.12)	0.0213				
2nd Trimester	-0.58 (2.03)	0.7742				
3rd Trimester	-0.35 (2.04)	0.8648				
Average PM_{10} (per 10 units)						
Whole Pregnancy	-6.62 (4.24)	0.1186	-13.02 (4.81)	0.0069	-13.47 (4.78)	0.0049
1st Trimester	2.97 (1.55)	0.0557				
2nd Trimester	-2.32 (1.73)	0.1809				
3rd Trimester	-3.12 (1.41)	0.0270				

Temporal Autocorrelation

The unexpected trend observed in birthweight according to PM_{10} exposure quartile in the 1st trimester in unadjusted analyses can be explained by the significant and strongly negative correlation (r=-0.75375, P<0.0001, data not shown) between mean PM_{10} exposure in the 1st and 3rd trimesters. PM_{10} demonstrates predictable temporal trends across seasons, peaking in the winter due to emissions from coal heating and the temperature inversion caused by geographical features, and dropping in the summer. Higher PM_{10} exposure during the 1st trimester is likely not causing higher birthweight, but rather predicting lower PM_{10} exposure during the 3rd trimester, 6 months later, which could be associated with higher birthweight. The 3rd trimester may thus be the critical period during which higher or lower PM_{10} truly has an effect on birthweight. This is consistent with the results of a number of previous studies on exposure windows.

PM_{10} exposure during the 2nd trimester, on the other hand, is only weakly correlated with PM_{10} during trimesters 1 (r=-0.05895, P<0.0001) and 3 (r=-0.01876, P=0.1908). Trimesters 2 and 3 were thus modeled simultaneously in later regressions. PM_{10} exposure during the whole pregnancy, an average of PM_{10} exposure during the three trimesters, was most highly correlated with PM_{10} exposure during the 2nd trimester, which represents the midpoint of the 1st and 3rd trimesters in terms of time and air pollution and thus serves as an approximation of the mean PM_{10} exposure during the whole pregnancy.

As SO_2 during the 1st trimester is very closely associated with PM_{10} during the 1st (r=0.82643, P<0.0001) and 3rd (r=-0.76432, P<0.0001) trimesters, it is possible the positive effect associated with SO_2 during the 1st trimester is truly reflective of the negative effect of PM_{10} during the 3rd trimester on birthweight. Both the counterintuitive effects of PM_{10} and SO_2 during the 1st trimester could be explained by the effect of PM_{10} during the 3rd trimester on birthweight.

SO_2 correlations were similar to those seen for PM_{10}. Of mean SO_2 exposures by trimester, Trimesters 1 and 3 were highly negatively correlated (r=-0.62972, P<0.0001), while whole pregnancy and trimester 2 SO_2 were highly positively correlated. Trimesters 1 and 3 were not highly correlated with whole pregnancy and trimester 2 SO_2, though all pairwise associations were significant. As such, SO_2 exposures during the 2nd and 3rd trimesters (weakly correlated with one another) were used for exposure window analysis.

Months closer in time are more correlated for each of the pollutants. Because the seasonal trends in NO_2 were less interpretable and it was not significant in reduced multivariate linear regressions, NO_2 was not further considered.

Exposure Window Regressions

When mean PM_{10} exposure during trimesters 2 and 3 were introduced into the reduced model in place of PM_{10} exposure during the whole pregnancy, both were significant (Table 4). A 10 $\mu g/m^3$ increase in mean PM_{10} exposure during the 2nd trimester was associated with an 8 g (sd 2 g) decrease in birthweight (P=0.0002) and the same increase during the 3rd trimester was associated with a 4 g (sd 1 g) decrease in birthweight (P=0.0019). Given IQRs of 51.7 and 61.1 for mean PM_{10} exposure during the trimesters 2 and 3, air pollution could have a cumulative and sizable effect on birthweight over time. Mean PM_{10} exposure by month was also considered. Because months 1 and 7, 2 and 8, and 3 and 9 were highly negatively correlated with one another (r<-0.50, P<0.0001), months 1, 2, and 3 were excluded. When months 4-9 were added one by one to the reduced model described before, all but month 7 had significant and negative effects on birthweight. When all were added simultaneously, the newly reduced model showed that months 4 and 9 had significant and negative effects on birthweight (Table 4).

In the co-exposure model, neither SO_2 exposures during trimester 2 or trimester 3 were found to be significant in after controlling for PM_{10} exposures. For SO_2 exposure by month, when months 4-9 were added simultaneously, the newly reduced model showed that months 4, 6, and 8 had significant but opposing effects on birthweight. Given the potential for additional endogeneity and the conflicting results for SO_2, only PM_{10} was considered for interaction effects.

Table 4. Effects of mean PM_{10} exposure by trimester and month on birthweight.

	Simple		**Full**		**Reduced**	
PM_{10} Exposure	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
Trimester 2	-7.11 (2.10)	0.0007	-8.01 (2.12)	0.0002	-8.01 (2.12)	0.0002
Trimester 3	-3.66 (1.40)	0.0089	-4.39 (1.41)	0.0019	-4.39 (1.41)	0.0019
Month 4	-2.74 (1.31)	0.0367	-4.71 (1.65)	0.0044	-5.24 (1.47)	0.0004
Month 5	-3.97 (1.48)	0.0072	-1.98 (1.83)	0.2789		
Month 6	-2.84 (1.43)	0.0465	-1.78 (1.87)	0.3407		
Month 7	-1.89 (1.20)	0.1138	-0.72 (1.73)	0.6778		
Month 8	-2.36 (1.08)	0.0284	-1.00 (1.63)	0.5374		
Month 9	-2.56 (1.07)	0.0167	-3.42 (1.46)	0.0190	-4.50 (1.20)	0.0002
SO_2 Exposure	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
Trimester 2	1.27 (2.26)	0.5755	1.23 (2.27)	0.5866		
Trimester 3	0.77 (2.03)	0.7045	0.72 (2.03)	0.7226		
Month 4	2.48 (1.93)	0.1996	6.83 (3.20)	0.0331	6.47 (2.47)	0.0087
Month 5	0.35 (1.93)	0.8580	-1.86 (3.97)	0.6386		
Month 6	-0.05 (1.79)	0.9790	-5.58 (3.86)	0.1486	-4.71 (2.36)	0.0460
Month 7	0.75 (1.70)	0.6582	1.96 (3.85)	0.6101		
Month 8	2.04 (1.68)	0.2255	8.05 (3.97)	0.0428	6.38 (2.33)	0.0062
Month 9	0.52 (1.93)	0.7866	-3.90 (3.65)	0.2853		

*The analysis of trimesters was conducted separately from the analysis of months. All models for PM_{10}, including the simple models, were adjusted for household income, newborn sex, gestational diabetes, preeclampsia, vaginal bleeding, maternal and paternal BMI, and average SO_2 during the whole pregnancy. All models for SO_2 were adjusted for the same covariates and average PM_{10} during the whole pregnancy in place of average SO_2. The coefficients and significances on the covariates were not qualitatively different from those presented in Table 3.

Dietary Effects

PCA identified four factors from the 33 food items on the questionnaire and generated factor scores for each. Factor 1 included staples and other basic goods (ex. rice, flour, green vegetables, tomatoes, and potatoes); factor 2 included non-meat sources of protein (ex. milk, yogurt, eggs, soymilk, and tofu); factor 3 included additional vegetables (ex. mushrooms, bamboo shoots, wood-ear, seaweed, and garlic); and factor 4 included meats (beef, lamb, chicken, fish, and seafood). Higher factor scores indicated a greater variety of foods consumed within a category. Factor scores were significantly associated with household income level, but not with maternal BMI, which may be determined not by quality or variety of food, but by quantity, not measured here. Factor scores were also significantly associated with lower birthweight in the case of factor 1, and higher birthweight for factors 2 and 4. However, the effect sizes per unit change in the factor scores were small, and the IQRs for factor scores 1-4 were 0.35, 1.05, 1.35, and 1.36, so the total effects of food variety on birthweight were not anticipated to be large.

Table 5. Associations between factor scores and household income, maternal BMI, as well as effects on birthweight.

Factor, Interpretation	**Household income***		**Maternal BMI***		**Birthweight (Simple)****		**Birthweight (Full)****		**Birthweight (Reduced)****	
	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
1, Staples	-0.0265 (0.0105)	0.0113	0.0002 (0.0055)	0.9738	-12.61 (5.76)	0.0285	-12.82 (5.75)	0.0258	-12.74 (5.75)	0.0268
2, Non-meat protein	0.1095 (0.0103)	<0.0001	0.0031 (0.0055)	0.5643	12.84 (5.77)	0.0260	13.15 (5.76)	0.0226	13.03 (5.76)	0.0237
3, Vegetables	0.0265 (0.0105)	0.0113	-0.0064 (0.0055)	0.2427	7.12 (5.86)	0.2246	7.88 (5.86)	0.1787		
4, Meat	0.0825 (0.0104)	<0.0001	-0.0073 (0.0055)	0.1815	12.66 (5.82)	0.0297	13.18 (5.82)	0.0235	12.92 (5.82)	0.0264

*Factor scores were regressed on household income and maternal BMI. These regressions did not adjust for covariates.

**Birthweight was regressed on factor scores, adjusting for newborn sex, gestational diabetes, preeclampsia, vaginal bleeding, maternal and paternal BMI, average SO_2 during the whole pregnancy, and average PM_{10} during the whole pregnancy (the results were not qualitatively different when average PM_{10} during trimesters 2 and 3 were used instead). Income was not included in the model due to its previously described correlation with dietary factors. The coefficients and significances on the covariates were not qualitatively different from those presented in Table 3.

Interactions

Using a model that included household income, newborn sex, gestational diabetes, preeclampsia, vaginal bleeding, maternal and paternal BMI, average SO_2 during the whole pregnancy, average PM_{10} during the whole pregnancy, and dietary factors 1, 2, and 4, mean PM_{10} exposure during the whole pregnancy was not found to have significant interactions with income, maternal BMI, newborn sex, or dietary factors.

Discussion

Comparison of air pollution trends, effect sizes, and windows of exposure

The temporal trends in each of the air pollutants was consistent with previous findings in Lanzhou, with a bimodal distribution for PM_{10} and unimodal distributions for SO_2 and NO_2, with concentrations highest in summer and lowest in winter[11], and levels above Chinese and international standards[56].

We found evidence for a negative impact of air pollution on birthweight. Specifically, PM_{10} exposure during the 2nd and 3rd trimesters appears to be a better candidate for having effects on birthweight than SO_2 or NO_2. Previous studies have disagreed on the size and even direction of the effects of air pollution on birthweight and other birth outcomes. Our results are consistent with a WHO review finding associations between PM and both PTB and LBW in developing countries with high levels of air pollution[15]. However, they run counter to those of some studies that find a positive or null association between PM exposure and birthweight, including a study of 1.5 million births in Texas[16], a study of twins[7], and the Beijing Olympics natural experiment[19]. These differences can be reconciled after considering collinearity among multiple exposures, as well as residual confounding by differences in PM composition and by temporal autocorrelation[42], for example between the seemingly opposing effects of PM_{10} during the 1st and 3rd trimesters on birthweight. The methodologies applied by different studies, and the sample sizes used, also vary widely.

The finding that PM_{10} but not SO_2 is associated with LBW is consistent with a systematic review that also found inconclusive results for NO_2 across publications[42]. Studies in Japan and China found associations between SO_2 and risk of LBW[52,53], but another in Germany following power plant desulfurization found increases in LBW[31]. Apparently paradoxical results can frequently be explained or rationalized by complex correlation structures among different air pollutants, and different exposure windows.

PM_{10} does not penetrate as deeply into the respiratory tracts and lungs as does $PM_{2.5}$ or $PM_{0.1}$, and though it may impair lung structure and function, PM_{10}'s effects may be more dependent on its specific composition[51]. A study of eight European cohorts found that higher concentrations of sulfur, nickel, and zinc in PM_{10} and $PM_{2.5}$ were associated with increased risk of LBW[36]. Another study in the northeastern and mid-Atlantic U.S. found associations between birthweight and exposure to aluminum, elemental carbon, nickel, and titanium in $PM_{2.5}$, even at levels compliant with EPA standards, and null results for other chemical components of particulate matter[13].

Though the overall effects of a particular pollutant during pregnancy may not be significant, their effect sizes having been diluted by averaging over time, the effects during a particular trimester may still be important. As other studies have emphasized, it continues to be necessary to identify critical exposure windows[25], the specific active constituents of air pollution, and the mechanisms by which they exert effects on fetal outcomes[24,27].

Molecular, cellular, and physiological mechanisms

Exposure to air pollution may act through different mechanisms at different stages of the pregnancy, and on different organ systems. For instance, the placenta is less permeable to toxins earlier in the pregnancy, so early effects are more likely to be indirect, due to maternal responses, rather than the translocation of particles from the respiratory tract to the fetus[18]. The different mechanisms and physiological manifestations associated with different exposure windows, however, are complex and not well-characterized. One study from a low-pollution setting in China reports an association between exposure to PM_{10} and SO_2 in the second and third months of pregnancy and birth defects[30]. We did not consider birth defects due to sample size limitations.

A number of studies have also considered residential proximity to traffic and roadways, finding associations with LBW and also uncovering potential epigenetic mechanisms such as DNA[23] and mtDNA[20] methylation and shortened telomere length[6] in the placenta, which may serve as intermediate indicators of other mechanisms acting on disease progression. As placental weight was also lower in mothers living near major roads, the impairment of placental oxygen and nutrient transport functions were suggested to be part of the causal pathway between pollution exposure and birth outcomes including PTB and LBW[55], perhaps by inducing an anti-angiogenic state[46]. Indeed, proximity has also been related to maternal and fetal obstetrical complications including preeclampsia, preterm premature rupture of membrane and, subsequently, PTB and potentially LBW[54]. Maternal smoking, another prenatal exposure associated with LBW, was similarly found to heighten reduce antioxidant capacity and elevate oxidative stress in fetal placental tissue[4] and cord blood[3].

Some studies have also investigated the effects of in utero exposure to air pollution in animal models, finding associations with placental injury and hemorrhage as well as inflammatory cell infiltration and oxidative stress[49], and differential cytokine levels[9], gene expression, and hormone activation in pathways mediating inflammatory signaling, the antioxidant response, and endothelial function[45], with corresponding morphological changes in the umbilical cord[47]. These may serve as systemic mechanisms underlying reduced birthweight and later risk of cardiovascular, neurological, metabolic, and immunological conditions in humans[12,26].

Many covariates on placenta and umbilical cord are available from the Lanzhou birth cohort for future study, but fetal conditions such as placental abruption, placenta previa, and cord entanglement were also found to be significantly and negatively associated with birthweight in simple linear regressions, but were not included as it was not possible to preclude reverse causation or confounding by underlying biological mechanisms. Their inclusion improved the fit of the reduced model in Table 1 from R^2=0.0510 to R^2=0.2235, and the inclusion of placenta weight alone improved R^2 to 0.2189 (13 g increase in birthweight for 10 g increase in placenta weight, $P<0.05$) without otherwise qualitatively changing the results (data not shown). This validates the essential role of the placenta in fetal development, but also suggests that placenta weight may be a proxy for developmental processes that also affect birthweight.

With better data, the molecular, cellular, and physiological bases, including the relation to maternal and fetal conditions, for changes to birthweight can be further elucidated. Preliminary analyses on these data suggest that preeclampsia and placental conditions may mediate the connection between PM_{10} and birthweight (data not shown), consistent with some previous findings.

There is also the open question of whether air pollution exerts its influence on birthweight via PTB or IUGR. Some studies have found that PM affects birthweight without inducing PTB[35], while others, including studies on indoor air pollution, found that certain cooking fuels[1] and other chemicals lowered birthweight[21,34]. In this cohort, the present findings on term birthweight and a previous investigation of PTB[58] suggest that the effect of particulate matter on birthweight is mediated by both PTB and IUGR. Given the importance of indoor air pollution, including polychlorinated biphenyls, disinfection byproducts, and pesticides[33], it is important to consider multilevel environmental exposures in tandem.

A number of proposed mechanisms by which PM exposure might affect birthweight, including inflammation, oxidative stress, maternal-fetal hemodynamics, and displacement of the oxygen-hemoglobin dissociation curve[27,42], could also plausibly be affected by nutritional status and dietary profiles[22]. However, effect modification by nutrition was not found in our study, possibly due to biases in self-reported data or limited power. Other effect modifiers, such as race and smoking, were not considered due to low rates of smoking among Chinese women, and low numbers of non-Han women. A more detailed accounting of possible molecular and cellular mechanisms as well as physiological effects is necessary.

Limitations and potential methodological improvements

We accounted for temporal autocorrelation, the fact that months are more closely correlated with adjacent months or months a full year away, in only a crude way. Multicollinearity due to multiple exposures and temporal autocorrelation and seasonality for each pollutant should be investigated more explicitly in future studies.

Notably, NO_2, SO_2, and PM_{10} are heavily influenced by one another. Certain estimates were not robust to sensitivity analysis; for example, PM_{10} was in some instances not significant except in the presence of NO_2 or SO_2, both of which are positively associated with birthweight in contrast to PM_{10}, which is negatively associated with birthweight. Given that PM_{10} is positively correlated with both NO_2 and SO_2, sharing many of the same sources, it is possible that NO_2 or SO_2 are suppressing the effects of PM_{10}. If this is indeed the case, it points to the need for a fuller accounting of other environmental pollutants which may be correlated with PM_{10}, confounding the relationship with birthweight. However, NO_2 and SO_2 are widely associated with lower birthweight, rather than higher, and so residual confounding is another serious possibility. Additionally, there is still the potential for confounding by seasonal variables such as temperature and meteorological factors.

Apart from seasonal effects, we should also consider fixed effects in the trends of PM_{10}, SO_2, and NO_2, as well as whether or not differences in the fractions of women giving birth during each season bias the correlation matrix. For example, whole pregnancy NO_2 is most closely correlated to 3rd trimester NO_2, indicating that 3rd trimester NO_2 best approximates the average of 1st, 2nd, and 3rd trimester NO_2. This could be the case if a disproportionate number of infants in the sample were conceived in a particular month and a particular location, for example, if many infants were conceived in December in an area where NO_2 is highest in January-March, lowest in April-June, and at intermediate values in July-September.

As previously mentioned, future research will need to more fully account for seasonal trends in pregnancy and in different air pollutant concentrations using statistical methods. Smoothing splines, mixed regressions, and autoregressive methods may be applied in future analyses to better control for multicollinearity and potential misattribution/misinterpretation due to temporal autocorrelation. Land-use regression models and traffic proximity could also be applied to the Lanzhou context[37].

Our study, like many others, was also limited by its sample size and its power in isolating the small and easily overshadowed effects of air pollution on birthweight. Small effect sizes are difficult to examine without sufficiently specified regression models. Larger sample sizes and higher quality data on covariates (ex. food frequency) will allow us to improve our model. A longer follow-up time as well as a more geographically diverse sample population would have provided more heterogeneity in air pollution exposure. Further, the spatial resolution of this study was limited by the small number of environmental monitoring stations, and exposure assessment based on inverse distance weighting interpolation is not necessarily accurate for those living far from the monitoring stations. As time goes on, technical improvements will become possible. For example, the air pollution monitoring stations now also collect data on $PM_{2.5}$, O_3, and CO. Multilevel predictors, perhaps from prospective personal exposure and biological monitoring, and outcomes, including utero and placental conditions, could then be integrated using mediation or structural equation modeling.

Future: Pollution Policy and Natural Experiments

Though Lanzhou long topped lists of cities most affected by air pollution in China, the local government launched a major initiative in 2012 to significantly reduce air pollution by enforcing existing statutes, by relocating heavy industries to specially-designated, less densely-populated areas, and by transitioning coal-burning heating stations to natural gas. Though seldom discussed in English-language reporting, the 'Lanzhou Model' of pollution control is widely considered to have been a success in improving air quality. Such policy changes occurring across China may present key opportunities to understand the burden of air pollution on the Chinese populace, and serve as natural experiments for the impacts of different interventions. Though the timeframe of the pollution control initiative was outside of the scope of this study, we are hopeful that our findings may serve as a reference for comparison of future results.

Indeed, there is now strong evidence that sustained improvements in outdoor air quality through consistent monitoring, the enforcement of regulations, environmentally-conscious urban design and other policies, or even temporary improvements in air quality, will result in improved health for the Chinese populace[19,28,29,40].

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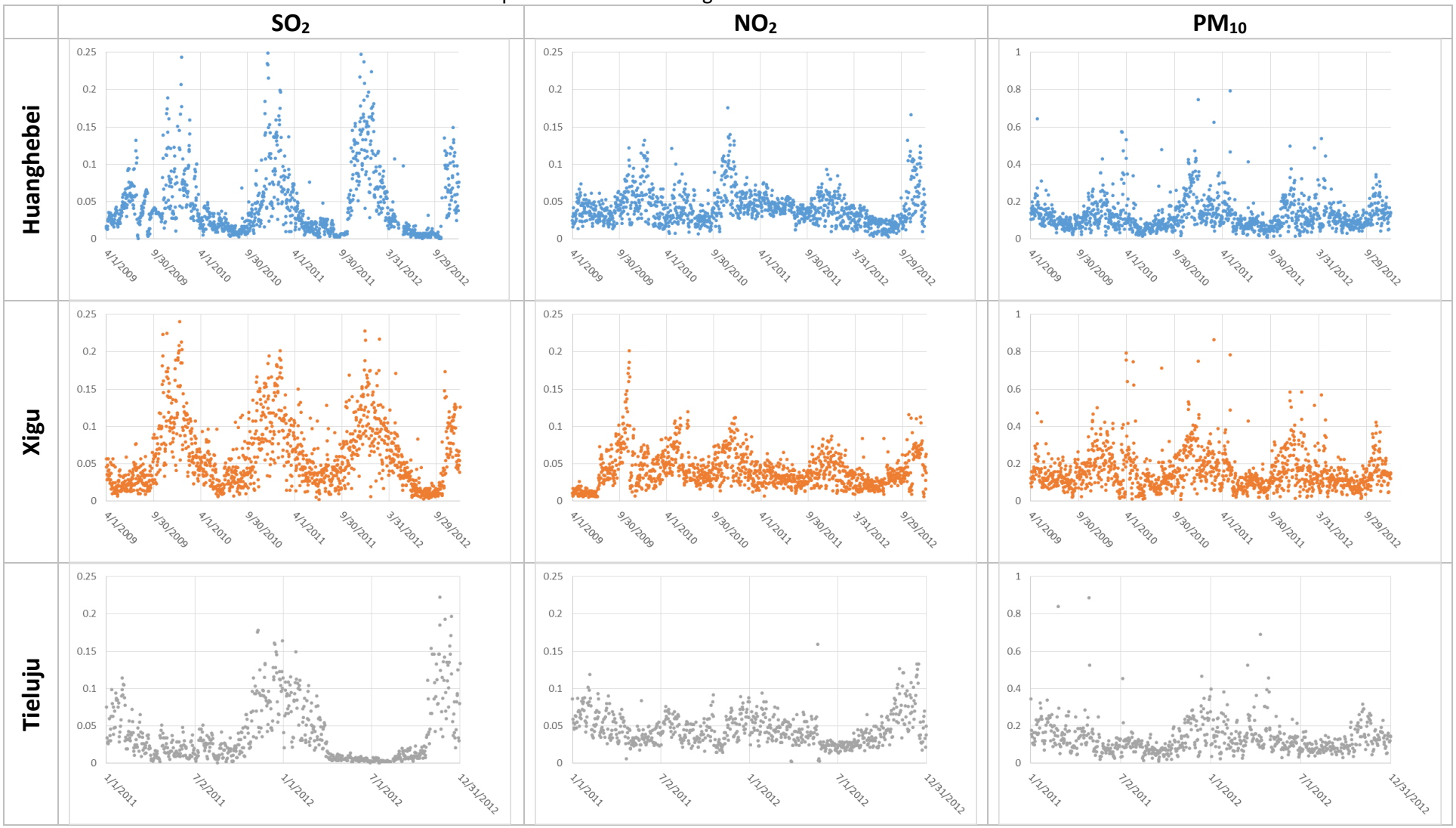
SO2
NO2
PM10
Huanghebei
Xigu
Tieluju
0.25
0.2
0.15
0.1
0.05
0
1
0.8
0.6
0.4
0.2
4/1/2009
9/30/2009
4/1/2010
9/30/2010
4/1/2011
9/30/2011
3/31/2012
9/29/2012
1/1/2011
7/2/2011
1/1/2012
7/1/2012
12/31/2012

Figure 1. Temporal and seasonal trends in SO_2, NO_2, and PM_{10}, stratified by location. The monitoring stations at Huanghebei and Xigu measured air pollution from April 1, 2009 until December 31, 2012, while the stations at Tieluju and Xizhan measured from January 1, 2011 until December 31, 2012. Raw data is presented here with impossible (negative) values removed. Data was not averaged across the different monitoring stations or aggregated by week or month to maintain spatial differences and temporal resolution, though for a given pollutant, merged raw data across all four stations are presented.

Supplemental Table 1a. PM_{10}, SO_2, and NO_2 Correlation Matrix by Trimester

		PM_{10}				SO_2				NO_2			
		preg	1st	2nd	3rd	preg	1st	2nd	3rd	preg	1st	2nd	3rd
PM_{10}	preg	1.000	0.076	0.729	0.334	0.493	0.031	0.487	0.146	0.350	0.148	0.343	0.073
	1st	0.076	1.000	-0.059	-0.754	-0.160	0.826	-0.268	-0.717	-0.284	0.571	-0.265	-0.583
	2nd	0.729	-0.059	1.000	-0.019	0.583	0.094	0.773	-0.064	0.228	0.077	0.554	-0.198
	3rd	0.334	-0.754	-0.019	1.000	0.160	-0.764	0.104	0.817	0.411	-0.412	0.131	0.738
SO_2	preg	0.493	-0.160	0.583	0.160	1.000	0.178	0.773	0.398	0.616	0.164	0.637	0.173
	1st	0.031	0.826	0.094	-0.764	0.178	1.000	-0.064	-0.630	-0.073	0.639	-0.096	-0.493
	2nd	0.487	-0.268	0.773	0.104	0.773	-0.064	1.000	0.110	0.404	0.064	0.693	-0.070
	3rd	0.146	-0.717	-0.064	0.817	0.398	-0.630	0.110	1.000	0.487	-0.437	0.256	0.756
NO_2	preg	0.350	-0.284	0.228	0.411	0.616	-0.073	0.404	0.487	1.000	0.343	0.472	0.676
	1st	0.148	0.571	0.077	-0.412	0.164	0.639	0.064	-0.437	0.343	1.000	-0.209	-0.128
	2nd	0.343	-0.265	0.554	0.131	0.637	-0.096	0.693	0.256	0.472	-0.209	1.000	-0.023
	3rd	0.073	-0.583	-0.198	0.738	0.173	-0.493	-0.070	0.756	0.676	-0.128	-0.023	1.000

Supplemental Table 1b. PM_{10} Temporal Autocorrelation Matrix

Month	1	2	3	4	5	6	7	8	9	10
1	1.000	0.566	0.214	-0.029	-0.172	-0.452	-0.662	-0.485	-0.087	-0.006
2	0.566	1.000	0.583	0.163	-0.052	-0.227	-0.471	-0.673	-0.502	-0.170
3	0.214	0.583	1.000	0.525	0.063	-0.114	-0.276	-0.504	-0.656	-0.463
4	-0.029	0.163	0.525	1.000	0.476	0.020	-0.073	-0.216	-0.465	-0.493
5	-0.172	-0.052	0.063	0.476	1.000	0.456	0.079	0.026	-0.129	-0.227
6	-0.452	-0.227	-0.114	0.020	0.456	1.000	0.542	0.159	0.106	0.016
7	-0.662	-0.471	-0.276	-0.073	0.079	0.542	1.000	0.557	0.202	0.129
8	-0.485	-0.673	-0.504	-0.216	0.026	0.159	0.557	1.000	0.560	0.221
9	-0.087	-0.502	-0.656	-0.465	-0.129	0.106	0.202	0.560	1.000	0.553
10	-0.006	-0.170	-0.463	-0.493	-0.227	0.016	0.129	0.221	0.553	1.000

Supplemental Table 1c. SO_2 Temporal Autocorrelation Matrix

Month	1	2	3	4	5	6	7	8	9	10
1	1.000	0.716	0.321	-0.132	-0.404	-0.518	-0.495	-0.442	-0.358	-0.197
2	0.716	1.000	0.704	0.296	-0.146	-0.396	-0.515	-0.485	-0.503	-0.384
3	0.321	0.704	1.000	0.714	0.324	-0.101	-0.373	-0.499	-0.564	-0.501
4	-0.132	0.296	0.714	1.000	0.721	0.368	-0.034	-0.304	-0.486	-0.480
5	-0.404	-0.146	0.324	0.721	1.000	0.750	0.432	0.038	-0.236	-0.369
6	-0.518	-0.396	-0.101	0.368	0.750	1.000	0.763	0.460	0.107	-0.104
7	-0.495	-0.515	-0.373	-0.034	0.432	0.763	1.000	0.760	0.475	0.176
8	-0.442	-0.485	-0.499	-0.304	0.038	0.460	0.760	1.000	0.786	0.482
9	-0.358	-0.503	-0.564	-0.486	-0.236	0.107	0.475	0.786	1.000	0.768
10	-0.197	-0.384	-0.501	-0.480	-0.369	-0.104	0.176	0.482	0.768	1.000

Supplemental Table 1d. NO_2 Temporal Autocorrelation Matrix

Month	1	2	3	4	5	6	7	8	9	10
1	1.000	0.513	0.101	-0.227	-0.444	-0.304	-0.045	0.032	0.000	-0.050
2	0.513	1.000	0.491	0.078	-0.205	-0.378	-0.252	-0.022	0.079	0.032
3	0.101	0.491	1.000	0.499	0.112	-0.177	-0.336	-0.240	-0.026	0.066
4	-0.227	0.078	0.499	1.000	0.529	0.156	-0.145	-0.273	-0.220	-0.094
5	-0.444	-0.205	0.112	0.529	1.000	0.532	0.184	-0.106	-0.236	-0.225
6	-0.304	-0.378	-0.177	0.156	0.532	1.000	0.602	0.252	-0.062	-0.177
7	-0.045	-0.252	-0.336	-0.145	0.184	0.602	1.000	0.684	0.319	0.066
8	0.032	-0.022	-0.240	-0.273	-0.106	0.252	0.684	1.000	0.718	0.422
9	0.000	0.079	-0.026	-0.220	-0.236	-0.062	0.319	0.718	1.000	0.752
10	-0.050	0.032	0.066	-0.094	-0.225	-0.177	0.066	0.422	0.752	1.000