ISSN: 2837-4835

Research Article

International Internal Medicine Journal

Role for Environmental Factors on the Relationship Between Seasons of Conception and Preterm Birth: An Observational Study in China

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Submitted: 2024, Jun 01; **Accepted**: 2024, Jun 17; **Published**: 2024, Jun 30

Citation: Liang, Y., Wang, Z., Bai, S., Du, S., Zhao, X., et al. (2024). Role for Environmental Factors on the Relationship Between Seasons of Conception and Preterm Birth: An Observational Study in China. *Int Internal Med J, 2*(6), 01-12.

Abstract

Background: *The relationship between season and the risk of preterm birth is not consistent. Importantly, the role of environmental factors in it is not clear.*

Methods*: Based on the baseline of the Jinan birth cohort, the mothers from the birth cohort were the subjects, and they were interviewed face-to-face by the questionnaire. The individual exposure levels of temperature and humidity during the first 30 days of pregnancy were calculated by an inverse distance weighting method. The effect of season on the risk of preterm birth was obtained by logistic regression model, and the mediating effect of environmental factors in the association between season and preterm birth was obtained by sequential test.*

Results: *A total of 4.4 % (263/5984) of mothers had premature children. The rates of preterm birth were higher in winter (6.0 %) and summer (4.5 %) than that in spring (3.1 %). In the multivariable logistic regression model, the adjusted odds ratio and 95 % confidence interval for the risk of preterm birth at conception in winter and summer were 2.228 (1.512-3.316) and1.541 (1.055-2.277). However, after further adjustment for humidity, only the association between winter conception and preterm birth remained statistically significant (OR: 2.353, 95% CI: 1.594-3.511). Moreover, the humidity partially mediated the relationship (41.2 %) between conception in winter and preterm birth, and humidity in winter was negatively associated with the risk of preterm birth (indirect effect = -0.007, P < 0.001).*

Conclusions: *For women living in the temperate regions, conception in summer and winter may increase the risk of preterm birth, and this association persisted in winter after adjusting for environmental factors. During the first 30 days of pregnancy, lower levels of humidity exposure in winter contributed to and mediated the relationship. The results may provide epidemiological evidence for pregnancy planning and care of women from the perspective of environmental factors.*

Keywords: Preterm Birth, Season, Mediating Effect, Birth Cohort

List of Abbreviations

OR Odds ratio
CI Confidence interval
O3 Ozone
PM2.5 Particulate matter with an aerodynamic diameter of less than 2.5 mm
IDW Inverse distance weighting
SD Standard deviation
IQR Interquartile range
VIF Variance inflation factors

1. Background

Preterm birth is a common adverse pregnancy outcome. The World Health Organization defines preterm birth as the birth of fewer than 37 weeks of pregnancy or the birth before the 259th day of pregnancy [1]. It was suggested that preterm birth was one of the causes of death for children under the age of 5 [2]. In addition, not only does preterm birth affect the health of newborns such as developing respiratory diseases, but also has long-term effects on the growth and development of children such as causing the poor development of the nervous system in childhood [3-5]. The global estimated prevalence of preterm birth was approximately 9.6 %, with a 95 % confidence interval (CI) of 9.1 % - 10.1 % in 2005 and 11.1% (95 % CI: 9.1 %-13.4 %) in 2010 [6,7]. Therefore, preventing the occurrence of premature birth is of great significance for promoting the health of children and reducing the associated social burden.

The occurrence of preterm birth is affected by many factors such as maternal age, abnormal pregnancy, tobacco smoke exposure during pregnancy, fetal congenital diseases and temperature, among which season is an important factor related to the environment, social activities and lifestyle habits [8-13]. Some studies tried to illuminate the relationship between season and preterm birth, and the seasonal pattern of preterm birth has been found around the world. A study conducted in the United States found that the highest prevalence of preterm birth occurred among the mothers who were pregnant in winter (11.3 %) and spring (11.0 %) [14]. Another study from Greece demonstrated that the occurrence of preterm birth increased in spring (6.2 %) and summer (6.2 %) [15]. Epidemiological evidence from South Korea indicated that the prevalence of preterm births peaked in summer (5.4 %) and winter (5.1 %) [16]. Given the inconsistent results reported in these studies, more research evidence is needed to confirm the link between season and preterm birth. There are multiple potential reasons for this. Firstly, the results came from different countries with different geographical location and social customs [17,18]. In addition, seasonal variables were defined differently: some chose the season of conception (14), others the season of birth [14-16]. Finally, there is a lack of evidence on the association between the season of conception according to the 24 solar terms and the risk of preterm birth. Thus, the seasonal patterns of preterm birth still need to be explored.

A number of studies have found association between environmental factors and preterm birth. Some studies have pointed that exposure to PM2.5, O3 and high temperature could affect the risk of preterm birth [19-21]. Meanwhile, the exposure levels of some environmental factors are different in different seasons. Specifically, people are more likely to be exposed to high temperatures in summer and low temperatures in winter, and more likely to be exposed to high levels of PM10 and PM2.5 in winter as well as O3 in summer [20,22]. Therefore, it is important to consider the effect of the environmental factors on the risk of preterm birth when we explore the relationship between the season and preterm birth.

Therefore, this study was based on the baseline data from the Jinan Birth Cohort to achieve three goals: 1) to examine the association between season of conception and the risk of preterm birth; 2) to explore whether the association between season of conception and preterm birth persisted after adjusting for climatic factors (temperature and humidity) as well as atmospheric pollutants (PM2.5 and O3); and 3) to explore whether there were mediating effects of other environmental factors between season of conception and preterm birth. Not only will the findings shed light on the role of environmental factors in seasonal influences on preterm birth, but also provide a new scientific basis for pregnant planning and pregnancy care of women.

2. Methods

2.1. Study Population

The present study was a cross-sectional study. The research population was from the baseline survey of the birth cohort study of which the purpose was to examine the effect of exposure to air pollutants in early life on childhood asthma. Fifteen out of 116 community vaccination clinics in Jinan City, Shandong province, China, were selected as the study sites of the birth cohort. From January 2018 to December 2019, when infants younger than one month visited outpatient clinics for vaccinations, infants and their mothers were recruited as study subjects for the birth cohort. The inclusion criteria were: i) the infants had no congenital disease; ii) the mothers had been living in Jinan City during pregnancy; iii) the mothers did not have serious mental illness or language communication difficulties; iiii) the mothers giving birth to a single child; iiiii) the mothers who gave birth between November 1, 2018 and October 31, 2019 [23,24]. Each mother was given a face-to-face questionnaire to obtain the relevant variables for the study.

2.2. Dependent Variable and Independent Variable

Preterm birth, the dependent variable of this research, is defined as the birth less than 37 weeks of gestation [1]. The gestational week for each mother was calculated by the date of birth minus the date of the first day for the last menstruation. And the gestational week was double determined by B ultrasound diagnose and the date of the first day of last menstruation and the date of delivery.

The season of conception was the independent variable. The date of conception was calculated based on the date of birth and gestational age. The season in which this date occurred was defined as the season of conception. The seasons are divided according to the Lichun, Lixia, Liqiu and Lidong of the 24 solar terms in the traditional Chinese calendar. Specifically, two solar terms in one month, and six solar terms are in each season, twenty-four solar terms are in one year. The solar terms are determined by the position of the sun on the returning ecliptic, the apparent path of the sun on the celestial sphere during the year. It coincides with the twelve signs of the zodiac in foreign astrology. At the same time we compared the results with those of seasons routinely divided according to months.

2.3. Assessment of Exposure to Environmental Factors

Monitoring data of ambient temperature, relative humidity (humidity) and air pollutants of subjects during the first 30 days of pregnancy were obtained from 17 Jinan Environmental Monitoring Station, which covered the study area. The first 30 days of pregnancy was from the first day of conception to the following 29 days. The daily mean of ambient temperature and humidity for each subject was obtained by calculating the mean of the average daily temperature and humidity of environmental monitoring stations in Jinan City. From the same environmental monitoring stations, we obtained average daily monitoring values of O3 (ozone), and PM2.5 (particulate matter with an aerodynamic diameter of less than 2.5 mm). Based on the beginning date of pregnancy and the family address for each subject, the individual daily mean of air pollutant concentration was estimated by an inverse distance weighting (IDW) method [21]. Afterwards, we calculated the arithmetic mean of the daily exposure levels during the first 30 days of pregnancy for each individual as the exposure level to environmental factors.

2.4. Covariates

Covariate information was obtained through the questionnaire, which included general characteristics of the mother, maternal pregnancy information, infant information and information of the family. The general characteristics of the mother included parity, delivery method, age, education level, housewife and regular menstrual cycle. According to the parity, we divided the subjects into primipara and multipara. Age was divided into four groups: ≤25 years, 25-30 years, 30-35 years, and >35 years. Maternal pregnancy information mainly included pregnancy complications, pregnancy-induced hypertension, abnormal pregnancy, passive smoking, vitamin D supplement, folic acid supplement, calcium supplement, work, and exercise. Pregnancy complications included abnormal umbilical cord, amniotic fluid embolism and uterine rupture. Abnormal pregnancy included placenta previa, threatened preterm labor, gestational diabetes mellitus and prenatal bleeding. Passive smoking was defined as exposure to tobacco smoke for more than 30 minutes per week. Exercise was defined as any planned, organized, and repetitive physical activity, including walking, brisk walking, swimming, yoga/Pilates/ maternity gymnastics, squats and others. Infant information just included the gender of infant [25]. Information of the family included number of family members, total monthly income (RMB) and address. Address was defined as the geographical location of the residence where the mother lived for the longest period of her pregnancy. All variable information, including dependent variables, independent variables, and covariates except for environmental monitoring data, was obtained through face-to-face interviews using questionnaires at the baseline survey.

2.5. Statistical Analysis

For continuous variables, when they were normally distributed, the mean and standard deviation (SD) were used to describe them, and Student's t test and Analysis of Variance were used to test for differences between groups; when they are not normally distributed, the median and interquartile range (IQR) are used to describe them, and rank sum test was used to examine the differences between groups. For categorical variables, rates and constituent ratios were used to describe them, and comparisons between groups were performed by Chi-square test. We constructed the binary logistic regression models for univariate and multivariate analyses. In the multifactor model, we adjusted for covariables that might be associated with preterm birth, covariates were grouped into three groups according to basic maternal information, adverse pregnancy symptoms and behavioral factors, progressively adjusted. Environmental factors were also separately included in the multifactor logistic regression model for adjustment. In addition, we calculated the variance inflation factors (VIF) of the covariables in the model for collinearity diagnosis and excluded the covariables of which VIF over 10. The odds ratio (OR) and corresponding 95 % confidence interval (CI) were used to described the effect of variates on preterm birth. We adopted *Pearson* correlation coefficient to conduct the correlation analysis of continuous variables. The mediating effect of environmental factors on the association between season and preterm birth was analyzed by sequential test [22,23].

Statistical analyses were performed with R version 3.6.1 (http://www.r-project.org/) using *gmodels, EnvExpInd, mediation*, and car packages. P values of < 0.05 were considered statistically significant.

2.6. Sensitivity Analysis

Furthermore, because the study subjects were from 15 community vaccination clinics which were selected in the birth cohort study, in order to verify whether a selection bias, infants from each clinic were excluded successively, and a multivariable analysis was conducted again to prove the stability of the results.

Also, in order to control for the effect of moving during pregnancy, the variable of moving during pregnancy was firstly adjusted in the model. Secondly, after excluding study participants who moved during pregnancy, the analysis was conducted again.

2.7. Quality Control

In each procedure of the study, rigorous quality control was carried out. The questionnaire was designed by experts in reproductive epidemiology. After designing, the questionnaire was improved through pre-survey. The investigators at each site had a 3-day training course on maternal and infant knowledge and investigation skills. During the investigation and data input and sorting, there were quality control personnel on the site to supervise. In addition, Epidata 3.1 was used for data entry and logical proofreading.

3. Results

3.1. The Characteristics of the Subjects

6,640 pairs of infants and mothers were included in the baseline of the birth cohort. After excluding 139 multiple pregnancies, we selected the mothers who gave birth between November 1, 2018 and October 31, 2019 as the subjects. In the end, 5,984 mothers were included in the study (Figure S1). We presented the distribution of outpatient clinics in Jinan, the location of air monitoring stations and the home addresses of the study participants in Figure 1. The study area is located in the mid-latitude zone and has a temperate monsoon climate. It is characterized by four distinct seasons, with a dry spring with little rain, a warm and rainy summer, a cool and dry autumn and a cold and snowy winter.

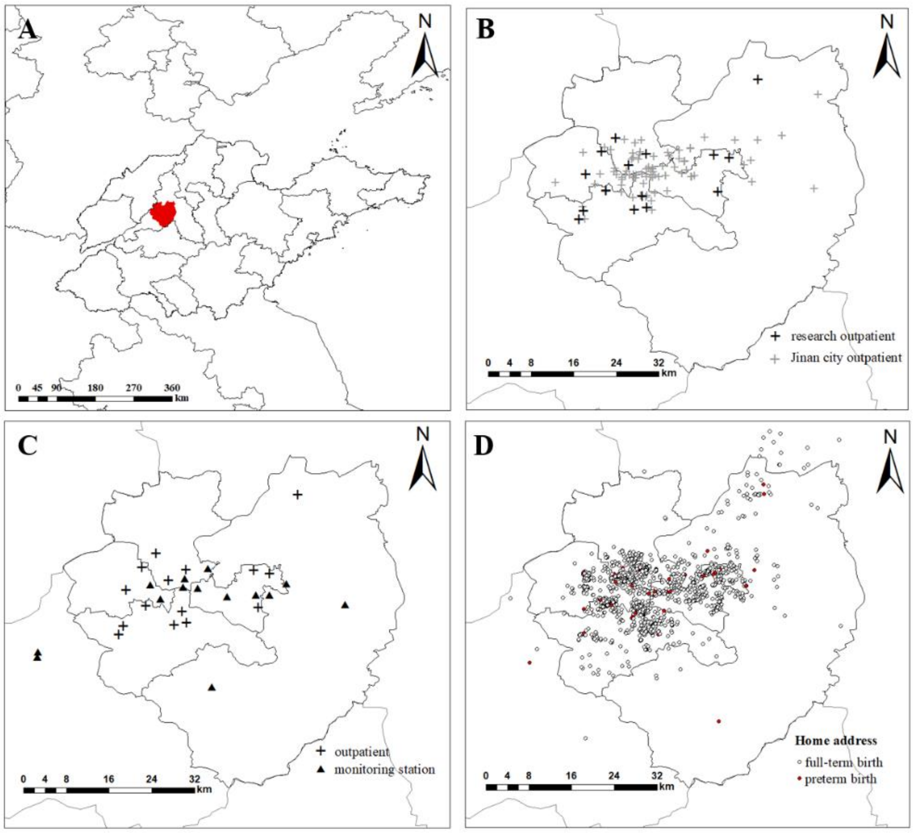


Figure 1: The locations for Study Area(A), Outpatient Clinics (B, C), Monitoring Stations(C), and Home Addresses of Subjects(D)

3.2. The Distributions of Preterm Birth in the Population

The range of gestational age for the subjects was 188 days to 309 days, and the median and IQR of gestational age were 275 days and 11 days. Among 5984 subjects, 263 mothers gave birth to premature children, and the rate of premature children was 4.4 %.

The distributions of preterm birth in different subgroups were showed in Table 1. Compared with the mothers without preterm birth, mothers with preterm birth were more likely to be housewives, older mothers, primiparas, and the mothers with cesarean section, pregnancy complications, pregnancy-induced hypertension, abnormal pregnancy, did not exercise during pregnancy, and the mothers who took vitamin D supplements during pregnancy ($P < 0.05$).

Classification		Total		Preterm birth		P
		n	proportion (%)	n	rate (%)	
Maternal general information						
age (year)	≤25	722	12.1	24	3.3	<0.001
	25~30	2422	40.5	86	3.6	
	30~35	1981	33.1	96	4.8	
	＞35	859	14.4	56	6.6	
education level	below college degree	1558	26.0	81	5.2	0.084
	college degree or above	4426	74.0	182	4.1	
housewife	no	4731	79.1	193	4.1	0.025
	yes	1253	20.9	70	5.6	
regular menstrual cycle	no	701	11.7	34	4.9	0.598
	yes	5283	88.3	229	4.3	
Infant						
gender	male	3102	51.8	150	4.8	0.097
	female	2882	48.2	113	3.9	
Family						
number of family members	≤3	1576	26.3	57	3.6	0.092
	>4	4408	73.7	206	4.7	
total monthly income (RMB)	≤6000	744	12.4	42	5.6	0.366
	6000~12000	2819	47.1	119	4.2	
	12000~18000	1627	27.2	69	4.2	
	>18000	794	13.3	33	4.2	
Maternal pregnancy information						
primipara	no	3035	50.7	150	4.9	0.042
	yes	2949	49.3	113	3.8	
delivery method	normal delivery	3275	54.7	103	3.1	<0.001
	cesarean section	2709	45.3	160	5.9	
pregnancy complications	no	5881	98.3	254	4.3	0.046
	yes	103	1.7	9	8.7	
pregnancy-induced hypertension	no	5800	96.9	228	3.9	<0.001
	yes	184	3.1	35	19.0	
abnormal pregnancy	no	5684	95.0	206	3.6	<0.001
	yes	300	5.0	57	19.0	
passive smoking	no	5114	85.5	227	4.4	0.756
	yes	870	14.5	36	4.1	
vitamin D supplement	no	3589	60.0	140	3.9	0.027
	yes	2395	40.0	123	5.1	
folic acid supplement	no	388	6.5	22	5.7	0.254

	yes	5596	93.5	241	4.3	
calcium supplement	no	1024	17.11	49	4.8	0.558
	yes	4960	82.89	214	4.3	
work	no	2298	38.4	102	4.4	0.948
	yes	3686	61.6	161	4.4	
exercise	no	1784	29.8	99	5.5	0.006
	yes	4200	70.2	164	3.9	

Table 1: Characteristics of Subjects and the Distribution of Preterm Birth in Different Subgroups

3.3. Preterm Birth in Different Seasons of Conception

The distribution of solar terms in the time range of maternal conception was described in Table S1, and the distribution of seasons was showed in Figure S2. The proportion of mothers who became pregnant, the proportion and the incidence of preterm birth in different months (according to the solar terms) were presented in Figure 2. Preterm births occurred in 3.1 % (45/1429) of the mothers who conceived in spring, 4.5 % (79/1745) in summer, 4.2 % (66/1584) of in autumn, and 6.0 % (73/1226) in winter. Stratification according to 24 solar terms, the preterm birth rate was higher among the subjects who conceived in summer (4.5 % vs 3.1 %, OR= 1.458, 95 % CI: 1.009-2.132) and winter (6.0 % vs 3.1 %, OR=1.947, 95 % CI:1.338-2.864), when comparing with that in spring. More information was showed in Table 2.

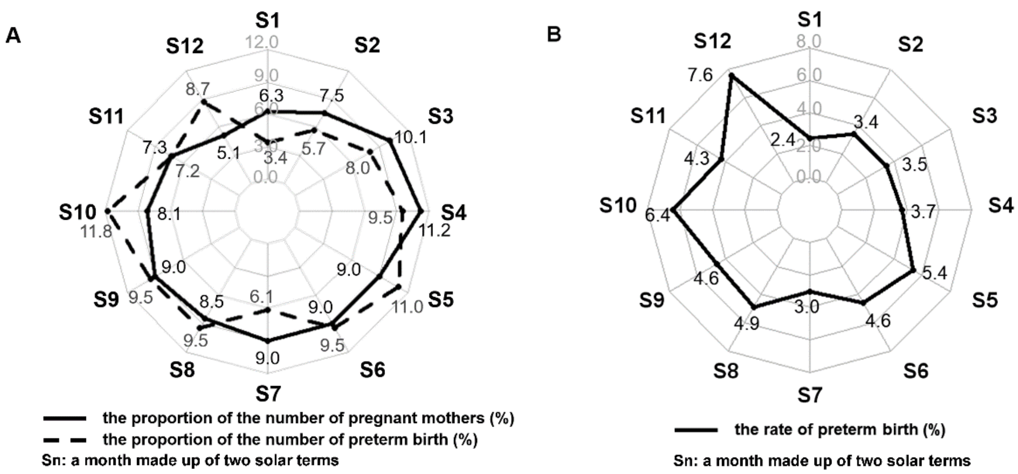


Figure 2: The Proportion of Mothers who Conceived and the Proportion and Rate of Preterm Birth in Different Months

Season of conception	Simple	Preterm birth (%)	*P*	*OR* (95 % *CI*)
Spring	1429	45 (3.1)	-	1
Summer	1745	79 (4.5)	0.047	1.458 (1.009-2.132)
Autumn	1584	66 (4.2)	0.140	1.337 (0.912-1.978)
Winter	1226	73 (6.0)	0.001	1.947 (1.338-2.864)

Table 2: The Rate of Preterm Birth in Different Seasons of Conception

3.4. The Exposure Levels of the Environmental Factors During the First 30 Days of Gestation

The median values of concentrations of temperature, humidity, SO_2, NO_2, CO, O_3, PM_{10}, and $PM_{2.5}$ exposure during the first 30 days of gestation were 18.257 ℃, 52.908 %, 12.935 μg/m^3, 39.598 μg/m^3, 818.214 μg/m^3, 115.721 μg/m^3, 106.496 μg/m^3, and 42.892 μg/m^3, respectively (Table 3). There was a statistically significant difference in maternal exposure to humidity between mothers who delivered preterm and those who did not (P = 0.015). The median and *IQR* were 53.805 % (10.473 %) in the preterm birth group, and 52.849 % (10.656 %) in the non-preterm birth group (Table 3). Except for humidity, there were no significant differences in temperature and six air pollutants during the first 30 days of pregnancy between the two groups (P > 0.05, Table 3).

Environmental factor	Total		Mothers with preterm birth		Mothers without preterm birth		*P*
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Temperature (℃)	16.874 (9.623)	18.257 (17.145)	16.112 (10.031)	16.777 (20.543)	16.909 (9.603)	18.310 (16.920)	0.284
Humidity (%)	54.514 (7.482)	52.908 (10.634)	55.433 (6.965)	53.805 (10.473)	54.471 (7.503)	52.849 (10.656)	0.015
O_3 (μg/m^3)	111.256 (45.139)	115.721 (78.314)	113.753 (44.78)	121.676 (75.320)	111.141 (45.156)	115.580 (78.538)	0.340
$PM_{2.5}$ (μg/m^3)	51.536 (21.056)	42.892 (32.265)	53.654 (22.153)	44.340 (42.434)	51.439 (21.001)	42.828 (31.744)	0.212

Table 3: The Exposure Levels of Environmental Factors During the first 30 days of Gestation Between Groups

3.5. The Relationship between Seasons of Conception and the Risk of Preterm Birth

The results of multivariable analysis were shown in Table 4. The adjusted OR (95 % CI) for the risk of preterm birth associated with conception in winter was 2.003 (1.374-2.951) in Model 1, 2.264 (1.539-3.368) in Model 2, and 2.228 (1.512-3.316) in Model 3, respectively, compared with conception in spring. The OR (95 % CI) of conception in summer was 1.482 (1.024-2.169) in Model 1, 1.571 (1.077-2.320) in Model 2, and 1.541 (1.055-2.277) in model 3, respectively. And conception in autumn was not significantly associated with the risk of preterm birth (P > 0.05).

Season of conception	Model 1 [a]		Model 2 [b]		Model 3 [c]	
	P	OR (95 % CI)	*P*	OR (95 % CI)	*P*	OR (95 % CI)
Spring		1.000 (reference)		1.000 (reference)		1.000 (reference)
Summer	0.039	1.482 (1.024-2.169)	0.021	1.571 (1.077-2.320)	0.027	1.541 (1.055-2.277)
Autumn	0.118	1.362 (0.927-2.018)	0.065	1.453 (0.980-2.172)	0.073	1.438 (0.970-2.151)
Winter	<0.001	2.003 (1.374-2.951)	<0.001	2.264 (1.539-3.368)	<0.001	2.228 (1.512-3.316)

[a] Adjusted for covariates related to basic maternal information: primipara, delivery method, age, housewife.

[b] Adjusted for the covariates in Model 1, continued adjustment for covariates related to abnormal symptoms in pregnancy: pregnancy complications, pregnancy-induced hypertension, and abnormal pregnancy during pregnancy.

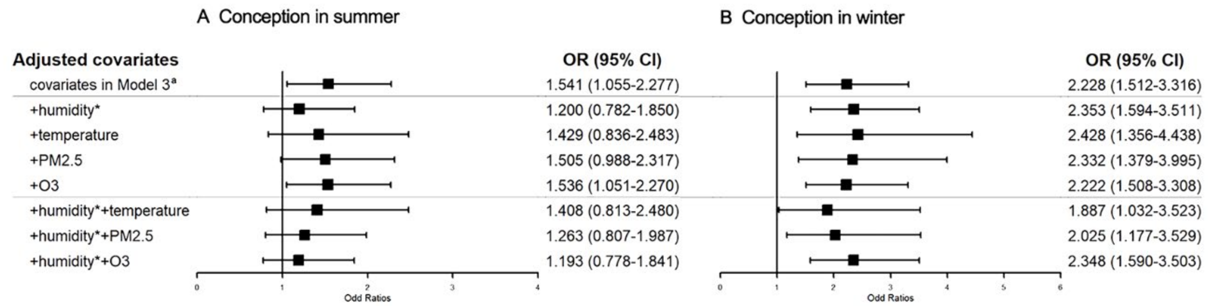
[c] Adjusted for the covariates in Model 2, continued adjustment for covariates related to behavioural factors: passive smoking, vitamin D supplement, and exercise during pregnancy.

Table 4: Multifactor Logistic Regression Models for the Association between Seasons of Conception and the Risk of Preterm Birth

3.6. The Roles of Environmental Factors on the Association Between Seasons of Conception and the Risk of Preterm Birth

Based on the covariates in Model 3, we adjusted for the environmental factors to examine the relationship between conception in summer or winter and the risk of preterm birth, and the results were showed in Figure 3. For conception in summer, the *ORs* and 95 % *CIs* were 1.200 (0.782-1.850) adjusted for humidity, and 1.429 (0.836-2.483) adjusted for temperature, and 1.505 (0.988-2.317) adjusted for $PM_{2.5}$, and 1.536 (1.051-2.270) adjusted for O_3, and 1.408 (0.813-2.480) adjusted for humidity and temperature, and 1.263 (0.807-1.987) adjusted for humidity and $PM_{2.5}$, and 1.193 (0.778-1.841) adjusted for humidity and O_3, respectively. For conception in winter, the *ORs* and 95 % *CIs* of the risk of preterm birth were 2.353 (1.594-3.511) adjusted for humidity, and 2.428 (1.356-4.438) adjusted for temperature, and 2.332 (1.379-3.995) adjusted for $PM_{2.5}$, and 2.222 (1.508-3.308) adjusted for O_3, and 1.887 (1.032-3.523) adjusted for humidity and temperature, and 2.025 (1.177-3.529) adjusted for humidity and $PM_{2.5}$, and 2.348 (1.590-3.503) adjusted for humidity and O_3, respectively. In addition, the OR (95 % CI) of the risk of preterm birth associated with each 10 % increase in humidity was 1.020 (1.003-1.038).

Covariance diagnostics were performed before inclusion in the model for correction, and none of the variables for which adjustments were made were free of multicollinearity with each other, while correlation analyses were carried out, humidity was positively correlated with temperature and negatively correlated with $PM_{2.5}$, but had no correlation with O_3. The correlation coefficient was 0.602 between humidity and temperature (P<0.001), and -0.576 between humidity and $PM_{2.5}$ (P<0.001). And the correlation coefficient between humidity and O_3 was 0.012 (P=0.400).



ª Including primipara, delivery method, age, housewife a.nd pregnancy complications, pregnancy-induced hypertension and abnormal pregnancy during pregnancy and passive smoking, vitamin D supplement and exercise during pregnancy.

* The covariate was significantly associated with preterm birth (*P*<0.05).

Figure 3: The ORs and 95 % CIs for the Risk of Preterm Birth Related to Season of Conception in Multifactor Logistic Regression Models. A: the Risk of Conception in Summer with Adjusting for Different Environmental Factors; B: the Risk of Conception in Winter with Adjusting for Different Environmental Factors

3.7. The Result for the Mediating Effect of Humidity

The effect of humidity in the association between season of conception and risk of preterm birth was showed in Figure 4 and Table S3. For the independent variable in each model, conception in spring and in autumn was the control group. There was no statistical significance in mediating effect of the humidity in the relationship between conception in summer and preterm birth (P > 0.05). The humidity partially mediated the relationship between conception in winter and preterm birth (Indirect effect= □0.007, P < 0.001), which was explained 41.2% of the relationship.

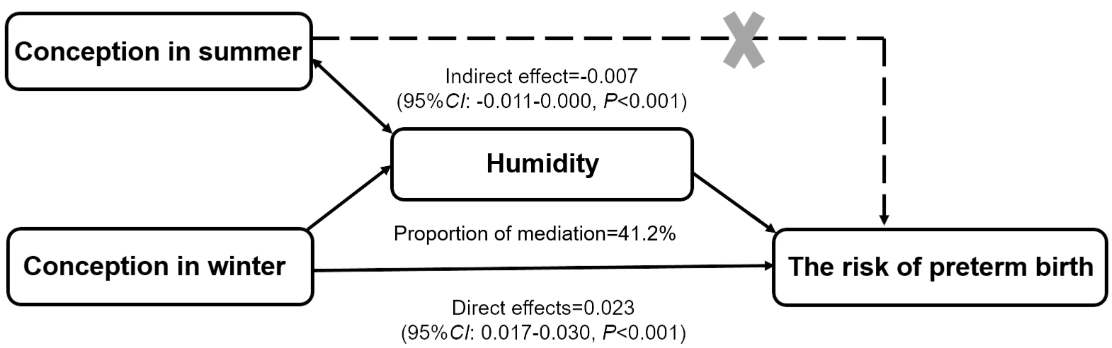


Figure 4: The Mediating Effect of Humidity on the Relationship Between Season of Conception and the Risk of Preterm Birth

3.8. The Result of the Sensitivity Analysis

To test the robustness of the results, we performed some sensitivity analysis, and the results were showed in Figure S3. After excluding clinics one by one, the effect of maternal conceiving in winter on preterm birth still existed (OR > 2). And conceiving in other seasons was still not associated with preterm birth.

To control for the effect of moving during pregnancy on the study results, the variable moving during pregnancy was adjusted for in the model, and the risk of winter pregnancy on preterm birth remained (aOR = 2.009, 95%CI 1.378-2.960). Secondly, after excluding study participants who moved during pregnancy, the analysis was repeated and winter pregnancy remained a risk factor for preterm birth (aOR = 2.094, 95%CI 1.422-3.123) (Table S4).

4. Discussion

Although some studies have explored the association between season and preterm birth, most of them have used the season of delivery as the independent variable. As far as we know, only two studies have revealed the relationship between season of conception and preterm birth. A study from Pennsylvania, the United States, noted that mothers who conceived in autumn and summer were less likely to have a premature birth than those who conceived in spring and winter (autumn: OR=0.91, 95 % CI: 0.85-0.96; summer: OR=0.92, 95 % CI: 0.86-0.98) (14). Another Danish national cohort study found that a slight increase in risk was observed in autumn (AHR, 1.05; 95% CI, 1.02-1.09) compared with winter [24]. Our finding was not quite the same as the result of the previous research. In the present study, mothers who conceived in winter were more likely to give birth prematurely after adjusting for environmental factors such as temperature, humidity and air pollutants (OR=2.353, 95 % CI: 1.594-3.511). Demonstrating that the effect of seasonal patterns on the risk of preterm birth cannot be attributed entirely to meteorological factors and air quality. Other factors such as race/ethnicity, lifestyle, and economic level may also play an important role in the association between season and preterm birth. Therefore, there may be different seasonal patterns in the risk of preterm birth in different regions, and the association between seasonal and preterm birth risk should be further studied in more regions [26-29]. The study area of this study is the northern Chinese city, Jinan, which is located in the mid-latitude zone and has a temperate monsoon climate due to the influence of solar radiation, atmospheric circulation and geography. It is characterized by a pronounced monsoon and four distinct seasons, with a dry spring with little rain, a warm and rainy summer, a cool and dry autumn, and a cold and snowy winter. The results of this study are therefore can be extrapolated to regions with similar seasonal patterns.

In this study, IDW method was used to assess the pollutant exposure levels of the subjects. It is widely used and has been employed in a number of studies to estimate the concentrations of major air pollutants to which subjects are exposed, with relatively smooth interpolation results for small measurement areas with relatively dense sampling points and small area variations[29-32]. But IDW modelling method may cause an exposure bias as the number of monitoring stations was sparse with an ignorance in the land used conditions [33]. In contrast, our research is a small area study and is located in an urban area with relatively consistent land use, making it more accurate and reasonable to use IDW to assess pollutant exposure concentrations.

Our results showed that the association between summer conception and preterm birth disappeared after adjusting for exposure levels of environmental factors other than O3 in the first 30 days of pregnancy, but the association between winter conception and preterm birth persisted. In other words, the increased risk of preterm birth for mothers conceived during the summer can be attributed to environmental factors, of which humidity may have played a key role, as the association between summer conception and risk of preterm birth disappeared after adjusting for humidity as well as humidity-related temperature and PM2.5. Meanwhile, O3 was not correlated with humidity, adjusting for O3 did not affect the association. Our results adjusting for humidity and one of the other environmental factors also supported this view. Some studies pointed that eclampsia and preeclampsia were more prevalent in hot, cold and humid seasons or months [34,35]. Based on the evidence to date, we conjecture that the humidity may affect the cardiovascular system of pregnant women, which further causes premature birth. Given that most studies on the relationship between environmental factors and preterm birth have focused on temperature, air pollutants, and greenery, the relationship between humidity and preterm birth and its mechanistic will require more evidence in the future [13]. More importantly, after adjusting for environmental factors, the association between winter conception and risk of preterm birth persisted. To further explored the mechanisms, we analyzed the mediating effect of humidity on the relationship between seasons of conception and the risk of preterm birth. Interestingly, we found that humidity partially mediated the relationship between conception in winter and the risk of preterm birth, and more specifically, that exposure to low humidity in winter may increase the risk of preterm birth (proportion of mediation = 41.2%, indirect effect = □0.007, $P < 0.001$). Except for the humidity, there may be other reasons for the relationship between conception in winter and preterm birth. On the one hand, some researches showed that the virus was more likely to be transmitted in winter [36-38]. Infections such as influenza infection and malaria in pregnancy might affect intrauterine growth and lead to preterm birth [39,40]. Therefore, we reckoned that a high risk of infection contributes to more preterm births in mothers who fertilize in winter than in other seasons. On the other hand, nutrition may be another reason for preterm birth among the women who conceive in winter pregnancies. When winter comes, changes in the diet of mothers, such as having a high-fat diet and difference in vegetable and fruit intake, may lead to a rapid weight gain of the mothers, affect the blood perfusion of the placenta in the future, and lead to premature birth [41,42]. Furthermore, lack of prenatal health care may lead to adverse birth outcomes. In winter, the end of the year, woman will be busier in that they need to sum up their work and prepare for the New Year and the Spring Festival. A study found that mothers who became pregnant in October or November were less likely to get prenatal care in the first trimester [43]. It is necessary to explore the mechanism for the effect of conception in winter on preterm birth in further studies.

In this study, we chose the seasons based on the solar terms in the traditional Chinese calendar as the independent variables. In the traditional Chinese calendar, the solar year is divided equally into 24 parts, which was called the 24 solar terms. The 24 solar terms have not only had a profound influence in China, but have also spread to the Korean Peninsula, Japan, Southeast Asia and other regions. Even in countries where there are no 24 solar terms, the twelve constellations in astrology correspond to twelve of the 24 solar terms, one by one. The solar terms are determined by the position of the sun on the returning ecliptic, the apparent path of the sun on the celestial sphere during the year. The position of the sun's annual trajectory is therefore relatively fixed for each of the solar terms. Lichun, Lixia, Liqiu and Lidong are when the sun reaches 315°, 45°, 135° and 225° of the ecliptic respectively, representing the beginning of spring, summer, autumn and winter. It scientifically reveals the laws of astronomical and meteorological changes in China, combines astronomy, agriculture, phenology and folklore skillfully, and is used to indicate climate change, to make decisions about the timing of crop sowing and harvesting, and derives a large number of seasonal cultures related to it [44-47]. In contrast, the seasons cannot be accurately delineated according to the months, as the same date each year corresponds to a different annual trajectory of the sun. Some studies have examined the relationship between seasons or climate change based on the traditional Chinese calendar and human health [48-50]. Therefore, we speculate that to explore the relationship between season based on solar terms and preterm birth could discover a more appropriate link of them in Chinese people.

There were mainly three advantages in the present study. First, we looked at the relationship between season and preterm birth in more detail and found for the first time that humidity partially mediated the relationship. It provides a reference for the following mechanism research. Second, compared with the birth season in other studies, the conception season based on traditional Chinese calendar solar terms was selected as the research variable in our study, which was more in line with the seasonal pattern of exposure of the study subjects, and was of more preventive significance and value in the exploration of etiology. Third, we considered more season-related covariates in this study. We assessed individual exposure levels for environmental factors, performed a differential analysis to select the factors that might affect preterm birth, and included them in the multivariable model for adjustment.

However, our study still had some limitations. Mothers of all live-born infants were included in the study, but infants who died in the perinatal period due to preterm delivery were not included in the study, which may lead to some selection bias. Besides, some covariates such as maternal pregnancy information was reported only by relying on maternal recollections, which may have a certain degree of recall bias. Thirdly, due to the uneven distribution of monitoring stations, the assessment of exposure to environmental factors for study subjects located at a distance from the monitoring stations may not be sufficiently precise. In addition, as climatic factors, air quality and other factors vary from region to region, the conclusions of this study need to be extrapolated with caution.

5. Conclusions

For women living in temperate regions, conception in summer and winter may increase the risk of preterm birth. The increased risk of preterm birth during summer conception was strongly associated with environmental factors. However, in addition to the mediating effect of humidity, other unknown factors played a role in the increased risk of preterm birth during winter conception, and the possible causes of preterm birth in women during winter conception need to be further investigated.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Preventive Medicine of Shandong University (Approved number: 20170315). Informed consent was obtained from all subjects and/or their legal guardian(s). All methods were carried out in accordance with relevant guidelines and regulations.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study was funded by the National Natural Science Foundation of China (81773386).

Author Contributions

Yuxiu Liang: Investigation, Software, Writing-Original draft preparation. Zhaojun Wang: Resources. Shuoxin Bai: Investigation, Visualization, Data Curation. Shuang Du: Investigation, Software. Shaoqian Lin and Xiaodong Zhao: Supervision, Investigation. Zhiping Wang: Project administration, Methodology, Conceptualization.

Acknowledgments

Thanks to the Jinan Center for Disease Control and Prevention and the staff of the community vaccination clinic for the investigation as well as the Jinan Ecological Environment Bureau for reviewing environmental data. We also thank all mothers and infants for their cooperation.

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