Correlation between exposure to fine particulate matter and hypertensive disorders of pregnancy in Shanghai, China

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Research

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Abstract

Background Association between fine particulate matter (PM 2.5) and hypertensive disorders of pregnancy (HDP) is inconsistent and appears to change in each trimester. We aim to investigate the association of exposure to ambient PM 2.5 in early pregnancy with HDP. A retrospective cohort study was performed among 8,776 women with singleton pregnancy who attended the antenatal clinic before 20 gestational weeks in a tertiary women's hospital during 2014 - 2015. Land use regression models were used to predict individual levels of PM 2.5 exposure.

Results The average PM 2.5 concentration during the first 20 gestational weeks ranged from 28.6 to 74.8 μg m -3 [median, 51.4 μg m -3 ; interquartile range, 47.3 - 57.8 μg m -3]. A total of 440 (5.0%) women was diagnosed with HDP. The restricted cubic spline showed an exposure-response relationship between the PM 2.5 concentration and risk of HDP. We observed an association between PM 2.5 exposure during the first trimester with HDP (RR = 3.89 per 10 μg m -3 , 95% CI: 1.45 - 10.43), but not during the second trimester (RR = 0.71 per 10 μg m -3 , 95% CI: 0.40 - 1.27). Compared with their counterparts, nulliparous women who were exposed to high levels of PM 2.5 in the index pregnancy had a higher risk of developing HDP [the relative excess risk due to interaction was 0.92 (0.46 - 1.38)].

Conclusion Our findings suggest that PM 2.5 exposure during the first trimester is associated with the development of HDP, and the association is modified by parity.

Background

Hypertensive disorders of pregnancy (HDP), including gestational hypertension, preeclampsia, and eclampsia, exert substantial adverse effects on both maternal and foetal health (1, 2). It complicates up to 10% pregnancies (3, 4) and ranks as the second leading causes of maternal mortality in China (5). Despite the serious consequences, the biological mechanisms underlying HDP remain unclear.

Fine particulate matter (median aerodynamic diameter ≤ 2.5 μm; $PM_{2.5}$), has been proposed to be associated with the incidence of hypertension in the general population (6–8). Air pollutants have been linked with endothelial dysfunction and vasoconstriction, increased blood pressure (9) $PM_{2.5}$ generally has been associated with increased risks of cardiovascular diseases within hours to days of exposure in susceptible individuals (10). Because cardiovascular changes that occur as part of a normal pregnancy, pregnant women might be more vulnerable to the adverse effects of $PM_{2.5}$, while its association with HDP is inconsistent and appears to change in each trimester (11–14). Two systematic reviews, both of which were published in 2014, reported contradictory effect estimates between HDP and $PM_{2.5}$ exposure during pregnancy (15, 16). A case-control study of 298 predominantly Hispanic women reported an association between $PM_{2.5}$ exposure during the first trimester, but not the second trimester, and an increased risk of HDP among non-obese women (17). Additionally, two studies other based on the registry data suggested an association between second-trimester exposure to $PM_{2.5}$ and an increased risk of HDP (13, 18). The inconsistent findings may be due to the differences in $PM_{2.5}$ concentrations and the

ethnicity of the population (14). We are not aware of any studies that have evaluated the association between HDP and exposure to a higher concentration of $PM_{2.5}$.

In this retrospective cohort study, we sought to investigate the association between exposure to ambient $PM_{2.5}$ in early pregnancy with HDP. We hypothesize that the risk of HDP increases as the $PM_{2.5}$ concentration increases and varies according to the trimester of pregnancy.

Results

Of the 8,776 women in the study population, 440 (5.01%) women were diagnosed with HDP. Table 1 shows the demographic characteristics of the participants. At baseline, the mean age of the participants was 30.1 (standard deviation = 3.6) years at conception, 7,117 (81.1%) were nulliparous, 1,659 (18.9%) were multiparous, 1,053 (12.0%) were overweight or obese (BMI $\geq$ 24 kg m^{-2}), and 1,408 (16.0%) were underweight. Notably, 3,136 (35.7%) women became pregnant in the spring, 1,778 (20.3%) in the summer, 1,541 (17.6%) in the autumn and 2,321 (26.5%) in the winter. Greater than thirty percent of women (n = 2,749) reported a history of chronic diseases in either of their parents. Compared to normotensive women, women with HDP tended to be overweight or obese and were more likely to be nulliparous or have a parental history of chronic diseases.

Table 1
Basic Characteristics of the participants (n = 8,776)

Characteristics	Total (n = 8,776)	No HDP (n = 8,336)	HDP (n = 440)	P value
Gestational age at enrollment (days)	104.0 ± 8.7	104.0 ± 8.6	104.3 ± 8.9	0.46
Maternal age at enrollment (year)	30.2 ± 3.6	30.2 ± 3.6	30.4 ± 3.7	0.14
Maternal height (centimeters)	161.7 ± 4.8	161.7 ± 4.8	161.7 ± 5.0	0.85
Maternal weight before pregnancy (kg)	54.8 ± 7.8	54.6 ± 7.5	59.8 ± 10.9	< 0.01
Pre - conception BMI (kg m^{-2})				
Underweight (< 18.5)	1,408 (16.0)	1,372 (16.5)	36 (8.5)	
Normal (18.5–23.9)	6,315 (72.0)	6,054 (73.6)	261 (59.3)	
Overweight or obesity (≥ 24)	1,053 (12.0)	910 (10.9)	143 (32.5)	< 0.01
Season of conception				
Spring	3,136 (35.7)	2,951 (35.4)	185 (42.1)	
Summer	1,778 (20.3)	1,695 (20.3)	83 (18.9)	
Autumn	1,541 (17.6)	1,492 (17.9)	49 (11.1)	
Winter	2,321 (26.5)	2,198 (26.4)	123 (27.9)	< 0.01
Parity				
Nulliparous	7,117 (81.1)	6,735 (80.8)	382 (86.8)	
Multiparous	1,659 (18.9)	1,601 (19.2)	58 (13.2)	< 0.01
Baby sex				
Male	4,510 (51.4)	4,284 (51.4)	226 (51.4)	
Female	4,266 (48.6)	4,085 (48.6)	214 (48.6)	0.99
Parental history of chronic diseases				
No	6,027 (68.7)	5,777 (69.3)	250 (56.8)	
Yes	2,749 (31.3)	2,559 (30.7)	190 (43.2)	< 0.01
Prenatal care insurance type				
Government-sponsored	6,900 (78.6)	6,535 (78.4)	365 (83.0)	
Self-pay	1,876 (21.4)	1,801 (21.6)	75 (17.0)	0.02

Table 2 shows the average concentration to $PM_{2.5}$ exposure among the study participants in different exposure periods. The $PM_{2.5}$ concentration measured throughout the 20-week period ranged from 28.6 to 74.8 μg m^{-3} (median, 51.4 μg m^{-3}; IQR: 47.3–57.8 μg m^{-3}). Median (IQR) $PM_{2.5}$ concentrations recorded in the first and second trimester of pregnancy were 54.6 μg m^{-3} (IQR: 46.5–60.1 μg m^{-3}) and 52.0 μg m^{-3} (IQR: 44.3–56.3 μg m^{-3}), respectively. The $PM_{2.5}$ concentration is higher among women with HDP compared to women without HDP in first trimester and the whole 1–20 gestational weeks ($P < 0.05$).

Table 2
Summary of estimated PM2.5 concentration (μg m^{-3})

Gestational period	Median (Q1 - Q3)			P value
	Total	No HDP	HDP	
0–12 gestational weeks	54.6 (46.5–60.1)	54.4 (46.3–60.0)	57.2 (50.1–60.6)	< 0.01
13–20 gestational weeks	52.0 (44.3–56.3)	52.0 (44.3–56.3)	52.1 (44.2–56.5)	0.68
0–20 gestational weeks	51.4 (47.3–57.8)	51.3 (47.3–57.8)	54.1 (47.8–58.3)	0.03

The restricted cubic spline of the exposure-response relationship between $PM_{2.5}$ exposure at different gestational periods and the risk of HDP (Figure. 1). The adjusted RR for HDP increased monotonically following an increase in the $PM_{2.5}$ concentration in an exposure-response relationship pattern for each exposure period examined, which indicated a linear association between them. After adjusting for the effects of maternal age, parity, parental history of chronical diseases, health insurance, sex of foetus, and season of conception, we observed an increased risk of HDP associated with $PM_{2.5}$ exposure during the first trimester, but not during the second trimester and or the entire 0–20 gestational week period (Table 3). The adjusted RR was 3.89 per 10 μg m^{-3} (95% CI: 1.45–10.43) for the first trimester, 0.61 per 10 μg m^{-3} (95% CI: 0.33–1.11) for the second trimester, and 0.71 per 10 μg m^{-3} (95% CI: 0.40–1.27) for the entire 0–20 gestational week period.

Table 3
Association of $PM_{2.5}$ and HDP by gestational periods

	No of cases	(%)	Crude RR (95% CI)	Adjusted RR (95% CI)	P for trend
0–12 gestational weeks					
Continuous	440	5.1	4.03 (2.11–7.72)	3.89 (1.45–10.43)	
Q1 (< 46.36)	76	3.5	Reference (1.00)	Reference (1.00)	
Q2 (46.36–54.54)	103	4.7	1.33 (0.99–1.79)	1.30 (0.93–1.82)	
Q3 (54.54–60.06)	129	5.9	1.67 (1.26–2.22)	1.66 (1.11–2.48)	
Q4 (≥ 60.06)	132	6.0	1.70 (1.28–2.26)	1.67 (1.10–2.53)	< 0.01
13–20 gestational weeks					
Continuous	440	5.0	1.11(0.66–1.87)	0.71 (0.40–1.27)	
Q1 (< 44.41)	113	5.1	Reference (1.00)	Reference (1.00)	
Q2 (44.41–52.03)	105	4.8	0.93 (0.71–1.21)	0.85 (0.65–1.12)	
Q3 (52.03–56.35)	109	5.0	0.98 (0.75–1.27)	0.88 (0.67–1.15)	
Q4 (≥ 56.35)	113	5.2	1.02 (0.78–1.32)	0.85 (0.64–1.12)	0.82
0–20w gestational weeks					
Continuous	440	5.0	2.22 (1.05–4.68)	1.00 (0.38–2.61)	
Q1 (< 47.35)	97	4.4	Reference (1.00)	Reference (1.00)	
Q2 (47.35–51.42)	103	4.7	1.06 (0.80–1.40)	0.90 (0.67–1.23)	
Q3 (51.42–57.81)	111	5.1	1.14 (0.87–1.50)	0.89 (0.65–1.24)	
Q4 (≥ 57.81)	129	5.9	1.33 (1.03–1.74)	1.01 (0.73–1.41)	0.02

When the exposure was categorized into four groups, participants exposed to the second, third and fourth quartiles of $PM_{2.5}$ had RR of 1.30 (95% CI: 0.93–1.82), 1.66 (95% CI: 1.11–2.48) and 1.67 (95% CI: 1.10–2.53), respectively, for HDP compared with participants exposed to the first quartile of ambient $PM_{2.5}$ concentrations. The P-value for the Cochran-Armitage trend test was < 0.01. The association pattern of $PM_{2.5}$ with preeclampsia or gestational hypertension was similar to the main analysis (data available upon request).

No multiple and addictive interactions were observed between maternal age, pre-conception BMI, parental history of hypertension, season of delivery and $PM_{2.5}$ concentration in the first trimester on the risk of

HDP (Table 4). An additive interaction and multiplicative interaction between $PM_{2.5}$ exposure and parity were detected, which indicated that parity modified the effect of $PM_{2.5}$ exposure on the risk of HDP.

Table 4
Interaction of covariates and PM2.5 exposure during first trimester with the risk of HDP

Covariates	Multiplicative scale	Additive scale
	RR (95% CI)	RERI (95% CI)
Maternal age (≥ 35 years)	0.69 (0.33–1.16)	0.32 (-0.18–0.81)
Parity (Nulliparous)	2.28 (1.28–4.06)	0.92 (0.46–1.38)
Parental history of chronical diseases (Yes)	1.04 (0.69–1.55)	0.20 (-1.22–1.62)
Season of conception (Spring or winter)	0.89 (0.31–1.92)	-0.09 (-1.62–1.44)
Pre-conception BMI (Underweight)	1.89 (0.86–4.11)	0.32 (-0.20–0.83)
Pre-conception BMI (Overweight or obesity)	1.01 (0.65–1.56)	0.82 (-0.77–2.40)

Discussion

We estimate the association between $PM_{2.5}$ exposure during specific gestational periods and risk of HDP in a retrospective hospital-based cohort study. Based on the results, pregnant women might be at higher risk of developing HDP following exposure to $PM_{2.5}$ in the first trimester. Furthermore, the association shows an exposure-response pattern and is modified by parity.

We observed a prevalence of 5% for HDP in this cohort, which is consistent with findings that reported a prevalence of 4.2% for HDP in China (19). Previous studies have reported inconsistent results for the association between $PM_{2.5}$ exposure and risk of HDP. Two previous studies reported a null association between these parameters during any period of pregnancy (11, 20), but the different models for estimating exposure made the data incomparable.

Although air quality in Shanghai is better than other large cities in China and the government has taken strategy to control air pollution since 2013 (21), the level of $PM_{2.5}$ in this study was still higher than reported in previous studies performed in other countries. Dadvand et al. used LUR model to predict the $PM_{2.5}$ concentration in 8,398 women and reported that first and third trimester exposure to $PM_{2.5}$ is associated with the risk of preeclampsia (22). Mobasher et al. also reported a positive association between $PM_{2.5}$ exposure and HDP during the first trimester and throughout pregnancy (17). These findings are consistent with our results on the elevated risk of HDP following $PM_{2.5}$ exposure in the first trimester. The average $PM_{2.5}$ concentrations reported in their studies (16.5 and 18.1 μg m^{-3}, respectively) are much lower than the concentration recorded in our study (51.4 μg m^{-3}).

Few studies have tested the interaction effect of demographic characteristic and $PM_{2.5}$ exposure on the HDP. According to Mobasher et al., the association between $PM_{2.5}$ and HDP is modified by BMI. Kannan et al. also reported a positive association between $PM_{2.5}$ exposure and increased pulse pressure for participants categorized as obese (BMI $\geq$ 30 kg m^{-2}) (23). Due to the ethnic differences between American women and Asian women, the criteria used to establish BMI categories and the prevalence for overweight or obesity are different in the two studies. We identified a modifying effect of parity instead of pre-conception BMI. The association is more obvious for the nulliparous women. The childbearing policy also leads to a different distribution in parity among western countries and China. Specifically, more nulliparous women were included in our study (81% vs. 56%). Previous study performed among Asian-American women showing that nulliparity is significantly associated with gestational hypertension (24). Another study involving 49 hospitals in Canada also reported that a history of term pregnancy conveys a substantial “protection” against preeclampsia (25). However, the mechanism of the interaction of parity and $PM_{2.5}$ exposure on risk of HDP requires further study.

The potential mechanisms underlying the associations between $PM_{2.5}$ exposure and HDP remain unclear. However, first trimester trophoblast cells that are exposed to $PM_{2.5}$ respond with reduced growth, oxidative stress, inflammation and endoplasmic reticulum stress (26, 27). In addition, an animal study observed the induction of a persistent intrauterine inflammatory state following $PM_{2.5}$ exposure, and the greatest effect was observed for the first trimester exposure (28). Histopathological changes and vascular injuries of the placenta were also observed in mice exposed to $PM_{2.5}$ (29). All these changes were reported to underlie the pathogenesis of HDP (30).

To our knowledge, this study represents the first attempt to estimate the association between exposure to high concentrations of $PM_{2.5}$ and its interaction with demographic characteristics with HDP in the Chinese population, which consolidated the evidence on the association of $PM_{2.5}$ with hypertension. While some limitations should also be noted. First, although the baseline characteristics are comparable between the included women and excluded women, single geographic region of shanghai limits the generalizability of our finds. Second, on the exact blood pressure and diagnosis date of HDP were unavailable, which might result in exposure misclassification. Women with higher exposure during the late second trimester but not in the first trimester would be classified as unexposed and bias the result towards the null. Meanwhile, the estimates were robust when we included or excluded the $PM_{2.5}$ exposure in the late period of the second trimester (20–28 gestational weeks, data available upon request). Third, the deidentified electronic medical system does not have data on life-style factors (maternal smoking, alcohol drinking), diet habit, and other potential risk factors for HDP and might induce residual confounding. Regarding to smoking, although it might be a strong effect modified factor in this study, the proportion of active smoking is rare among Chinese pregnant women. Meanwhile, the passive smoking rate of pregnant women also sharply decreased to 7.8% consequently since public places smoking control regulations issued in 2010 (31). In addition, a case-control study of approximately 2,500 births in Los Angeles County indicated that associations between air pollution and preterm birth were insensitive to adjustment for occupation or income et al.(32). Finally, although our cohort was compiled during

2014–2015 in a single institute, no change of definition of HDP were warrants, potential measurement bias could induce non-differential misclassification on the outcome, which could bias the estimates towards the null again.

Conclusion

In conclusion, exposure to $PM_{2.5}$ during the first trimester tends to be associated with an increased risk of HDP, and parity might modify the association. Specifically, the effect estimate is more obvious for nulliparous women than multiparous women.

Methods

Study population

We performed a hospital-based, retrospective cohort study among pregnant women with a singleton pregnancy, who were attending the antenatal clinic from January 2014 to December 2015 in Shanghai first maternity and infant hospital in Shanghai, China. Since HDP is generally clinically diagnosed beginning at 20 gestational weeks and we did not have detailed information on the diagnosis date of HDP, women with an initial visit at a gestational week before 20 weeks were included in the study (n = 21,944). Detailed of the study population have also been described previously (33).

All women were invited to provide personal sociodemographic and health information at the initial antenatal appointment, including age at conception, residence address, employment status (employed or unemployed), health insurance (with or without), parity (nulliparous or multiparous), height (in centimetres), weight before pregnancy (in kilograms). The pre-conception body mass index (BMI) was calculated by dividing the weight (in kilograms) by the height (in metres squared) and was categorized into three groups: underweight (BMI < 18.5 kg m^{-2}), normal weight (BMI 18.5 - 23.9 kg m^{-2}) and overweight or obese (BMI ≥ 24 kg m^{-2}). Gestational age was assessed based on the date of the last menstrual period and the results of the early ultrasound. We also asked women if either of their parents had a history of chronic diseases, including heart diseases, diabetes, hypertension and kidney diseases.

Women with missing or implausible pre-pregnancy weight or weight at initial clinic (< 34 or > 150 kg), or height (< 100 cm) were excluded (n = 13,157). In addition, women with a diagnosis of chronic hypertension before pregnancy were also excluded from the study (n = 11). Finally, 8,776 women were included in the study. We also analysed the difference of basic characteristic between women included women and excluded women. Compared to the excluded women, the included women were more likely to have government-sponsored health care insurance. Other characteristics, including age, gestational age, baby sex, season of conception are comparable between the two groups (data available on request).

Fine particulate matter (PM2.5) exposure assessment

A land-use regression (LUR) model, a feasible way to describe the relationship between land use and $PM_{2.5}$ pollution level, was used to predict outdoor $PM_{2.5}$ levels at the residential address of each participating woman (34, 35). The dependent variable in LUR model was the mean values of $PM_{2.5}$ concentration collected by Shanghai Environmental Monitor Centre at 35 monitoring locations. The independent variables included longitude, distance from monitors to the ocean, highway intensity, waterbody area, and industrial land area. Forward stepwise multiple regression method was employed to fit the model. The adjusted R squared value for the model was 0.88. This method was described in more detail by C Liu et al. 2016 (34). A map showing the locations of participants relative to the monitors is provided in our previous article (36). We defined a prior three exposure windows of $PM_{2.5}$ according to the birthdate and gestation weeks in this study, including the first trimester (gestational week 1 through week 12), early second trimester (week 13 to week 20) and the period before a potential diagnosis of HDP (1-20 gestational weeks). We log-transformed the $PM_{2.5}$ concentrations measured in the different gestational period to improve normality and variance homogeneity (37). Concentrations of $PM_{2.5}$ were analysed as continuous or categories variables according to the interquartile range (IQR) in the study.

Outcome

The outcome of the study was HDP. Women with an onset of hypertension (systolic blood pressure and/or diastolic blood pressure ≥ 140/90 mmHg) after 20 weeks of gestation were diagnosed with HDP during the study period (2014 - 2015). Information on HDP was identified from electronic medical records and the maternal hospital discharge summary. In our main analysis, we combined gestational hypertension, pre-eclampsia, eclampsia, and hemolytic anemia□elevated liver function and low platelet count syndrome (HELLP syndrome) as a whole group.

Statistical analysis

Descriptive statistics for participant characteristics are presented as the means [standard deviations (SD)] for continuous variables and frequencies with percentages for categorical variables. The distribution of $PM_{2.5}$ exposure was presented as medians and IQR during each of the specified time windows.

Firstly, we assessed the possibility of a non-linear relationship between $PM_{2.5}$ exposure and the risk of HDP using restricted cubic splines (38). Then, we estimated the relative risks (RR) and 95% confidence interval (CI) between $PM_{2.5}$ exposure during the index gestational period and the risk of HDP using Poisson regression analysis by PROC GENMOD in SAS 9.4. The RR per 10 μg m^{-3} or per IQR and 95% CI for an increase in the $PM_{2.5}$ concentration during a specific gestational period were obtained. Covariates in the adjusted multivariate analysis included maternal age, parity, parental history of chronical diseases, health insurance, sex of foetus, and season of conception. We rerun the analyses for gestational hypertension and preeclampsia.

In a sensitivity analysis, we explored other covariates that are known to or might modify the association between $PM_{2.5}$ exposure during the first trimester and the risk of HDP on the additive and multiplicative scales, including maternal age (< 35 or ≥ 35 years), pre-conception BMI (underweight, overweight or obese, and normal weight), parental history of hypertension (yes, no), season of conception (spring and winter, summer and autumn), and parity (nulliparous or multiparous). The multiplicative interaction was evaluated by including the interaction index in the models. The additive interaction was evaluated by the relative excess risk due to the interaction (RERI) (39). If an additive interaction was not observed, the 95% CI of the RERI would include zero.

All statistical tests were two-sided and used an α level of 0.05. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Figures were prepared with Stata/SE15 (StataCorp, College Station, TX, USA).

Abbreviations

$PM_{2.5}$: fine particulate matter; HDP: hypertensive disorders of pregnancy; IQR: interquartile range; BMI: body mass index; LUR: land-use regression; SD: standard deviations; RR: relative risk; CI: confidence interval.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine. The study was performed in accordance with the approved guidelines.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from Shanghai First maternity and Infant hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Shanghai First maternity and Infant hospital.

Conflict of interest

The authors report no conflicts of interest.

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Author contributions

XJS wrote original draft. YZ made a substantial contribution in study design and methodology. YYY interpreted the data and edited the draft. Jing Hua is was a major contributor in validating of the dataset. All authors read and approved the final manuscript.

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Tables

Table 1. Basic Characteristics of the participants (n=8,776)

Characteristics	Total (n = 8,776)	No HDP (n = 8,336)	HDP (n = 440)	*P* value
Gestational age at enrollment (days)	104.0 ± 8.7	104.0 ± 8.6	104.3 ± 8.9	0.46
Maternal age at enrollment (year)	30.2 ± 3.6	30.2 ± 3.6	30.4 ± 3.7	0.14
Maternal height (centimeters)	161.7 ± 4.8	161.7 ± 4.8	161.7 ± 5.0	0.85
Maternal weight before pregnancy (kg)	54.8 ± 7.8	54.6 ± 7.5	59.8 ± 10.9	< 0.01
Pre - conception BMI (kg m^{-2})				
Underweight (< 18.5)	1,408 (16.0)	1,372 (16.5)	36 (8.5)	
Normal (18.5 - 23.9)	6,315 (72.0)	6,054 (73.6)	261 (59.3)	
Overweight or obesity (≥ 24)	1,053 (12.0)	910 (10.9)	143 (32.5)	< 0.01
Season of conception				
Spring	3,136 (35.7)	2,951 (35.4)	185 (42.1)	
Summer	1,778 (20.3)	1,695 (20.3)	83 (18.9)	
Autumn	1,541 (17.6)	1,492 (17.9)	49 (11.1)	
Winter	2,321 (26.5)	2,198 (26.4)	123 (27.9)	< 0.01
Parity				
Nulliparous	7,117 (81.1)	6,735 (80.8)	382 (86.8)	
Multiparous	1,659 (18.9)	1,601 (19.2)	58 (13.2)	< 0.01
Baby sex				
Male	4,510 (51.4)	4,284 (51.4)	226 (51.4)	
Female	4,266 (48.6)	4,085 (48.6)	214 (48.6)	0.99
Parental history of chronic diseases				
No	6,027 (68.7)	5,777 (69.3)	250 (56.8)	
Yes	2,749 (31.3)	2,559 (30.7)	190 (43.2)	< 0.01
Prenatal care insurance type				
Government-sponsored	6,900 (78.6)	6,535 (78.4)	365 (83.0)	
Self-pay	1,876 (21.4)	1,801 (21.6)	75 (17.0)	0.02

Table 2. Summary of estimated PM2.5 concentration (μg m^{-3})

Gestational period	Median (Q1 - Q3)			*P* value
	Total	No HDP	HDP	
0 - 12 gestational weeks	54.6 (46.5 - 60.1)	54.4 (46.3 - 60.0)	57.2 (50.1 - 60.6)	< 0.01
13 - 20 gestational weeks	52.0 (44.3 - 56.3)	52.0 (44.3 - 56.3)	52.1 (44.2 - 56.5)	0.68
0 - 20 gestational weeks	51.4 (47.3 - 57.8)	51.3 (47.3 - 57.8)	54.1 (47.8 - 58.3)	0.03

Table 3. Association of $PM_{2.5}$ and HDP by gestational periods

	No of cases	(%)	Crude RR (95% CI)	Adjusted RR (95% CI)	*P* for trend
0 - 12 gestational weeks					
Continuous	440	5.1	4.03 (2.11 - 7.72)	3.89 (1.45 - 10.43)	
Q1 (< 46.36)	76	3.5	Reference (1.00)	Reference (1.00)	
Q2 (46.36 - 54.54)	103	4.7	1.33 (0.99 - 1.79)	1.30 (0.93 - 1.82)	
Q3 (54.54 - 60.06)	129	5.9	1.67 (1.26 - 2.22)	1.66 (1.11 - 2.48)	
Q4 (≥ 60.06)	132	6.0	1.70 (1.28 - 2.26)	1.67 (1.10 - 2.53)	<0.01
13 - 20 gestational weeks					
Continuous	440	5.0	1.11(0.66 - 1.87)	0.71 (0.40 - 1.27)	
Q1 (< 44.41)	113	5.1	Reference (1.00)	Reference (1.00)	
Q2 (44.41 - 52.03)	105	4.8	0.93 (0.71 - 1.21)	0.85 (0.65 - 1.12)	
Q3 (52.03 - 56.35)	109	5.0	0.98 (0.75 - 1.27)	0.88 (0.67 - 1.15)	
Q4 (≥ 56.35)	113	5.2	1.02 (0.78 - 1.32)	0.85 (0.64 - 1.12)	0.82
0 - 20w gestational weeks					
Continuous	440	5.0	2.22 (1.05 - 4.68)	1.00 (0.38 - 2.61)	
Q1 (< 47.35)	97	4.4	Reference (1.00)	Reference (1.00)	
Q2 (47.35 - 51.42)	103	4.7	1.06 (0.80 - 1.40)	0.90 (0.67 - 1.23)	
Q3 (51.42 - 57.81)	111	5.1	1.14 (0.87 - 1.50)	0.89 (0.65 - 1.24)	
Q4 (≥ 57.81)	129	5.9	1.33 (1.03 - 1.74)	1.01 (0.73 - 1.41)	0.02

Table 4. Interaction of covariates and PM2.5 exposure during first trimester with the risk of HDP

Covariates	Multiplicative scale	Additive scale
	RR (95% CI)	RERI (95% CI)
Maternal age (≥ 35 years)	0.69 (0.33 - 1.16)	0.32 (-0.18 - 0.81)
Parity (Nulliparous)	2.28 (1.28 - 4.06)	0.92 (0.46 - 1.38)
Parental history of chronical diseases (Yes)	1.04 (0.69 - 1.55)	0.20 (-1.22 - 1.62)
Season of conception (Spring or winter)	0.89 (0.31 - 1.92)	-0.09 (-1.62 - 1.44)
Pre-conception BMI (Underweight)	1.89 (0.86 - 4.11)	0.32 (-0.20 - 0.83)
Pre-conception BMI (Overweight or obesity)	1.01 (0.65 - 1.56)	0.82 (-0.77 - 2.40)

Figures

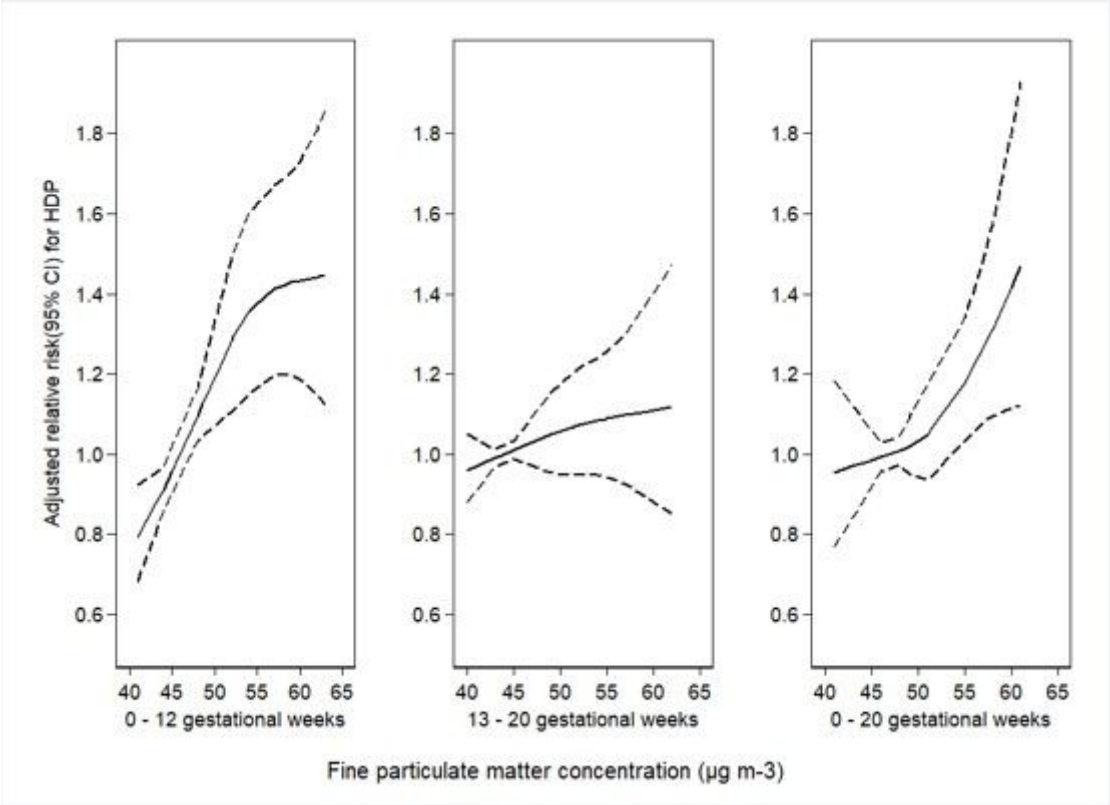

Figure 1

Nonlinear exposure - response association between trimester exposure of PM2.5 and adjusted RR (95% CI) for HDP. Dash lines corresponded to pointwise 95% predicted intervals.