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

CURRENT STATUS: POSTED

Xiujuan Su
Tongji University School of Medicine

Yan Zhao
Shanghai First Maternity and Infant Hospital

Yingying Yang
Shanghai First Maternity and Infant Hospital

Jing Hua
Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine

huajing_mih@163.com Corresponding Author
ORCID: https://orcid.org/0000-0003-3716-4845

DOI:
10.21203/rs.2.24053/v1

SUBJECT AREAS
Toxicology

KEYWORDS
fine particulate matter (PM2.5), hypertensive disorders of pregnancy, hypertension, parity, relative excess risk due to interaction
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; PM₂.₅), 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) PM₂.₅ 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 ≥ 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)                    | 1408 (16.0)       | 1372 (16.5)        | 36 (8.5)      |         |
| Normal (18.5–23.9)                     | 6315 (72.0)       | 6054 (73.6)        | 261 (59.3)    |         |
| Overweight or obesity (≥ 24)           | 1053 (12.0)       | 910 (10.9)         | 143 (32.5)    | < 0.01  |
| Season of conception                    |                   |                    |               |         |
| Spring                                 | 3136 (35.7)       | 2951 (35.4)        | 185 (42.1)    |         |
| Summer                                 | 1778 (20.3)       | 1695 (20.3)        | 83 (18.9)     |         |
| Autumn                                 | 1541 (17.6)       | 1492 (17.9)        | 49 (11.1)     |         |
| Winter                                 | 2321 (26.5)       | 2198 (26.4)        | 123 (27.9)    | < 0.01  |
| Parity                                 |                   |                    |               |         |
| Nulliparous                            | 7117 (81.1)       | 6735 (80.8)        | 382 (86.8)    |         |
| Multiparous                            | 1659 (18.9)       | 1601 (19.2)        | 58 (13.2)     | < 0.01  |
| Baby sex                               |                   |                    |               |         |
| Male                                   | 4510 (51.4)       | 4284 (51.4)        | 226 (51.4)    |         |
| Female                                 | 4266 (48.6)       | 4085 (48.6)        | 214 (48.6)    | 0.99    |
| Parental history of chronic diseases    |                   |                    |               |         |
| No                                     | 6027 (68.7)       | 5777 (69.3)        | 250 (56.8)    |         |
| Yes                                    | 2749 (31.3)       | 2559 (30.7)        | 190 (43.2)    | < 0.01  |
| Prenatal care insurance type           |                   |                    |               |         |
| Government-sponsored                  | 6900 (78.6)       | 6535 (78.4)        | 365 (83.0)    |         |
| Self-pay                               | 1876 (21.4)       | 1801 (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) | No HDP (Q1 - Q3) | HDP (Q1 - Q3) | P value |
|----------------------------|------------------|------------------|---------------|---------|
| Total                      | 54.6 (46.5–60.1) | 54.4 (46.3–60.0) | 57.2 (50.1–60.6) | < 0.01  |
| 0–12 gestational weeks     |                  |                  |               |         |
| 13–20 gestational weeks    |                  |                  |               |         |
| 0–20 gestational weeks     |                  |                  |               |         |

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 chronic    | 1.04 (0.69–1.55)     | 0.20 (-1.22–1.62)       |
| dical diseases (Yes)            | 0.89 (0.31–1.92)     | -0.09 (-1.62–1.44)      |
| Season of conception (Spring    | 1.89 (0.86–4.11)     | 0.32 (-0.20–0.83)       |
| or winter)                      |                      |                         |
| Pre-conception BMI (Underweight)| 1.89 (0.86–4.11)     | 0.32 (-0.20–0.83)       |
|                                |                      |                         |
| Pre-conception BMI (Overweight  | 1.01 (0.65–1.56)     | 0.82 (-0.77–2.40)       |
| or obesity)                     |                      |                         |

### 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 ≥ 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
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 $\geq$ 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 $\mu$g 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 chronic 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.

**Funding**

This study was supported by the National Natural Science Foundation of China (grant number 81602860); Key Laboratory of Public Health Safety (Fudan University), Ministry of Education, China (grant number GW2019-10); and Shanghai Municipal Commission of Health and Family Planning (grant number 20174Y0010).

**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 the dataset. All authors read and approved the final manuscript.

**References**

1. Hammad IA, Meeks H, Fraser A, et al. Risks of cause-specific mortality in offspring of pregnancies complicated by hypertensive disease of pregnancy. Am J Obstet Gynecol. 2019. doi:10.1016/j.ajog.2019.07.024

2. Robledo CA, Mendola P, Yeung E, et al. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environ Res. 2015;137:316-22. doi:10.1016/j.envres.2014.12.020

3. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA. 2002;287(24):3183-6. doi:10.1001/jama.287.24.3183

4. Wang IK, Chang SN, Liao CC, et al. Hypertensive disorders in pregnancy and preterm delivery and subsequent stroke in Asian women: a retrospective cohort study. Stroke.
5. Feng XL, Zhu J, Zhang L, et al. Socio-economic disparities in maternal mortality in China between 1996 and 2006. Bjog-Int J Obstet Gy. 2010;117(12):1527-36. doi:10.1111/j.1471-0528.2010.02707.x

6. Lin H, Guo Y, Zheng Y, et al. Long-Term Effects of Ambient PM2.5 on Hypertension and Blood Pressure and Attributable Risk Among Older Chinese Adults. Hypertension. 2017;69(5):806-12. doi:10.1161/HYPERTENSIONAHA.116.08839

7. Yang BY, Guo Y, Bloom MS, et al. Ambient PM1 air pollution, blood pressure, and hypertension: Insights from the 33 Communities Chinese Health Study. Environ Res. 2019;170:252-9. doi:10.1016/j.envres.2018.12.047

8. Zhang Z, Guo C, Lau AKH, et al. Long-Term Exposure to Fine Particulate Matter, Blood Pressure, and Incident Hypertension in Taiwanese Adults. Environ Health Perspect. 2018;126(1):017008. doi:10.1289/EHP2466

9. Integrated Science Assessment (ISA) For Particulate Matter (Final Report, Dec 2009). EPA/600/R-08/139F (2009).

10. Brook RD, Rajagopalan S, Pope CA, 3rd, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010;121(21):2331-78. doi:10.1161/CIR.0b013e3181dbece1

11. Savitz DA, Elston B, Bobb JF, et al. Ambient Fine Particulate Matter, Nitrogen Dioxide, and Hypertensive Disorders of Pregnancy in New York City. Epidemiology. 2015;26(5):748-57. doi:10.1097/EDE.0000000000000349

12. Mendola P, Wallace M, Liu D, Robledo C, Mnnist T, Grantz KL. Air pollution exposure and preeclampsia among US women with and without asthma. Environ Res. 2016;148:248-55. doi:10.1016/j.envres.2016.04.004
13. Xu X, Hu H, Ha S, Roth J. Ambient air pollution and hypertensive disorder of pregnancy. J Epidemiol Community Health. 2014;68(1):13-20. doi:10.1136/jech-2013-202902

14. Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. Paediatr Perinat Epidemiol. 2012;26(2):91-100. doi:10.1111/j.1365-3016.2011.01245.x

15. Hu H, Ha S, Roth J, Kearney G, Talbott EO, Xu X. Ambient Air Pollution and Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis. Atmos Environ (1994). 2014;97:336-45. doi:10.1016/j.atmosenv.2014.08.027

16. Pedersen M, Stayner L, Slama R, et al. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. Hypertension. 2014;64(3):494-500. doi:10.1161/HYPERTENSIONAHA.114.03545

17. Mobasher Z, Salam MT, Goodwin TM, Lurmann F, Ingles SA, Wilson ML. Associations between ambient air pollution and Hypertensive Disorders of Pregnancy. Environ Res. 2013;123:9-16. doi:10.1016/j.envres.2013.01.006

18. Nobles CJ, Williams A, Ouidir M, Sherman S, Mendola P. Differential Effect of Ambient Air Pollution Exposure on Risk of Gestational Hypertension and Preeclampsia. Hypertension. 2019;74(2):384-90. doi:10.1161/HYPERTENSIONAHA.119.12731

19. Hu J, Li Y, Zhang B, et al. Impact of the 2017 ACC/AHA Guideline for High Blood Pressure on Evaluating Gestational Hypertension-Associated Risks for Newborns and Mothers. Circ Res. 2019;125(2):184-94. doi:10.1161/CIRCRESAHA.119.314682

20. Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA. Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in western Washington State. Environ Health Perspect. 2011;119(6):886-92.
21. Chen Z, Wang JN, Ma GX, Zhang YS. China tackles the health effects of air pollution. Lancet. 2013;382(9909):1959-60. doi:10.1016/S0140-6736(13)62064-4

22. Dadvand P, Figueras F, Basagana X, et al. Ambient air pollution and preeclampsia: a spatiotemporal analysis. Environ Health Perspect. 2013;121(11-12):1365-71. doi:10.1289/ehp.1206430

23. Kannan S, Dvonch JT, Schulz AJ, et al. Exposure to fine particulate matter and acute effects on blood pressure: effect modification by measures of obesity and location. J Epidemiol Community Health. 2010;64(1):68-74. doi:10.1136/jech.2008.081836

24. Li C, Binongo JN, Kancherla V. Effect of Parity on Pregnancy-Associated Hypertension Among Asian American Women in the United States. Matern Child Health J. 2019;23(8):1098-107. doi:10.1007/s10995-019-02746-z

25. Xiong X, Fraser WD, Demianczuk NN. History of abortion, preterm, term birth, and risk of preeclampsia: a population-based study. Am J Obstet Gynecol. 2002;187(4):1013-8. doi:10.1067/mob.2002.126282

26. Familari M, Naav A, Erlandsson L, et al. Exposure of trophoblast cells to fine particulate matter air pollution leads to growth inhibition, inflammation and ER stress. PloS one. 2019;14(7):e0218799. doi:10.1371/journal.pone.0218799

27. Liu Y, Wang L, Wang F, Li C. Effect of Fine Particulate Matter (PM2.5) on Rat Placenta Pathology and Perinatal Outcomes. Med Sci Monit. 2016;22:3274-80. doi:10.12659/msm.897808

28. Nachman RM, Mao G, Zhang X, et al. Intrauterine Inflammation and Maternal Exposure to Ambient PM2.5 during Preconception and Specific Periods of Pregnancy: The Boston Birth Cohort. Environ Health Perspect. 2016;124(10):1608-15. doi:10.1289/EHP243
29. Yue H, Ji X, Zhang Y, Li G, Sang N. Gestational exposure to PM2.5 impairs vascularization of the placenta. Sci Total Environ. 2019;665:153-61. doi:10.1016/j.scitotenv.2019.02.101

30. Phipps E, Prasanna D, Brima W, Jim B. Preeclampsia: Updates in Pathogenesis, Definitions, and Guidelines. Clin J Am Soc Nephrol. 2016;11(6):1102-13. doi:10.2215/CJN.12081115

31. Shi L, Dong Y, Pei S, Cai Y, Huang H. Passive smoking status and its influencing factors among pregnant women in Shanghai. Journal of Shanghai Jiaotong University (Medical Science). 2017;37(2):141.

32. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol. 2007;166(9):1045-52. doi:10.1093/aje/kwm181

33. Su X, Zhao Y, Cao Z, Yang Y, Duan T, Hua J. Association between isolated hypothyroxinaemia in early pregnancy and perinatal outcomes. Endocr Connect. 2019. doi:10.1530/EC-19-0088

34. Liu C, Henderson BH, Wang D, Yang X, Peng ZR. A land use regression application into assessing spatial variation of intra-urban fine particulate matter (PM2.5) and nitrogen dioxide (NO2) concentrations in City of Shanghai, China. Sci Total Environ. 2016;565:607-15. doi:10.1016/j.scitotenv.2016.03.189

35. Ross Z, Jerrett M, Ito K, Tempalski B, Thurston GD. A land use regression for predicting fine particulate matter concentrations in the New York City region. Atmos Environ. 2007;41(11):2255-69. doi:10.1016/j.atmosenv.2006.11.012

36. Zhao Y, Cao Z, Li H, et al. Air pollution exposure in association with maternal thyroid function during early pregnancy. J Hazard Mater. 2018;367:188-93. doi:10.1016/j.jhazmat.2018.12.078
37. Baumgartner J, Schauer JJ, Ezzati M, et al. Indoor air pollution and blood pressure in adult women living in rural China. Environ Health Perspect. 2011;119(10):1390-5. doi:10.1289/ehp.1003371

38. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med. 1989;8(5):551-61.

39. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol. 2005;20(7):575-9.

Tables

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

| Characteristics                                      | Total (n = 8,776) | No HDP (n = 8,336) | HDP (n = 440) |
|------------------------------------------------------|------------------|--------------------|---------------|
| Gestational age at enrollment (days)                 | 104.0 ± 8.7      | 104.0 ± 8.6        | 104.3 ± 8.9   |
| Maternal age at enrollment (year)                    | 30.2 ± 3.6       | 30.2 ± 3.6         | 30.4 ± 3.7    |
| Maternal height (centimeters)                        | 161.7 ± 4.8      | 161.7 ± 4.8        | 161.7 ± 5.0   |
| Maternal weight before pregnancy (kg)                | 54.8 ± 7.8       | 54.6 ± 7.5         | 59.8 ± 10.9   |
| 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)    |
| 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)    |
| 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)     |
| 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)    |
| 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)    |
| 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)     |
Table 2. Summary of estimated PM2.5 concentration (μg m\(^{-3}\))

| Gestational period       | Total          | Median (Q1 - Q3) | HDP            |
|--------------------------|----------------|------------------|----------------|
|                          |                |                  |                |
| 0 - 12 gestational weeks | 54.6 (46.5 - 60.1) | 54.4 (46.3 - 60.0) | 57.2 (50.1 - 60.6) |
| 13 - 20 gestational weeks| 52.0 (44.3 - 56.3) | 52.0 (44.3 - 56.3) | 52.1 (44.2 - 56.5) |
| 0 - 20 gestational weeks | 51.4 (47.3 - 57.8) | 51.3 (47.3 - 57.8) | 54.1 (47.8 - 58.3) |

Table 3. Association of PM\(_{2.5}\) and HDP by gestational periods

| Gestational period       | 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)   | <0.1        |
| 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)   | 0.8         |
| 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)   | 0.0         |
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 - 0.82) |
| Pre-conception BMI (Overweight or obesity)     | 1.01 (0.65 - 1.56)   | 0.82 (-0.77 - 2.43) |

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.
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.