Pregnancy Hypertension 15 (2019) 16–22

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

# Dose-response relationship between maternal blood pressure in pregnancy and risk of adverse birth outcomes: Ma'anshan birth cohort study

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ARTICLE INFO

*Keywords:*
Adverse birth outcomes
Birth cohort study
Dose-response relationship
Maternal blood pressure

ABSTRACT

*Objectives:* This study depicts the dose-response relationship between blood pressure (BP) during pregnancy and adverse birth outcomes in different trimesters.
*Study design:* We used restricted cubic spline to quantify the dose-response relationship between maternal BP in different trimesters and risk of adverse birth outcomes (small for gestational age, SGA; and pre-term birth, PTB). The data were from the Ma'anshan birth cohort study in China (N = 3273).
*Main outcome measures:* Risk of SGA and PTB.
*Results:* There were dose-response associations of both systolic blood pressure (SBP) and diastolic blood pressure (DBP) with risk of SGA in the third trimester and with PTB in both second and third trimesters. In the third trimester, compared with SBP of 120 mmHg, the odds ratios (ORs) and 95% confidence intervals (CI) of SGA were 1.12 (1.01–1.19), 1.32 (1.10–1.60), 1.65 (1.20–2.27) and 2.05 (1.30–3.24) for SBP of 125, 130, 135 and 140 mmHg, respectively. The corresponding ORs and 95% CIs of PTB were 1.15 (1.00–1.32), 1.59 (1.28–1.98), 2.35 (1.66–3.33) and 3.47 (2.10–5.73), respectively. Compared with DBP of 70 mmHg, the ORs and 95% CIs of SGA were 1.44 (1.16–1.78) and 3.04 (2.06–4.50) for DBP of 80 and 90 mmHg, respectively. The corresponding ORs and 95% CIs of PTB were 1.32 (0.93–1.90) and 3.58 (2.21–5.78), respectively.
*Conclusions:* A consistent set of dose-response relationships between maternal BP and adverse birth outcomes were observed. Most importantly, we found that moderately elevated maternal BP, even within a normal range, increased the risk of adverse birth outcomes.

## 1. Introduction

Adverse birth outcomes such as preterm birth (PTB) and birth birthweight that is small for gestational age (SGA) are associated with perinatal mortality and morbidity [1–4]. These outcomes also increase the risk of developing heart and metabolic disease in childhood and adulthood [5–8]. It is therefore important to understand and the risk factors associated with these outcomes.

Hypertensive disorders and pre-eclampsia in pregnancy are leading causes of maternal and perinatal mortality, and they account for 8 ∼ 10% of pregnancy complications [9,10], and contribute largely to adverse birth outcomes [11,12]. However, previous studies have mostly focused on clinically overt hypertension (typically defined as a systolic blood pressure [SBP] ≥ 140 mmHg and/or diastolic blood pressure [DBP] ≥ 90 mmHg). The effects of lower levels of SBP and DBP have not been studied extensively, although an updated guideline [13] by the American College of Cardiology/American Heart Association has modified the diagnostic criteria for hypertension from 140/90 mmHg to 130/80 mmHg. The rationale for this change was observational data that related SBP/DBP and risk of cardiovascular disease (CVD). They now suggest that the risk for CVD increases even between normal blood pressure (BP), elevated BP (120–129/ < 80 mmHg) and stage 1

*Abbreviations:* BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; PTB, pre-term birth; LBW, low birth weight; OR, odds ratio; RCS, restricted cubic spline; SBP, systolic blood pressure; SGA, small for gestational age

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https://doi.org/10.1016/j.preghy.2018.09.004
Received 25 June 2018; Received in revised form 20 August 2018; Accepted 5 September 2018
Available online 06 September 2018

hypertension (130–139/80–89 mmHg). It is unclear whether the new hypertension diagnostic criteria apply to pregnant women. Thus, there is a need to better understand the association between maternal BP and adverse birth outcomes.

To the best of our knowledge, only one study [14] has considered BP as a continuous risk factor for adverse birth outcomes such as PTB and SGA. Thus, the dose-response relationship between BP during pregnancy and the risk for PTB and SGA remains unclear. In the current study, a prospective birth cohort study in China was used a restricted cubic spline (RCS) function to estimate the dose-response relationship between maternal DBP and SBP and adverse birth outcomes (including PTB, SGA). We also identified critical periods (i.e., different trimesters) during pregnancy of aberrant maternal BP levels influencing adverse birth outcomes.

## 2. Materials and methods

### 2.1. Cohort study

The Ma'anshan Birth Cohort (MABC) Study is a population-based prospective study conducted in Ma'anshan city in the Anhui province in China. The MABC recruited 3474 pregnant women at their first prenatal visit between May 2013 and September 2014. Among these cases, 3273 women with single live births were included in this study. The flow chart of the excluding process was presented in Fig. 1. This study was approved by the ethics committee of Anhui Medical University. Written informed consent was obtained from each pregnant woman.

### 2.2. Data collection

Extensive data were collected using a structured self-reported questionnaire, supervised by trained interviewers. These data included age, race, education, social, economic status, smoking, alcohol consumption and anthropometric measures. Participants were asked if they had used multivitamin and/or mineral supplements in different periods (one month before pregnancy, the first/second/third trimester of pregnancy). Participants who indicated regular use were asked about the frequency of taking supplements (e.g. daily, weekly). Hypertensive disorders and diabetes status were obtained from medical records.

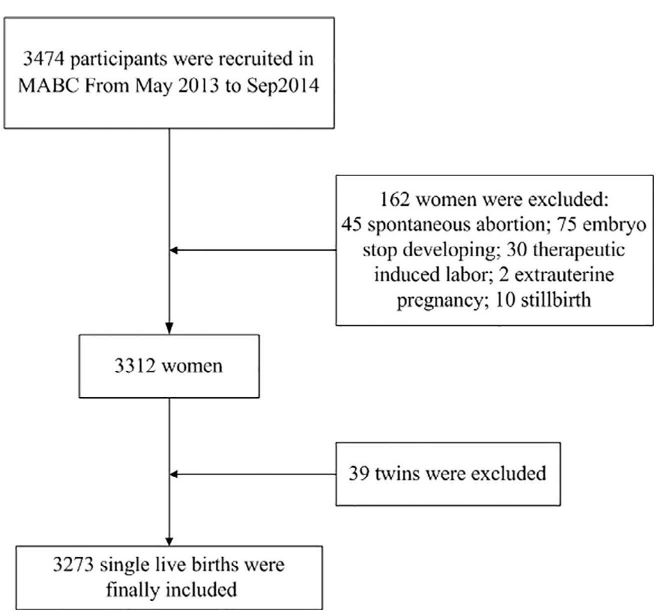


**Fig. 1.** Flow chart of participant inclusion and exclusion of our study.

### 2.3. Blood pressure measurement

BP was measured in a study visit during each trimester using a calibrated mercury sphygmomanometer following a standardized protocol. All participants were seated in an upright position with back support and were asked to relax for 5 min. A cuff was placed around the non-dominant upper arm, which was supported at the level of the heart, with the bladder midline over the brachial artery pulsation. We assigned average of two sequential BP values to each record, with a minimum two-minute rest period between measurements.

### 2.4. Definition of PTB, SGA

Preterm birth (PTB) was defined as a gestational age of less than 37 weeks at delivery. PTB was categorized for spontaneous and iatrogenic PTB. Small for gestational age (SGA) at birth was defined as a gestational-age-adjusted birth weight below the tenth percentile [15] in our cohort.

### 2.5. Covariates

Pre-pregnancy BMI (kg/m$^2$) was categorized as four groups: < 18.5, 18.5–24, 24–28, ≥28 [16]. Weight gain during pregnancy was divided into three groups: appropriate, insufficient and excessive according to the Institute of Medicine (IOM) guidelines [17]. Smoking at early pregnancy was defined as ongoing smoking or former smoker who quit after knowing about pregnancy. Alcohol drinking was categorized as never, occasionally and regularly. Multiple vitamin intake frequency was categorized as never (1 ~ 2 times/week), moderate (3 ~ 6 times/week) and daily. Three time periods were studied (pre-pregnancy, first trimester, second trimester), as there was too many missing cases in the third trimester. Hypertensive disorders were categorized as normal, gestational hypertension, pre-eclampsia and chronic hypertension before pregnancy. Gestational hypertension was defined as a blood pressure higher than 140/90 mmHg without proteinuria, diagnosed after 20 weeks of gestation. Diabetes status was categorized as no diabetes, gestational diabetes and pre-gestational diabetes (i.e., diabetes before pregnancy). The diagnosis of gestational diabetes was considered about 28 weeks of gestation, when any of the following criteria were met on the 75 g oral glucose tolerance test (OGTT): fasting plasma glucose ≥5.1 mmol/L, at 1 h ≥ 10 mmol/L, and at 2 h ≥ 8.5 mmol/L [18]. Education level was divided into five groups: primary school or below, middle school, high school, junior college, and undergraduate or above. Monthly income levels (Chinese Yuan) was divided into four groups: < 1000, 1000–2500, 2500–4000 and ≥4000.

### 2.6. Statistical analysis

A RCS function with four knots was used to delineate the dose-response relationships between maternal blood pressure (both DBP and SBP) and adverse outcomes. RCS can fit both nonlinear and linear associations between exposures and outcome(s). A $P$ value for non-linearity was computed by testing the null hypothesis that the coefficient of the second spline was equal to zero, otherwise the linear trend was assessed. To estimate the risks of SGA and PTB for different SBP/DBP, BP was treated as continuous variable in multivariable logistic regression models. Odds ratios (ORs) and 95% confidence intervals (CIs) for every point of BP were calculated. The fully adjusted model included age, pre-pregnancy BMI, weight gain, diabetes, parity and fetal sex, smoking, drinking, education, income, pre- pregnancy multivitamin intake, first-trimester multivitamin intake, second-trimester multivitamin intake and gestational weeks (when BP was measured). When analyzing SGA, we excluded infants who were large for their gestational age (LGA) and used appropriate for gestational age (AGA) infants as control. We further used post-estimation command, xblc [19], to facilitate tabular and graphical presentation of these relationships.

**Table 1**
Maternal characteristics of participants in current birth cohort study.

| Variables | Mean (SD) | N (%) |
|---|---|---|
| Age | 26.4 (3.6) | |
| Pre-pregnancy BMI | 20.9 (2.9) | |
| *Systolic blood pressure* | | |
| First-trimester | 108.4 (10.7) | |
| Second-trimester | 113.1 (9.9) | |
| Third-trimester | 115.8 (10.3) | |
| *Diastolic blood pressure* | | |
| First-trimester | 69.7 (8.4) | |
| Second-trimester | 67.2 (7.8) | |
| Third-trimester | 69.9 (8.6) | |
| *Gestational weeks* | | |
| First-trimester | 10.0 (2.1) | |
| Second-trimester | 25.6 (1.1) | |
| Third-trimester | 34.1 (1.1) | |
| *Hypertensive disorders* | | |
| Normal | | 3066 (93.7) |
| Hypertension | | 137 (4.2) |
| Pre-eclampsia | | 57 (1.7) |
| Chronic hypertension | | 6 (0.2) |
| Missing | | 7 (0.2) |
| *Parity* | | |
| Nulliparous | | 2898 (88.5) |
| Multiparous | | 375 (11.5) |
| *Pre-pregnancy BMI category* | | |
| < 18.5 | | 611 (18.7) |
| 18.5 ~ 24 | | 2264 (69.2) |
| 24 ~ 28 | | 317 (9.7) |
| ≥28 | | 81 (2.5) |
| *Weight gain* | | |
| Appropriate | | 932 (28.5) |
| Insufficient | | 279 (8.5) |
| Excessive | | 2007 (61.3) |
| Missing | | 55 (1.7) |
| *Education* | | |
| Primary school or below | | 38 (1.2) |
| Middle school | | 622 (19.0) |
| High school | | 735 (22.5) |
| Junior college | | 1016 (31.0) |
| Undergraduate or above | | 862 (26.3) |
| *Income (Chinese Yuan)* | | |
| < 1000 | | 55 (1.7) |
| 1000 ~ 2500 | | 812 (24.8) |
| 2500 ~ 4000 | | 1402 (42.8) |
| ≥4000 | | 1004 (30.7) |
| *Smoking in early pregnancy* | | |
| No | | 3176 (97.0) |
| Yes | | 96 (3.0) |
| *Drinking* | | |
| Never | | 3012 (92.0) |
| Occasionally | | 256 (7.8) |
| Regularly | | 5 (0.2) |
| *Pre-pregnancy multi-vitamin intake* | | |
| Never | | 3031 (92.6) |
| 1 ~ 2 times/week | | 27 (0.8) |
| 3 ~ 6 times/week | | 39 (1.2) |
| Every day | | 172 (5.3) |
| Missing | | 4 (0.1) |
| *First-trimester multi-vitamin intake* | | |
| Never | | 2468 (75.4) |
| 1 ~ 2 times/week | | 84 (2.6) |
| 3 ~ 6 times/week | | 157 (4.8) |
| Every day | | 559 (17.1) |
| Missing | | 5 (0.1) |
| *Second-trimester multi-vitamin intake* | | |
| Never | | 2902 (88.7) |
| 1 ~ 2 times/week | | 63 (1.9) |
| 3 ~ 6 times/week | | 40 (1.2) |
| Every day | | 210 (6.4) |
| Missing | | 58 (1.8) |
| *Fetal sex* | | |
| Male | | 1666 (50.9) |
| Female | | 1601 (48.9) |
| Missing | | 6 (0.2) |
| *Diabetes* | | |
| No | | 2841 (86.8) |
| Gestational diabetes | | 419 (12.8) |
| Pre-pregnancy diabetes | | 13 (0.4) |
| *Size for gestational age* | | |
| Appropriate | | 2409 (73.6) |
| Small | | 316 (9.7) |
| Large | | 540 (16.5) |
| Missing | | 8 (0.2) |
| *Pre-term birth* | | |
| No | | 3136 (95.8) |
| Yes | | 134 (4.1) |
| Missing | | 3 (0.1) |
| *PTB types* | | |
| Spontaneous PTB | | 82 (61.2) |
| Iatrogenic PTB | | 52 (38.8) |

*Abbreviations:* BMI, body mass index.

Subgroup analysis was conducted according to the type of PTB. Analyses were conducted using SPSS v16.0 and Stata 10.0. All $P$ values were two-sided and statistical significance was set at $P < 0.05$.

## 3. Results

Table 1 shows the characteristics of study participants. The average maternal age was 26.3. Gestational weeks at birth varied from 27 to 43, with an average of 38. We observed 316 infants with SGA (9.7%), and 134 infants with PTB (4.1%).

### 3.1. SBP/DBP and risk of SGA

Higher levels of both SBP or DBP were associated with higher risk of SGA (Tables 2 and 3). SBP ($p_{nonlinear} = 0.08$) was marginally non-linearly associated with risk of SGA. DBP ($p_{nonlinear} = 0.001$) was significantly nonlinearly associated with risk of SGA in the third trimester (Fig. S1). However, SBP/DBP in neither of the first or second trimester was significantly associated with risk of SGA. We found even within a normal range, participants with a SBP of 125 mm Hg or above and DBP of 80 mm Hg or above in the third trimester, had a higher risk of SGA.

### 3.2. SBP/DBP and risk of PTB

The risk of PTB was higher with an elevated SBP or DBP (Tables 4 and 5). The magnitude of associations between higher BP and PTB increased with time onwards, with the strongest association observed in the third trimester. Individuals with SBP of 125 mm Hg or above had an increased risk of PTB in both second and third trimesters. Both SBP ($p_{nonlinear} = 0.05$) and DBP ($p_{nonlinear} = 0.02$) in the third trimester were nonlinearly associated with risk of PTB (Fig. S2). In the second trimester, both SBP ($p_{nonlinear} = 0.18$; $P < 0.001$ for linear trend) and DBP ($P_{nonlinear} = 0.103$; $p = 0.017$ for linear trend) were found to be linearly associated with risk of PTB. SBP/DBP was not significantly related to risk of PTB in the first trimester. Subgroup analysis based on PTB type is presented in the Supplementary Table 1. The effect of elevated BP was more evident in iatrogenic than spontaneous PTB across three trimesters.

**Table 2**
Relationships between systolic blood pressure in each trimester and risk of SGA.

| SBP (mmHg) | First-trimester | | | | Second-trimester | | | | Third-trimester | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | $P^*$ | $P^\dagger$ | OR | 95%CI | $P^*$ | $P^\dagger$ | OR | 95%CI | $P^*$ | $P^\dagger$ |
| | **Crude** | | 0.61 | 0.47 | **Crude** | | 0.36 | 0.30 | **Crude** | | **0.01** | – |
| 110 | 0.99 | 0.85, 1.16 | | | 1.20 | 0.92, 1.56 | | | 1.27 | 0.97, 1.66 | | |
| 120 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 125 | 1.05 | 0.92, 1.21 | | | 1.03 | 0.93, 1.14 | | | 1.08 | 1.00, 1.16 | | |
| 130 | 1.12 | 0.83, 1.49 | | | 1.10 | 0.86, 1.41 | | | 1.32 | 1.13, 1.55 | | |
| 135 | 1.20 | 0.75, 1.92 | | | 1.19 | 0.80, 1.77 | | | 1.68 | 1.28, 2.20 | | |
| 140 | 1.25 | 0.69, 2.27 | | | 1.28 | 0.74, 2.23 | | | 2.14 | 1.45, 3.15 | | |
| 145 | 1.35 | 0.62, 2.92 | | | 1.38 | 0.68, 2.81 | | | 2.72 | 1.64, 4.53 | | |
| | **Model 1** | | 0.41 | **0.02** | **Model 1** | | 0.21 | 0.40 | **Model 1** | | **0.01** | – |
| 110 | 0.90 | 0.76, 1.05 | | | 1.10 | 0.84, 1.45 | | | 1.14 | 0.87, 1.51 | | |
| 120 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 125 | 1.13 | 0.98, 1.31 | | | 1.10 | 0.99, 1.22 | | | 1.14 | 1.05, 1.23 | | |
| 130 | 1.30 | 0.96, 1.74 | | | 1.26 | 0.98, 1.62 | | | 1.46 | 1.23, 1.73 | | |
| 135 | 1.52 | 0.94, 2.46 | | | 1.46 | 0.97, 2.19 | | | 1.96 | 1.47, 2.61 | | |
| 140 | 1.69 | 0.93, 3.10 | | | 1.70 | 0.97, 2.97 | | | 2.62 | 1.73, 3.97 | | |
| 145 | 1.99 | 0.90, 4.38 | | | 1.97 | 0.96, 4.03 | | | 3.52 | 2.04, 6.05 | | |
| | **Model 2** | | 0.53 | **0.03** | **Model 2** | | 0.20 | 0.61 | **Model 2** | | 0.08 | **0.03** |
| 110 | 0.91 | 0.77, 1.08 | | | 1.10 | 0.83, 1.45 | | | 1.12 | 0.84, 1.49 | | |
| 120 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 125 | 1.10 | 0.95, 1.28 | | | 1.10 | 0.99, 1.23 | | | 1.10 | 1.01, 1.19 | | |
| 130 | 1.22 | 0.91, 1.66 | | | 1.28 | 0.99, 1.66 | | | 1.32 | 1.10, 1.60 | | |
| 135 | 1.39 | 0.85, 2.27 | | | 1.50 | 0.99, 2.27 | | | 1.65 | 1.20, 2.27 | | |
| 140 | 1.51 | 0.81, 2.80 | | | 1.75 | 0.98, 3.12 | | | 2.05 | 1.30, 3.24 | | |
| 145 | 1.71 | 0.76, 3.83 | | | 2.05 | 0.98, 4.29 | | | 2.55 | 1.41, 4.64 | | |

$P^*$ for non-linear. $P^\dagger$ for linear trend.
Model 1 adjusted for age, pre-pregnancy BMI, weight gain, diabetes, parity and fetal sex. Model 2 adjusted for Model 1 plus smoking, drinking, education, income, pre-pregnancy multi-vitamin intake, first-trimester multi-vitamin intake, second-trimester multi-vitamin intake and gestational weeks when blood pressure was measured. Abbreviations: SBP, systolic blood pressure; CI, confidence interval; OR, odds ratio; SGA, small for gestational age; BMI, body mass index.

## 4. Discussion

Our study suggested that there are significant dose-response relationships between SBP and/or DBP during pregnancy and risk of adverse birth outcomes. Most importantly, even with BP in the normal range, individuals with SBP of 125 mm Hg or above and DBP of 80 mm Hg or above already had a higher risk of SGA and/or PTB. In addition, our results indicated different sensitive periods for adverse birth outcomes. For example, higher BP in the third trimester was significantly associated with an increased risk of SGA. Further, BP in both the second and the third trimester was significantly associated with an elevated risk of PTB. Overall, the magnitude of associations between higher BP

**Table 3**
Relationships between diastolic blood pressure in each trimester and risk of SGA.

| DBP (mmHg) | First-trimester | | | | Second-trimester | | | | Third-trimester | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | $P^*$ | $P^\dagger$ | OR | 95%CI | $P^*$ | $P^\dagger$ | OR | 95%CI | $P^*$ | $P^\dagger$ |
| | **Crude** | | 0.12 | 0.80 | **Crude** | | 0.06 | 0.54 | **Crude** | | **< 0.001** | – |
| 60 | 1.11 | 0.86, 1.43 | | | 1.34 | 1.03, 1.74 | | | 1.28 | 1.01, 1.62 | | |
| 70 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 80 | 0.96 | 0.79, 1.18 | | | 1.18 | 0.94, 1.48 | | | 1.26 | 1.04, 1.54 | | |
| 90 | 1.34 | 0.81, 2.22 | | | 1.65 | 0.96, 2.86 | | | 2.67 | 1.88, 3.80 | | |
| 100 | 1.88 | 0.78, 4.53 | | | 2.32 | 0.96, 5.58 | | | 5.71 | 3.11, 10.46 | | |
| | **Model 1** | | 0.06 | 0.17 | **Model 1** | | 0.08 | 0.33 | **Model 1** | | **< 0.001** | – |
| 60 | 0.99 | 0.76, 1.28 | | | 1.17 | 0.89, 1.54 | | | 1.15 | 0.90, 1.46 | | |
| 70 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 80 | 1.08 | 0.87, 1.34 | | | 1.31 | 1.04, 1.66 | | | 1.43 | 1.17, 1.76 | | |
| 90 | 1.79 | 1.06, 3.03 | | | 1.99 | 1.13, 3.52 | | | 3.32 | 2.28, 4.83 | | |
| 100 | 3.01 | 1.22, 7.46 | | | 3.02 | 1.21, 7.54 | | | 7.77 | 4.10, 14.75 | | |
| | **Model 2** | | 0.19 | 0.28 | **Model 2** | | 0.19 | 0.46 | **Model 2** | | **0.001** | – |
| 60 | 0.97 | 0.74, 1.26 | | | 1.13 | 0.86, 1.48 | | | 1.09 | 0.85, 1.40 | | |
| 70 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 80 | 1.06 | 0.85, 1.32 | | | 1.28 | 1.00, 1.63 | | | 1.44 | 1.16, 1.78 | | |
| 90 | 1.58 | 0.91, 2.74 | | | 1.84 | 1.02, 3.33 | | | 3.04 | 2.06, 4.50 | | |
| 100 | 2.37 | 0.91, 6.17 | | | 2.66 | 1.03, 6.88 | | | 6.49 | 3.33, 12.65 | | |

$P^*$ for non-linear. $P^\dagger$ for linear trend.
Model 1 adjusted for age, pre-pregnancy BMI, weight gain, diabetes, parity and fetal sex. Model 2 adjusted for Model 1 plus smoking, drinking, education, income, pre-pregnancy multi-vitamin intake, first-trimester multi-vitamin intake, second-trimester multi-vitamin intake and gestational weeks when blood pressure was measured.
Abbreviations: DBP, diastolic blood pressure; CI, confidence interval; OR, odds ratio; SGA, small for gestational age; BMI, body mass index.

**Table 4**
Relationships between systolic blood pressure in each trimester and risk of PTB.

| SBP (mmHg) | First-trimester | | | | Second-trimester | | | | Third-trimester | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | $P^*$ | $P^†$ | OR | 95%CI | $P^*$ | $P^†$ | OR | 95%CI | $P^*$ | $P^†$ |
| | | | 0.59 | **0.01** | **Crude** | | 0.09 | < **0.001** | **Crude** | | < **0.001** | – |
| 110 | 0.81 | 0.66, 0.99 | | | 0.93 | 0.63, 1.38 | | | 1.20 | 0.80, 1.79 | | |
| 120 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 125 | 1.20 | 1.03, 1.40 | | | 1.29 | 1.17, 1.42 | | | 1.22 | 1.09, 1.37 | | |
| 130 | 1.45 | 1.05, 2.00 | | | 1.79 | 1.44, 2.23 | | | 1.88 | 1.58, 2.24 | | |
| 135 | 1.82 | 1.08, 3.06 | | | 2.53 | 1.77, 3.62 | | | 3.11 | 2.36, 4.09 | | |
| 140 | 2.12 | 1.10, 4.08 | | | 3.57 | 2.16, 5.89 | | | 5.14 | 3.45, 7.65 | | |
| 145 | 2.66 | 1.13, 6.27 | | | 5.04 | 2.65, 9.59 | | | 8.50 | 5.02, 14.39 | | |
| | **Model 1** | | 0.64 | 0.07 | **Model 1** | | 0.39 | < **0.001** | **Model 1** | | **0.01** | – |
| 110 | 0.87 | 0.70, 1.08 | | | 0.91 | 0.60, 1.40 | | | 1.13 | 0.74, 1.72 | | |
| 120 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 125 | 1.16 | 0.99, 1.35 | | | 1.21 | 1.09, 1.34 | | | 1.20 | 1.06, 1.35 | | |
| 130 | 1.35 | 0.97, 1.87 | | | 1.54 | 1.22, 1.96 | | | 1.74 | 1.44, 2.14 | | |
| 135 | 1.62 | 0.94, 2.77 | | | 1.99 | 1.35, 2.93 | | | 2.70 | 1.99, 3.65 | | |
| 140 | 1.83 | 0.93, 3.59 | | | 2.56 | 1.50, 4.39 | | | 4.19 | 2.71, 6.47 | | |
| 145 | 2.20 | 0.91, 5.32 | | | 3.30 | 1.65, 6.59 | | | 6.50 | 3.66, 11.53 | | |
| | **Model 2** | | 0.81 | 0.08 | **Model 2** | | 0.18 | < **0.001** | **Model 2** | | < **0.05** | – |
| 110 | 0.88 | 0.70, 1.10 | | | 0.96 | 0.62, 1.48 | | | 1.11 | 0.70, 1.77 | | |
| 120 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 125 | 1.12 | 0.96, 1.32 | | | 1.25 | 1.12, 1.39 | | | 1.15 | 1.00, 1.32 | | |
| 130 | 1.27 | 0.90, 1.78 | | | 1.67 | 1.30, 2.15 | | | 1.59 | 1.28, 1.98 | | |
| 135 | 1.47 | 0.85, 2.55 | | | 2.27 | 1.51, 3.41 | | | 2.35 | 1.66, 3.33 | | |
| 140 | 1.62 | 0.81, 3.24 | | | 3.08 | 1.76, 5.42 | | | 3.47 | 2.10, 5.73 | | |
| 145 | 1.88 | 0.76, 4.65 | | | 4.19 | 2.03, 8.62 | | | 5.13 | 2.65, 9.94 | | |

$P^*$ for non-linear. $P^†$ for linear trend.
Model 1 adjusted for age, pre-pregnancy BMI, weight gain, diabetes, parity and fetal sex. Model 2 adjusted for Model 1 plus smoking, drinking, education, income, pre-pregnancy multi-vitamin intake, first-trimester multi-vitamin intake, second-trimester multi-vitamin intake and gestational weeks when blood pressure was measured.
Abbreviations: SBP, systolic blood pressure; CI, confidence interval; OR, odds ratio; PTB, pre-term birth; BMI, body mass index.

and adverse birth outcomes increased over time, with the strongest associations observed in the third trimester.

Our study was both comparable to and distinct from previous studies. Our results are consistent with a number of studies that have demonstrated that hypertensive disorders in pregnancy impose an increased risk of diverse adverse outcomes [12,20]. Our results also corroborate the idea that pre-hypertension women have a higher risk of different adverse outcomes [14]. However, while previous studies suggested that DBP is more important than SBP in predicting adverse birth outcomes, both were equally significant in the current study.

**Table 5**
Relationships between diastolic blood pressure in each trimester and risk of PTB.

| DBP (mmHg) | First-trimester | | | | Second-trimester | | | | Third-trimester | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | $P^*$ | $P^†$ | OR | 95%CI | $P^*$ | $P^†$ | OR | 95%CI | $P^*$ | $P^†$ |
| | **Crude** | | 0.24 | < **0.05** | **Crude** | | 0.08 | < **0.001** | **Crude** | | **0.01** | – |
| 60 | 0.97 | 0.66, 1.42 | | | 0.90 | 0.62, 1.31 | | | 0.88 | 0.57, 1.36 | | |
| 70 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 80 | 1.44 | 1.09, 1.89 | | | 1.76 | 1.39, 2.21 | | | 1.62 | 1.20, 2.18 | | |
| 90 | 2.56 | 1.51, 4.34 | | | 3.35 | 1.96, 5.72 | | | 4.20 | 2.81, 6.28 | | |
| 100 | 4.60 | 1.85, 11.41 | | | 6.40 | 2.68, 15.25 | | | 11.03 | 5.77, 21.07 | | |
| | **Model 1** | | 0.30 | 0.12 | **Model 1** | | 0.08 | **0.01** | **Model 1** | | < **0.05** | – |
| 60 | 1.08 | 0.72, 1.62 | | | 1.03 | 0.69, 1.54 | | | 0.94 | 0.59, 1.49 | | |
| 70 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 80 | 1.27 | 0.94, 1.71 | | | 1.58 | 1.24, 2.02 | | | 1.47 | 1.07, 2.02 | | |
| 90 | 2.00 | 1.13, 3.54 | | | 2.75 | 1.58, 4.80 | | | 4.01 | 2.60, 6.17 | | |
| 100 | 3.15 | 1.19, 8.38 | | | 4.80 | 1.95, 11.80 | | | 11.10 | 5.56, 22.18 | | |
| | **Model 2** | | 0.59 | 0.15 | **Model 2** | | 0.10 | **0.02** | **Model 2** | | **0.02** | – |
| 60 | 1.02 | 0.68, 1.54 | | | 1.02 | 0.68, 1.53 | | | 0.71 | 0.39, 1.27 | | |
| 70 | 1.00 | 1.00 | | | 1.00 | 1.00 | | | 1.00 | 1.00 | | |
| 80 | 1.24 | 0.91, 1.68 | | | 1.56 | 1.21, 2.01 | | | 1.32 | 0.93, 1.90 | | |
| 90 | 1.74 | 0.95, 3.19 | | | 2.66 | 1.47, 4.79 | | | 3.58 | 2.21, 5.78 | | |
| 100 | 2.46 | 0.87, 6.91 | | | 4.53 | 1.75, 11.77 | | | 9.84 | 4.56, 21.26 | | |

$P^*$ for non-linear. $P^†$ for linear trend.
Model 1 adjusted for age, pre-pregnancy BMI, weight gain, diabetes, parity and fetal sex. Model 2 adjusted for Model 1 plus smoking, drinking, education, income, pre-pregnancy multi-vitamin intake, first-trimester multi-vitamin intake, second-trimester multi-vitamin intake and gestational weeks when blood pressure was measured.
Abbreviations: DBP, diastolic blood pressure; CI, confidence interval; OR, odds ratio; PTB, pre-term birth; BMI, body mass index.

Further, most previous studies found that only BP during the third trimester contributed to an elevated risk of adverse birth outcomes, but our study indicated elevated BP levels in other trimesters might also relate to different adverse outcomes. The study by Steer et al [21] found a "U" shape between birth weight and DBP, suggesting that both higher and lower BP were associated with lower birth weights. However, in our study, the nonlinear shape was more like a "J" shape, with a significant negative effect of high BP but a marginal effect of low BP. This result should be interpreted with caution, as the relatively low sample size and low statistical power for this analysis might in part explain these discrepancies. Further investigations in different populations are needed to clarify the dose-response relationship between maternal BP and adverse birth outcomes.

The association between poor fetal growth and hypertensive disorders has previously been explained by the notion that the dysfunctional placenta causes both hypertensive disorders and poor birth outcomes [22,23]. However, a different point of view [14,24] has been recently proposed, which is that both impaired maternal perfusion of the placenta (an extrinsic defect) and impaired placental development (an intrinsic defect) may lead to SGA and stillbirth. If this view is correct, hypertensive disorder (an indicator of maternal cardiovascular function), might also contribute to these adverse birth outcomes rather than just reflect impaired placental function. Other recent evidence that has demonstrated an association between indicating a history of PTB and higher BP [25] in late midlife and future risk of maternal cardiovascular disease [26] might also support aforementioned point.

High BP has been hypothesized to be unfavorable to fetal growth because of uteroplacental hypoperfusion. Our data show that a moderate elevation in BP (i.e., SBP as low as 125 mmHg or DBP as low as 80 mmHg), is a risk for adverse birth outcomes. Consistent with our study, a large historical cohort study [27] in the rural Chinese population found a strong linear relationship between preconception BP and risk of PTB. However, another two similar studies suggested that preconception BP was not associated with risk for a range of adverse birth outcomes including SGA, PTB and LBW [28,29]. A recent Cochrane systematic review [30] showed that antihypertensive drugs did not reduce the risk of infant death, PTB and SGA among women of mild to moderate hypertension during pregnancy. That conclusion was supported in a recent meta-analysis [31]. Whether elevated BP is a marker of some other condition or is truly causal and contributes to an increased risk of infant adverse outcomes needs further investigation. This research will have significant effect on future preventive strategies and clinical decision making on maternal care.

This study has several strengths. First, previous studies generally focused on the impact of hypertensive disorders on the risk of adverse birth outcomes [12,32]. Few studies [14] have considered BP on a continuum and assessed the dose-response relationships between maternal BP and adverse birth outcomes. Second, this study assessed both linear and nonlinear relationships between maternal blood pressure in different trimesters and risks of multiple adverse birth outcomes, which is novel. The majority of previous studies have only evaluated linear data trends, and so the shape of the nonlinear relationship remains poorly understood. One similar study by Steer et al. [21] only examined DBP as a risk factor for birth weight and perinatal mortality, and their data suggested an inverse U-shaped association between DBP and risk of birth weight and perinatal mortality, whereas, other adverse birth outcomes for instance SGA and PTB were not referred to. Finally, our large and consistent data base allowed us to adjust for many potential confounders including pre-pregnancy BMI and gestational weight gain. Gestational weight gain was not always adjusted for in other studies, which might bias observed associations. Gestational weight gain is important to evaluate, as excessive weight gain is related to the risk of both hypertensive disorders in pregnancy [33] and adverse birth outcomes [34,35].

Our study had several limitations. First, BP was measured at one visit in each trimester, which could affect its reliability. Second, information on some potential confounders (e.g., family history of hypertension) was not available, and so we were unable to examine if these variables also contribute to adverse birth outcomes. Third, majority of our subjects were Han Chinese, and their results may not generalize to other population. Replication of the current study in a different sample is an important next step for the field.

In summary, our study suggested that maternal BP during pregnancy is significantly associated with the risk of adverse birth outcomes in a dose-response manner. Even a moderately elevated maternal BP, within a normal range, increases the risk of adverse birth outcomes. Further studies are needed to attempt to replicate the current results and explore the underlying mechanisms of the observed relationships.

## 5. Source of funding

This work was supported by the National Natural Science Foundation of China (NSCF-81330068) and the National Natural Science Foundation of China (NSCF-81573168). The sponsors were not involved in any aspect of this manuscript preparation.

## 6. Conflict of interest

No potential conflicts of interest relevant to this article were reported.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.preghy.2018.09.004.

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