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Clinical Research Paper

High normal blood pressure increase risks of developing adverse pregnancy outcomes

Dian He[1,6,*], Haibing Li[1,6,*], Shaowen Wu[2,*], Yifei Lu[5], Jun Li[3], Yan He[1,6], Chengchao Zhang[4], Zihe Zheng[5] and Weiyuan Zhang[2]

[1]Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing, China

[2]Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China

[3]Division of Health System, Policy and Management, JC School of Public Health and Primary Care, Chinese University of Hong Kong, Sha Tin, Hong Kong

[4]302 Military Hospital of China, Beijing Shi, China

[5]Epidemiology Department, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

[6]Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China

[*]These authors contributed equally to this work

Correspondence to: Dian He, **email:** hedian@ccmu.edu.cn
Zihe Zheng, **email:** zzheng11@jhu.edu
Weiyuan Zhang, **email:** zhangwy9921@hotmail.com

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ABSTRACT

This study evaluated the effects of high normal blood pressure (HNBP) in early pregnancy on adverse pregnancy outcomes. We conducted a multi-center and national representative retrospective cohort study. We defined high normal blood pressure as systolic blood pressure between 130-140mmHg or diastolic blood pressure between 85-90mmHg. We used multivariable logistic regression to examine the association of HNBP and risks of pregnancy outcomes. Of 69 687 normotensive women in early pregnancy, 5 798 (8.3%) fulfilled our definition of HNBP, 20 394 (29.3%) were in normal blood pressure group, and the rest 43 495 (62.4%) women had optimal blood pressure. The incidence rates of gestational hypertension, preeclampsia, gestational diabetes mellitus (GDM), premature birth, small for gestational age (SGA), caesarean section, placental abruption and perinatal mortality were 1.6%, 2.3%, 4.2%, 6.1%, 7.1%, 54.9%, 0.5% and 0.7% respectively. Compared to women who had optimal blood pressure, those with HNBP had significantly higher odds of preeclampsia (OR = 4.179, 95% CI 3.584, 4.873), gestational hypertension (OR = 6.050, 95% CI 5.071, 7.219), GDM (OR = 1.077, 95% CI 1.007, 1.153), premature birth (OR = 1.504, 95% CI 1.329, 1.702), SGA (OR = 1.329, 95% CI 1.177, 1.500) and cesarean delivery (OR = 1.583, 95% CI 1.379, 1.817). Our restricted cubic spline results supported positive dose-response relationships between continuous blood pressure and the odds of these pregnancy complications. HNBP in early pregnancy significantly increased the risk of developing preeclampsia, gestational hypertension, GDM, premature birth, SGA and cesarean delivery. Our study provided robust epidemiological evidences for monitoring HNBP in early pregnancy to reduce the risks of adverse pregnancy outcomes.

INTRODUCTION

High blood pressure (BP) in early pregnancy increases the risk of hypertensive disorders during pregnancy, cerebral hemorrhage, hepatic failure and acute renal failure in late pregnancy [1–4]. However, some studies proposed that pregnant women with high normal blood pressure (HNBP, defined as systolic blood pressure between 130-140 mmHg or diastolic blood pressure between 85-90 mmHg) could also benefit from early hypertension management [5]. Previous studies found that HNBP was significantly associated with the development of gestational hypertension (adjusted odds ratio [OR] 1.81, 95% confidence interval [CI] 1.16, 3.25) and preeclampsia (adjusted OR 6.05, 95% CI 3.46, 12.6) [6]. Other studies reported significant associations of HNBP with small for gestational age (SGA), stillbirth and high perinatal mortality [7, 8]. However, the effect of HNBP on pregnancy risks is in debate. A study reported no difference in the risks of pregnancy loss, high-level neonatal care, or overall maternal complications between two groups of targeted diastolic blood pressure of 100mmHg versus 85 mmHg [9, 10].

Given these conflicting findings of HNBP and the risks of adverse pregnancy outcomes, more evidences are needed for clarifying the most preferable pregnancy blood pressure management in clinical practice. Thus, our primary objective is to study the associations between HNBP and common adverse pregnancy outcomes, including gestational hypertension, preeclampsia, gestational diabetes mellitus (GDM), premature birth, SGA, cesarean delivery, placental abruption and perinatal mortality. The second objective of our study is to examine the potential modification effect of pre-pregnancy body mass index (BMI) on the associations between HNBP and the above adverse outcomes.

RESULTS

Of 112 386 participants, we excluded 2 969 women with chronic hypertension, 15 240 women missing blood pressure measurement in early pregnancy, 19 531 women missing pre-pregnancy BMI, 4 959 women missing GWG. A total of 69 687 women were included in the analysis. We did not find significant differences between included women and excluded women in this analysis.

Of the 69, 687 participants, 5, 798 (8.3%) were categorized into the HNBP group, 20, 394 (29.3%) into the normal blood pressure group, and 43, 495 (62.4%) into the optimal BP group (Table 1). The incidences of HNBP in the underweight, normal weight, and overweight-obese groups were 4.7%, 7.1% and 15.5%, respectively (Figure 1). Early pregnancy blood pressure levels were significantly correlated with pre-pregnancy BMI ($p < 0.001$), and women with higher pre-pregnancy BMI level also had higher blood pressure level. Other maternal characteristics were significantly different across the three blood pressure groups, except for smoking status and family history of hypertension.

Among the 69, 687 normotensive pregnant women, the incidences of gestational hypertension, preeclampsia, GDM, premature birth, SGA, cesarean delivery, placental abruption and perinatal mortality were 1.6%, 2.3%, 4.2%, 6.1%, 7.1%, 54.9%, 0.5% and 0.7% respectively. The incidence rates of these outcomes in HNBP group were higher than those in the other two groups (all p values < 0.001, in Table 2), except for placental abruption or perinatal mortality. Normotensive women with HNBP were more likely to develop preeclampsia or gestational hypertension earlier than other two groups (Figure 2).

We performed multivariable analyses to examine whether BP levels were associated with developing the above outcomes. We adjusted for maternal age, years of education, smoking, alcohol consumption, height, pre-pregnancy BMI, GWG, nulliparous status, family history of hypertension, levels of hospitals and human development index (Table 3). Results shown that pregnant women in HNBP group or the normal blood pressure group were more likely to develop preeclampsia, with odds ratios equaled to 4.179 (95% CI 3.584, 4.873) and 2.503 (95% CI 2.215, 2.828) respectively (Figure 3). Similarly, HNBP was significantly associated with the increased odds of gestational hypertension (OR = 6.050, 95% CI 5.071, 7.219), GDM (OR = 1.583, 95% CI 1.379, 1.817), premature birth (OR = 1.504, 95%CI 1.329, 1.702), SGA (OR = 1.329, 95% CI 1.177, 1.500) and CS (OR = 1.077, 95%CI 1.007, 1.153) respectively. However, we did not observe significant associations existed between BP levels and placental abruption (OR = 0.907, 95%CI 0.554, 1.485) or perinatal mortality (OR = 1.506, 95% CI 0.980, 2.316). We also found that pre-pregnancy BMI levels were significantly associated with the risks of preeclampsia, gestational hypertension, GDM, premature birth and SGA (Table 3). However, the interaction effects of BP and pre-pregnancy BMI on above pregnancy outcomes were not statistically significant in our study (all p value > 0.05).

Using blood pressure as a continuous variable, multivariable logistic regression models reveal that both higher SBP and DBP were significantly associated with the increased odds of preeclampsia, the effect of which was independent of pre-pregnancy BMI (Table 4). Per 5 mmHg increase in SBP, there was 29% increased odds of preeclampsia (OR = 1.290, 95%CI 1.254, 1.327); and per 5 mmHg increase in DBP, there was 46.6% increased odds of preeclampsia (OR = 1.466, 95%CI 1.409, 1.525). Associations were observed between SBP/ DBP with gestational hypertension, GDM, premature birth, SGA and cesarean delivery (Table 4). In order to test the robustness of our findings, we restricted our analysis to women with BMI between 18.5 kg/m^2 and 24.9 kg/m^2 (n = 44 673), and results in this subgroup were consistent with the overall population (Table 4).

Using SBP equals to 120 mmHg or DBP equals to 80 mmHg groups as the reference, we applied restricted

cubic spline regression to analyze the dose-response relationship between continuous blood pressure change (SBP and DBP) and the odds of the above pregnancy outcomes (Figure 4). Based on the blood pressure-outcome association trajectory, we found that there were significant nonlinear dose-response relationships between the adverse pregnancy outcomes and the continuous blood pressure change. Compared to other outcomes, preeclampsia and gestational hypertension had stronger dose-response relationship (steeper trajectory) with blood pressure level (Figure 4).

DISCUSSION

In this large, national representative retrospective cohort study, we found that blood pressure level of normotensive women was associated with the development of gestational hypertension, preeclampsia, GDM, premature birth, SGA and caesarean section, where stronger associations were seen with gestational hypertension and preeclampsia. Higher blood pressure increased women's risks of developing adverse pregnancy outcomes [11]. Results of sensitivity analyses were consistent with our main findings. Although pre-pregnant BMI was also an independent risk factor for above pregnancy outcomes, we did not observe significant interaction effects of blood pressure with pre-pregnancy BMI on the outcomes.

We found stronger associations between BP level in early pregnancy and the development of preeclampsia and gestational hypertension. After adjusting for confounders, the risks of preeclampsia or gestational hypertension were 2.5–6 times higher comparing women in the normal blood pressure or HNBP group to those with optimal blood pressure. A retrospective cohort study demonstrated that the adjusted ORs of normal blood pressure and HNBP for the subsequent occurrence of preeclampsia were 5.1 (95% CI 2.2, 12) and 8.3 (95% CI 3.1, 22) respectively; and the adjusted ORs for gestational hypertension were 7.0 (95% CI 2.6, 19) and 7.4 (95% CI 2.1, 25) respectively [12]. Several studies showed that blood pressure level of early pregnancy in women who developed preeclampsia or gestational hypertension at a later time was higher than those who did not [12, 13]. Magee's study reported that women in the group with less-tight blood pressure control group (targeted diastolic blood pressure of 100mmHg) had a significantly higher frequency of severe maternal hypertension than those in the tighter control group (85 mmHg) [9]. Additional evidence showed that tighter blood pressure control during pregnancy brings benefit to mothers without increasing the neonates' risks, along with lowering the cost of pregnancy health care [5]. Thence, some researcher proposed that a cut off value of DBP equaled to 81 mmHg was the optimal threshold for early gestational blood pressure level, which allowed for identifying pregnant women with higher risks of gestational [14].

In addition, we also found that women with higher blood pressure level were more likely to develop preeclampsia or gestational hypertension at earlier time than those with lower blood pressure level. Previous studies showed that chronic hypertension was a well-established risk factor for developing preeclampsia prior to 34th gestational week [15, 16, 17]. In our study, women in the HNBP group had higher percentage developing preeclampsia or gestational hypertension before 32 weeks of gestation (Figure 2).

We observed that the incidence of SGA neonates was 1.3 times higher in the HNBP group compared to the optimal blood pressure group. A previous study suggested the risk of SGA had 1.8-fold increase among mothers with high blood pressure even when preeclampsia was absent

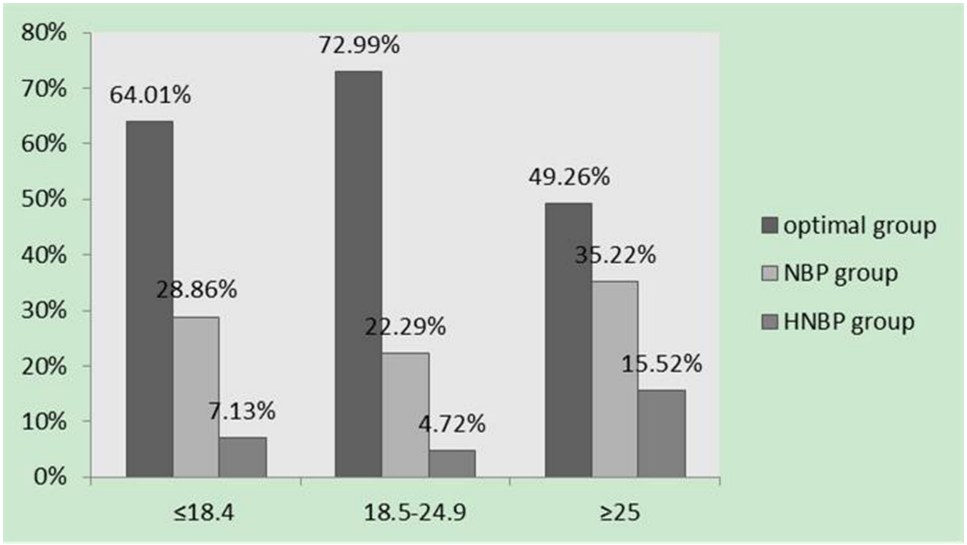

Figure 1: Proportions of blood pressure levels in body mass index groups (NBP: normal blood pressure; HNBP: high normal blood pressure).

[11]. Anna-Karin et al. found that prehypertension was associated with increased risk of SGA birth with adjusted OR of 1.69 (95% CI 1.51, 1.90). Additionally, risks of SGA birth increased by 2.0% (95% CI 1.5, 2.8) per each one mm Hg rise in DBP during pregnancy [8]. The possible biological rationale for this association is that high blood pressure, along with placental gene expression and function, affects critical components of maternal metabolism [18]. Study found that impaired maternal perfusion of the placenta (an extrinsic defect) and impaired placental development (an intrinsic defect) could cause SGA [19].

We also observed associations between HNBP and the development of preterm birth and cesarean section. To our best knowledge, there was no study reported the association between HNBP with preterm birth or cesarean section. However, studies indicated that, even in the absence of superimposed preeclampsia, women with chronic hypertension had an increased risk of preterm or cesarean delivery [20]. Panaitescu's study indicated that chronic hypertension was associated with 3.7-fold increased risk of iatrogenic preterm birth and 1.8-fold increased risk of cesarean section [11]. A meta-analysis studies showed that women with chronic hypertension had 30% higher risks of cesarean delivery (OR = 1.3, 95%CI 1.1, 1.5), and 170% increased risks for preterm delivery (OR = 2.7, 95%CI 1.9, 3.6) [21]. However, the pathogenesis of spontaneous preterm birth among women with hypertension remains unclear.

Among our normotensive study population, we found positive association between blood pressure and the risks of GDM. There was no study explored the association between HNBP and the development of GDM among normotensive pregnancy women. A prospective study based on 109,932 pregnancies shown that chronic hypertension was associated with increased risk of GDM (OR = 1.61, 95% CI 1.27, 2.05) [11]. Another study reported that gestational hypertension was associated with increased risk of post-delivery diabetes mellitus (HR = 1.52, 95% CI 1.21, 1.89) [3]. Insulin resistance, chronic inflammation and endothelial dysfunction may contribute to the biological rationale of the association [21–22].

The associations between blood pressure levels and occurrences of placental abruption (OR = 0.907, 95%CI 0.554, 1.485) or perinatal mortality (OR = 1.506, 95% CI 0.980, 2.316) were not statistically significant in our study. A previous study found that each mmHg increase in DBP from early to late pregnancy did not alter the risk of stillbirth (95% CI-1.4, 1.7) [8]. As far as we known, few publications had focuses on the association of HNBP and placental abruption. Researchers proposed that high blood pressure might lead to an imbalance in proangiogenic and antiangiogenic factors, notably an increase in soluble fms-like tyrosine kinsase-1 (sFlt-1), thereby leading to placental abruption [23].

The prevalence of high blood pressure among pregnant women has been increasing over time. This is primarily attributed to the increased prevalence of obesity and the delayed childbearing age [24]. A large number of pregnancy women unaware of their blood pressure level or HNBP condition. Early health education and counseling about the risks of hypertensive disease during pregnancy are needed for prospective mothers. Our findings provided robust epidemiological evidences and new insight to the relationship between maternal blood pressure in early pregnancy and adverse pregnancy outcomes. Based on this large and national representative cohort study, we recommended that health care providers should spend more efforts on the monitoring and follow-up with HNBP women during early pregnancy, especially for those who are overweight or older.

Our study had several strengths. First, we obtained the information of blood pressure, weight, height,

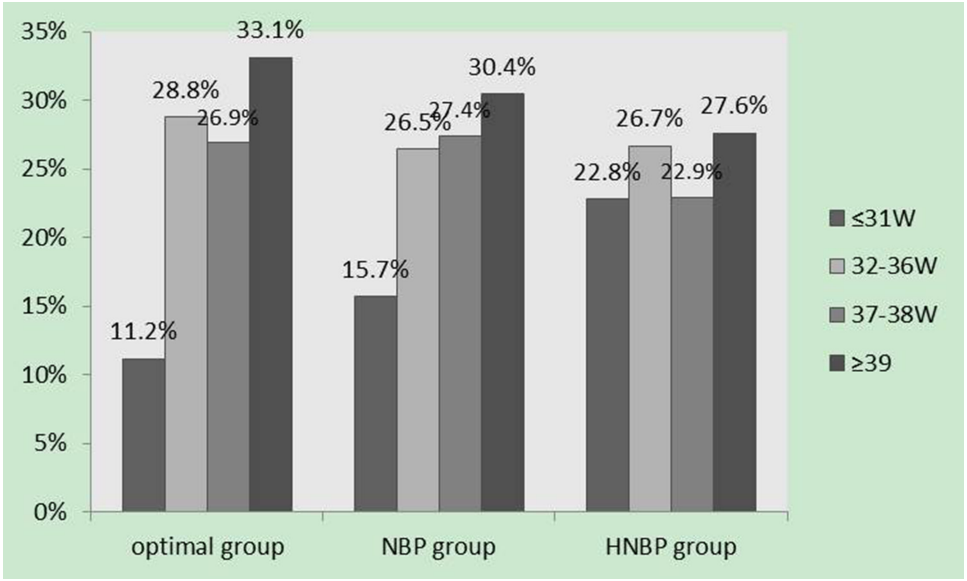

Figure 2: Proportions of onset time classifications of PE or GH in blood pressure groups (W = weeks; NBP: normal blood pressure; HNBP: high normal blood pressure).

gestational age, and adverse pregnancy outcomes directly from clinic medical records from each research center, which was an objective data source compared to self-report. Second, we are confident that the classification of blood pressure categories was accurate since the measurements were conducted at the time of women's first hospital visit. Third, the national representative nature of our study population lowered the cohort selection bias and increased the external validity of our conclusion.

The limitations of our study are as following. In this study, we did not to examine the effect of HNBP on the onset time of adverse outcomes that occurred during pregnancy. In future studies, we would like to prospectively evaluate and quantify the relationship between pre-pregnancy blood pressure level and the onset time of different adverse outcomes, especially preeclampsia and gestational hypertension. Second, we were not able to conclude causality, but associations, between blood pressure and pregnancy complications. Third, since the study was based on Chinese population, readers are advised to be careful when generalizing the results to other circumstance.

In conclusion, these results provide robust epidemiological evidences: high normal blood pressure of normotensive pregnancy women significantly increased risks of development of gestational hypertension, preeclampsia, GDM, premature birth, SGA and caesarean section, where the risks increased by 5 times for developing gestational hypertension, and increased by 3 times for preeclampsia. HNBP in combination with other clinical indicators can predict the probability of occurrence of these adverse pregnancy outcomes. Thence, we

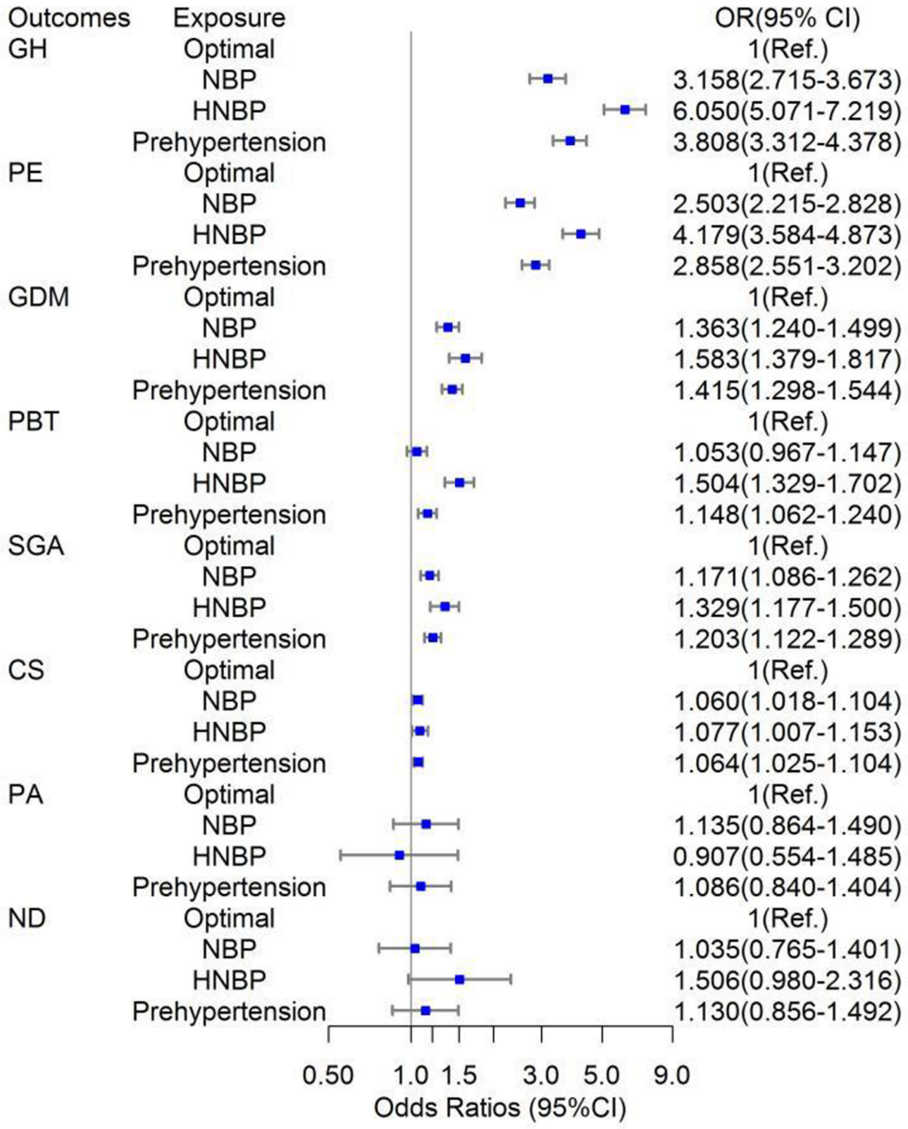

Figure 3: Odds ratios of high-normal, normal, prehypertension groups associated with occurrences of adverse pregnancy outcomes. (GH: Gestational hypertension; PE: Pre-eclampsia; GDM: Gestational Diabetes Mellitus; PB: Premature birth; SGA: small for gestational age; CS: Caesarean Section; NBP: normal blood pressure; HNBP: high normal blood pressure; prehypertension: HNBP or NBP).

recommend health care providers increase the monitoring for high normal blood pressure during early pregnancy in the clinical practice.

MATERIALS AND METHODS

Study design

We conducted a retrospective study using a multicenter and national representative cohort study, which was originally designed for investigating the prevalence of common pregnancy and birth complications in China. In the retrospective study, data on the relevant events for each individual are collected from existing records, and can immediately be analyzed to determine the relative risk of the cohort compared to the control group. In 2011, 38 general hospitals or gynecology and obstetrics specialty hospitals were selected from 14 provinces and regions across China. These research sites covered most provinces in China and provided more than

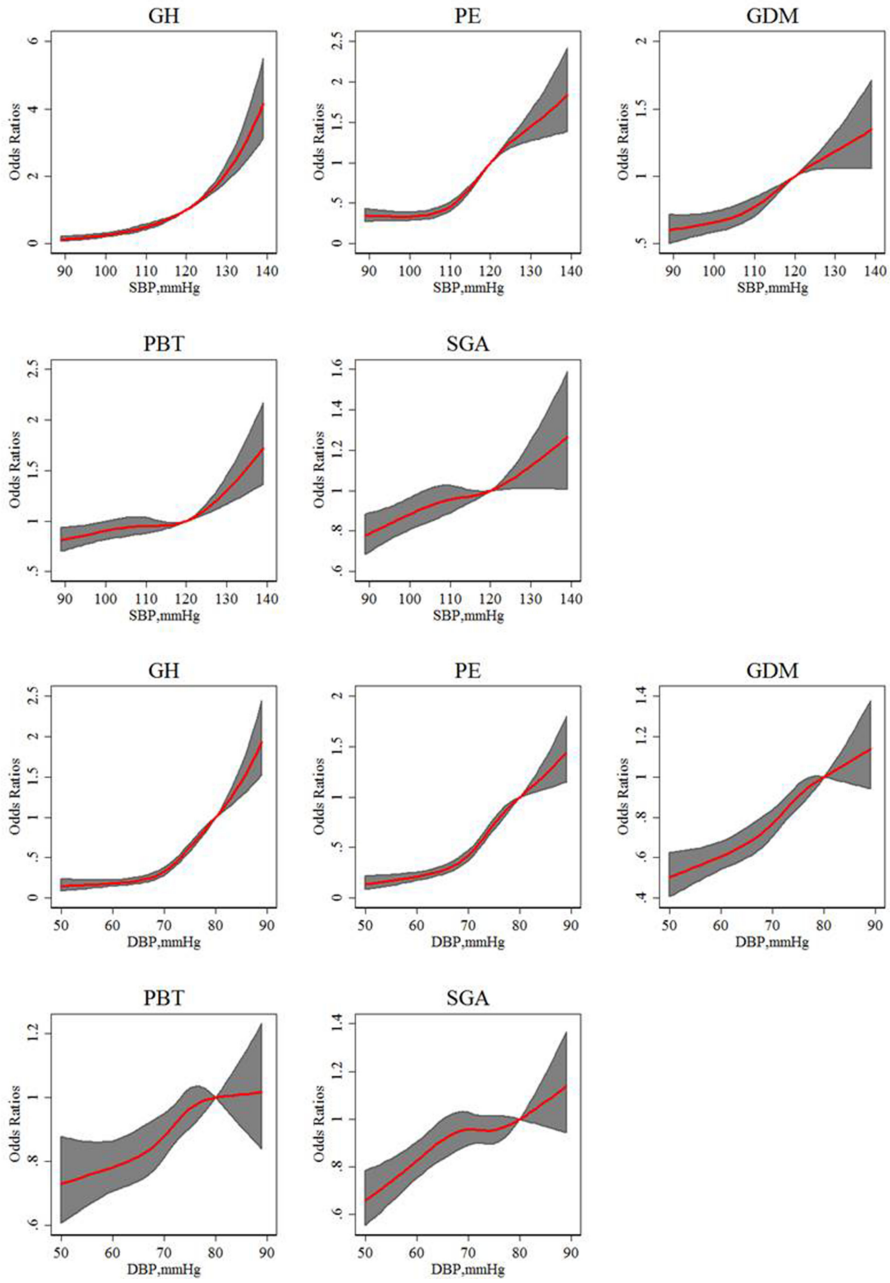

Figure 4: Risk of pregnancy outcomes according to SBP or DBP as a continuous variable. Gray areas are 95% confidence intervals. Odds ratios were estimated using logistic regression modeling, adjusting for maternal age, years of education, smoking, alcohol consumption, height, pre-pregnancy BMI, GWG, nulliparous, family history of hypertension, levels of hospitals and HDI. (GH: Gestational hypertension; PE: Pre-eclampsia; GDM: Gestational Diabetes Mellitus; PB: Premature birth; SGA: small for gestational age; BMI: body mass index; GWG: gestational weight gain; HDI: human development index).

Table 1: Maternal characteristics in three groups divided by the blood pressure value around 12 weeks of pregnancy ($N = 69\ 687$)

	Optimal	Normal	High normal	*p*-value
	43495 (62.4%)	20394 (29.3%)	5798 (8.3%)	
Age (years)				< 0.001
≤ 24	9877 (22.8)	4999 (24.6)	1223 (21.3)	
25–29	18934 (43.8)	8448 (41.7)	2320 (40.3)	
30–34	10698 (24.7)	4753 (23.4)	1525 (26.5)	
≥ 35	3720 (8.6)	2080 (10.3)	686 (11.9)	
Years of education				< 0.001
≥ 13	21273 (49.6)	8081 (40.3)	2428 (42.6)	
10–12	12846 (29.9)	6812 (34.0)	1912 (33.5)	
≤ 9	8798 (20.5)	5139 (25.7)	1361 (23.9)	
Smoking				0.984
Smoker	153 (0.4)	70 (0.3)	20 (0.3)	
Non-smoker	43342 (99.6)	20324 (99.7)	5778 (99.7)	
Drinking				< 0.001
No	42835 (98.5)	20175 (98.9)	5743 (99.1)	
Yes	660 (1.5)	219 (1.1)	55 (0.9)	
Height (cm)				< 0.001
≤ 159	10924 (28.2)	4693 (26.5)	1208 (24.6)	
160–164	17812 (45.9)	7958 (44.9)	2232 (45.4)	
165–169	8130 (21.0)	4067 (22.9)	1138 (23.2)	
≥ 170	1908 (4.9)	1023 (5.8)	335 (6.8)	
Pre-pregnancy BMI				< 0.001
≤ 18.4	5227 (14.1)	1596 (9.5)	338 (7.4)	
18.5–24.9	28593 (76.9)	12893 (76.3)	3187 (69.6)	
≥ 25	3355 (9.0)	2399 (14.2)	1057 (23.1)	
GWG				< 0.001
Below	9114 (25.4)	4558 (27.6)	1098 (24.9)	
Adequate	15360 (42.9)	6605 (40.0)	1737 (39.5)	
Above	11367 (31.7)	5348 (32.4)	1567 (35.6)	
Nulliparous				< 0.001
Yes	36563 (84.1)	16682 (81.8)	4809 (82.9)	
No	6932 (15.9)	3712 (18.2)	989 (17.1)	
Family history of hypertension				0.070
No	42804 (98.4)	20115 (98.6)	5701 (98.3)	
Yes	691 (1.6)	279 (1.4)	97 (1.7)	
Levels of hospitals				< 0.001
Two-level	12504 (28.7)	7060 (34.6)	1751 (30.2)	
Three-level	30991 (71.3)	13334 (65.4)	4047 (69.8)	
HDI				< 0.001
High-level	24558 (56.5)	7907 (38.8)	2550 (44.0)	
Middle-level	6418 (14.8)	4842 (23.7)	1111 (19.2)	
Low-level	12519 (28.8)	7645 (37.5)	2137 (36.9)	

BMI: body mass index (kg/m^2); GWG: gestational weight gain; HDI: Human Development Index.

Table 2: Percentage of maternal and neonatal outcomes stratified by the blood pressure value around 12 weeks of pregnancy (N = 69 687)

	Optimal	Normal	High normal	*p*-value
	N = 43495 (%)	N = 20394 (%)	N = 5798 (%)	
Gestational hypertension	358 (0.8)	460 (2.3)	284 (4.9)	< 0.001
Pre-eclampsia	581 (1.3)	705 (3.5)	337 (5.8)	< 0.001
Gestational diabetes	1636 (3.8)	919 (4.5)	364 (6.3)	< 0.001
Premature Birth	2500 (5.8)	1294 (6.3)	451 (7.8)	< 0.001
SGA	2828 (6.7)	1552 (7.8)	472 (8.3)	< 0.001
Caesarean Section	23025 (52.9)	11800 (57.9)	3455 (59.6)	< 0.001
Placental Abruption	196 (0.5)	105 (0.5)	28 (0.5)	0.540
Perinatal mortality	303 (0.7)	164 (0.8)	47 (0.8)	0.263

Pre-eclampsia: including mild and severe preeclampsia; SGA: small for gestational age; Perinatal mortality: including neonatal death and stillbirth.

Table 3: Odds ratios of blood pressure levels or Pre-pregnancy BMI levels associated with occurrences of adverse pregnancy outcomes

	Blood pressures			Pre-pregnancy BMI			Interaction *P* value*
	AOR (95%CI)			AOR (95%CI)			
	Optimal	Normal	High-normal	Normal	Below	Above	
Gestational hypertension	1 (Ref.)	3.158 (2.715–3.673)	6.050 (5.071–7.219)	1 (Ref.)	0.786 (0.612–1.009)	1.605 (1.372–1.877)	0.454
Pre-eclampsia	1 (Ref.)	2.503 (2.215–2.828)	4.179 (3.584–4.873)	1 (Ref.)	0.937 (0.770–1.140)	1.391 (1.209-1.600)	0.157
Gestational Diabetes	1 (Ref.)	1.363 (1.240–1.499)	1.583 (1.379–1.817)	1 (Ref.)	0.683 (0.584–0.798)	2.113 (1.900–2.350)	0.081
Premature Birth	1 (Ref.)	1.053 (0.967–1.147)	1.504 (1.329–1.702)	1 (Ref.)	1.259 (1.128–1.405)	1.051 (0.934–1.183)	0.051
SGA	1 (Ref.)	1.171 (1.086–1.262)	1.329 (1.177–1.500)	1 (Ref.)	1.610 (1.472–1.760)	0.712 (0.624-0.813)	0.058
Caesarean Section	1 (Ref.)	1.060 (1.018–1.104)	1.077 (1.007–1.153)	1 (Ref.)	0.752 (0.713–0.793)	1.593 (1.499–1.692)	0.521
Placental Abruption	1 (Ref.)	1.135 (0.864–1.490)	0.907 (0.554–1.485)	1 (Ref.)	1.087 (0.754–1.567)	0.726 (0.474–1.114)	0.859
Perinatal mortality	1 (Ref.)	1.035 (0.765–1.401)	1.506 (0.980–2.316)	1 (Ref.)	1.141 (0.744–1.750)	0.997 (0.627–1.585)	0.259

Pre-eclampsia: including mild and severe preeclampsia; SGA: small for gestational age; Perinatal mortality: including neonatal death and stillbirth; *Interaction *p* value: the interaction effect between blood pressure and pre-pregnancy BMI associated with adverse pregnancy outcomes; AOR: adjusted odds ratio.

120 000 women's records. The chosen hospitals included 19 tertiary hospitals and 19 secondary hospitals, which are the most common medical institutions in mainland China.

Data collection

We included pregnant women who delivered babies during January 1st 2011 and December 31st 2011 in the selected hospitals as study population. We collected participants' clinical information from their clinical medical records. Data collection was conducted by trained medical staffs and all the collected information was crosschecked by study investigators for quality control. These clinical medical records include sociodemographic information, disease history, the occurrence of pregnancy complications, as well as perinatal and neonatal outcomes. Data had been routinely updated from participants' first prenatal visit (around 12th gestational week). The detailed

Table 4: Odds ratios of SBP or DBP by increment of 5 mmHg associated with occurrences of adverse pregnancy outcomes by categories of pre-pregnancy BMI

	Overall population		Population with 18.5 ≤ BMI < 24.9	
	SBP OR (95%CI)	DBP OR (95%CI)	SBP OR (95%CI)	DBP OR (95%CI)
Gestational hypertension	1.444 (1.396–1.494)	1.592 (1.520–1.668)	1.459 (1.400–1.521)	1.604 (1.516–1.696)
Pre-eclampsia	1.290 (1.254–1.327)	1.466 (1.409–1.525)	1.311 (1.268–1.356)	1.476 (1.409–1.547)
Gestational Diabetes	1.102 (1.080–1.124)	1.140 (1.110–1.170)	1.090 (1.065–1.117)	1.122 (1.088–1.158)
Premature Birth	1.050 (1.032–1.069)	1.055 (1.029-1.080)	1.047 (1.025–1.069)	1.069 (1.039–1.099)
SGA	1.044 (1.028–1.061)	1.059 (1.037–1.082)	1.042 (1.023–1.061)	1.064 (1.037–1.091)
Caesarean Section	1.002 (0.994–1.011)	1.026 (1.014–1.037)	1.005 (0.995–1.014)	1.029 (1.016–1.042)
Placental Abruption	1.00 (0.945–1.058)	1.040 (0.962–1.125)	1.025 (0.960–1.095)	1.050 (0.960–1.148)
Perinatal mortality	1.071 (1.000–1.147)	1.073 (0.977–1.180)	1.051 (0.972–1.136)	1.075 (0.966–1.196)

Pre-eclampsia: including mild and severe preeclampsia; SGA: small for gestational age; Perinatal mortality: including neonatal death and stillbirth; BMI: pre-pregnancy BMI; SBP: Systolic BP; DBP: Diastolic BP.

study design can be found in previous publication [25].

This study has been approved by the Ethics Committees of each selected hospital, and followed the guidelines of the Helsinki agreement and its amendments. The National Research Ethics Service had previously approved the anonymous use of these data for research purposes.

Definition of exposures

Blood pressure was measured around the 12th gestational week using electronic sphygmomanometer or mercury sphygmomanometer with patients in the sitting position holding her right arm at heart level. Applying conservative exposure definition, we used the lower blood pressure reading for individuals who had more than one blood pressure measurement [26]. We categorized participants into 3 groups according to their blood pressure level as optimal (SBP < 120 mmHg and DBP < 80 mmHg), normal (130 mmHg > SBP ≥ 120 mmHg or 85 mmHg >DBP ≥ 80 mmHg), and high-normal (140 mmHg > SBP ≥ 130 mmHg or 90 mmHg > DBP ≥ 85 mmHg). Normal or high-normal group was further defined as prehypertension group. Women with high blood pressure (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) were excluded from our analysis [4].

Definition of outcomes

The outcomes of interest in our study were gestational hypertension, preeclampsia, GDM, premature birth, SGA, cesarean delivery, placental abruption and perinatal mortality. According to the classification system by the National High Blood Pressure Education Program (NHBPEP) Working Group, hypertension disorder during pregnancy was categorized into six subtypes: gestational hypertension (GH), mild preeclampsia, severe preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension and chronic hypertension in pregnancy [27]. Gestational hypertension was defined as hypertension without proteinuria occurring after the 20th week of gestation (ICD-9 codes 642D and 642X, and ICD-10 code O13). We combined mild preeclampsia and severe preeclampsia cases as preeclampsia (ICD-9 codes 642E-642H and ICD-10 codes O11 and O14)2. GDM was diagnosed using the oral glucose tolerance test at 24-28 weeks of pregnancy in accordance with the IADPSG criteria (ICD-9 code 648W and ICD-10 code O244) [28]. SGA was determined as infants who had birth weights below the 10th percentile of Chinese birth weight reference curve, adjusted for gestational age and gender. Premature birth was defined as childbirth occurred prior to 37 completed gestational weeks. We included stillbirth and neonatal death in the analysis of perinatal mortality.

Potential confounders

Pre-pregnancy BMI (kg/m^2) was calculated using maternal weight and height recorded around 12th gestational week. We categorized BMI into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight and obese (≥ 25.0 kg/m^2) [29]. Because less than 2% of our study population

was obese, we combined the overweight and obese groups to increase statistical power. We calculated gestational weight gain (GWG) as the difference between maternal weight prior to delivery and maternal weight recorded at the first prenatal visit (around 12th gestational week). We categorized GWG into adequate, inadequate and excessive weight gain groups based on the 2009 IOM GWG guidelines [30].

Other potential confounders that we included and adjusted in our analysis were maternal age at children birth, maternal years of education, smoking status, drinking status, height, whether nulliparous, family history of hypertension, type of hospital (tertiary versus secondary hospitals) and human development index (HDI).

Statistical analysis

We examined the difference of maternal characteristics across different blood pressure groups using chi^2 test. We used multivariable logistic regression model to explore the associations between blood pressure in early pregnancy and the odds of pregnancy outcomes. Multivariable logistic regression analysis was performed to determine independent risk factors for the development of pregnancy outcomes. We also examined the interaction effect of blood pressure and pre-pregnancy BMI categories on the risks of pregnancy outcomes. Then we used SBP and DBP as continuous variables to analyze the association between continuous BP (per 5 mmHg increase) and pregnancy outcomes. Additionally, we conducted sensitivity analyses restricted to women whose BMI ranged from 18.5 kg/m^2 to 24.9kg/m^2 in order to validate the associations between BP with pregnancy outcomes. We used restricted cubic spline regression to analyze the dose-response relationship between continuous blood pressure and the odds ratios of individual pregnancy outcomes. In multivariable regression models, we selected potential confounding factors based on clinicians' opinions and positive results in univariate analyses *($P < 0.05$)*. Two-sided $P < 0.05$ was used as the cut-off value for statistical significance. We used SAS software (version 9.4, SAS Institute Inc, Cary, NC) for all analyses.

Abbreviations

GH: Gestational hypertension; PE: Pre-eclampsia; GDM: Gestational diabetes mellitus; PBT: Premature birth; SGA: Small for gestational age; CS: Caesarean section; PA: Placental abruption; NBP: Normal blood pressure; HNBP: High normal blood pressure; Prehypertension: HNBP or NBP; BMI: body mass index; GWG: Gestational weight gain; HDI: Human development index; SBP: Systolic BP; DBP: Diastolic BP; AOR: Adjusted odds ratio.

Author contributions

Shaowen Wu, Jun Li and Yifei Lu directed data collection and management. Haibing Li and Dian He participated in data analysis and interpretation. Yan He and Weiyuan Zhang coordinated and supervised this investigation. Dian He, Chengchao Zhang and Zihe Zheng participated in drafting of this manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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