BMC Medicine

RESEARCH

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The interdependence of mid-trimester blood pressure and glucose levels in shaping fetal growth and neonatal outcomes: implications for risk–benefit assessment and co-management

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Abstract

Background Maternal hypertension and hyperglycemia are closely related but have distinct impacts on fetal growth and are managed independently. How the interdependence of blood pressure (BP) and glucose levels quantitatively influences risk patterns for abnormal fetal growth and neonatal complications remains unexplored.

Methods Maternal BP and fasting plasma glucose (FPG) levels were measured between 20 and 28 weeks of gestation in a cohort including 56,881 singleton pregnancies. Linear and quantile regression analyses were used to evaluate the relationship between BP and FPG. We examined the dose–response relationships between BP and FPG with small-for-gestational age (SGA) and large-for-gestational age (LGA) by using restricted cubic spline (RCS) curves. Additionally, multivariable fractional polynomial interaction (MFPI) analysis was conducted to assess the effects of higher versus lower BP levels across the full range of FPG levels. Heatmaps were created to visualize the contributions of BP and FPG by categorizing them into ordered groups.

Results Quantile regression revealed consistent positive correlations between mean arterial pressure (MAP) and FPG, with a steeper increase in MAP coefficients above the 0.5 quantile of FPG. MAP had a non-linear positive association with SGA risk, while FPG showed a non-linear negative association. Heatmaps revealed the highest SGA risk with high BP (MAP ≥ 85 mmHg)/low glucose (< 85 mg/dL) combinations and the lowest risk with low BP (MAP < 85 mmHg)/high glucose (≥ 85 mg/dL), with equivalent risk at both high BP/high glucose and low BP/low glucose. In hypertensive patients, SGA risk worsened continuously as glucose levels decreased. LGA risk was not influenced by BP levels. Neonatal complications decreased by approximately 47% as MAP declined from the highest to lowest category, and by about 17% with decreasing glucose levels.

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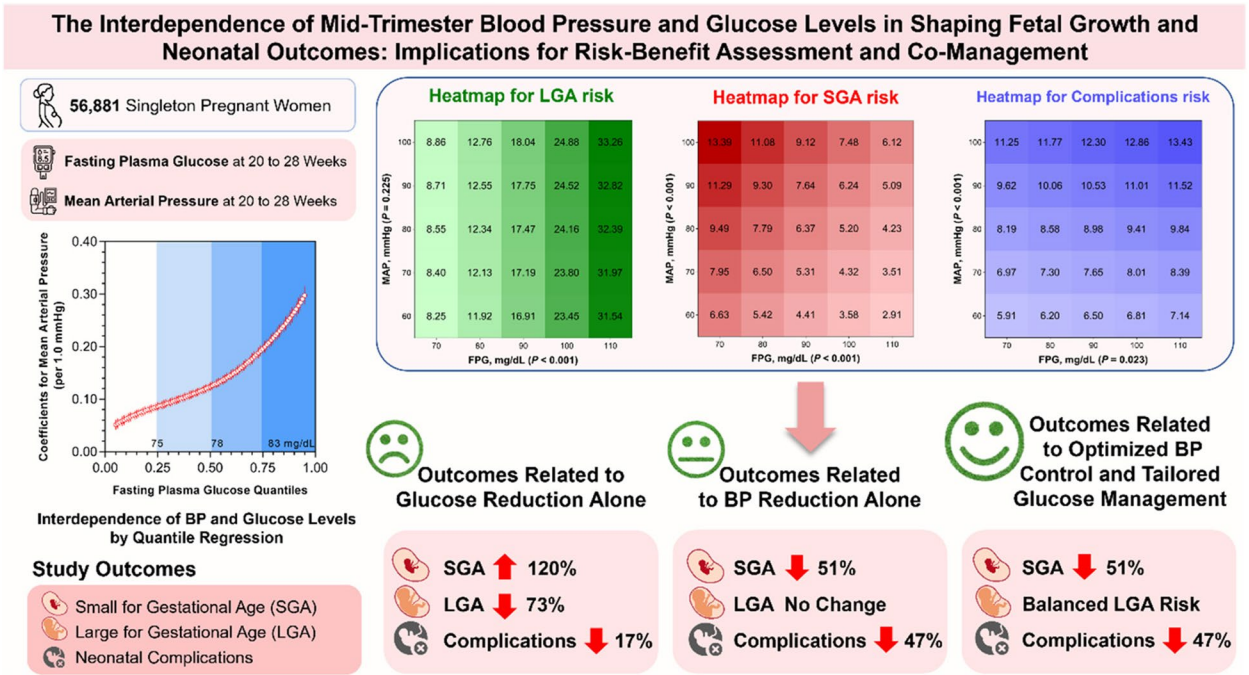
Conclusions Based on a large pregnancy cohort in China, this study revealed an interdependent association between maternal BP and glucose levels and their combined impact on the risk of SGA. It provided quantitative evidence of how this interdependence shapes the transition of risk patterns for SGA, neonatal complications, and LGA. These findings underscore the need for an integrated approach to co-managing BP and glucose levels during pregnancy.

Keywords Blood pressure, Fasting plasma glucose, Hypertensive disorders in pregnancy, Gestational diabetes, Small-for-gestational age infants, Large-for-gestational-age infants, Neonatal complications

Graphical Abstract



Background

Abnormal fetal growth, as defined by either small for gestational age (SGA) or large for gestational age (LGA), significantly increases short-term and long-term health issues [1, 2]. Blood pressure (BP) and glucose levels are modifiable risk factors for abnormal fetal growth. Elevation in BP, particularly in the form of hypertensive disorders of pregnancy (HDP), is one of the main drivers of SGA infants [3]. This is thought to be primarily mediated by chronic placental insufficiency as it is much more prevalent in early-onset disease [4]; however, the level of BP may be important in the placental insufficiency-fetal growth pathway as adverse pregnancy outcomes have been noted to be worse in HDP pregnancies with higher maternal BP. Maternal hyperglycemia, however, is strongly associated with the development of LGA infants [5], due to the corresponding excess fetal glucose and fat storage [6]. Maternal hyperglycemia and hypertension often co-exist. Part of this can be explained by higher maternal BMI, a shared risk factor for both conditions [7]. Nevertheless, maternal hyperglycemia and hypertension have differential effects on fetal growth and it is not clear which takes precedence. A recent population-based study indicated that the most common primary reasons for HDP infant admission were respiratory disease (28.3%), prematurity (22.7%), and hypoglycemia (16.4%) [8]. Notably, these diseases are often the study outcomes of gestational diabetes mellitus (GDM)-related randomized controlled trials [9–11].

In terms of BP management during pregnancy, a major concern with achieving tight BP targets among patients with HDP is the potential for a drop in BP leading to fetal growth restriction [12, 13]. However, findings from the Control of Hypertension in

Pregnancy Study (CHIPS) [14] and the Chronic Hypertension and Pregnancy (CHAP) Trial [15], which set a DBP target of < 85 mmHg and a SBP/DBP target of < 140/90 mmHg, respectively, did not find evidence to support this hypothesis. Regarding glucose management, current criteria to diagnose GDM (FPG ≥ 92 mg/dL or 5.1 mmol/L) are primarily based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [16], which showed no single glycemic threshold for birth weight and neonatal complications, but rather a continuous relationship with maternal hyperglycemia. As BP and glucose levels are pharmacologically manageable, these findings highlight the importance of simultaneously monitoring both to optimize fetal outcomes.

In observational studies, the classical approach to examining the impact of covariates on the outcome of interest is to add these covariates to the model independently, following the "ceteris paribus" assumption that other variables remain constant [17]. However, given the complex relationship between BP and glucose levels during pregnancy, their contributions to fetal outcomes should be re-examined beyond the "ceteris paribus" framework. This study addresses this knowledge gap by simultaneously analyzing the associations between maternal BP and glucose levels, as well as their combined impact on fetal growth and neonatal complications, in a large pregnancy cohort in China.

Methods

Population and study design

This retrospective cohort study was based on a pregnancy cohort from southern China (Guangzhou), including women who consecutively delivered at Guangdong Women and Children Hospital between January 1, 2013, and December 31, 2022. All enrolled women had their first booking and perinatal visits at this hospital, where they were expected to deliver. Guangdong Women and Children Hospital is one of the largest tertiary hospitals specializing in maternal and child health in Guangdong province, with ~ 10,000 deliveries annually [18]. The inclusion criteria included a singleton delivery, and the exclusion criteria included twin/multiple delivery, pre-pregnancy diabetes, chronic hypertension, delivery outcomes occurred before 28 weeks of gestation, as well as those who had missing values for glucose or BP levels between gestational weeks of 20 to 28, birth weight, or delivery week. The study flowchart is shown in Fig. 1. This study complies with the Declaration of Helsinki and was approved by the Ethics Committees of Guangdong Women and Children Hospital (202,301,105). Informed consent was waived due to the retrospective nature.

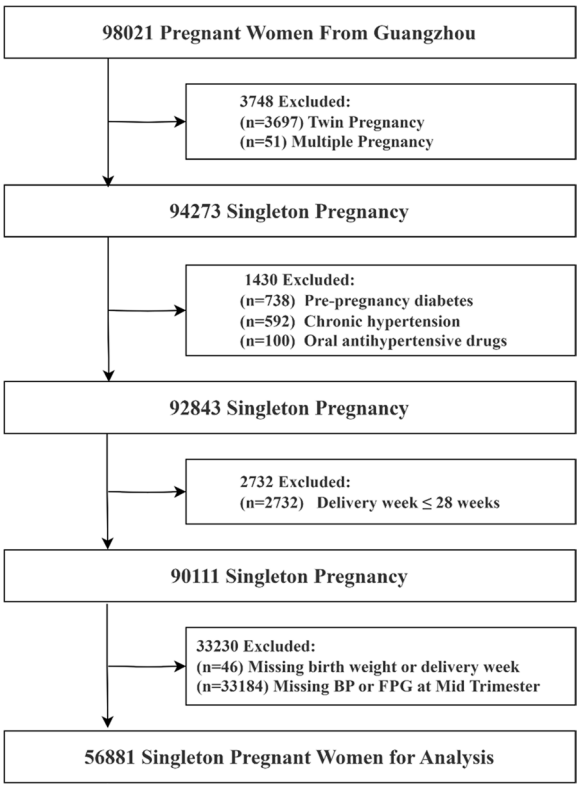


Fig. 1 Study flowchart

Exposures, covariates, and outcomes

The exposures were the averaged levels of fasting plasma glucose (FPG) and the averaged levels of office BP measurements [systolic BP, diastolic BP, and mean arterial pressure (MAP)] measured between 20 and 28 weeks of gestation. If there was only one measurement during this period, that single value was used. If there were multiple measurements, the mean of those values was calculated and used. Office BP was measured with the pregnant women in a sitting position, using an appropriately sized cuff for arm circumference by a trained nurse by using electronic sphygmomanometers. MAP was calculated as (SBP + DBP × 2)/3. The FPG test was performed after an overnight fast of at least 8 h, with blood sample drawn from the vein by a trained nurse. The diagnosis of HDP followed Chinese practicing guideline [19], which was generally consistent with the US guidelines [20, 21]. Notably, we used the FPG threshold of ≥ 92 mg/dL (5.1 mmol/L) to define GDM during our study period [22, 23].

Covariates for adjustment included maternal age, body mass index (BMI), parity, gravidity, history of polycystic ovary syndrome, history of kidney diseases, use of assisted reproductive technology, and other rare conditions known to increase the risk of birth weight

abnormalities (systemic lupus erythematosus, antiphospholipid syndrome, thrombotic diseases). BMI was defined as weight (kg) divided by height^2 (m^2). The prenatal BMI refers to measurements taken during routine antepartum check-ups ~ 20 weeks of gestation. "Gravidity" refers to the total number of pregnancies a woman has had, regardless of their outcome (including live births, stillbirths, and miscarriages). "Parity" refers specifically to the number of pregnancies resulting in live births or stillbirths at or beyond 24 weeks of gestation. The primary study outcomes were the delivery of SGA or LGA infants, defined as the gestational age adjusted birth weight below or above the 10th percentile using a global reference for fetal weight and birth weight percentiles [24], respectively, which takes into account the mean local birth weight and standard deviation. The secondary study outcomes were neonatal complications including preterm delivery, stillbirth/neonatal death, respiratory distress syndrome, hypoglycemia, and shoulder dystocia/neonatal brachial plexus injury.

Statistical analysis

A detailed description of the statistical analysis is provided in the Additional Methods. Data were described as the mean ± SD for continuous variables that were normally distributed or median with 25th to 75th percentiles for non-normally distributed continuous variables, and frequencies and percentages for categorical variables. We first analyzed the clinical features of all participants by 6 categories according to the MAP (< 85 mmHg and ≥ 85 mmHg) and tertiles of FPG within each MAP category. The binary classification of MAP at 85 mmHg was selected based on its dose–response relationship with SGA (see below). We applied linear and quantile regression analyses to evaluate the relationship between the levels of BP and FPG (Stata command "sqreg"). The covariates for adjustment were mentioned in the "Exposures, covariates, and outcomes" section. BMI was standardized to 20 weeks' gestation with an interpolation procedure [25]. For pregnant women with missing values for BMI (10.35%), we used the "missForest" function in R for multiple imputation. The "missForest" function is an imputation method based on random forests, designed to handle missing data effectively. It predicts missing values by iteratively building decision trees for both continuous and categorical variables. This method uses observed values to predict missing ones while accounting for variable relationships within the dataset. The imputation type is model-based, relying on random forest predictions to ensure accuracy and robustness [26]. The dose–response relationship between BP/FPG and study outcomes was examined by using restricted cubic spline (RCS) curves. Using multivariable fractional polynomial interaction (MFPI) analysis [27], we further assessed the impact of higher vs. lower BP levels, along with other binary classifications such as HDP vs. non-HDP and preeclampsia vs. non-preeclampsia, on study outcomes across the full spectrum of FPG levels. We constructed heatmaps to visualize the contribution of BP and FPG in their associations with study outcomes by presenting BP and FPG values as ordered categorical variables (10 mmHg for BP and 10 mg/dL for FPG) [28]. Moreover, in both SBP and FPG, and DBP and FPG combinations, we assessed the effects on the outcome with and without mutual adjustment for DBP and SBP, respectively. We used Stata version 16.0 (StataCorp, College Station, TX) and R version 4.0 (https://www.r-project.org/) for all analysis. All the statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics by mid-trimester BP and FPG *Categories*

A total of 56,881 singleton pregnant women were included for analysis (Fig. 1). Table 1 presents the clinical characteristics after grouping participants by two MAP categories (< 85 mmHg and ≥ 85 mmHg) and FPG tertiles. In general, as FPG increased within each MAP category, there was a corresponding increase in maternal age and BMI, women were more likely to have been pregnant before if they are at higher FPG and MAP levels (Table 1). In each MAP category, as FPG levels decreased from the highest to the lowest tertile, the incidence of SGA increased, with the highest incidence observed in participants with MAP ≥ 85 mmHg/lowest FPG (≤ 76 mg/dL) tertile, and the lowest incidence in those with MAP < 85 mmHg/highest FPG (≥ 82 mg/dL) tertile. Similarly, the incidence of LGA decreased as FPG levels declined, following a parallel trend across both MAP categories (Table 1). Regarding neonatal complications (Additional file 1: Table S1), those with higher MAP (≥ 85 mmHg) had an increased risk compared to the lower MAP category (11.18% vs. 8.05%, a 17.3% increase). Within each MAP category, there was a slight upward trend in complications as FPG levels increased: for lower MAP (< 85 mmHg), approximately an 11% increase, and for higher MAP, approximately a 12.6% increase from the lowest to highest FPG tertile. Detailed information on neonatal complications across MAP and FPG categories is provided in Additional file 1: Table S1.

Association between mid-trimester BP and FPG levels

Linear regression analysis, with or without covariate adjustment, revealed positive correlations between FPG and MAP levels (Pearson $r = 0.149$; adjusted $\beta = 0.131$, P for Pearson $r < 0.001$, P for adjusted $\beta < 0.001$, Fig. 2A)

Table 1 Baseline characteristics and outcomes by baseline FPG within each category of baseline MAP

	MAP < 85 mmHg			MAP ≥ 85 mmHg			*P*
	FPG tertile 1 (≤ 76 mg/dL) *N* = 17,406	FPG tertile 2 (77–81 mg/dL) *N* = 15,353	FPG tertile 3 (≥ 82 mg/dL) *N* = 12,088	FPG tertile 1 (≤ 76 mg/dL) *N* = 3568	FPG tertile 2 (77–81 mg/dL) *N* = 3862	FPG tertile 3 (≥ 82 mg/dL) *N* = 4604	
Age, y	29.3 (4.1)	30.1 (4.2)	31.0 (4.3)	29.2 (4.2)	30.1 (4.4)	31.1 (4.7)	< 0.001
BMI at 20 weeks of gestation, kg/m^2	21.7 (2.5)	22.3 (2.6)	23.2 (2.8)	22.7 (3.2)	23.4 (3.2)	24.5 (3.5)	< 0.001
Primipara	10,427 (59.9%)	8164 (53.2%)	5574 (46.1%)	2278 (63.8%)	2278 (59.0%)	2411 (52.4%)	< 0.001
Gravidity							< 0.001
1	7656 (44.0%)	5750 (37.5%)	3726 (30.8%)	1595 (44.7%)	1529 (39.6%)	1506 (32.7%)	
2	5423 (31.2%)	5154 (33.6%)	4166 (34.5%)	1087 (30.5%)	1246 (32.3%)	1543 (33.5%)	
3	4327 (24.9%)	4449 (29.0%)	4196 (34.7%)	886 (24.8%)	1087 (28.1%)	1555 (33.8%)	
Medical history							
ART	726 (4.2%)	728 (4.7%)	666 (5.5%)	242 (6.8%)	277 (7.2%)	364 (7.9%)	< 0.001
Kidney diseases	383 (2.2%)	298 (1.9%)	260 (2.2%)	80 (2.2%)	102 (2.6%)	133 (2.9%)	0.002
PCOS	111 (0.6%)	95 (0.6%)	77 (0.6%)	35 (1.0%)	40 (1.0%)	53 (1.2%)	< 0.001
Other conditions	63 (0.4%)	44 (0.3%)	32 (0.3%)	17 (0.5%)	18 (0.5%)	16 (0.3%)	0.19
Medical conditions of the indexed pregnancy							
GDM	1522 (8.7%)	1813 (11.8%)	3418 (28.3%)	355 (9.9%)	549 (14.2%)	1665 (36.2%)	< 0.001
HDP	308 (1.8%)	318 (2.1%)	301 (2.5%)	420 (11.8%)	473 (12.2%)	736 (16.0%)	< 0.001
GH	136 (0.8%)	166 (1.1%)	146 (1.2%)	228 (6.4%)	272 (7.0%)	435 (9.4%)	< 0.001
PE	172 (1.0%)	152 (1.0%)	155 (1.3%)	192 (5.4%)	201 (5.2%)	301 (6.5%)	< 0.001
SGA	1827 (10.5%)	1174 (7.6%)	692 (5.7%)	459 (12.9%)	386 (10.0%)	373 (8.1%)	< 0.001
LGA	1539 (8.8%)	1875 (12.2%)	2301 (19.0%)	334 (9.4%)	486 (12.6%)	880 (19.1%)	< 0.001
Neonatal complications	1372 (7.9%)	1173 (7.6%)	1064 (8.8%)	369 (10.3%)	440 (11.4%)	536 (11.6%)	< 0.001

Values are mean ± SD or *n* (%)

Other conditions included systemic lupus erythematosus, antiphospholipid syndrome, and thrombotic diseases

For continuous variables that are normally distributed (e.g., age and BMI), we used one-way analysis of variance (ANOVA). For categorical variables, we applied Pearson's chi-square test

Abbreviations: BMI Body mass index, *ART* Assisted reproduction technology, *PCOS* Polycystic ovary syndrome, *GDM* Gestational diabetes mellitus, *HDP* Hypertensive disorders of pregnancy, *GH* Gestational hypertension, *PE* Preeclampsia, *SGA* Small for gestational age, *LGA* Large for gestational age

and between MAP and FPG levels (Pearson $r = 0.149$; adjusted $\beta = 0.093$, P for Pearson $r < 0.001$, P for adjusted $\beta < 0.001$, Fig. 2B). Linear regression provides only an average estimate, which can obscure important details in the relationship between MAP and FPG. To overcome this limitation, we applied quantile regression, a method that allows us to examine how the relationship between MAP and FPG varies across different quantiles of their distributions. Figure 2C shows that in the adjusted model, the positive association between FPG and MAP is quantile-dependent. As MAP levels increase across the distribution, the regression coefficient for FPG rises steadily, ranging from approximately 0.10 at the 0.05 quantile to around 0.15 at the 0.95 quantile. Figure 2D illustrates a quantile-dependent relationship between MAP and FPG levels in the adjusted model, where the regression coefficient for MAP increases more steeply as FPG levels exceed 0.50 quantile (~ 78 mg/dL). This suggests that the influence of MAP on FPG becomes more pronounced at higher glucose levels, further reinforcing the interdependent relationship between these two factors.

Interdependent associations between BP and FPG levels on risks for abnormal fetal growth

RCS analyses revealed non-linear positive associations between the levels of SBP and DBP and the risk for SGA, with the threshold values of > 120 mmHg and > 65 mmHg, respectively (Additional file 1: Fig. S1A and B). A similar pattern was observed for MAP, with a threshold value of > 85 mmHg for the increased SGA risk (Additional file 1: Fig. S1C). We also presented the corresponding OR estimates based on the cutoffs of BP (Table 2). Notably, FPG levels and SGA risk exhibited a non-linear negative association, without a clear inflection point (Additional file 1: Fig. S1D). Therefore, we set the reference point at 78 mg/dL (the median value), below which a steeper

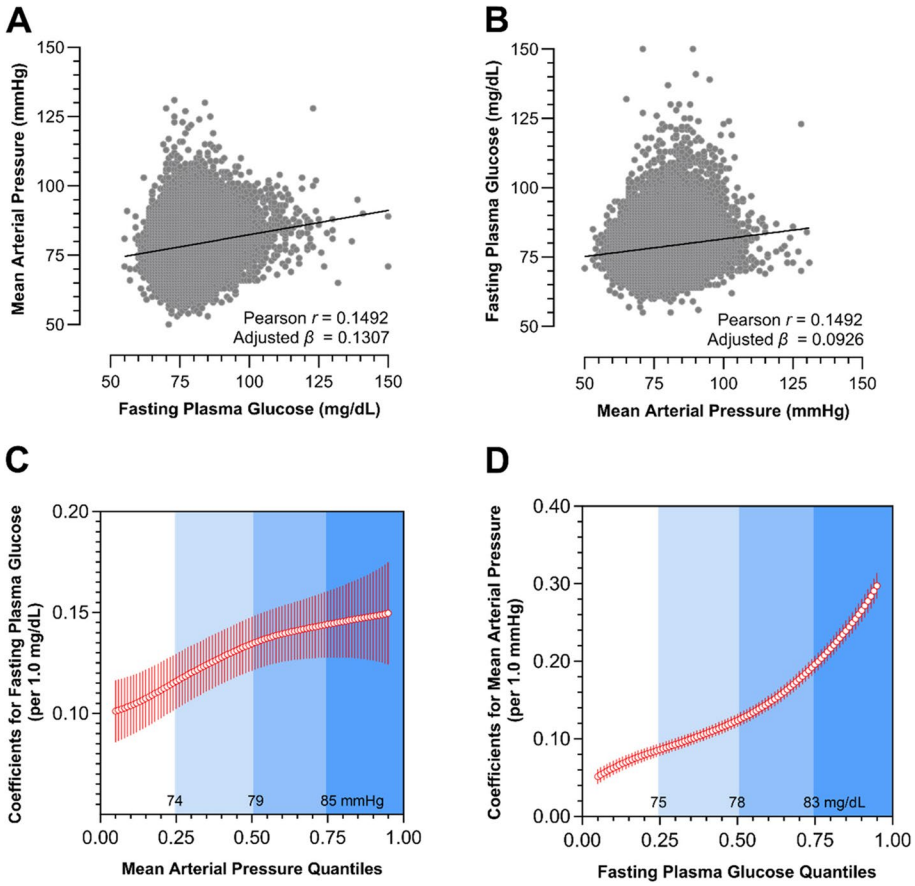


Fig. 2 Linear and quantile regression analyses between MAP and FPG. Pearson correlation analyses and multiple linear regression analyses after the adjustment of covariates [maternal age, BMI, parity, gravidity, polycystic ovary syndrome, kidney diseases, assisted reproductive technology, and other relatively rare conditions (systemic lupus erythematosus, antiphospholipid syndrome, thrombotic diseases)] **A** (*P* for Pearson $r < 0.001$, *P* for adjusted $\beta < 0.001$) and **B** (*P* for Pearson $r < 0.001$, *P* for adjusted $\beta < 0.001$). Quantile regression analyses showing the changes of coefficients for FPG (**C**) and MAP (**D**) from lower (0.05 quantile) to higher (0.95 quantile) quantiles of MAP and FPG, respectively, after covariate adjustment (mentioned above). Data are presented as estimated coefficients (red-circled dots) with 95% confidence intervals (vertical red lines) after Lowess smoothing

increase in the risk for SGA was observed (Additional file 1: Fig. S1D).

To explore the interdependent association between BP and FPG levels on the risk of abnormal growth, we first analyzed the relative risks of higher versus lower BP on SGA across the full spectrum of FPG levels. We used thresholds derived from RCS analysis, which had a significant impact on SGA risk, to convert SBP (≥120 mmHg vs. <120 mmHg), DBP (≥65 mmHg vs. <65 mmHg), and MAP (≥85 mmHg vs. <85 mmHg) from continuous to binary variables, representing higher versus lower BP levels. We then employed MFPI analysis to explore how these higher versus lower BP levels affect SGA risk across FPG levels. Before mutual adjustment for BP levels (i.e., DBP for SBP and SBP for DBP, Additional file 1: Fig. S2), both lower SBP and DBP were associated with a reduced risk of SGA, as long as FPG levels did not exceed their respective threshold values (92 mg/dL for SBP and 97 mg/dL for DBP). After adjusting for DBP, neither higher (≥120 mmHg) nor lower (<120 mmHg) SBP was associated with SGA risk across the full spectrum of FPG levels (Fig. 3A). Notably, after adjusting for SBP, higher DBP (≥65 mmHg) was consistently associated with an increased risk of SGA compared to lower DBP (<65 mmHg) when FPG levels were below 97 mg/dL (Fig. 3B). Furthermore, using MAP to account for the influence of both SBP and DBP, a similar risk pattern and FPG threshold were observed for individuals with higher MAP levels (Fig. 3C).

We next calculated the absolute risks for SGA in a matrix of FPG-BP combinations at 10 mmHg and 10 mg/dL interval. Figure 3D shows that after adjusting for DBP, the SBP-FPG combination revealed that only decreased FPG levels were associated with an increased risk of

Table 2 Multivariable-adjusted logistic models showing associations between BP (20–28 weeks) and SGA, LGA, and neonatal complications risk

Outcome	Exposure	*n/N*	Incidence rate	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
SGA	**SBP**						
	SBP < 120 mmHg	3898/45,267	8.61%	Reference		Reference	
	SBP ≥ 120 mmHg	1013/11,614	8.72%	1.01 (0.94–1.09)	0.704	1.19 (1.11–1.28)	< 0.001
	DBP						
	DBP < 65 mmHg	2817/35,759	7.88%	Reference		Reference	
	DBP ≥ 65 mmHg	2094/21,122	9.91%	1.29 (1.21–1.37)	< 0.001	1.40 (1.31–1.48)	< 0.001
	MAP						
	MAP < 85 mmHg	3693/44,847	8.23%	Reference		Reference	
	MAP ≥ 85 mmHg	1218/12,034	10.12%	1.25 (1.17–1.34)	< 0.001	1.45 (1.35–1.56)	< 0.001
LGA	**SBP**						
	SBP < 120 mmHg	5704/45,267	12.60%	Reference		Reference	
	SBP ≥ 120 mmHg	1711/11,614	14.73%	1.17 (1.11–1.25)	< 0.001	1.12 (1.05–1.19)	< 0.001
	DBP						
	DBP < 65 mmHg	4600/35,759	12.86%	Reference		Reference	
	DBP ≥ 65 mmHg	2815/21,122	13.33%	1.03 (0.98–1.08)	0.267	1.00 (0.95–1.06)	0.904
	MAP						
	MAP < 85 mmHg	5715/44,847	12.74%	Reference		Reference	
	MAP ≥ 85 mmHg	1700/12,034	14.13%	1.11 (1.04–1.17)	0.001	1.05 (0.99–1.12)	0.115
Neonatal complications	**SBP**						
	SBP < 120 mmHg	3703/45,267	8.18%	Reference		Reference	
	SBP ≥ 120 mmHg	1251/11,614	10.77%	1.35 (1.27–1.45)	< 0.001	1.27 (1.19–1.36)	< 0.001
	DBP						
	DBP < 65 mmHg	2801/35,759	7.83%	Reference		Reference	
	DBP ≥ 65 mmHg	2153/21,122	10.19%	1.34 (1.26–1.42)	< 0.001	1.27 (1.20–1.35)	< 0.001
	MAP						
	MAP < 85 mmHg	3609/44,847	8.05%	Reference		Reference	
	MAP ≥ 85 mmHg	1345/12,034	11.18%	1.44 (1.35–1.54)	< 0.001	1.35 (1.26–1.44)	< 0.001

Covariates are as in Fig. 2

Abbreviations: *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *MAP* Mean arterial pressure, *SGA* Small for gestational age, *LGA* Large for gestational age

SGA (SBP *P* for trend = 0.376; FPG *P* for trend < 0.001). In Fig. 3E and F, the highest absolute risks for SGA were concentrated in the upper left corner of the heatmaps, where DBP/MAP levels were highest and FPG levels were lowest. Conversely, the lowest risks were observed in the lower right corner, where DBP/MAP levels were lowest and FPG levels were highest. Additionally, the lower left and upper right corners exhibited similar risk levels, indicating that both low BP/low FPG and high BP/high FPG combinations were associated with comparable SGA risk.

In contrast to the FPG-BP and SGA relationship, the RCS curves revealed no threshold effect of BP levels on LGA risk (Additional file 1: Fig. S3). Similarly, before adjusting for covariates, higher BP was associated with an increased risk of LGA. However, after adjusting for covariates, BP was no longer associated with the risk of LGA (Table 2). MFPI analysis further confirmed that no clear benefit of higher vs. lower BP across the full spectrum of FPG levels (Additional file 1: Fig. S4). Additionally, the heatmaps of FPG-BP combinations and LGA risk revealed no significant association between BP levels and LGA, with LGA risk being largely dependent on FPG levels (Additional file 1: Fig. S5).

Associations of the levels of BP and FPG, and neonatal complications

RCS analyses revealed linear positive associations of SBP and DBP with the risks of neonatal complications (Additional file 1: Fig. S6A and B). Additionally, a non-linear positive association was observed between MAP levels and the risk of neonatal complications, though no clear inflection point was identified (Additional file 1: Fig. S6C). Notably, FPG levels exhibited a non-linear, J-shaped positive association with the risk of neonatal

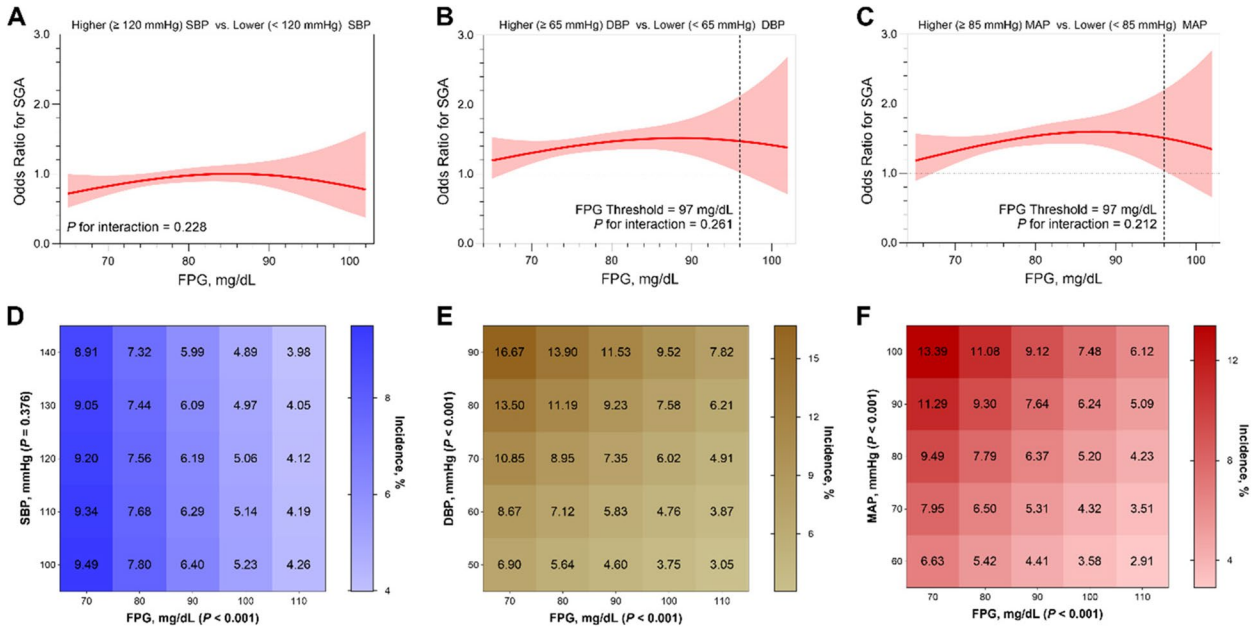


Fig. 3 The interdependent impact of BP and glucose on SGA risk. **A** (SBP, adjusted for DBP), **B** (DBP, adjusted for SBP), and **C** (MAP) show the effect of higher vs. lower BP on SGA risk across the FPG spectrum using multivariable fractional polynomial interaction analysis. Red lines represent odds ratios with 95% confidence intervals; the dotted line at Y = 1.0 indicates no change in odds ratio. Covariates are as in Fig. 2. **D**, **E**, and **F** show heatmaps of SBP-FPG, DBP-FPG, and MAP-FPG combinations, respectively, displaying absolute SGA risk at 10 mmHg/10 mg/dL intervals. Numbers in each square represent absolute risk, derived from logistic regression models with covariate adjustment (Fig. 2)

complications, with a threshold of 85 mg/dL, above which the risk significantly increased (Additional file 1: Fig. S6D). Using MFPI analysis and adjusting for DBP, there was no clear benefit of higher (≥120 mmHg) vs. lower (<120 mmHg) SBP across the full spectrum of FPG levels in terms of neonatal complications (Fig. 4A). This finding is further supported by the heatmaps of FPG-SBP combinations (Fig. 4D). However, higher levels of DBP (≥65 mmHg) and MAP (≥85 mmHg) were consistently associated with increased risks of neonatal complications. The heatmap of FPG-DBP combinations and neonatal complication risks (Fig. 4E) revealed an approximately 45% reduction in absolute risk as DBP decreased from 90 to 50 mmHg (12.05 to 6.62% for FPG at 70 mg/dL category; 14.29 to 7.94% for FPG at 110 mg/dL category) across all FPG categories. In contrast, only about a 16% reduction in absolute risk was observed as FPG decreased from 110 to 70 mg/dL (7.95 to 6.62% for DBP at 50 mmHg category; 14.29 to 12.05% for DBP at 90 mmHg category). Neonatal complications decreased by approximately 47% as MAP declined from the highest to lowest category, and by about 17% with decreasing glucose levels (Fig. 4F).

Sensitivity analyses

We first examined the relative risks of higher versus lower MAP on neonatal complications and SGA across the FPG levels (Additional file 1: Fig. S7), as well as the absolute risk for neonatal complications in the heatmap of FPG-BP combinations, after excluding preterm deliveries and in a separate analysis including only preterm deliveries (Additional file 1: Fig. S8). These results were generally consistent with the main findings (Figs. 3 and 4). In analyses where HDP/preeclampsia was used as an exposure instead of BP levels, similar risk patterns for SGA and neonatal complications were observed (Additional file 1: Fig. S9). Notably, in individuals with HDP or preeclampsia, the continuous exacerbation of risks for SGA and composite neonatal complications as FPG levels decrease suggests an aggravating effect of low glucose levels in the presence of hypertensive disorders. In quantile regression analyses of BP parameters and birth weight, SBP was not associated with birth weight in the upper quantiles (>0.75 quantile), which correspond to LGA outcome (>0.9 quantile). Moreover, both DBP and MAP demonstrated consistent negative associations with birth weight after glucose adjustment (Additional file 1: Fig. S10).

Discussion

Maternal BP and glucose levels are typically managed independently according to current clinical guidelines. However, our study demonstrates the interdependent relationship between maternal BP and glucose levels,

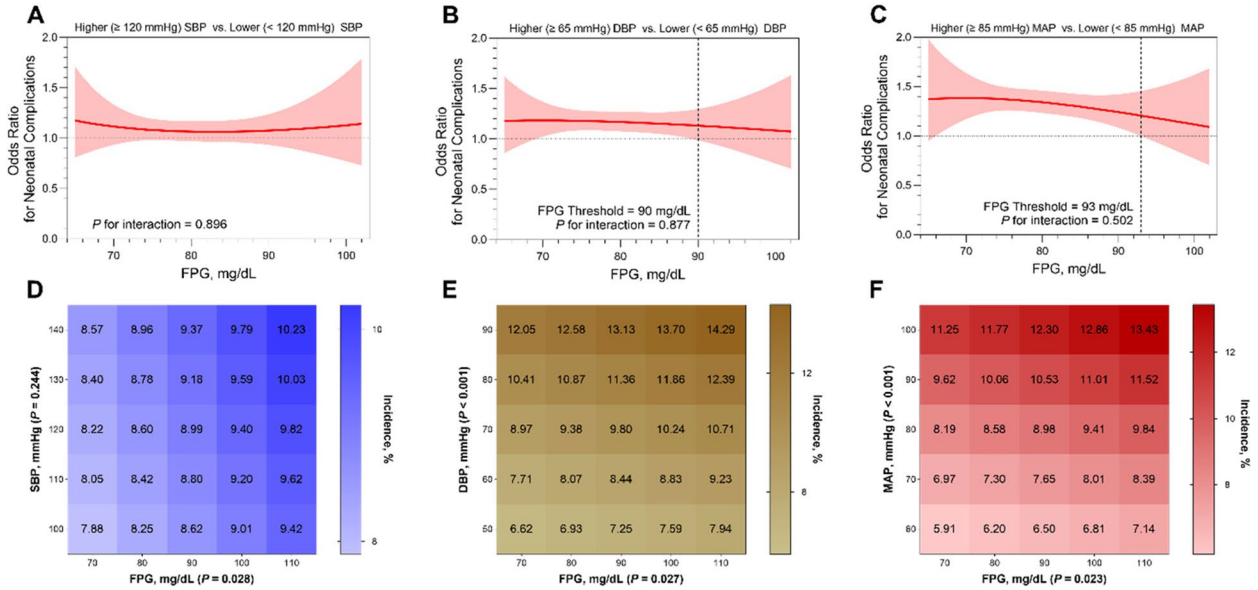


Fig. 4 The interdependent impact of BP and glucose on neonatal complication risk. **A** (SBP, after adjusting for DBP), **B** (DBP, after adjusting for SBP), and **C** (MAP) show the effect of higher vs. lower BP on neonatal complications across FPG levels using multivariable fractional polynomial interaction analysis. Red lines represent odds ratios with 95% confidence intervals, and the dotted line at Y = 1.0 indicates no change in risk. Covariates are as in Fig. 2. **D**, **E**, and **F** show heatmaps of SBP-FPG, DBP-FPG, and MAP-FPG combinations, respectively, displaying absolute neonatal complication risk at 10 mmHg/10 mg/dL intervals. Numbers in each square indicate absolute risk, derived from logistic regression models with covariate adjustment (Fig. 2)

highlighting their combined influence on fetal growth and neonatal outcomes. Using data from a large pregnancy cohort in China, we simultaneously analyzed mid-trimester BP and FPG levels, resulting in three novel findings. First, we uncovered a complex relationship between maternal BP and glucose, with quantile regression revealing consistent positive correlations between BP (MAP) and glucose, and a steeper increase in their association at higher glucose levels. Second, we identified the interdependent effect of BP and glucose on SGA risk. MAP above 85 mmHg was linked to a higher risk of SGA, while FPG exhibited a non-linear negative association. The highest SGA risk was observed with high MAP (≥ 85 mmHg)/low FPG (< 85 mg/dL) combinations, and the lowest risk with low MAP (< 85 mmHg)/high FPG (≥ 85 mg/dL), with equivalent risk at high MAP/high FPG and low MAP/low FPG combinations. In contrast, LGA risk was driven mainly by glucose levels, without a significant role for BP. Third, we demonstrated the combined effect of BP and glucose on neonatal complications. Neonatal complications decreased by approximately 47% as MAP declined from the highest to lowest category, and by about 17% with decreasing glucose levels. Taken together, these findings highlight the interdependent impact of BP and glucose on fetal growth. The stronger association between BP and glucose at higher glucose levels, along with BP's greater influence on neonatal complications, emphasizes the need for an integrated management approach during pregnancy.

Unlike traditional linear regression, which estimates the effect of an independent variable on the mean of the dependent variable, quantile regression estimates the effect across different quantiles (e.g., the 0.05, 0.5, and 0.95 quantiles). This approach is particularly useful for uncovering relationships that vary across the distribution, such as stronger effects at the extremes compared to the middle. By employing this method, we can capture the complex relationship between BP and glucose levels. MAP, representing organ-level perfusion (including placental perfusion), incorporates both SBP and DBP and serves as a key maternal factor in preeclampsia prediction [29, 30]. As such, it is an optimal surrogate marker for assessing the impact of BP changes on fetal growth. Although the overall Pearson correlation ($r = 0.149$) between MAP and glucose is often considered "weak," our quantile regression analyses revealed notably steeper MAP coefficients at higher glucose quantiles (e.g., the 0.75 quantile), where a 1 mmHg increase in MAP was associated with approximately a 0.3 mg/dL rise in glucose. This indicates that even a modest global correlation may have clinically relevant implications among individuals with elevated glucose levels, suggesting the potential benefits of co-managing both BP and glycemia. In our analysis, although the steeper rise in MAP coefficients at

higher glucose levels does not suggest a direct causal role of elevated MAP in increasing glucose, it indicates that higher glucose levels may be more strongly influenced by elevated BP. In support of this, a previous study showed that high BP before and during early pregnancy is associated with an increased risk of GDM [31]. Therefore, it is of great interest to explore in future studies what impact BP-lowering therapy will have on glucose levels in GDM patients.

Our heatmaps of BP/glucose combinations revealed distinct SGA risk patterns, with the highest risk at high MAP/low FPG and the lowest at low MAP/high FPG. Although GDM is typically linked to the development of LGA, recent studies showed that 6 to 7% of infants born to mothers with GDM are actually SGA [32, 33]. In GDM patients, neonatal complications were more frequent in the SGA infants than in the appropriate-for-gestational age or LGA infants [34]. This risk is linked to higher rates of hypertensive disorders [35], lower FPG levels [36], and episodes of hypoglycemia [32]. Consistent with our findings, this evidence suggests that inadequate BP control, along with low glucose levels, potentially due to overtreatment of GDM, are key risk factors contributing to the increased likelihood of SGA. Moreover, our findings demonstrated a consistent increase in SGA risk among HDP and preeclamptic patients as FPG levels decreased. This aligns with the heatmaps for SGA risk, which revealed coupled changes in BP and glucose levels influencing the risk pattern for SGA. These results emphasize that strict glucose control, particularly in the presence of hypertensive disorders or poorly controlled BP, is associated with worsening fetal growth.

Current criteria in China to diagnose GDM (FPG ≥ 92 mg/dL or 5.1 mmol/L) are mainly based on the HAPO study, which showed that there is no single glycemic threshold for adverse pregnancy outcomes, but rather a continuous relationship with maternal hyperglycemia. The IADPSG took the decision to set the thresholds for GDM diagnosis at 1.75 the odds for complications (relating to birth weight) compared with the mean value [37]. As a result, the expert consensus on lowering glycemic threshold standards aims to prevent as many pregnancy complications as possible [16, 38]. However, recent studies either using a two-step screening strategy [9] or adopting a higher criteria for GDM diagnosis (FPG ≥ 99 mg/dL or 5.5 mmol/L) [10] did not show significant differences in either perinatal or maternal complications between two groups. Our findings align with recent evidence showing that from the lowest to highest FPG categories, the relative risk for neonatal complications increased by only about 20% within each BP category. Notably, our heatmaps revealed an approximately 80% increase in neonatal complications from the lowest to highest BP categories within each glucose category. This suggests that strict control of BP levels may have more favorable impact on the reduction of neonatal complications as compared with glucose control. GDM management aims primarily to prevent fetal overgrowth (LGA) during pregnancy, which is strongly linked to maternal hyperglycemia. Our findings suggest that a fetal growth-based strategy can complement existing GDM management guidelines, especially in cases where LGA risk is evident. Heatmap analyses reveal that glucose levels are the primary determinant of LGA, while BP levels have a limited role in influencing fetal overgrowth. This strategy reinforces the need for tailored glucose control, particularly in pregnancies demonstrating signs of fetal overgrowth, to optimize outcomes for both mother and child. Thus, this evidence supports the idea that GDM management based on fetal growth, rather than a universal strict glycemic criterion, may improve pregnancy outcomes [39]. Current practicing guidelines to improve pregnancy outcomes, however, often focus on glucose and BP management independently. The consensus on BP management during pregnancy advocates for strict control [15]. However, there is considerable variability in glucose management across countries, with high diagnosis rates of GDM being particularly common in countries adopting one-step screening strategy [9]. Given the close relationship between glucose and BP levels during pregnancy, future studies should test the hypothesis that a tailored FPG target, specifically for those with well-controlled BP, may reduce SGA risk and improve preeclampsia-related outcomes. Since LGA is mainly dependent on glucose levels, we propose the following framework for integrated management of maternal hypertension and hyperglycemia: tailored management strategies should consider prioritizing BP control in cases where elevated BP poses significant risks, while ensuring that glucose levels are adequately managed to mitigate the risk of LGA and neonatal complications. We propose that the possible biological mechanism is that the elevation in maternal plasma glucose levels are acting as a compensatory response to fetal growth restriction caused by HDP. There are of course many factors apart from BP and glucose control affecting fetal growth and neonatal complications, including the risk factor common to both HDP and GDM of increased maternal BMI; however, this is not readily modifiable during pregnancy and despite major research and clinical efforts on weight management in pregnancy has shown very modest impact on pregnancy outcomes [40]. This framework may offer a clinically feasible approach to preventing fetal growth abnormalities and neonatal complications.

In this study, we included a representative cohort from a leading high-volume maternity and child health

hospital in China, which captured a full spectrum of pregnancies with diverse and general characteristics, adding robustness to the findings. The present study had the following limitations. Firstly, as an observational study, this study did not collect data on certain covariates, including gestational weight gain, household income, and education level, which may influence the observed associations. Moreover, we cannot establish the casual link of interactions between maternal glucose and BP levels and the risk for SGA and neonatal complications, which should be regarded as hypothesis generating. Future studies should consider incorporating these factors to provide a more comprehensive understanding of the interplay between maternal characteristics and pregnancy outcomes. Secondly, the duration of participant enrollment in the Guangzhou cohort spanned a 10-year period, during which the treatment strategy may be updated according to the state-of-art guidelines. However, major breakthroughs in the diagnosis and treatment of HDP and GDM occurred during the past 2 years [9, 10, 15], which have not been translated into clinical practice by the end of 2022. Therefore, the clinical outcomes in our cohorts would be less likely affected during the past 10 years. Thirdly, our cohorts were all based on the Chinese population. External validation studies from other populations are needed to confirm these findings.

Conclusions

Based on a large pregnancy cohort in China, this study revealed an interdependent association between maternal BP and glucose levels and their combined impact on the risk of SGA. It provided quantitative evidence of how this interdependence shapes the transition of risk patterns for SGA, neonatal complications, and LGA. These findings underscore the need for an integrated approach to co-managing BP and glucose levels during pregnancy. Tailored management strategies should consider prioritizing BP control in cases where elevated BP poses significant risks, while ensuring that glucose levels are adequately managed to mitigate the risk of LGA and neonatal complications.

Abbreviations

SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
FPG	Fasting plasma glucose
BMI	Body mass index
SGA	Small for gestational age infants
LGA	Large for gestational age infants
HDP	Hypertensive disorders of pregnancy
GH	Gestational hypertension
PE	Preeclampsia
GDM	Gestational diabetes mellitus
IADPSG	The International Association of Diabetes and Pregnancy Study Group
CHIPS	Control of Hypertension in Pregnancy Study
CHAP	Chronic Hypertension and Pregnancy Trial

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03990-7.

Additional file 1: Additional Methods. Figures S1–S10. Table S1. Fig. S1 Restricted cubic splines in multivariable-adjusted logistic models showing the associations between BP and FPG measured between 20 and 28 weeks of gestation, and risk for SGA infants. Fig. S2 Impact of higher BP versus lower BP on SGA risk according to a full spectrum of FPG levels. Fig. S3 Restricted cubic splines in multivariable-adjusted logistic models showing the associations between BP and FPG measured between 20 and 28 weeks of gestation, and risk for LGA infants. Fig. S4 Impact of higher BP versus lower BP on LGA according to a full spectrum of FPG levels. Fig. S5 Two-dimensional heatmaps showing the absolute risk of LGA in relationships to BP-FPG with scales of 10 mmHg/10 mg/dL intervals. Fig. S6 Restricted cubic splines in multivariable-adjusted logistic models showing associations between BP and FPG measured between 20 and 28 weeks of gestation, and risk for neonatal complications. Fig. S7 Impact of higher BP versus lower BP on neonatal complications/preterm delivery according to a full spectrum of FPG levels. Fig. S8 Two-dimensional heatmaps showing the absolute risk of neonatal complications/preterm delivery in relationships to BP-FPG with scales of 10 mmHg/10 mg/dL intervals. Fig. S9 HDP versus non-HDP, PE versus non-PE on SGA and neonatal complications according to a full spectrum of FPG levels. Fig. S10 Quantile regression analyses of BP parameters and birth weight. Table S1 Detailed neonatal complications by baseline FPG tertile within each category of baseline MAP

Acknowledgements

The authors would like to thank the staff of the Guangdong Women and Children Hospital Data Platform for their contributions to data extraction and preparation.

Authors' contributions

X.Z., A.Y., L.Lv., and C.H2. participated in the study concept and design. X.Z., L.Lv., A.H., A.Y., C.H2., T.L., J.Y. participated in the interpretation of the results and critical revision of the manuscript. X.Z., and J.Y. drafted the manuscript. J.Y., L.L., C.H1., H.S., Y.F., L.Z., performed the statistical analysis. Q.Y., H.D., J.W., and C.H2. contributed to the data collection and data management. J.Y., C.H1., H.S., Y.F., and L.Z., contributed to the data cleaning and data preprocessing. X.Z., A.Y. and C.H2. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Funding

National Natural Science Foundation of China (72274133, 82321001, 82071674), Guangdong Basic and Applied Basic Research Foundation (2019A1515110389), Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-069C).

Data availability

The data and analytic methods will be made available for onsite audits by third parties for the purposes of reproducing the results or replicating the procedure.

Declarations

Ethics approval and consent to participate

This study complies with the Declaration of Helsinki and was approved by the Ethics Committees of Guangdong Women and Children Hospital (202301105). Informed consent was waived due to the retrospective nature.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 9 October 2024 Accepted: 6 March 2025
Published online: 14 March 2025

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