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ORIGINAL RESEARCH

Blood Pressure Levels During Pregnancy and Gestational Diabetes Mellitus: A Prospective Cohort Study and Mendelian Randomization Analysis

Meng Yang[1,*], Zhongqiang Cao[1,*], Hong Mei[1], Liqin Hu[1], Wanting Zhu[2], Jieqiong Zhou[2], Jiuying Liu[2], Yuanyuan Zhong[2], Yan Zhou[2], Xiaoyuan Feng[3], Feiyan Xiang[1], Han Xiao[1], Aifen Zhou[1]

[1]Institute of Maternal and Child Health, Wuhan Children's Hospital (Wuhan Maternal and Child Health Care Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; [2]Department of Obstetrics, Wuhan Children's Hospital (Wuhan Maternal and Child Health Care Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; [3]Department of Echocardiography, Wuhan Children's Hospital (Wuhan Maternal and Child Health Care Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Aifen Zhou; Han Xiao, Institute of Maternal and Child Health, Wuhan Children's Hospital (Wuhan Maternal and Child Health Care Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430000, People's Republic of China, Email april1972@163.com; tjxiaohan1980@163.com

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Background: We aimed to investigate the association and causality between blood pressure (BP) during pregnancy and gestational diabetes mellitus (GDM).

Methods: In a Chinese birth cohort study, 5,952 participants with repeated measurements of BP were included. Logistic regression models were used to estimate the associations between BP and BP trajectories with the risk of GDM. Polygenic risk scores (PRS) were used in a one-sample Mendelian randomization (MR) analysis conducted on a subset of the cohort. Linkage disequilibrium score regression and a two-sample MR analysis were performed to explore genetic correlation and causal relationship between BP and GDM in both Europeans and East Asians.

Results: Elevated first and mean systolic blood pressure (SBP) during pregnancy were both associated with an increased risk of GDM. Individuals with a High-stable SBP trajectory throughout pregnancy had a higher risk of GDM (OR, 1.43[95% CI, 1.07–1.88]) compared to those with a low-stable SBP trajectory. The top quintile of genetically predicted SBP was associated with an increased risk of GDM compared to the lowest quintile (OR, 1.54[95% CI, 1.05–2.27]). A modest genetic correlation between SBP and GDM was observed in Europeans (r_g=0.12, p=0.0002). The MR analysis provided consistent evidence for a causal effect of SBP on GDM in Europeans (OR, 1.42[95% CI, 1.12–1.82]).

Conclusion: Our findings highlight the crucial role of elevated SBP in the development of GDM. Further genetic correlation and MR studies provide compelling evidence suggesting a potential causal relationship, thereby enhancing our understanding of the etiology of GDM.

Keywords: blood pressure, gestational diabetes mellitus, shared genetics, Mendelian randomization

Introduction

Gestational diabetes mellitus (GDM) is an increasingly prevalent medical disorder, characterized by impaired glucose tolerance (hyperglycemia) during pregnancy, affecting approximately 14% of all pregnancies worldwide.[1–3] GDM has long been associated with obstetric and neonatal complications, and it is gradually being recognized as a risk factor for future cardiometabolic disease in both mothers and their offspring.[4–6] Given the lack of effective treatments, identifying modifiable risk factors is of great significance to delay onset or reduce the risk for incident GDM. Hypertension before

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and during early pregnancy has been associated with the risk of GDM.[7,8] However, previous studies failed to capture the dynamic changes in blood pressure (BP) during pregnancy as they have only assessed BP at a single time point. Hence, the longitudinal associations of BP with subsequent risk of GDM are unclear. In addition, the association may be influenced by unidentified confounding factors shared by both traits (ie, residual confounding) or by the possibility that elevated BP could be a consequence of GDM preceding overt clinical symptoms (ie, reverse causation). Therefore, it is crucial to further investigate whether the observed association is causal.

The emergence of genome-wide association studies (GWAS) in the past two decades has facilitated the development of methods that utilize GWAS summary statistics to examine the shared genetic architecture between different traits. One such method is GWAS-based linkage disequilibrium score regression (LDSC), which allows for the estimation of genetic correlations at the level of single-nucleotide polymorphism (SNP) between traits.[9,10] Mendelian randomization (MR) is another approach that employs genetic variants as instrument variables to assess potential causal relationships between traits. By simulating the random assignment process in randomized controlled trials, MR helps address concerns regarding residual confounding and reverse causation.[11,12] Additionally, the availability of large-scale biobanks such as the United Kingdom Biobank (UKB) and Japan Biobank (BBJ), which encompass diverse ethnicities, has provided opportunities to investigate genetic heterogeneity across different racial groups.

The present study aimed to investigate the associations between specific BP indicators, including the first BP, mean BP and BP trajectories during pregnancy, and the subsequent risk of GDM in a large population-based cohort. To validate the associations between BP and GDM, a one-sample MR analysis was conducted using polygenic risk scores (PRS) based on a subset of cohort data. Furthermore, using publicly available GWAS summary statistics data, LDSC and two-sample MR analyses were employed to explore potential causal relationships between BP and GDM in Europeans and East Asians.

Methods

Study Population

This study is based on a prospective birth cohort conducted at Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), as previously documented.[13,14] Women diagnosed with pre-existing diabetes or with diabetes in pregnancy according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria were excluded. Participant selection for the current study is depicted in Figure 1. The final analysis included 5,952 eligible women who had undergone at least one BP measurement during early pregnancy (<24 weeks). Table S1 presents information on the number and proportions of pregnant women who underwent BP assessments during different gestational periods, as well as the number of measurements conducted per woman. The difference between enrolled and non-enrolled participants are provided in Table S2.

BP Measurements and BP Trajectories

The first BP measurement refers to the BP obtained during the participant's initial clinical visit between 7 to 24 weeks of gestation. Mean BP was calculated as the average of multiple BP measurements taken from the participant during their prenatal visits between 7–24 weeks of pregnancy. Maternal hypertension was defined as BP >140/90 mmHg at enrollment (first study visit). Group-based trajectory modeling (GBTM) is a specific type of finite mixture modeling that assumes the presence of distinct subgroups within a population that exhibit similar trajectories over time.[15–18] In this study, GBTM was utilized to analyze and characterize the patterns of BP trajectories between 7 and 24 weeks of gestation. Detailed information on BP measurements and GBTM is provided in the Supplemental Methods.

Ascertainment of GDM and Its Subtypes

The study participants underwent universal testing for GDM using an OGTT between 24 and 28 weeks of gestation. The diagnostic criteria for GDM were based on the recommendations by the IADPSG. These criteria include a fasting plasma glucose (FPG) of ≥5.1 mmol/L, or 1-hour post-load plasma glucose (1hPG) of ≥10.0 mmol/L, or 2-hour post-load plasma glucose (2hPG) of ≥8.5 mmol/L.[19] Normal glucose tolerance (NGT) was defined as FPG <5.11 mmol/l, 1hPG

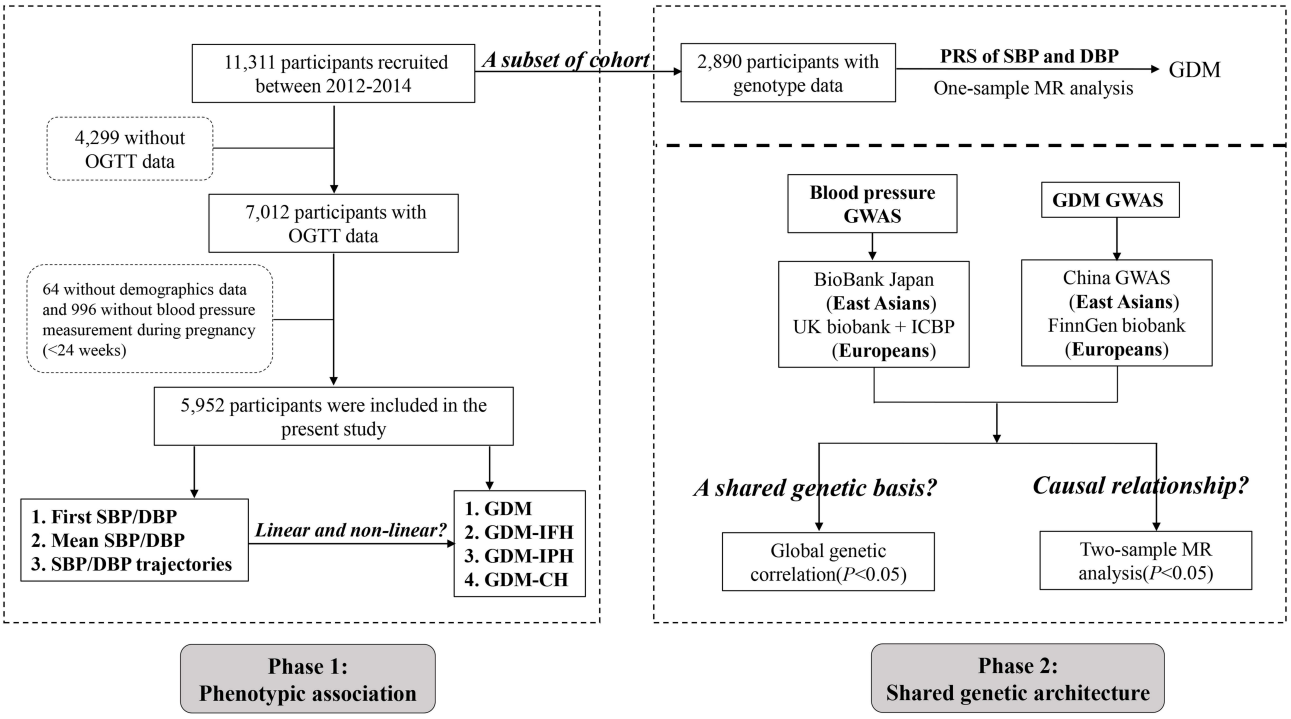

Figure 1 Flowchart of the overall study design.

<10.00 mmol/l and 2hPG <8.50 mmol/l. As described in the Supplemental Methods, participants diagnosed with GDM were further categorized into three subtypes:[20] isolated fasting hyperglycemia (GDM-IFH) group, isolated post-load hyperglycemia (GDM-IPH) group, and combined hyperglycemia (GDM-CH) group.

Covariates

At baseline, participants completed a structured questionnaire that included demographic and lifestyle factors. These factors included maternal age, educational level (≤9/10-12/13-15/≥16 schooling years), physical activity (Never or rarely, 1–2 days/week, 3–4 days/week, 5–6 days/week, 7 days/week), active or passive smoking (yes/no), multiparity (yes/no), gravidity (1/2/≥2), and family history of diabetes (yes/no). Pre-pregnancy BMI was calculated using self-reported weight and height. Maternal weight gain during pregnancy was calculated using the participant's weight at the time of GDM diagnosis minus their self-reported pre-pregnancy weight. Information on the number of prenatal visits throughout the entire pregnancy was obtained from the Maternal and Child Information System.

Genotyping and Calculation of PRS

Genotype data were collected from a subset of 2,890 pregnant women selected from our birth cohort. These data were obtained from peripheral venous blood samples during non-invasive prenatal testing (NIPT) screening.[21] Quality control of genetic data is described in the Supplemental Methods. Genotype dosages were utilized to compute PRS for systolic blood pressure (SBP) and diastolic blood pressure (DBP). The conduction of PRS was based on GWAS summary statistics from a meta-analysis conducted in China.[22] Genetic risk score analyses is described in the Supplemental Methods.

GWAS Datasets

The source of GWAS data on BP and GDM for two-sample MR analysis in the East Asian and European populations are detailed in the Supplemental Methods.

Sample Size Calculation

This study included 5,952 pregnant women (820 GDM cases, 13.8%), which provided adequate power (>80%) to detect an odds ratio (OR) of approximately 1.15–1.20 per 1-SD increase in systolic blood pressure at a two-sided $\alpha = 0.05$. The events-per-variable ratio exceeded 40, indicating sufficient model stability.

Statistical Analysis

Prospective Cohort Study Analysis

We initially described the baseline characteristics of participants based on GDM status. Continuous variables were compared using t-tests, while categorical variables were compared using chi-square tests. Next, we conducted multivariate adjusted logistic regression analyses to estimate ORs for the association between BP and the risks of GDM and its subtypes. Two forms of BP were considered: the first visit BP and the mean BP between 7–24 weeks of gestation. In the logistic regression models, we included SBP and DBP as both continuous variables (to estimate the effect size per 10 mmHg increase) and categorical variables (to estimate the effect size per tertile increase). Meanwhile, BP trajectories were derived using GBTM with a Stata plugin program (Stata Proc Traj), which enabled us to examine the associations of dynamic changes in BP and the risks of GDM and its subtypes. All models were adjusted for aforementioned covariates. Restricted cubic splines (RCS) and sensitivity analyses were performed as specified in the Supplemental Methods.

Individual-Level Data MR Analysis Using PRS

The unpaired two-sample Wilcoxon test was employed to compare the PRS for BP between GDM cases and controls. Logistic regression analysis was then conducted to examine the associations between BP PRS and the risk of GDM in the subset of cohort data. The risk of GDM was estimated across equal strata of increasing PRS by calculating OR relative to the first quintile.

Genetic Correlation and Two-Sample MR Analysis

To investigate the shared genetic components between BP and GDM, we employed LDSC to estimate their global genetic correlation. Two sample MR analyses were conducted using "TwoSampleMR" R package in the East Asian and European populations. Detailed methods are provided in the Supplemental Methods.

The MR analysis followed the STROBE-MR reporting guideline. All statistical analyses were performed using Stata 15.0 and R 4.1.0. Two-side *p* values of less than 0.05 were considered statistically significant.

Results

Characteristics of the Study Population

Among the 5,952 participants in the study, their ages ranged from 18 to 50 years with a mean age of 28.49±3.40 years. Approximately 21.5% of the women reported exposure to active or passive smoking during pregnancy. In total, 820 pregnancies were affected by GDM (13.8%). Compared with NGT women, those diagnosed with GDM tended to be older and multiparous, and have a higher pre-pregnancy BMI and frequency of prenatal visits (Table 1).

Association Between First and Mean BP During Pregnancy with GDM

After controlling for potential confounders, each 10 mmHg increase in the first SBP was significantly associated with an increased risk of GDM (adjusted OR, 1.11[95% CI, 1.04–1.19]), GDM-IPH (adjusted OR, 1.11[95% CI, 1.01–1.21]) and GDM-CH (adjusted OR, 1.18[95% CI, 1.02–1.38]). Additionally, when exploring tertiles of BP, the highest tertile of the first SBP showed significant associations with increased risks of GDM (adjusted OR, 1.37[95% CI, 1.14–1.66]), GDM-IFH (adjusted OR, 1.40[95% CI, 1.01–1.94]) and GDM-CH (adjusted OR, 1.60[95% CI, 1.04–2.47]). Notably, the second tertile of the first SBP also exhibited a significant association with an increased risk of GDM-IFH (adjusted OR, 1.45[95% CI, 1.05–2.01]). However, the first DBP did not show any significant associations with the risk of GDM or its subtypes (Table 2). Similarly, statistically significant associations were observed between elevated mean SBP and increased risks of GDM and its subtypes (Table S3).

Table 1 Baseline Characteristics of the Study Population

Characteristic	Total (N=5,952)	GDM (N=820)	NGT (N=5,132)	*p* value
Maternal age (year)	28.49±3.40	29.58±3.76	28.32±3.31	<0.001
Prepregnancy BMI (kg/m^2), %				<0.001
<18.5	1261 (21.2)	115 (14.0)	1146 (22.3)	
18.5–24	3961 (66.5)	536 (65.4)	3425 (66.7)	
24-28	629 (10.6)	144 (17.6)	485 (9.5)	
>28	101 (1.7)	25 (3.0)	76 (1.5)	
Education level (schooling years), %				0.004
≤9	490 (8.2)	92 (11.2)	398 (7.8)	
10-12	1013 (17.0)	150 (18.3)	863 (16.8)	
13-15	4118 (69.2)	536 (65.4)	3582 (69.8)	
≥16	331 (5.6)	42 (5.1)	289 (5.6)	
Active or passive smoking (yes), %	1278 (21.5)	172 (21.0)	1106 (21.6)	0.744
Gestational weight gain (~24 week) (kg)	17.33±4.92	17.42±4.86	16.74±5.25	<0.001
Multiparity (yes), %	548 (9.2)	118 (14.4)	430 (8.4)	<0.001
Gravidity, %				<0.001
=1	3491 (58.7)	398 (48.5)	3093 (60.3)	
=2	1446 (24.3)	221 (27.0)	1225 (23.9)	
>2	1015 (17.1)	201 (24.5)	814 (15.9)	
Physical activity during pregnancy, %				0.554
Never or rarely	625 (10.5)	82 (10.0)	543 (10.6)	
1-2 days/week	545 (9.2)	67 (8.2)	478 (9.3)	
3-4 days/week	448 (7.5)	71 (8.7)	377 (7.3)	
5-6 days/week	96 (1.6)	12 (1.5)	84 (1.6)	
7 days/week	4238 (71.2)	588 (71.7)	3650 (71.1)	
Fasting glucose (mmol/L)	4.44±0.49	5.00±0.80	4.35±0.35	<0.001
OGTT1-h (mmol/L)	7.26±1.63	9.29±1.87	6.93±1.32	<0.001
OGTT2-h (mmol/L)	6.48±1.29	8.13±1.61	6.22±1.01	<0.001
Family history of diabetes, %	125 (2.1)	29 (3.5)	96 (1.9)	0.003
Number of visits during overall pregnancy, %				0.043
=5	665 (11.2)	108 (13.2)	557 (10.9)	
6-9	2616 (44.0)	372 (45.4)	2244 (43.7)	
≥10	2671 (44.9)	340 (41.5)	2331 (45.4)	
First SBP(mmHg)	112.53±11.01	114.08±11.25	112.29±10.95	<0.001
First DBP(mmHg)	72.33±9.23	72.89±9.32	72.24±9.21	0.062
Hypertension, %	151 (2.5)	25 (3.0)	126 (2.5)	0.377

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; DBP, diastolic blood pressure.

In the RCS model, a linear dose-response relationship between mean SBP and the risk of GDM was observed (p<0.001 for overall association, p=0.25 for non-linear association) (Figure S1A). However, no significant linear or non-linear relationship was found between DBP and the risk of GDM (Figure S1B). Stratified analysis showed no significant interaction effects between BP and stratified factors on the risk of GDM (Table S4). These results remained essentially unchanged when the analysis was restricted to non-hypertensive women (Tables S5 and S6).

Association Between Blood Pressure Trajectories During Pregnancy with GDM

Figure S2 depicts the trajectory patterns of SBP and DBP during pregnancy. Tables S7 and S8 exhibit the elevated accuracy in assigning individuals to their corresponding trajectory groups. The trajectory groups were labeled as the High-stable group, Moderate-stable group, and Low-stable group.

Compared to the reference group (Low-stable SBP), the High-stable group demonstrated a significantly higher risk of GDM (adjusted OR, 1.43[95% CI, 1.07–1.88]) and GDM-CH (adjusted OR, 2.37 [95% CI, 1.30–4.35]). However, no

Table 2 Associations Between BP at the First Visit During Pregnancy and Risks of GDM and Its Subtypes

Outcome	n/N	per 10mmHg		Tertile 1	Tertile 2		Tertile 3	
		OR (95% CI)	*p*-value		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
First SBP								
GDM	820/5952	**1.11(1.04–1.19)**	**<0.001**	1(ref)	1.10(0.99–1.46)	0.06	**1.37(1.14–1.66)**	**<0.001**
GDM-IFH	260/5952	1.04(0.93–1.17)	0.47	1(ref)	**1.45(1.05–2.01)**	**0.02**	**1.40(1.01–1.94)**	**0.04**
GDM-IPH	423/5952	**1.11(1.01–1.21)**	**0.03**	1(ref)	1.07(0.83–1.38)	0.59	1.22(0.95–1.57)	0.11
GDM-CH	137/5952	**1.18(1.02–1.38)**	**0.03**	1(ref)	1.06(0.66–1.71)	0.79	**1.60(1.04–2.47)**	**0.03**
First DBP								
GDM	820/5952	1.05(0.96–1.13)	0.29	1(ref)	1.15(0.95–1.39)	0.14	1.15(0.96–1.39)	0.12
GDM-IFH	260/5952	1.06(0.92–1.21)	0.41	1(ref)	1.17(0.85–1.60)	0.33	1.18(0.86–1.61)	0.29
GDM-IPH	423/5952	1.01(0.90–1.12)	0.91	1(ref)	1.13(0.88–1.45)	0.33	1.06(0.82–1.35)	0.67
GDM-CH	137/5952	1.12(0.93–1.34)	0.25	1(ref)	1.14(0.73–1.80)	0.55	1.38(0.90–2.11)	0.13

Notes: Tertiles 1, 2, and 3 for SBP were <108 mmHg, 108–117mmHg, and >117mmHg, respectively. Tertiles 1, 2, and 3 for DBP were <66 mmHg, 66–72 mmHg, and >79 mmHg, respectively. Values in bold indicate statistically significant. n indicates the number of cases; N indicates the total study population. Adjusted for age, pre-pregnancy BMI, parity, gravidity, number of visits during pregnancy, education level, family history of diabetes, gestational weight gain and physical activity.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; IFH, isolated fasting hyperglycemia; IPH, isolated post-load hyperglycemia; CH, combined hyperglycemia; OR, odds ratio; CI, confidence interval.

increased risk of GDM-IFH and GDM-IPH was observed in the High-stable group. Similarly, in comparison to the Low-stable SBP group, the Moderate-stable group also exhibited a significantly higher risk of GDM (adjusted OR, 1.31[95% CI, 1.09–1.57]). On the other hand, there were no significant associations observed between the different DBP trajectory groups and the risk of GDM (Table 3).

One-Sample MR Analysis Based on PRS

In our subset cohort, we constructed PRS for SBP and DBP using the SNPs from Chinese-specific GWAS results. Figure 2 illustrates the associations between BP PRS and GDM. We observed a higher PRS for SBP in participants with

Table 3 Associations Between Different BP Trajectories During Pregnancy and Risks of GDM and Its Subtypes

Outcome	n/N	Low-Stable	Moderate-Stable		High-Stable	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
SBP trajectory						
GDM	820/5952	1(ref)	**1.31(1.09–1.57)**	**<0.001**	**1.43(1.07–1.88)**	**0.01**
GDM-IFH	260/5952	1(ref)	1.18(0.88–1.63)	0.28	1.14(0.70–1.83)	0.59
GDM-IPH	423/5952	1(ref)	1.27(1.00–1.63)	0.06	1.28(0.86–1.86)	0.21
GDM-CH	137/5952	1(ref)	1.52(0.96–2.51)	0.08	**2.37(1.30–4.35)**	**<0.001**
DBP trajectory						
GDM	820/5952	1(ref)	1.12(0.93–1.36)	0.24	1.09(0.84–1.42)	0.48
GDM-IFH	260/5952	1(ref)	1.09(0.80–1.52)	0.57	0.88(0.56–1.36)	0.56
GDM-IPH	423/5952	1(ref)	1.11(0.87–1.45)	0.39	1.14(0.81–1.61)	0.44
GDM-CH	137/5952	1(ref)	1.12(0.71–1.82)	0.63	1.40(0.79–2.49)	0.24

Notes: Trajectories low-stable, moderate-stable, and high-stable for mean SBP were 79–108.8, 104–130, 121.5–153 mmHg, respectively. Trajectories low-stable, moderate-stable, and high-stable for mean DBP were 44–67.3, 63–84, 77.5–102.3 mmHg, respectively. Values in bold indicate statistically significant. n indicates the number of cases; N indicates the total study population. Adjusted for age, pre-pregnancy BMI, parity, gravidity, number of visits during pregnancy, education level, family history of diabetes, gestational weight gain and physical activity.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; IFH, isolated fasting hyperglycemia; IPH, isolated post-load hyperglycemia; CH, combined hyperglycemia; OR, odds ratio; CI, confidence interval.

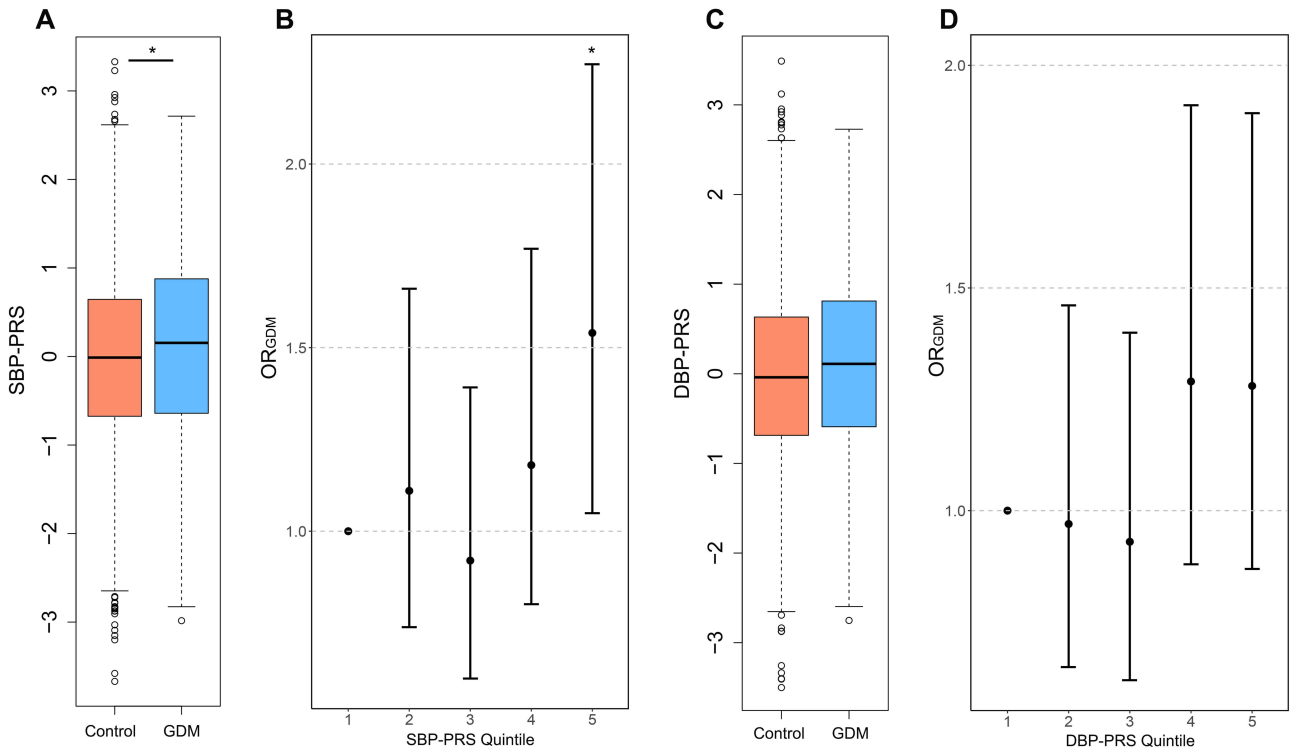

Figure 2 One-sample Mendelian randomization analyses between PRS for BP on the risk of GDM. Comparisons of the SBP-PRS (**A**) and DBP-PRS (**C**) of the subjects with GDM and Control. Relationship of SBP-PRS quintile (**B**) and DBP-PRS quintile (**D**) with GDM. *p<0.05.
Abbreviations: PRS, polygenic risk score; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus.

GDM compared to those without GDM (p=0.036). Specifically, the top quintile of PRS for SBP showed a significant association with an increased risk of GDM compared to the lowest quintile of PRS in our dataset (OR=1.54, 95% CI, 1.05–2.27). However, no significant difference was found in PRS for DBP between participants with GDM and those without GDM.

Genome-Wide Genetic Correlation and Two-Sample MR Analysis

Using cross-trait LDSC, we estimated the r_g between SBP and GDM to be 0.26 (p=0.19) in East Asians and 0.12 (p=0.0002) in Europeans. Similarly, for the genetic correlation between DBP and GDM, the r_g was 0.39 (p=0.24) in East Asians and 0.05 (p=0.09) in Europeans (Figure S3).

In the East Asian population, the MR analyses did not provide any evidence of causal effects of SBP and DBP on GDM (Table S9 and Figures S4–S11). However, the IVW method indicated that a higher genetic liability to SBP (each 10mmHg increase) was significantly associated with an increased risk of GDM (OR=1.42, 95% CI, 1.12–1.82) in the European population. The estimates from the other three MR approaches were directionally consistent, although they had larger statistical uncertainties (Figure 3 and Figures S12–S14). The intercepts from the MR-Egger regression analyses were close to zero, suggesting no strong evidence of pleiotropy for SBP (intercept=−0.00025). Additional analyses excluding SNPs related to BMI supported the robustness of these findings (Table S10). The leave-one-out analysis demonstrated the absence of outlying variants which was further validated by MR-PRESSO (OR=1.22, 95% CI, 1.03–1.44). On the other hand, no evidence of causal effects of DBP on GDM was found, indicating that genetically predicted DBP did not seem to influence GDM risk (IVW OR=1.00, 95% CI, 0.74–1.37). Similar null effects were identified in the other three MR models (Figure 3 and Figures S15–S17).

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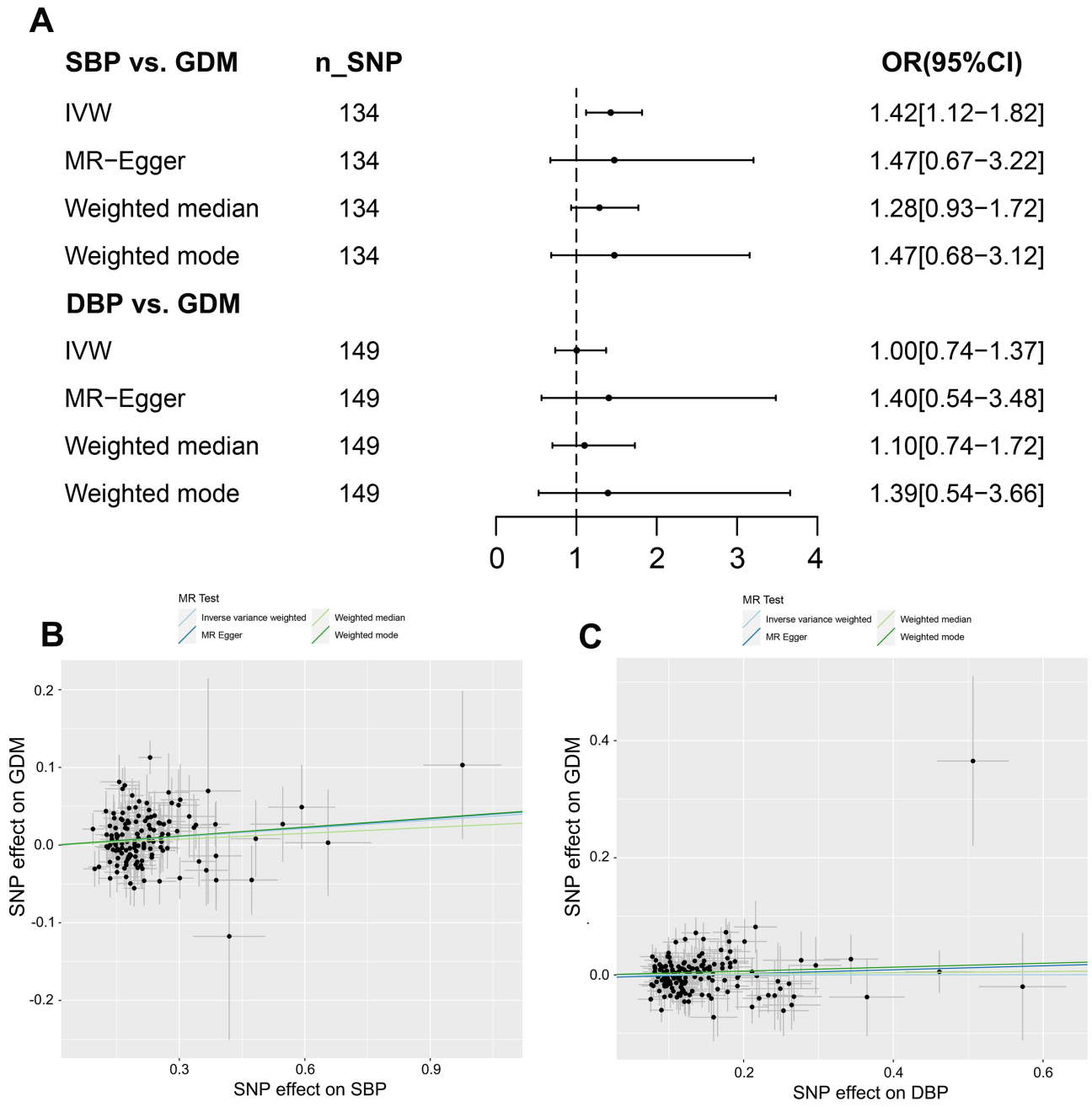

Figure 3 Two-sample Mendelian randomization analyses of the associations of BP and GDM in Europeans. (**A**) Forest plots show causal-effect estimates of 10-mmHg SBP or DBP on GDM. Scatter plots in which the SNP-outcome associations are plotted against the SNP-SBP (**B**) and SNP-DBP (**C**) associations, allowing visualization of the causal-effect estimate for each individual SNP on estimated GDM.

Abbreviations: IVW, inverse variance weighted; SNP, single-nucleotide polymorphism; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus.

Discussion

In this prospective study, we have identified a significant association between elevated SBP and an increased risk of GDM. Importantly, we have also observed that women with Moderate-stable and High-stable SBP trajectories during pregnancy were more likely to develop GDM compared to those following a low-stable trajectory. These findings emphasized the pivotal role of elevated SBP, rather than DBP, in the development of GDM. Furthermore, our genetic correlation study revealed a shared genetic basis between SBP and GDM, further supporting the potential underlying

mechanisms linking these two conditions. The evidence from our MR studies strengthens the possibility that elevated SBP during pregnancy may indeed have a causal role in the development of GDM.

The association between hypertension and GDM has been studied in recent decades. A retrospective cohort study conducted in China, involving 47874 women with singleton live births, revealed that stage 1 hypertension, as defined by the revised American Heart Association guidelines, was associated with an increased risk of GDM.[8] Similarly, another nested case-control study, with 381 cases and 942 controls, found that during early pregnancy, women with prehypertension had a slightly increased risk of GDM, while women with hypertension had a twofold increased risk compared to those with normal BP.[7] However, the impact of BP levels on the risk of GDM were not consistent across studies. For example, the Rhea study conducted in Greece from 2007 to 2009 reported that a 10 mmHg increase in both SBP and DBP was associated with a 49% and 34% higher risk of developing GDM, respectively.[23] In contrast, the CARDIA (Coronary Artery Risk Development) study found no significant association between pre-pregnancy BP and GDM.[24] Another study conducted in China suggested that first-trimester SBP, but not DBP, was significantly associated with the risk of GDM, which is consistent with our findings.[25] However, this study only included high-risk women referred to a clinic providing antenatal care and had limited information on confounding factors. The findings from our study extended the existing literature by using data from a large birth cohort and demonstrating that elevated first and mean SBP during pregnancy are associated with an increased risk of GDM.

In our study, we found that women with Moderate-stable and High-stable SBP trajectories during pregnancy had an increased risk of GDM. These findings align with a previous study on type 2 diabetes, which included 4,625 individuals aged 18–60 years and included multiple measurements of BP. The results of that study showed that the long-term trajectory of SBP could serve as a significant predictor for the development of diabetes over time.[26] Our findings emphasize the importance of effectively managing SBP levels during pregnancy to reduce the risk of GDM.

Furthermore, we observed a modest association between higher SBP and a specific GDM subtype characterized by elevated fasting blood glucose levels. However, the association was stronger for GDM subtypes involving postprandial blood glucose or a combination of fasting and postprandial blood glucose. Recent studies have indicated that individuals with isolated impaired fasting glucose and isolated impaired glucose tolerance exhibited different characteristics in terms of insulin sensitivity in the liver and muscle.[27–29] Additionally, our previous study also revealed differential effects of protein powder consumption on the GDM subtypes.[30] These findings suggest that distinct molecular pathways and physiological processes may contribute to the development of different subtypes of GDM. Understanding these variations is crucial for the development of targeted prevention and management strategies.

Given the inherent challenges posed by residual confounding and reverse causation in the observational study, we employed the individual-level MR using PRS to test the causality of the association. The one-sample MR analysis produced consistent estimates with our observational findings and provided compelling evidence supporting a causal role of elevated SBP in the risk of GDM. Such methodological features strengthened the robustness and internal validity of our findings. Moreover, we conducted genetic correlation analysis and two-sample MR analysis using publicly available GWAS summary data. Although the genetic correlation coefficient between BP and GDM was higher in East Asian populations, statistically significant results were only found in European populations. Similarly, the two-sample MR analysis yielded consistent evidence of a causal effect of high SBP on GDM in European populations. This discrepancy may be attributed to the relatively smaller sample sizes and low statistical power of GWAS studies of GDM conducted in East Asian populations. It is important to note that the genetic correlation analysis provides insights into the shared genetic architecture between BP and GDM, indicating a potential underlying biological link. However, the lack of significant findings in East Asian populations highlights the need for larger-scale studies or population-specific investigations to further elucidate the causal relationship between SBP and GDM in these populations.

We did not observe a significant association between elevated DBP and the risk of GDM. This finding aligns with prior research showing that, once systolic blood pressure (SBP) or pulse pressure is accounted for, diastolic blood pressure (DBP) often demonstrates a weaker or non-independent association with cardiovascular outcomes and target organ damage, whereas SBP remains the dominant predictor.[31,32] Contemporary cardiovascular risk assessment tools and hypertension guidelines likewise place greater prognostic weight on SBP than on DBP.[33,34] Our results are consistent

with this pattern and further support the greater relevance of SBP, compared with DBP, in relation to GDM risk in this cohort.

The mechanisms by which elevated SBP may contribute to the development of GDM likely involve multiple interrelated pathophysiological pathways. Chronic elevation of BP can induce endothelial dysfunction, leading to impaired placental perfusion and reduced nutrient and oxygen exchange, which may disrupt glucose homeostasis during pregnancy.[35,36] Elevated SBP is also associated with systemic inflammation and oxidative stress, both of which can impair insulin signaling and β-cell function.[37,38] Moreover, women with higher SBP levels often exhibit greater insulin resistance even before conception, reflecting shared cardiometabolic risk factors such as visceral adiposity and dyslipidemi.[39,40] Collectively, these mechanisms suggest that elevated SBP may not only serve as a marker of preexisting metabolic dysfunction but also actively contribute to the pathogenesis of GDM through endothelial, inflammatory, and insulin-resistance–related pathways.

The major implication of our findings is that effectively managing BP, particularly SBP, during pregnancy could be beneficial in reducing the risk of GDM in non-hypertension women. A meta-analysis including 19 randomized controlled trials suggested that SBP lowering may be an effective strategy for the prevention of new-onset type 2 diabetes.[41] Considering the unique physiological state of pregnant women, promoting lifestyle-based interventions, such as dietary control and appropriate exercise, might be a viable approach to reduce BP during pregnancy and consequently prevent GDM.

To the best of our knowledge, this was the first comprehensive study to evaluate longitudinal BP patterns and their association with GDM, with a particular emphasis on establishing causal relationships through both one-sample and two-sample MR analyses. The representative population and pragmatic study design enable these findings to provide scientific evidence for routine prenatal care. Several strengths contribute to the robustness of this study. First, we evaluated BP levels throughout pregnancy in a large prospective cohort, enabling the longitudinal assessment of their association with GDM development. Second, our study yielded robust and consistent findings regarding the associations between various aspects of SBP and GDM. Finally, the incorporation of genetic correlation and MR analyses enhances our ability to infer causal effects in a more reliable and rigorous manner.

However, some limitations need to be acknowledged. Firstly, the use of trajectory analysis methods may introduce misclassification, potentially leading to biased results by obscuring the true trajectory patterns and associations. Nevertheless, it is crucial to recognize that misclassification is not an inherent flaw of the analysis method itself but rather reflects the complexity and variability inherent in human behavior and development. Secondly, reliance on self-reported pre-pregnancy weight introduces the possibility of misclassification, which can result in inaccurate estimates of measures. However, previous studies have suggested that the bias associated with self-reported weight tends to be relatively small and may not significantly impact the investigated associations.[42] Thirdly, despite our efforts to account for established risk factors for GDM in our analyses, residual confounding from unidentified factors shared by blood pressure and GDM is possible. However, we attempted to address this issue through MR analysis, a method that aids in the inference of causality. Fourthly, this cohort was conducted in a single location in China, which may limit the generalizability of the findings to other populations. Although the two-sample MR analysis included data from European populations, differences in genetic backgrounds and environmental exposures across ethnic groups suggest that further validation in more diverse populations is warranted. Lastly, the MR analysis did not yield statistically significant results in the East Asian population. Further studies using larger and more powerful genome-wide association datasets are needed to clarify the causal relationship between blood pressure and GDM in diverse ethnic backgrounds.

In conclusion, our study, utilizing individual data from a large prospective cohort and incorporating genetic analysis and MR analysis, provides novel evidence underscoring the substantial impact of SBP on the development of GDM. These findings suggest that maintaining lower SBP levels could be a potential strategy for preventing the onset of GDM in pregnant women. The comprehensive approach employed in our study strengthens the validity of the results and contributes to our understanding of the etiology of GDM.

Contributions to the Literature

- Prior studies have largely overlooked the dynamic relationship between longitudinal blood presssure trajectories during pregnancy and GDM risk, particularly in Asian populations.
- This study innovatively integrates observational cohort data with polygenic risk scoring and multi-ancestry Mendelian randomization to disentangle associaative and causal mechanisms.
- Findings emphasize the clinical relevance of early pregnancy blood pressure monitoring as a modifiable risk factor for GDM prevention strategies.

Abbreviations

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; IADPSG, International Association of Diabetes and Pregnancy Study Groups; MR, mendelian randomization; BP, blood pressure; PRS, polygenic risk scores; GWAS, genome-wide association studies; LDSC, linkage disequilibrium score regression; GBTM, group-based trajectory modeling; RCS, restricted cubic splines; OR, odds ratio; CI, confidence interval.

Data Sharing Statement

Data set are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (approval number [2012]14) and the Ethics Committee of Wuhan Women and Children Medical and Healthcare Center (approval number 2010009). Written informed consent was obtained from all study participants. In accordance with the Administrative Measures for Ethical Review of Life Science and Medical Research Involving Humans (National Health Commission of the People's Republic of China, Document No. [2023] 4), analyses using publicly available, de-identified summary-level GWAS data are exempt from additional IRB approval; therefore, no further ethical review was required for this part of the study.

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Author Contributions

Conceptualization: H.X., A.Z.

Methodology: M.Y., L.H., H.X., A.Z.

Formal analysis: M.Y.

Data curation: Z.C., H.M., J.Z., J.L., Y.Z., Y.Y.Z., X.F., F.X.,W.Z.

Writing – original draft: M.Y.

Writing – review & editing: L.H., W.Z., H.X., A.Z.

Funding acquisition: M.Y., H.X., A.Z.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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