

# Effect of Maternal Pre-Pregnancy Body Mass Index on Longitudinal Fetal Growth and Mediating Role of Maternal Fasting Plasma Glucose: A Retrospective Cohort Study

Qinzheng Chen<sup>1</sup>, Zhen He<sup>1</sup>, Yaxin Wang<sup>2</sup>, Xuanjin Yang<sup>2</sup>, Nana Liu<sup>2</sup>, Suhan Zhang<sup>2</sup>, Liangkun Ma<sup>2</sup>, Xuezhong Shi<sup>1</sup>, Xiaocan Jia<sup>1</sup>, Yongli Yang<sup>1</sup>, Yin Sun<sup>2</sup>, Yuan He<sup>3</sup>

<sup>1</sup>Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, People's Republic of China; <sup>2</sup>Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric & Gynecologic Diseases, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences (CAMS) and PUMC, Beijing, People's Republic of China; <sup>3</sup>National Human Genetic Resources Center, National Research Institute for Family Planning, Beijing, People's Republic of China

Correspondence: Yin Sun, Department of Obstetrics and Gynecology, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences (CAMS) and PUMC, Beijing, 100730, People's Republic of China, Email yin\_sun\_pumch@163.com; Yongli Yang, Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, 450001, People's Republic of China, Email ylyang377@zzu.edu.cn

**Purpose:** To assess the impact of maternal pre-pregnancy body mass index (BMI) on longitudinal fetal growth, and the potential mediation effect of the maternal fasting plasma glucose in first trimester.

**Methods:** In this retrospective cohort study, we collected pre-pregnancy BMI data and ultrasound measurements during pregnancy of 3879 singleton pregnant women who underwent antenatal examinations and delivered at Peking Union Medical College Hospital. Generalized estimation equations, linear regression, and logistic regression were used to examine the association between pre-pregnancy BMI with fetal growth and adverse neonatal outcomes. Mediation analyses were also used to examine the mediating role of maternal fasting plasma glucose (FPG) in first trimester.

**Results:** A per 1 Kg/m<sup>2</sup> increase in pre-pregnancy BMI was associated with increase fetal body length Z-score ( $\beta$  0.010, 95% CI 0.001, 0.019) and fetal body weight ( $\beta$  0.017, 95% CI 0.008, 0.027). In mid pregnancy, pre-pregnancy BMI also correlated with an increase Z-score of fetal abdominal circumference, femur length (FL). Pre-pregnancy BMI was associated with an increased risk of large for gestational age and macrosomia. Mediation analysis indicated that the associations between pre-pregnancy BMI and fetal weight in mid and late pregnancy, and at birth were partially mediated by maternal FPG in first trimester (mediation proportion: 5.0%, 8.3%, 1.6%, respectively).

**Conclusion:** Maternal pre-pregnancy BMI was associated with the longitudinal fetal growth, and the association was partly driven by maternal FPG in first trimester. The study emphasized the importance of identifying and managing mothers with higher pre-pregnancy BMI to prevent fetal overgrowth.

**Keywords:** body mass index, fetal growth, adverse neonatal outcomes, fasting plasma glucose, mediation analysis, cohort study

## Introduction

Obesity has been one of the largest public health threats globally. A statistical report indicated that the number of people with overweight or obesity has reached 2 billion worldwide, with the proportion of women of reproductive age and children was constantly increasing.<sup>1,2</sup> The birth weight of neonates progressively increased over time.<sup>3</sup> The risk of childhood obesity and multiple diseases in adulthood (such as hypertension, diabetes, and tumours) are increased if an infant already has overweight or obesity at birth.<sup>4</sup> This phenomenon is referred to as the Developmental Origins of Health and Diseases (DOHaD) paradigm.<sup>5</sup> Fetal growth could be influenced by a multitude of factors, maternal factors such as maternal hormones, obesity, and nutritional deficiencies also are known to impact this process.<sup>6,7</sup> Maternal

obesity has been demonstrated to be associated with an increased risk of obstetric complications during the perinatal period, as well as an increased risk of metabolic syndrome in offspring.<sup>8–10</sup> However, few studies had taken into consideration the impact of maternal pre-pregnancy obesity on the early stages of offspring development, which is crucial for preventing fetal growth acceleration or deceleration.

Furthermore, it is well established that overweight/obesity is associated with abnormal glucose metabolism, and pre-pregnancy obesity may contribute to abnormal glucose metabolism in early pregnancy (the period from the last menstrual period to 12 weeks of gestation).<sup>11–13</sup> It has been reported that abnormal glucose metabolism during early pregnancy affected fetal growth, altering the trajectory of intrauterine growth, suggesting that plasma glucose may be a mediator in the association between pre-pregnancy weight and the change in fetal growth.<sup>14,15</sup> Therefore, we hypothesized that the association between pre-pregnancy BMI and fetal intrauterine growth in pregnant women was partly mediated by maternal early pregnancy fasting plasma glucose (FPG).

However, previous studies tended to use birth weight as the indicator for fetal growth, but it could not represent the specific growth characteristics of fetuses in the uterus. Thus, it is necessary to utilize ultrasound-based fetal measurements to assess fetal growth status. Furthermore, the impact of early pregnancy glucose levels on the association between pre-pregnancy BMI and fetal growth remains unclear. This study aims to delve into the impact of maternal nutritional status (pre-pregnancy BMI and plasma glucose) on fetal intrauterine growth during pregnancy, and explore the key factors influencing fetal intrauterine growth. Therefore, in this retrospective cohort study among 4860 mother-offspring pairs, we examined the associations between maternal pre-pregnancy BMI and fetal growth and the risk of adverse neonatal outcomes, and explored the mediation effect of maternal FPG in first trimester.

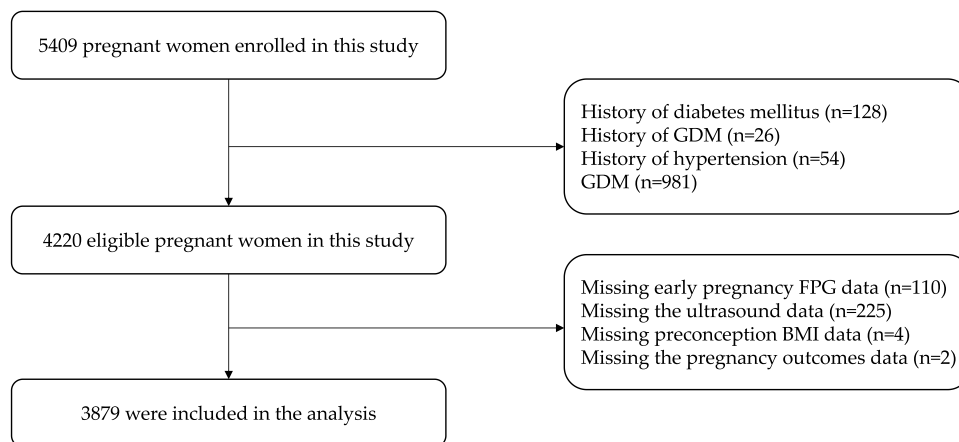
## Materials and Methods

### Study Population

This retrospective cohort study was conducted at Peking Union Medical College Hospital (PUMCH). From July 2020 to June 2022, a total of 5409 singleton pregnant women who underwent antenatal care throughout the pregnancy in the PUMCH were obtained. [Figure 1](#) details the participant's selection process. Demographic information and medical information of the mother-fetus pairs were collected via questionnaires and Hospital Information System (HIS). This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the Declaration of Helsinki. Written informed consent was acquired from all study participants, and this study was approved by the ethics committee of PUMCH (JS-2763).

### Exposure Measurement

Pre-pregnancy weight and height were obtained from questionnaires filled out by pregnant women at the PUMCH upon confirmation of pregnancy. The pre-pregnancy BMI ( $\text{kg}/\text{m}^2$ ) was calculated as body weight (kg) divided by height-squared



**Figure 1** Flowchart of the study population.

( $m^2$ ). Maternal FPG in first trimester (the last menstrual period to 12 weeks of gestation) was the plasma glucose level measured by blood taken before breakfast after overnight fasting (at least 8–10 h without any food, except drinking water) during the first antenatal visit of the early pregnancy. All the glucose level tests were measured by professional laboratory physicians using Biochemical detector (cobas c 701/702, Roche).

## Fetal Growth and Neonatal Outcome

As a part of the follow-up prenatal visits, pregnant women were routinely monitored with transabdominal sonography (EPIQ Elite, PHILIPS) to measure the fetal head circumference (HC), abdominal circumference (AC), femur length (FL) to the nearest millimetre. These measurements were performed during mid pregnancy (18 to 24 weeks of gestation) and late pregnancy (28 to 34 weeks of gestation). The ultrasound measurements were conducted by experienced sonographers. The estimated fetal weight (EFW) was calculated according to the Hadlock formula.<sup>16</sup> Information on fetal sex, gestational age, birth weight, and birth height were obtained from hospital medical records. Based on the INTERGROWTH-21st Standard, gestational age-adjusted z-scores for fetal biometry measurements, EFW, weight and height at birth were calculated.<sup>17</sup>

Preterm birth (PB) was defined as a gestational age at birth <37 weeks.<sup>18</sup> Large for gestational age (LGA) was defined as a birth weight exceeded the 90th percentile gestational age- and sex-specified birth weight according to growth standard curves of the birth weight of Chinese newborns of different gestation.<sup>19–21</sup> Low birth weight (LBW) was defined as a birth weight <2500 g,<sup>22</sup> whereas macrosomia was defined as a birth weight >4000 g.<sup>23</sup>

## Covariates

Information about maternal age, maternal parity, history of adverse pregnancy, gestational age, and infant sex were extracted from the medical record system. Maternal socioeconomic characteristics (eg, education level, occupation), lifestyle factors (eg, physical activity level), family history of diabetes, and family history of hypertension disease were collected by standardized structured questionnaire in first antenatal care. Gestational weight gain (GWG) refers to the difference between pre-pregnancy weight and weight before delivery, and it is categorized into appropriate and inappropriate GWG according to the guidelines provided by the Institute of Medicine (IOM) in 2009 on the range of GWG.<sup>24</sup>

## Statistical Analysis

Variables were presented as means with standard deviations (SD), medians with upper and lower quartiles, or percentages. Differences in variables were compared using t tests or Mann–Whitney *U*-tests for continuous variables and Chi-squared test for categorical variables.

Generalized estimating equation (GEE) models were used to handle repeatedly measured fetal growth data (body length and body weight) to estimate the effect of maternal pre-pregnancy BMI on the longitudinal fetal growth patterns.<sup>25</sup> The fetus length could not be estimated by ultrasound, so the longitudinal growth of body length was assessed using FL instead of birth height in mid and late pregnancy.<sup>26</sup> We utilized mid-pregnancy EFW, late pregnancy EFW, and birth weight to assess the longitudinal growth of body weight.

Multiple linear regression models were used to examine the association of maternal pre-pregnancy BMI with fetal biometry measurement in the mid and late pregnancy, and at birth. Multiple logistic regression models were used to estimate the associations of maternal pre-pregnancy BMI with the risk of adverse neonatal outcomes (PB, LGA, LBW, macrosomia).

Mediation analysis was conducted using the “mediation” package in R4.2.2 to assess whether maternal FPG in first trimester contributed to the association of maternal pre-pregnancy BMI with fetal biometric measurements.<sup>27</sup>

For all analyses, maternal pre-pregnancy BMI was included as a continuous variable in the models. All regression models were first adjusted for maternal age, education level, physical activity level, and gestational age (Model 1) and subsequently additionally adjusted for parity, GWG throughout pregnancy, maternal FPG in first trimester, family history of hypertension disease, and family history of diabetes (Model 2).

We also conducted stratified analyses to explore potential differences in the association based on maternal age <35 or ≥35, primiparous or multiparous, with or without family history of diabetes, and male or female infant.

Significance tests were two-sided, and  $P < 0.05$  was considered statistically significant. R version 4.2.2 (R Group for Statistical Computing) performed all analyses.

## Results

### Population Characteristics

Descriptive characteristics of maternal and offspring are listed in Table 1. A total of 4860 singleton pregnant women were included in the final analysis. The mean maternal age was  $32.55 \pm 4.18$  years, and the mean maternal pre-pregnancy BMI was  $22.72 \pm 3.25$  Kg/m<sup>2</sup>. The birth weight of the newborns were  $3269.06 \pm 445.49$  g, and 51.6% of the newborns were boys. The prevalence of PB and LGA were 4.70% and 12.80%, respectively.

**Table 1** Maternal and Offspring Characteristics of This Study

Characteristic	Overall 3879
<b>Maternal characteristics</b>	
Age, mean $\pm$ SD, years	32.55 $\pm$ 4.18
<35, n (%)	3000 (77.3)
$\geq$ 35, n (%)	879 (22.7)
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	22.72 $\pm$ 3.25
Nullipara, n (%)	3014 (77.7)
Education level, n (%)	
Primary education	1819 (46.9)
Bachelor	2005 (51.7)
Master or doctoral	55 (1.4)
Physical activity level, n (%)	
Low	3789 (97.7)
Middle	88 (2.3)
High	2 (0.1)
Family history of hypertension disease, n (%)	
No	2680 (69.1)
Yes	1199 (30.9)
Family history of diabetes, n (%)	
No	3178 (81.9)
Yes	701 (18.1)
FPG in first trimester, mean $\pm$ SD, mmol/L	4.67 $\pm$ 0.47
GWG throughout pregnancy, median [IQR], kg	7.20 [5.40, 9.10]
<b>Fetal biometry measurements</b>	
<b>Mid pregnancy</b>	
Gestational age, median [IQR], weeks	22.00 [21.00, 22.00]
HC, mean $\pm$ SD, mm	196.54 $\pm$ 9.02
AC, mean $\pm$ SD, mm	174.15 $\pm$ 9.37
FL, mean $\pm$ SD, mm	37.42 $\pm$ 2.34
EFW, mean $\pm$ SD, g	479.65 $\pm$ 61.17
<b>Late pregnancy</b>	
Gestational age, median [IQR], weeks	30.00 [29.00, 31.00]
HC, mean $\pm$ SD, mm	282.55 $\pm$ 41.74
AC, mean $\pm$ SD, mm	264.20 $\pm$ 45.51
FL, mean $\pm$ SD, mm	57.84 $\pm$ 9.30
EFW, mean $\pm$ SD, g	1597.38 $\pm$ 288.73

(Continued)

**Table 1** (Continued).

Characteristic	Overall 3879
<b>Neonatal characteristics</b>	
Gestational age at birth, median [IQR], weeks	39.00 [38.00, 40.00]
Sex, n (%)	
Female	1876 (48.4)
Male	2003 (51.6)
Birth height, mean $\pm$ SD, cm	49.31 $\pm$ 2.09
Birth weight, mean $\pm$ SD, g	3275.68 $\pm$ 440.22
PB, n (%)	183 (4.70)
LGA, n (%)	496 (12.80)
LBW, n (%)	153 (3.90)
Macrosomia, n (%)	163 (4.20)

**Notes:** Values were shown means (SD), medians [IQR], and numbers (percentage).  
**Abbreviations:** SD, Standard deviation; IQR, interquartile range; BMI, body mass index; FPG, fasting blood glucose; GWG, gestational weight gain; HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight; PB, premature birth; LGA, large for gestational age; LBW, low birth weight.

## Maternal Pre-Pregnancy BMI and Longitudinal Fetal Growth

**Table 2** presents the association between pre-pregnancy BMI and fetal longitudinal growth patterns using GEE analysis. After adjusting for maternal age, education level, physical activity level, and gestational age at assessment (Model 1), maternal pre-pregnancy BMI was positively associated with fetal growth pattern (body length Z-score:  $\beta$  0.010, 95% CI 0.002, 0.017; body weight Z-score:  $\beta$  0.019, 95% CI 0.010, 0.029). After further adjustment for parity, FPG, family history of hypertension disease, and family history of diabetes (Model 2), the association slightly weakened but remained significant (body length Z-score:  $\beta$  0.010, 95% CI 0.001, 0.019; body weight Z-score:  $\beta$  0.017, 95% CI 0.008, 0.027).

The maternal pre-pregnancy BMI was associated with fetal biometric measurements (**Table 3**). We found that for every 1 kg/m<sup>2</sup> increase in maternal pre-pregnancy BMI, there was an increase in z-scores for fetal AC ( $\beta$  0.012 95% CI 0.005, 0.018), FL ( $\beta$  0.009, 95% CI 0.001, 0.018), and EFW ( $\beta$  0.019, 95% CI 0.011, 0.028) during mid pregnancy after adjusted confounders. Similar to mid pregnancy, higher pre-pregnancy BMI was associated with an increase in z-scores for EFW ( $\beta$  0.014, 95% CI 0.007, 0.021) during late pregnancy, birth height ( $\beta$  0.018, 95% CI 0.008, 0.027), and birth weight ( $\beta$  0.033, 95% CI 0.025, 0.042) after adjusted confounders.

## Maternal Pre-Pregnancy BMI and Neonatal Outcome

**Table 4** presents the ORs with 95% CIs for neonatal outcomes associated with maternal pre-pregnancy BMI. After adjusting for confounding factors, every 1 kg/m<sup>2</sup> increase in maternal pre-pregnancy BMI was found to be associated with an increased risk of PB (OR 1.050, 95% CI 1.006, 1.107), LGA (OR 1.119, 95% CI 1.086, 1.153), and macrosomia

**Table 2** The Effects of the Pre-Pregnancy BMI on Fetal Longitudinal Growth Pattern (GEE Analysis)

Variable	Model 1		Model 2	
	Beta (95% CI)	P	Beta (95% CI)	P
Body length	0.010 (0.002, 0.017)	0.01	0.010 (0.001, 0.019)	0.034
Body weight	0.019 (0.010, 0.029)	<0.001	0.017 (0.008, 0.027)	0.001

**Notes:** Model 1 adjusted for maternal age, education level, physical activity level, and gestational age. Model 2 further adjusted for parity, GWG throughout pregnancy, FPG, family history of hypertension disease, and family history of diabetes.

**Abbreviations:** CI, confidence interval; GEE, generalized estimating equation.

**Table 3** The Effects of the Pre-Pregnancy BMI on Fetal Biometric Measurements During Each Pregnancy Period

Variable	Model 1		Model 2	
	Beta (95%CI)	P	Beta (95%CI)	P
Mid pregnancy				
HC	0.004 (−0.001, 0.009)	0.154	0.001 (−0.005, 0.006)	0.863
AC	0.010 (0.005, 0.016)	0.001	0.012 (0.005, 0.018)	0.001
FL	0.010 (0.002, 0.017)	0.013	0.009 (0.001, 0.018)	0.028
EFW	0.020 (0.012, 0.027)	<0.001	0.019 (0.011, 0.028)	<0.001
Late pregnancy				
HC	−0.015 (−0.057, 0.027)	0.480	−0.007 (−0.053, 0.040)	0.776
AC	0.001 (−0.031, 0.033)	0.970	0.003 (−0.032, 0.039)	0.851
FL	0.012 (−0.026, 0.049)	0.535	0.019 (−0.023, 0.060)	0.379
EFW	0.011 (0.005, 0.018)	<0.001	0.014 (0.007, 0.021)	<0.001
Birth size				
Height	0.022 (0.013, 0.031)	<0.001	0.018 (0.008, 0.027)	<0.001
Weight	0.041 (0.033, 0.049)	<0.001	0.033 (0.025, 0.042)	<0.001

**Notes:** Model 1 adjusted for maternal age, education level, physical activity level, and gestational age. Model 2 further adjusted for parity, GWG throughout pregnancy, FPG, family history of hypertension disease, and family history of diabetes.

**Abbreviations:** HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight; CI, confidence interval.

**Table 4** Associations of Pre-Pregnancy BMI with Adverse Neonatal Outcomes

Variable	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
PB	1.014 (0.969, 1.061)	0.556	1.050 (1.006, 1.107)	0.028
LGA	1.134 (1.103, 1.165)	<0.001	1.119 (1.086, 1.153)	<0.001
LBW	0.974 (0.911, 1.042)	0.443	0.980 (0.910, 1.055)	0.586
Macrosomia	1.150 (1.100, 1.202)	<0.001	1.138 (1.085, 1.194)	<0.001

**Notes:** Model 1 adjusted for maternal age, education level, and physical activity level. Model 2 further adjusted for parity, GWG throughout pregnancy, FPG, family history of hypertension disease, and family history of diabetes.

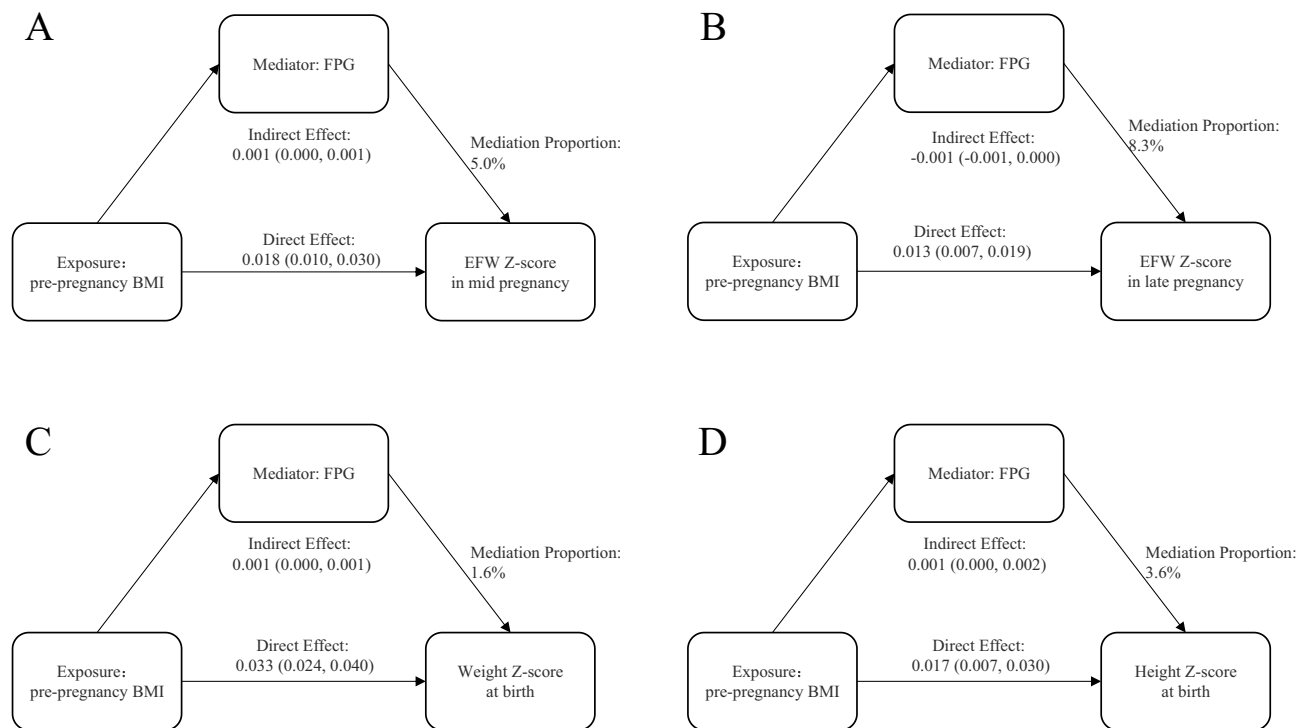
**Abbreviations:** PB, premature birth; LGA, large for gestational age; LBW, low birth weight; OR, odds ratio; CI, confidence interval.

(OR 1.138, 95% CI 1.085, 1.194). No significant association was observed between increasing maternal pre-pregnancy BMI and the risk of LBW after adjusting for confounding factors.

## Mediation Effects of Maternal FPG in First Trimester

A significant association was observed between maternal pre-pregnancy BMI and maternal FPG in first trimester ([Supplementary Table 1](#)). After confirming the above associations between maternal pre-pregnancy BMI with fetal biometric measurements, we constructed mediation models to explore the effects of maternal FPG in first trimester.

The results of the mediation analyses are shown in [Figure 2](#). When maternal PFG in first trimester was included as a mediator in the association of maternal pre-pregnancy BMI with EFW Z-score in mid pregnancy, the mediating effect (mediation proportion: 5.0%) was found. Similarly, the mediating effect (mediation proportion: 8.3%) of maternal PFG in first trimester in the association of pre-pregnancy BMI with EFW Z-score in late pregnancy, and the mediating effect



**Figure 2** The mediation effects of maternal FPG in first trimester on the association of maternal pre-pregnancy BMI with fetal biometry measurements. (A–D) respectively represented the mediation effects of maternal FPG in first trimester on the associations of pre-pregnancy BMI with EFV during mid pregnancy, EFV during late pregnancy, birth weight, and birth height. All models were conducted and adjusted for maternal age, education level, physical activity level, parity, GWG throughout pregnancy, family history of hypertension disease, and family history of diabetes.

(mediation proportion: 1.6%) of maternal FPG in first trimester in the association of pre-pregnancy BMI and birth weight Z-score, as well as birth height (mediation proportion: 3.6%) also presented.

## Stratified Analysis

A stratified analysis was conducted on factors such as maternal age, parity, family history of diabetes, and fetal sex. No significant difference between maternal pre-pregnancy BMI and fetal growth ([Supplementary Table 2](#)). In the association between pre-pregnancy BMI and neonatal outcomes, an interaction effect was found between a family history of diabetes in pregnant women, fetal sex, and pre-pregnancy BMI ([Supplementary Table 3](#)). Specifically, among pregnant women delivering female infants, there was a correlation between pre-pregnancy BMI and an increased risk of PB, whereas the opposite was observed in pregnant women delivering male infants. In pregnant women without a family history of diabetes, the ORs for LGA associated with pre-pregnancy BMI was significantly higher than in those with a family history of diabetes ([Supplementary Table 2](#)).

## Discussion

In this retrospective cohort study, we evaluated the relationship between pre-pregnancy BMI and fetal growth, and explored the mediation effect of early pregnancy FPG. We found pre-pregnancy BMI was positively associated with an increase in fetal biometric data (AC, FL, and EFV) during mid pregnancy, EFV during late pregnancy, birth height and weight, and the risk for LGA and macrosomia. Furthermore, we found that maternal FPG in first trimester partly mediated the association between pre-pregnancy BMI and EFV in mid and late pregnancy and birth weight. These findings indicated that controlling pre-pregnancy BMI was important for preventing excessive fetal growth.

During pregnancy, the developing fetus is particularly sensitive to the intrauterine environment, and maternal metabolic factors. Maternal pre-pregnancy obesity can impact the structure and hemodynamics of the maternal placenta, ultimately affecting fetal growth.<sup>28–32</sup> Our study revealed a positive correlation between pre-pregnancy BMI and

longitudinal fetal weight gain, as well as an association with increased AC and FL z-scores in mid pregnancy fetuses. Dr Spann et al had similar findings to ours, showing a positive correlation between pre-pregnancy BMI and EFW.<sup>33</sup> A nested study in the Generation R Study found that maternal pre-pregnancy BMI could affect fetal EFW starting from mid pregnancy.<sup>34</sup> Lindell et al also demonstrated exposure to higher maternal pre-pregnancy BMI was associated with increased EFW in late pregnancy.<sup>35</sup> In contradistinction, a previous study showed that no association was found between maternal pre-pregnancy BMI and any of the fetal biometric variables (HC, AC, FL, EFW).<sup>36</sup> There may be a variety of reasons why the result differed from ours, including sample sizes, differences in regional characteristics, and racial and ethnic differences. Furthermore, pregnant women with abnormal pre-pregnancy BMI might be subjected to dietary interventions to regulate their weight, potentially resulting in changes to fetal biometric characteristics.

We observed that maternal pre-pregnancy BMI was associated with an increased risk of macrosomia and LGA. A meta-analysis incorporating 60 studies revealed that overweight or obese mothers had a significantly increased risk of giving birth to macrosomia and LGA, while underweight mothers have an increased risk of delivering an SGA infant when compared to mothers with a normal weight range.<sup>37</sup> Another cohort study conducted in Poland reported the risk of delivering a macrosomic infant was three times higher for obese mothers compared to those with normal weight.<sup>38</sup> Similarly, a study undertaken in Switzerland showed that the risk of delivering LGA infants was 2-fold and 3.3-fold higher in overweight and obese pregnant women, respectively, when compared to women with a normal weight range.<sup>39</sup> Our study demonstrated that even within the normal range, an increase in pre-pregnancy BMI could result in an increased risk of macrosomia and LGA. One possible explanation for the observed associations was that a higher maternal BMI has affected the early growth of the placenta and its function in later stages, these changes could promote fetal growth and eventually lead to macrosomia and LGA infants.<sup>40–42</sup> Therefore, appropriate nutritional management and weight control during the perinatal period are crucial for preventing neonatal obesity.

In our study, we investigated the potential mediating role of maternal early pregnancy FPG in the association between pre-pregnancy BMI and fetal biometric measurements. Our results showed that FPG partially mediated this association, suggesting that pre-pregnancy BMI could not be considered a completely independent predictor of fetal growth. The mediation effect of maternal FPG in first trimester may be related to the placental transfer of glucose, the elevation of plasma glucose during pregnancy, resulting in excessive glucose flowing into the fetal circulation, ultimately leading to changes in fetal growth patterns.<sup>43,44</sup> Maternal obesity also plays a crucial role in this process.<sup>45</sup> In conclusion, these known mechanisms may constitute the hypothesis that FPG in early pregnancy partially mediated the effects of pre-pregnancy BMI on fetal growth.

There were several strengths of our study. Firstly, previous research has typically only examined fetal measurement data from a specific period, neglecting the longitudinal growth of fetuses. In this study, repeated measurements of fetal growth data were utilized to assess the impact of pre-pregnancy BMI on fetal longitudinal growth patterns to identify and control fetal growth acceleration or deceleration in early stages, to prevent adverse neonatal outcomes. In addition, we took into consideration the mediating impact of FPG during early pregnancy, and observed a mediation effect of pre-pregnancy FPG, indicating that the impact of pre-pregnancy BMI on fetal growth is partially mediated by early pregnancy FPG. Finally, our study considered the continuous distribution of pre-pregnancy BMI, while previous studies mainly explored the relationship between maternal overweight/obesity and fetal growth, making it difficult to determine the generalizability of conclusions.

The analysis has several limitations. Firstly, the study population was predominantly from the capital city of China, Beijing, with an average age of over 32 years and more than 90% having received higher education. However, this may not be representative of the wider national population, so caution should be exercised in generalizing the results to the entire country. Additionally, this study was susceptible to recall bias with regard to pre-pregnancy weight as well as measurement bias in ultrasound assessments, which may have influenced the results obtained. Finally, although this observational study controlled for many potential confounding factors, there was still the possibility of unmeasured or residual confounding that could limit the ability to make causal inferences. Therefore, in the future, it is possible to establish a multicenter designed study to increase the sample size, enhance sample representativeness, and improve the generalizability of results. Additionally, conducting long-term follow-up studies on mother-infant pairs will allow for a comprehensive assessment of the impact of maternal pre-pregnancy BMI on offspring growth and development.



## Conclusion

This study found that pre-pregnancy BMI and FPG in first trimester has a certain impact on fetal intrauterine growth, especially in terms of influencing mid-pregnancy fetal AC and weight. This finding emphasizes the importance of monitoring maternal nutritional status before and during early pregnancy to promote healthy fetal growth and development. Although our research results partially support previous studies, further in-depth research is also called for to comprehensively understand the effects of pre-pregnancy BMI and pregnancy plasma glucose on fetal health, which is crucial for improving maternal and child health.

## Abbreviations

SD, Standard deviation; IQR, interquartile range; CI, confidence interval; GEE, generalized estimating equation; BMI, body mass index; FPG, fasting blood glucose; GWG, gestational weight gain; HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight; PB, premature birth; LGA, large for gestational age; LBW, low birth weight.

## Data Sharing Statement

The datasets generated and/or analysed during the current study are not publicly available due to reasons of sensitivity but are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all study procedures were ethically approved by the ethics committee of PUMCH (JS-2763). Written informed consent was obtained from all of the participants.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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 report no conflicts of interest in this work.

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