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ORIGINAL ARTICLE

Pregestational diabetes mediates the association between maternal obesity and the risk of congenital heart defects

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Keywords
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ABSTRACT

Aims/Introduction: We aimed to explore whether the association between obesity and congenital heart defects (CHDs) can be mediated by maternal pregestational diabetes (PGDM).

Materials and Methods: We included 53,708 mother-infant pairs with deliveries between 2017 and 2019 from the Birth Cohort in Shenzhen. Mothers were categorized into four groups: the underweight group (body mass index [BMI] <18.5), normal weight group (18.5 ≤ BMI < 24), overweight group (24 ≤ BMI < 28) and obesity group (BMI ≥28). Multivariable logistic regression models were used to evaluate the association between BMI and CHDs. Mediation analysis was used to confirm the effect of PGDM on the association between maternal obesity and CHDs.

Results: The proportion of obese individuals in the Birth Cohort in Shenzhen was 2.11%. Overall, 372 (0.69%) infants were diagnosed with CHDs. Maternal obesity was associated with an increased risk of CHDs (odds ratio 1.97, 95% confidence interval 1.14–3.41). The mediation effect of PGDM on the association between maternal obesity and CHDs was significant (odds ratio 1.18, 95% confidence interval 1.06–1.32). The estimated mediation proportion was 24.83%.

Conclusions: Maternal obesity was associated with increased risk for CHDs, and PGDM partially mediated the association between maternal obesity and CHDs.

INTRODUCTION

Congenital heart defects (CHDs) are among the most common types of birth defects[1] and are leading causes of birth defects associated with morbidity, mortality and medical expenditures[2–4]. The prevalence of CHDs is approximately 5–15‰ of live births worldwide[1,5–7]. According to a meta-analysis carried out in China[8], the prevalence of CHDs was 4.905‰ from 2015 to 2019.

In recent decades, studies have focused on genetic abnormalities related to CHDs. However, at most, 15% of all CHD cases can be traced to a genetic cause (e.g., 8–10% have aneuploidy and 3–5% have single-gene defects); but the pathogenesis for 85% of CHDs remains unknown[9]. An increasing number of studies have focused on maternal factors, including obesity, pregestational diabetes, smoking, alcohol consumption and rubella infection[10–16]. A better understanding of the origins of CHDs is required to allow for prevention and earlier detection[9].

Obesity is a growing public health problem in both developed and developing countries. It has been projected that by 2025, 21% of women in the world will be severely obese (BMI ≥35 kg/m^2)[17]. Obesity in pregnancy adversely influences both fetal and neonatal outcomes[18], including increased risks of major congenital malformations. A population-based study carried out in Sweden showed that adjusted prevalence rate ratios of aortic branch defects, atrial septal defects and persistent ductus arteriosus increased with maternal obesity severity[19]. A meta-analysis involving 99,205 CHDs cases among 6,467,422 participants reported that increased maternal BMI was associated with the risk of developing CHDs in offspring[20]. However, some failed to observe any significant relationships between pregestational obesity and the risk of CHDs[21].

The prevalence of PGDM, another independent risk factor of CHDs, has been increasing globally[22]. Previous studies have

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shown that PGDM is a risk factor for CHDs and all CHDs subtypes[9]. In general, maternal obesity increases the risk of PGDM, and the prevalence of PGDM among obese pregnant women ranges between 0.6 and 3.8%[23,24], which is higher than that in the normal weight population. Given the increased prevalence of obesity and the increased risk of alterations in glucose metabolism among women who are obese, the effect of PGDM on the relationship between obesity and CHDs has not been well demonstrated.

The present study aimed to investigate the mediation effect of PGDM on the association between maternal obesity and CHDs.

MATERIALS AND METHODS

Data sources and study population

This cohort study was carried out in Shenzhen Maternity and Child Health Care Hospital. Regular antenatal examination was carried out, and the pregnancy outcomes were recorded. Data were collected from the hospital-based information system and Shenzhen Maternal and Child Information System.

We included mother–child pairs who: (i) had complete inspection and delivery information in the hospital; (ii) had complete newborn information; and (iii) had a single-child live birth. We excluded mother–child pairs who had: (i) stillbirths; (ii) multiple births; (iii) fetal chromosomal abnormalities; (iv) extracardiac birth defects; and (v) physical/chemical contact history and maternal CHDs history; and (vi) missing data on weight or height in the beginning of pregnancy.

The enrollment process was as follows (Figure 1). Twins and triplets (n = 1,944) were excluded. Women who delivered infants with chromosomal abnormalities/extracardiac defects (n = 1,896) and stillbirths (n = 50) were excluded. Those with physical/chemical contact history and maternal CHDs history (n = 444) were also excluded. Additionally, those with missing data on weight and height in the beginning of pregnancy (n = 631) were excluded. In total, 53,708 live singleton births

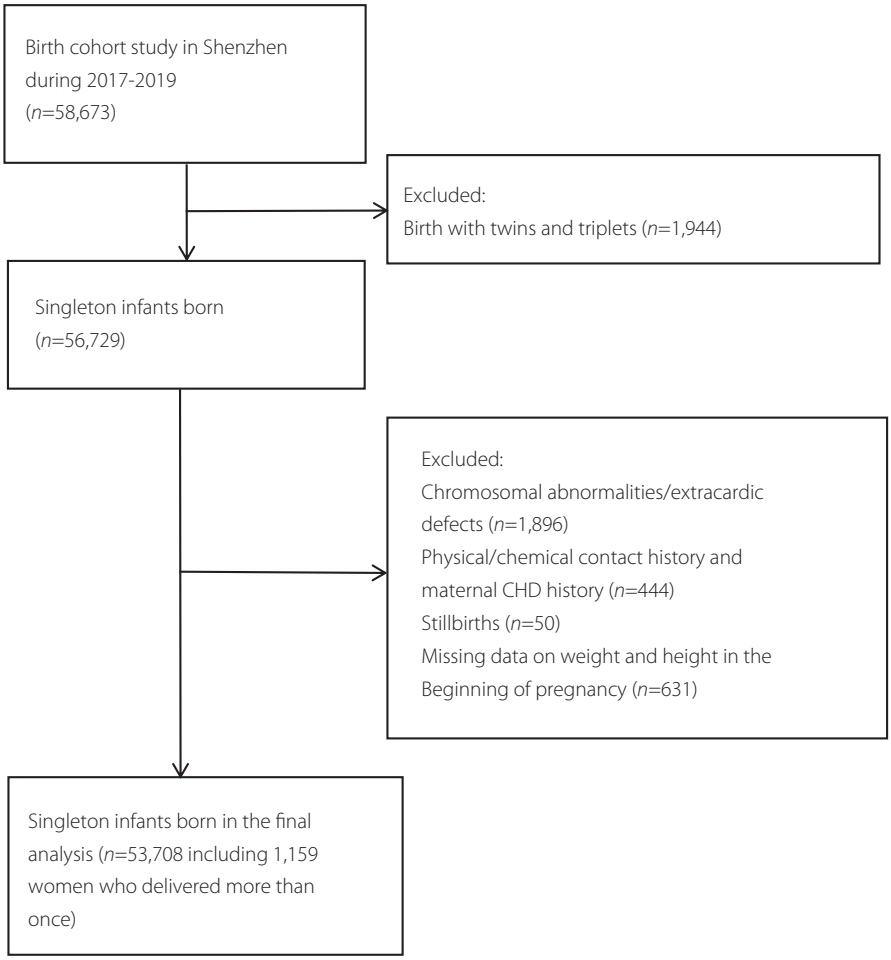

Figure 1 | Flow chart of participants.

from 2017 to 2019 (including 1,159 women who delivered more than once) were enrolled.

Exposure

Maternal BMI was calculated based on measured weight and height at the first antenatal visit (before 12 weeks of pregnancy). The specific measurement techniques were as follows. Women emptied their bowels and took off their shoes, hats, coats, all the clothes even bras, leaving only the underpants. The Omron (HNH-9) physical examination scale automatically measured height and weight, and calculated BMI. According to the recommendation of Chinese adult body mass index classification published by the China Obesity Working Group in 2001[25], mothers were categorized into four groups: the underweight group (BMI <18.5), normal weight group ($18.5 \leq$ BMI < 24), overweight group ($24 \leq$ BMI < 28) and obesity group (BMI ≥28).

Pregestational diabetes mediates was diagnosed when any of the following criteria was met[26]: (i) diabetes diagnosed before the index pregnancy, or in the first trimester or early second trimester; (ii) a fasting plasma glucose of ≥126 mg/dL; (iii) or a 2-h glucose of ≥200 mg/dL on a 75-g oral glucose tolerance test.

Outcomes

The main outcome was the presence of any heart defect in live-born infants. The diagnosis and classification of CHDs were confirmed by ultrasound in Shenzhen Maternity and Child Healthcare Hospital, Shenzhen, Guangdong, China. The offspring CHDs diagnosis was supplemented and corrected according to the information of the Shenzhen Maternal and Child Information System within 1 year after birth.

CHDs were classified by using a previously published algorithm that used a hierarchical approach to map CHDs into embryologically related defect phenotypes[27]. These phenotypes were heterotaxia, conotruncal defects (including truncus arteriosus, tetralogy of Fallot, transposition of the great arteries, other), atrioventricular septal defect, total anomalous pulmonary venous return, left ventricular outflow tract obstruction (including coarctation of the aorta, valvular aortic stenosis, other), right ventricular outflow tract obstruction (including valvular pulmonary stenosis, other), septal defect (including atrial septal defects [ASDs], ventricular septal defects [VSDs]) and complex CHDs. Patent ductus arteriosus was not included in the present study.

Covariates

Potential confounders were selected based on previous literature and the univariate analysis. Confounders included maternal age, maternal education level, mode of conception, parity, maternal gestational diabetes (GDM) and offspring sex.

There were no missing data on covariates.

Statistical analysis

For normally distributed variables, numbers and percentages were given. To compare proportions of two nominal variables, Pearson's χ^2-test and Fisher's exact test of independence were used. Odds ratios (ORs) with 95% confidence intervals (CIs) for all outcomes were calculated for offspring of mothers with underweight, overweight and obesity compared with mothers with normal weight. Generalized estimating equations were carried out using the 'geeglm' package to adjust for the correlation between mothers who gave birth more than once within the study period.

Multivariate regression analyses in two different models were used to estimate the ORs and 95% CI for CHDs in different BMI categories, using women with normal weight as the reference group. Model 1 was adjusted for maternal age, maternal education level, mode of conception, parity, GDM and offspring sex. Model 2 was adjusted for maternal age, maternal education level, mode of conception, parity, GDM, PGDM and offspring sex. Interaction and stratified analyses were conducted according to obesity and PGDM. Mediation analysis was carried out using the 'medflex' package in R 3.6.3, and the other analyses were carried out using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). P-value <0.05 was considered statistically significant.

RESULTS

General characteristics

The characteristics of mothers and births are presented in Table 1. Infants with low maternal education levels and maternal PGDM had increased rates of congenital heart defects ($P < 0.05$). However, compared with primipara mothers, multipara mothers had lower rates of offspring CHDs ($P < 0.05$). Rates of CHDs were not statistically different in groups according to maternal age, mode of conception, maternal GDM or sex of offspring.

Maternal obesity and the risk of CHDs

Figure 2 showed the distribution of BMI. The prevalence of obesity was just 2.11%. Overall, 372 (0.69%) offspring were diagnosed with congenital heart defects (Table 1). The incidence of CHDs in the underweight group, normal weight group, overweight group and obesity group was 0.64, 0.68, 0.72 and 1.24%, respectively.

In model 1, after adjusting for maternal age, maternal education level, mode of conception, parity, maternal GDM and offspring sex, the odds ratios for CHDs according to maternal BMI were 0.90 (95% CI 0.67–1.21) for underweight mothers and 1.11 (95% CI 0.81–1.53) for overweight mothers. The offspring of mothers who were obese (adjusted OR [aOR] 1.97, 95% CI 1.14–3.41) had a significantly higher risk of total CHDs (Figure 2).

The specific CHD phenotypes distributed in groups according to BMI were described in Table S1. In the present study, the proportion of complex heart defects was 7.26% (27/372). For obese mothers, significantly increased risks were observed for left ventricular outflow tract obstruction (aOR 5.69, 95% CI 1.62–19.90) and VSD (aOR 2.58, 95% CI 1.24–5.40; Table S2 and S3). At the same time, offspring of obese mothers were

Table 1 | Maternal and birth characteristics and congenital heart defects in live singleton births in Shenzhen, 2017–2019

Characteristics	Total (n = 53,708)	CHDs		P
		n (per 100) (n = 372)	Unadjusted odds ratio (95% CI)	
Maternal age (years)				
<20	82	2 (2.44)	3.33 (0.54–10.72)	0.10
20 to <25	2,640	19 (0.72)	0.97 (0.58–1.53)	0.89
25 to <30	17,186	128 (0.74)	1.00	
30 to <35	20,576	137 (0.67)	0.89 (0.70–1.14)	0.36
35 to <40	11,165	71 (0.64)	0.85 (0.63–1.13)	0.28
≥40	2,059	15 (0.73)	0.98 (0.55–1.62)	0.94
Maternal education level				
High school and below	17,949	186 (1.04)	1.99 (1.61–2.46)	<0.001
College	30,932	162 (0.52)	1.00	
Master and above	4,827	24 (0.50)	0.95 (0.60–1.43)	0.81
Mode of conception				
Naturally	51,984	354 (0.68)	1.00	
Assisted	1,724	18 (1.04)	1.54 (0.92–2.40)	0.07
Parity				
Primipara	24,824	195 (0.79)	1.00	
Multipara	28,884	177 (0.61)	0.77 (0.63–0.96)	0.02
PGDM				
No	53,338	356 (0.67)	1.00	
Yes	370	16 (4.32)	6.73 (3.87–10.85)	<0.001
GDM				
No	45,159	325 (0.72)	1.00	
Yes	8,549	47 (0.55)	0.76 (0.55–1.03)	0.08
Sex of offspring				
Female	25,220	193 (0.77)	1.00	
Male	28,488	179 (0.63)	0.82 (0.67–1.01)	0.06

CHD, congenital heart defect; CI, confidence interval; GDM, gestational diabetes; PGDM, pregestational diabetes.

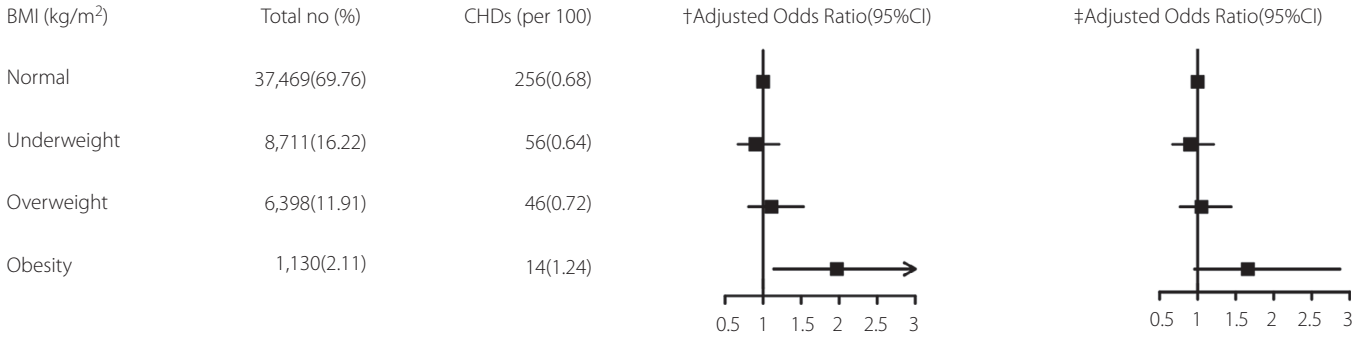

Figure 2 | Logistic regression of the correlation between body mass index (BMI) and congenital heart defects (CHDs) in live singleton offspring in Shenzhen, 2017–2019 (n = 53,708). †Model 1, adjusted for maternal age, maternal education level, mode of conception, parity, gestational diabetes and offspring sex. ‡Model 2, adjusted for maternal age, maternal education level, mode of conception, parity, gestational diabetes, pregestational diabetes and offspring sex. CI, confidence interval.

more likely to have tetralogy of Fallot (aOR 2.49, 95% CI 0.62–9.96), but the difference was not significant (Table S4). Comparisons of other phenotypes were hampered because of their rare incidence.

Maternal obesity and PGDM

The association between maternal obesity and PGDM was investigated and presented in Table 2. The adjusted risk ratios for PGDM according to maternal BMI were 0.65 (95% CI

Table 2 | Logistic regression of the correlation between body mass index and pregestational diabetes in live singleton offspring in Shenzhen, 2017–2019

BMI (kg/m^2)	Adjusted odds ratio (95% CI)†	*P*
Normal	1.00	–
Underweight	0.65 (0.42–1.01)	0.06
Overweight	2.84 (2.23–3.61)	<0.01
Obesity	7.53 (5.41–10.48)	0.01

†Total n = 53,708. Adjusted for maternal age, maternal education level, mode of conception, parity and offspring sex. BMI, body mass index; CI, confidence interval; PGDM, pregestational diabetes.

0.42–1.01) for underweight mothers and 2.84 (95% CI 2.23–3.61) for overweight mothers after adjusting for maternal age, maternal education level, mode of conception, parity and offspring sex. Maternal obesity (aOR 7.53, 95% CI 5.41–10.48) was significantly associated with increased risks of PGDM.

PGDM and the risk of CHDs

The proportion of offspring exposed to maternal pregestational diabetes was 0.69% (n = 370); the offspring of women with PGDM were 6.88-fold (95% CI 4.11–11.53, $P < 0.01$) more likely to have CHDs than the offspring of mothers without PGDM (Table 3).

Mediation effect of PGDM on the association between obesity and CHDs

The association between maternal obesity and offspring CHDs became weaker and non-significant when the model was additionally adjusted for maternal PGDM in model 2 compared with model 1 without adjustment for maternal PGDM (Figure 2).

First, we hypothesized that there was an interaction effect between maternal obesity and PGDM on offspring CHDs. Interaction and stratified analyses were carried out, but we found no interaction effect between maternal obesity and PGDM (P = 0.40; Table S5). Therefore, we carried out further mediation effect analysis.

The total effect was decomposed into a direct effect (OR 1.67, 95% CI 0.97–2.87) and an indirect effect (mediation effect; OR 1.18, 95% CI 1.06–1.32), which attributed the effect of maternal obesity on offspring CHDs through PGDM (Figures 3 and 4). The estimated mediation proportion was 24.83%.

Table 3 | Logistic regression of the correlation between pregestational diabetes and congenital heart defects in live singleton offspring in Shenzhen, 2017–2019

PGDM	Adjusted odds ratio (95%CI)†	*P*
No	1.00	–
Yes	6.88 (4.11–11.53)	<0.01

†Total n = 53,708. Adjusted for maternal age, maternal education level, mode of conception, parity and offspring sex. CHDs, congenital heart defect; CI, confidence interval; PGDM, pregestational diabetes.

DISCUSSION

This was a large population cohort study carried out in Shenzhen, China. The overall incidence of CHDs in live singleton offspring was 0.69%. Among the CHDs, septal defects (VSDs, ASDs) were the most common types of CHDs, accounting for 53.49% of CHDs. Possible explanations include selective termination of severe/complex CHD cases after prenatal diagnosis and differences in CHD classification.

Although the distribution of BMI in the present study was different from the distribution of BMI in European and USA study populations, and there were relatively few cases of obesity, we found that the overall risks of congenital heart defects, and the risk of left ventricular outflow tract obstruction and VSD progressively increased with maternal obesity. Additionally, we did not find significant differences in the offspring CHDs incidences in the underweight or overweight groups. The present results suggest that maternal obesity is a risk factor for the occurrence of offspring CHDs. This finding is consistent with findings from some studies that focused on CHDs, reporting increasing risks with maternal obesity[28,29].

However, this finding contrasts with a previous study in China. Xuelian *et al.*[21] reported that the risk of CHDs was significantly higher among mothers with prepregnancy underweight and low-to-average BMI, and they failed to observe any significant relationships between prepregnancy overweight or obesity and the risk of CHDs in offspring, even when using different cut-off values to define reference groups. This difference might be due to the relatively small number of overweight women in their study.

The mechanisms underlying the association between obesity and CHDs are largely unknown. It is well established that women who are overweight or obese can be affected by insulin resistance or abnormal glucose control[30]. Both animal and human studies have shown that hyperglycemia during pregnancy plays an important role in embryonic development[31]. This is why PGDM was introduced in the present study, and we wanted to know whether PGDM had an impact on the relationship between maternal obesity and CHDs. In previous studies, some researchers considered PGDM as a confounding factor, whereas some studies excluded PGDM populations[29]. To our knowledge, this is the first study to analyze the mediation effect of maternal PGDM on the association between maternal obesity and offspring CHDs. The present results showed that PGDM partially mediates the effect of maternal obesity on CHDs. If diabetes mellitus is well controlled in obese women before pregnancy, the risk of congenital heart defects in offspring can be reduced by 24.83%.

Additionally, adipose tissue is an active metabolic and endocrine organ[32], and there are some teratogenic mechanisms other than abnormal glucose metabolism, such as

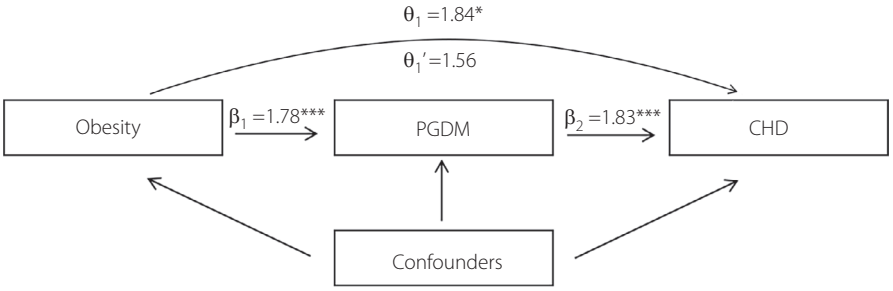

Figure 3 | The mediation effects. θ_1 is the adjusted odds ratio of maternal obesity on congenital heart defects (CHD) adjusting for maternal age, maternal education level, mode of conception, parity, gestational diabetes and offspring sex. θ_1' is the adjusted odds ratio of maternal obesity on CHDs additionally introducing pregestational diabetes (PGDM) into the model. β_1 is the coefficient of maternal obesity on PGDM adjusted for maternal age, maternal education level, mode of conception, parity, GDM and offspring sex. β_2 is the coefficient of PGDM on CHDs adjusted for maternal age, maternal education level, mode of conception, parity, GDM, offspring sex and maternal obesity. ***P*-value <0.05; ****P*-value <0.001.

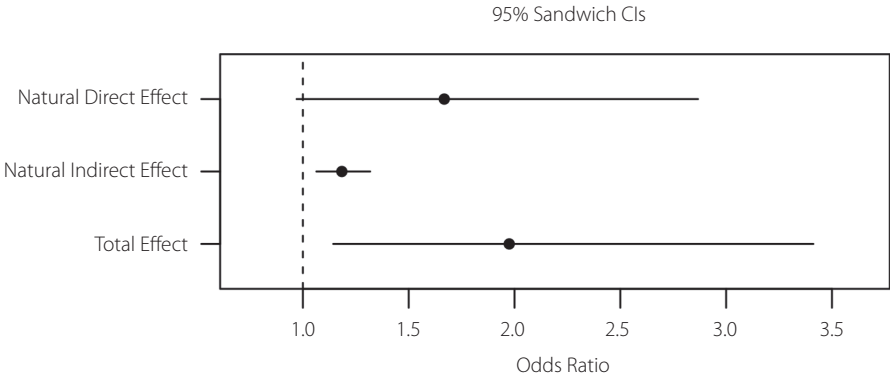

Figure 4 | The decomposition of effect of maternal obesity on congenital heart defects. CI, confidence interval.

inflammation, vascular dysfunction and abnormal placental metabolism[33], which might adversely influence organogenesis and fetal development. More research on mechanism is of great significance for precise prevention. These are the directions of our future research. In addition, the study of mechanism is also helpful to the treatment direction[34,35].

In the present study, maternal BMI was calculated on the basis of weight and height measured in early pregnancy, which reduces the risks of recall and selection bias. Because we gathered information from the Shenzhen Maternal and Child Information System, we had an opportunity to supplement and correct the information of infants with the diagnosis of CHDs within the first year of life. Most importantly, we first studied the mediation effect of PGDM on the relationship between maternal obesity and CHDs.

However, several limitations of the study should be acknowledged. First, we lacked information about CHDs in situations of stillbirth, miscarriage or induced abortions. Malformations are more common in pregnancies with miscarriage or stillbirth, and prenatal diagnosis of severe or complex CHDs might also lead to induced abortion. Therefore, it is ideal to diversify research population to stillbirth, miscarriage and induced abortions. Second, we did not classify the PGDM into type 1 or type 2 diabetes, which are different in pathophysiology. It would be of interest to classify the types of PGDM to identify a more precise mechanism. Finally, we were unable to collect data on enough cases of some specific rare phenotype for further analysis.

In conclusion, the present study notes that maternal obesity is an independent risk factor for overall congenital heart defects. In addition, we conclude that PGDM partially mediates the association between maternal obesity and CHDs. Screening of PGDM and the adjustment of glucose play an important role in reducing the risk for fetal heart defects in obese women. The mechanisms underlying the associations between maternal obesity and the risk of offspring CHDs need to be further investigated to provide individualized treatment plans for high-risk populations.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The Ethics Committee of Shenzhen Maternity and Child Health Care Hospital, Guangdong, China.

Informed consent: All the participants signed an informed consent form.

Approval date of registry and the registration no. of the study/-trial: Approval number: Shenzhen Maternal and Child Ethics Review No.23; Approval date: 2017-04-07.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Body mass index and incidence of specific congenital heart defects in live singleton offspring in Shenzhen, 2017–2019 (n = 53,708).

Table S2 | Logistic regression of the correlation between body mass index and left ventricular outflow tract obstruction in live singleton offspring in Shenzhen, 2017–2019 (n = 53,708).

Table S3 | Logistic regression of the correlation between body mass index and ventricular septal defects in live singleton offspring in Shenzhen, 2017–2019 (n = 53,708).

Table S4 | Logistic regression of the correlation between body mass index and tetralogy of Fallot in live singleton offspring in Shenzhen, 2017–2019 (n = 53,708).

Table S5 | Logistic regression to identify the interaction effect between maternal obesity and pregestational diabetes on the risk of offspring congenital heart defects (n = 53,708).