Maternal Obesity and the Risk of Congenital Heart Defects: the Mediation Effect of Pregestational Diabetes

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Abstract

Background Congenital heart defects (CHDs) are the most common birth defects worldwide. Maternal obesity has been proposed as a risk factor for CHDs, but the results are controversial and inconclusive. Pregestational diabetes (PGDM) is well known as a risk factor for CHDs and is closely related to obesity. However, the effect of PGDM on the association between maternal obesity and CHDs has not been investigated.

Objectives We aimed to explore the association between maternal obesity and CHDs and to further evaluate the mediation effect of PGDM on this association.

Methods We involved 53708 mother-infant pairs with deliveries between 2017 and 2019 from the Birth Cohort in Shenzhen (BiCoS). Mothers were categorized into four groups: the underweight group ($\text{BMI} < 18.5$), normal weight group ($18.5 \leq \text{BMI} < 24$), overweight group ($24 \leq \text{BMI} < 28$) and obesity group ($\text{BMI} \geq 28$). To evaluate the association between BMI and CHDs, we fit multivariable logistic regression models, adjusting for maternal age, maternal education level, mode of conception, parity, GDM and offspring sex. Mediation analysis was used to confirm the mediation effect of PGDM on the association between maternal obesity and CHDs.

Results The proportion of obese individuals in the BiCoS was 2.11%. Overall, 372 (0.69%) infants were diagnosed with CHDs. The prevalence of CHDs in underweight, normal weight, overweight and obese individuals was 0.64%, 0.68%, 0.72% and 1.24%, respectively. Maternal obesity was associated with an increased risk of CHDs ($\text{OR}=1.97$, 95% CI 1.14–3.41). The offspring of women with PGDM were 6.88 times (95% CI 4.11–11.53) more likely to have CHDs than the offspring of mothers without PGDM. The mediation effect of PGDM on the association between maternal obesity and CHDs was significant ($\text{OR}=1.18$, 95% CI 1.06–1.32). The estimated mediation proportion was 24.83%.

Conclusion Our findings suggested that maternal obesity was associated with CHDs and that 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 a leading cause 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 conducted in China^[8], the prevalence of CHDs was 4.905‰ from 2015–2019.

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, pre-gestational diabetes, smoking, alcohol

consumption and rubella infection^[10-16]. A better understanding of the origins of CHDs is needed 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 ($\text{BMI} \geq 35 \text{ kg/m}^2$)^[17]. Obesity in pregnancy adversely influences both foetal and neonatal outcomes^[18], including increased risks of major congenital malformations. A population-based study conducted 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 prepregnancy 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 demonstrated that PGDM is a risk factor for CHD and all CHD subtypes^[9]. Despite their different pathophysiological mechanisms, both type 1 and type 2 diabetes contribute to the risk of CHD^[23]. 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%^[24, 25], 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.

This study aims to explore the association between maternal obesity and CHDs. This is the first study to investigate the mediation effect of PGDM on the association between maternal obesity and CHDs.

Methods

Data sources and study population

This cohort study was conducted in Shenzhen Maternity and Child Health Care Hospital. Regular antenatal examination was performed, 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 1) had complete inspection and delivery information in the hospital, 2) had complete newborn information, and 3) had a single-child live birth. We excluded mother-child pairs who had 1) stillbirths, 2) multiple births, 3) foetal chromosomal abnormalities, 4) extracardiac birth defects, 5) physical/chemical contact history and maternal CHDs history, and 6) missing data on weight or height at the beginning of pregnancy.

The enrolment process was as follows (Fig 1): Twins and triplets ($n=1944$) were excluded. Women who delivered infants with chromosomal abnormalities/extracardiac defects ($n=1896$) 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, 53708 live singleton births from 2017 to 2019 (including 1159 women who delivered more than once) were enrolled.

This research was approved by the Ethics Committee of Shenzhen Maternity and Child Health Care Hospital, Guangdong, China (approval number: Shenzhen Maternal and Child Ethics Review No.23). All the participants signed an informed consent form.

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 and bras. The Omron (HNN-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 China Obesity Working Group in 2001^[26], 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 ($BMI \geq 28$).

PGDM was diagnosed when any of the following criteria were met^[27]: diabetes diagnosed before the index pregnancy or in the first trimester or early second trimester, a fasting plasma glucose of 126 mg/dL or greater, or a 2-hour glucose of 200 mg/dL or greater on a 75-g oral glucose tolerance test.

Outcomes

The main outcome was the presence of any heart defects in liveborn infants. The diagnosis and classification of CHDs were confirmed by ultrasound in our hospital. The offspring CHD diagnosis was supplemented and corrected according to the information of the Shenzhen Maternal and Child Information System within one 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^[28]. These phenotypes were heterotaxia, conotruncal defects (including truncus arteriosus, tetralogy of Fallot, transposition of the great arteries, other), atrioventricular septal defect (AVSDs), total anomalous pulmonary venous return (TAPVR), left ventricular outflow tract obstruction (LVOTO; including coarctation of the aorta, valvular aortic stenosis, other), right ventricular outflow tract obstruction (RVOTO, 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 our 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 chi-square 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 was performed using the "geeglm" package to adjust for the correlation between mothers who gave birth more than once within the study period. A multivariate analysis model was adjusted for maternal age, maternal education level, mode of conception, parity, GDM, and offspring sex. Interaction and stratified analyses were conducted according to obesity and PGDM. Mediation analysis was performed using the "medflex" package in R 3.6.3, and the other analyses were conducted using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered statistically significant.

Results

General characteristics

The characteristics of mothers and births were 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

Fig 2 showed the distribution of BMI. The prevalence of obesity was only 2.11%. Overall, 372 (0.69%) offspring were diagnosed with a congenital heart defect (Table 1). The incidence of CHDs in 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 congenital heart defects 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 (aOR=1.97, 95% CI 1.14–3.41) had a significantly higher risk of total CHDs (Fig 2).

The specific CHD phenotypes distributed in groups according to BMI were described in Supplementary Table 2. In our study, the proportion of complex heart defect was 7.26% (27/372). For obese mothers, significantly increased risks were observed for LVOTO (aOR = 5.69, 95% CI 1.62-19.90) and VSD (aOR =

2.58, 95% CI 1.24-5.40) (Supplementary Table 3, Supplementary Table 4). At the same time, offsprings of obese mothers were more likely to have TOF, but the difference was not significant (Supplementary Table 5). 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 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, maternal GDM 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 pre-gestational diabetes was

0.69% (n=370); the offspring of women with PGDM were 6.88 times (95% CI 4.11–11.53, $p<0.01$) more likely to have CHDs than the offspring of mothers without PGDM (Table 3).

The mediation effect of PGDM on the association between obesity and CHDs

The association between maternal obesity and offspring CHDs became weaker and nonsignificant when the model was additionally adjusted for maternal PGDM in model 2 compared to the model without adjustment for maternal PGDM (Fig 2).

First, we hypothesized that there was an interaction effect between maternal obesity and PGDM on offspring CHDs. Interaction and stratified analyses were conducted, but we found no interaction effect between maternal obesity and PGDM (Supplementary Table 1). Therefore, we conducted 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 (Fig 3, Fig 4). The estimated mediation proportion was 24.83%.

Discussion

This is a large population cohort study conducted in Shenzhen, China. The overall incidence of CHDs is 0.69%. Among the CHDs, septal defects (VSDs, ASDs) are the most common type of CHDs, accounting for 53.49% of CHDs. The incidence of complex CHDs is lower than that reported abroad. 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 study was different from the distribution of BMI in European and American study populations and there were relatively few cases of obesity, we found that the overall risks

of congenital heart defects and the risk of LVOTO progressively increased with maternal obesity. Additionally, we did not find a significant difference in the offspring CHDs incidences in the underweight/overweight groups. Our results suggest that maternal obesity is an independent risk factor for the occurrence of offspring CHDs. This finding is consistent with findings from some researches focused on CHDs, reporting increasing risks with maternal obesity^[29, 30].

However, this finding contrasts with previous studies in China. Xuelian^[21] et al reported that the risk of CHDs was significantly higher among mothers with prepregnancy underweight and low-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 may 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^[31]. Both animal and human studies have shown that hyperglycaemia during pregnancy plays an important role in embryonic development^[32]. This is why PGDM was introduced in our study, and we wanted to know whether PGDM plays a role in the relationship between maternal obesity and CHDs. In previous studies, some researchers considered abnormal PGDM as a confounding factor, while some studies have excluded PGDM populations^[30]. To our knowledge, this is the first time to analyse the mediation effect of maternal PGDM on the association between maternal obesity and offspring CHDs. Our results showed that PGDM mediated 24.83% of the effect of maternal obesity on CHDs.

Additionally, adipose tissue is an active metabolic and endocrine organ^[33], and there are some teratogenic mechanisms other than abnormal glucose metabolism, such as inflammation, vascular dysfunction, and abnormal placental metabolism^[34], which may adversely influence organogenesis and foetal development. These are the directions of our future research.

Strengths and limitations

In our 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 used data 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 may 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 have different pathophysiologies. It would be of interest to classify the types of PGDM to identify a more

precise mechanism. Third, we were unable to collect data on enough cases of some specific rare phenotype for further analysis.

Conclusions

In conclusion, our study notes that maternal obesity is an independent risk factor for overall congenital heart defects. Our findings support the potential importance of interventions to reduce prepregnancy obesity as an important strategy to reduce offspring congenital heart defects. In addition, according to our findings, we conclude that PGDM partially mediates the association between maternal obesity and CHDs. 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.

Declarations

Authors' contributions

Xiao-Xia Wu, Lin-Lin Wu and Jian-Min Niu made substantial contributions to conception and design; Xiao-Xia Wu was a major contributor in writing the manuscript. Ru-Xiu Ge and Le Huang analyzed and interpreted the patient data; Fu-Ying Tian revised it critically for important intellectual content; Yi-Xuan Chen made acquisition of data. All authors read and approved the final manuscript.

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Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication

All the participants signed an informed consent form for publication.

Ethics approval and consent to participate

This research was approved by the Ethics Committee of Shenzhen Maternity and Child Health Care Hospital, Guangdong, China (approval number: Shenzhen Maternal and Child Ethics Review No.23). All the participants signed an informed consent form to participate.

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Tables

Table 1 Maternal and Birth characteristics and CHDs in live singleton Birth in Shenzhen, 2017–2019

CHDs				
Characteristics	Total No (N=53708)	No(per 100) (n=372)	Unadjusted odds ratio (95%CI)	P value
Maternal age(years)				
<20	82	22.44	3.330.54-10.72	0.10
20~<25	2640	190.72	0.970.58-1.53	0.89
25~<30	17186	1280.74	1.00	
30~<35	20576	1370.67	0.890.70-1.14	0.36
35~<40	11165	710.64	0.850.63-1.13	0.28
≥40	2059	150.73	0.980.55-1.62	0.94
Maternal education level				
High school and below	17949	1861.04	1.99(1.61-2.46)	0.001
College	30932	1620.52	1.00	
Master and above	4827	240.50	0.95(0.60-1.43)	0.81
Mode of conception				
Naturally	51984	3540.68	1.00	
Assisted	1724	181.04	1.54(0.92-2.40)	0.07
Parity				
Primipara	24824	1950.79	1.00	
Multipara	28884	1770.61	0.770.63-0.96	0.02
PGDM				
No	53338	3560.67	1.00	
Yes	370	164.32	6.733.87-10.85	0.001
GDM				
No	45159	3250.72	1.00	
Yes	8549	470.55	0.760.55-1.03	0.08
Sex of Offspring				
Female	25220	1930.77	1.00	
Male	28488	1790.63	0.82(0.67-1.01)	0.06

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

Table 2 Logistic regression of the correlation between BMI and PGDM in live singleton offspring in Shenzhen, 2017–2019 (N=53708)

BMI (kg/m2)	*Adjusted odds ratio (95%CI)	P
normal	1.00	-
underweight	0.65(0.42-1.01)	0.06
over weight	2.84(2.23-3.61)	<0.01
obesity	7.53(5.41-10.48)	0.01

BMI indicates body mess index; PGDM indicates pregestational diabetes; CI indicates confidence interval.

*Adjusted for maternal age, maternal education level, mode of conception, parity, offspring sex

Table 3 Logistic regression of the correlation between PGDM and CHDs in live singleton offspring in Shenzhen, 2017–2019(N=53708)

PGDM	*Adjusted odds ratio (95%CI)	P
no	1.00	-
yes	6.88(4.11-11.53)	0.01

CHDs indicates congenital heart defect; PGDM indicates pregestational diabetes; CI indicates confidence interval.

*Adjusted for maternal age, maternal education level, mode of conception, parity, offspring sex

Figures

Figure 1

Flow chart of participants

Figure 2

Logistic regression of the correlation between BMI and CHDs in live singleton offspring in Shenzhen, 2017–2019 (N=53708) *: Model 1, adjusted for maternal age, maternal education level, mode of conception, parity, GDM, offspring sex **: Model 2, adjusted for maternal age, maternal education level, mode of conception, parity, GDM, PGDM, offspring sex BMI indicates body mess index; CHDs indicates congenital heart defects; CI indicates confidence interval.

Figure 3

The mediation effects. θ_1 is the aOR of maternal obesity on CHDs adjusting for maternal age, maternal education level, mode of conception, parity, GDM and offspring sex. θ_1' is the aOR of maternal obesity on CHDs additionally introducing PGDM into 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 CHDs CI indicates confidence interval.

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