Association of maternal weight gain in early pregnancy with congenital heart disease in offspring: a China birth cohort study

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ABSTRACT

Objectives Little study has reported the association of maternal weight gain in early pregnancy with fetal congenital heart disease (CHD). We aimed to explore the potential relationship based on a China birth cohort while adjusting by multiple factors.

Design Cohort study.

Setting China birth cohort study conducted from 2017 to 2021.

Participants The study finally included 114 672 singleton pregnancies in the 6–14 weeks of gestation, without missing data or outliers, loss to follow-up or abnormal conditions other than CHD. The proportion of CHD was 0.65% (749 cases).

Primary and secondary outcome measures Association between maternal pre-pregnancy weight gain and CHD in the offspring were analysed by multivariate logistic regression, with the unadjusted, minimally adjusted and maximally adjusted methods, respectively.

Results The first-trimester weight gain showed similar discrimination of fetal CHD to that period of maternal body mass index (BMI) change (DeLong tests: p=0.091). Compared with weight gain in the lowest quartile (the weight gain less than 0.0 kg), the highest quartile (over 2.0 kg) was associated with a higher risk of fetal CHD in unadjusted (OR 1.36, 95% CI: 1.02 to 1.72), minimally adjusted (adjusted OR (aOR) 1.29, 95% CI: 1.02 to 1.63) and maximally adjusted (aOR 1.29, 95% CI: 1.02 to 1.63) models. The association remains robust in pregnant women with morning sickness, normal pre-pregnancy BMI, moderate physical activity, college/university level, natural conception or with folic acid (FA) and/or multivitamin supplementation.

Conclusions and relevance Although the association of maternal pre-pregnancy weight gain on fetal CHD is weak, the excessive weight gain may be a potential predictor of CHD in the offspring, especially in those with morning sickness and other conditions that are routine in the cohort, such as normal pre-pregnancy BMI, moderate physical activity, college/university level, natural conception or with FA and/or multivitamin supplementation.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital disability, affecting 17.9 per 1000 newborns worldwide, and occupies the first place in the incidence of perinatal congenital disabilities in China, according to the report in 2012. The aetiology of CHD is complex and influenced by environmental and genetic factors. An umbrella review, including 165 meta-analyses of different environmental factors and CHD, found a significant summary association of severe obesity (relative risk: 1.38, 95% CI: 1.30 to 1.47).

Currently, most studies focus on the effect of maternal weight status before or during pregnancy on fetal CHD and less on the influence of maternal weight gain in early pregnancy. A meta-analysis, containing more than 1 150 000 cases obtained from 13 case–control studies and 4 cohort studies, indicated significant associations between maternal overweight status or maternal obesity and the risk for CHD in infants (overweight: OR=1.065, 95% CI: 1.021 to 1.100; obesity: OR=1.174, 95% CI: 1.146 to 1.203) but had little evidence of maternal underweight status. 
Advanced maternal age may be a potential risk factor for CHD,7 8 but some studies found little evidence.9 10

Although inappropriate gestational weight gain (GWG) is often associated with adverse perinatal outcomes, adequate GWG is relatively confusing.11–13 The US Institute of Medicine (IOM) provided recommendations on the total GWG as well as rates of GWG during the second and third trimesters, based on the pre-pregnancy body mass index (BMI).13

Little study has reported the influence of maternal weight gain in early pregnancy on the risk of fetal CHD adjusted by multiple factors. The potential association of it with fetal CHD might differ by these maternal factors. We hypothesised that maternal weight gain during early pregnancy was associated with the risk of CHD in offspring. Therefore, our study aimed to describe maternal weight gain in early pregnancy and analyse its influence on fetal CHD, adjusted by maternal age, maternal pre-pregnancy BMI, morning sickness and other confounding factors.

METHODS

Study design and data sources

All the data was obtained from the China birth cohort study (CBCS),14 a prospective longitudinal and the first national-based birth cohort study. The CBCS was conducted in 38 research centres in China.15 The quality control measures on data homogeneity are essential in a multicentre cohort study. The study cohort, followed-up strategies, data collection and data management can be found in the published paper. From the commencement of CBCS to 31 August 2021 about 144585 records were obtained in the CBCS electronic system (including full-term birth, preterm birth, stillbirth, miscarriage, induced labour, confirmed loss to follow-up, etc). Participants’ information was extracted from the CBCS electronic systems by their unique identification, containing information on the early pregnancy information questionnaire and the delivery outcome.

Exclusion criteria included missing early pregnancy information questionnaire (n=11 868), multiple pregnancies (n=2778), missing data or outliers for parental weight/height (n=167), loss to follow-up (n=176) and abnormal condition of mother and fetus other than fetal CHD (n=7029, including fetal malformation, miscarriage, pregnancy loss, premature birth, low birth weight, fetal macrosomia, etc), not within the range of 6–14 weeks of gestation (n=7895). Thus, the final analysis included 114672 singleton pregnancies according to the inclusion and exclusion criteria (figure 1).

Participation in the research was voluntary, and each subject obtained written informed consent. Besides, this study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (Reference No. 2018-KY-003-02).

Patient and public involvement statement

In CBCS, women were enrolled in early pregnancy and completed the baseline questionnaire with 97 questions.14

Figure 1 Flowchart of the selection of study participants. CHD, congenital heart disease.
Data collection and measurements

This study collected the following information: (1) Demographic characteristics include maternal weight before or in early pregnancy, age, ethnicity and occupation. (2) Lifestyle behaviours include maternal secondhand smoke exposure, drinking and smoking. (3) Current pregnancy information includes conception method, parity, morning sickness, folic acid (FA) and/or multivitamin supplementation and pregnancy outcome. The CHD in the offspring was evaluated by a trained obstetrician, paediatrician or cardiologist before discharge or within 3 days after birth, including live births, stillbirths and late miscarriages diagnosed with CHD. If controversy persists, suspected cases are further determined by echocardiography, MRI or autopsy. Unfortunately, we only obtained information on the presence or absence of CHD in offspring without the specific subtypes. Still, concerning a published article using data from the CBCS,15 the three most common types were ventricular septal defect, multiple CHD and tetralogy of Fallot.

Weight was accurately measured using an electronic scale (BW-150; UWE, Beijing, China), with participants wearing light clothes, no shoes and empty pockets.15 Based on the WHO criteria, BMI was categorised as obesity (BMI≥30.0 kg/m²), overweight (25.0–29.9 kg/m²), normal (18.5–24.9 kg/m²) and low (<18.5 kg/m²). The maternal first-trimester weight change was the weight of the early pregnancy (kg) minus that of the pre-pregnancy (kg). Gestational weeks were calculated by the survey date minus the last menstrual period. The maternal weight change in the first trimester was divided into four grades based on interquartile values. The BMI change was the maternal BMI (kg/m²) in early pregnancy minus pre-pregnancy (kg/m²). The occupation was divided into three classes: (1) Active (eg, farmer or manual worker); (2) moderate (eg, teachers, salespeople or clerks); (3) light (eg, unemployed). Morning sickness, FA and/or multivitamin supplementation were divided into two levels: Yes or No.

Statistical analysis

Data calculations and statistical analyses were performed using IBM SPSS Statistics V.22 and R V.4.2.2 (a free software environment for statistical computing and graphics). Quantitative data were expressed by the mean and SD or medium and quartile range, while qualitative data were described by frequency and percentage.

As appropriate, the \( \chi^2 \) test, t-test or Mann-Whitney U test was performed to calculate differences for numerical and categorical variables. The receiver-operating characteristics curve (ROC) and the area under ROC (AUC) were used to assess predictive performances of maternal weight change and maternal BMI change in the first trimester for fetal CHD, and the DeLong test to compare the AUCs of these two variables. The association on fetal CHD was analysed by performing multivariate logistic regression (LR) analyses, calculating OR or adjusted OR (aOR) with 95% CI in unadjusted, minimally adjusted and maximally adjusted methods. Sensitivity analysis was done in subgroups to identify the robustness of the association of the maternal weight change in early pregnancy with fetal CHD, which included morning sickness (Yes or No), FA and/or multivitamin supplementation (Yes or No), BMI before pregnancy (normal, low or overweight and obesity), age (<35 years or ≥35 years), educational level (college or university, high school or below and postgraduate), physical activity (moderate, light and active), gestational week (6 weeks~, 9 weeks ~ or 12 weeks~) and mode of conception (natural or assisted). Unadjusted and minimally adjusted LR analyses were performed, respectively. The minimally adjusted analyses were adjusted for the elements except for the stratification factor. A p value <0.05 was considered statistically significant.

RESULTS

Characteristics

This study ultimately included 114 672 singleton pregnancies, including 749 (0.65%) cases with fetal CHD. The mean of maternal first-trimester weight change was 1.1±2.4 kg, and the medium was 1.0 (0.0, 2.0).

Online supplemental table A1 in the online supplemental appendix shows the percentile of weight gain in different groups, including all participants, fetal CHD, maternal pre-pregnancy BMI, gestational week and morning sickness. Table 1 presents the significant differences in weight gain among gestational weeks, age, BMI, educational level, physical activity, smoking, drinking status, FA and/or multivitamin supplementation and morning sickness. After dividing first-trimester weight gain into four grades by the quartiles, the number and rate of CHD in the first quartile (Q1, <0.0 kg) was 99 (0.5%), 211 (0.7%) in the second (Q2, 0.0–0.9 kg), 168 (0.7%) in the third (Q3, 1.0–1.9 kg) and 271 (0.7%) in the fourth (Q4, 2.0 kg~) quartile (online supplemental appendix figure A1). The characteristics of the non-CHD and CHD group participants are shown in online supplemental appendix table A2. Compared with the non-CHD group, the pregnant women with CHD in offspring were older (mean age of 30.8 vs 29.7 years old, respectively), had less morning sickness (59.6% vs 53.5%) and a higher increase in maternal weight change (mean change of 1.3 kg vs 1.1 kg) and maternal BMI change (0.5 kg/m² vs 0.4 kg/m²).

Association of the change of weight and BMI in early pregnancy with CHD

The association of maternal weight gain with fetal CHD was similar to BMI in early pregnancy (AUC: 0.517 vs 0.519; DeLong tests: p=0.091). In addition, the association seemed to exist in the women with a normal level of...
<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Weight change (kg)</th>
<th>P value</th>
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<tr>
<td></td>
<td></td>
<td>Mean±SD</td>
<td>Medium (Q1, Q3)</td>
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<tr>
<td>Total</td>
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<td>1.0 (0.0, 2.0)</td>
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<td>&lt;35</td>
<td>99899</td>
<td>1.1±2.4</td>
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<td>≥35</td>
<td>14773</td>
<td>1.3±2.3</td>
<td>1.0 (0.0, 2.0)</td>
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<td>Maternal BMI before pregnancy (kg/m²)</td>
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<td></td>
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<td>Normal</td>
<td>83488</td>
<td>1.1±2.3</td>
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<td>Low</td>
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<td>1.3±2.1</td>
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<td>1.0 (0.0, 2.0)</td>
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<tr>
<td>Obesity</td>
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<td>1.2±3.6</td>
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<tr>
<td>Han</td>
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<td>1.1±2.4</td>
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<td>Minority</td>
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<td>Maternal physical activity, n (%)</td>
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<td>Light</td>
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<td>Parity, n (%)</td>
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<td>Multipara</td>
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<td>Nullipara</td>
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<td>1.2±2.4</td>
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<td>Maternal smoking, n (%)</td>
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<td>1.1±2.4</td>
<td>1.0 (0.0, 2.0)</td>
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<td>Yes</td>
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<td>1.8±2.6</td>
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<td>Maternal secondhand smoke exposure, n (%)</td>
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<td>Yes</td>
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<td>Maternal drinking, n (%)</td>
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<td>1.1±2.4</td>
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<td>Yes</td>
<td>3708</td>
<td>1.4±2.4</td>
<td>1.0 (0.0, 2.6)</td>
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<td>Mode of conception, n (%)</td>
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<td>1.0 (0.0, 2.0)</td>
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<td>Assisted reproduction</td>
<td>4423</td>
<td>1.2±2.5</td>
<td>1.0 (0.0, 2.4)</td>
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<td>Morning sickness</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>46346</td>
<td>1.4±2.1</td>
<td>1.0 (0.0, 2.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>68326</td>
<td>0.9±2.5</td>
<td>1.0 (0.0, 2.0)</td>
</tr>
<tr>
<td>FA and/or multivitamin supplementation</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>3199</td>
<td>0.9±2.5</td>
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<tr>
<td>Yes</td>
<td>111473</td>
<td>1.1±2.4</td>
<td>1.0 (0.0, 2.0)</td>
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<td>Gestational week (weeks)</td>
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<td>6~</td>
<td>31787</td>
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<td>1.0 (0.0, 2.0)</td>
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<td>9~</td>
<td>34566</td>
<td>1.0±2.4</td>
<td>1.0 (0.0, 2.0)</td>
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</table>

Continued
pre-pregnancy BMI (online supplemental appendix table A3).

The influence of the maternal weight gain in early pregnancy on CHD in offspring

Online supplemental table A2 presents the results of univariate analyses. Besides, table 2 shows the results of unadjusted (adjusted for none), minimally adjusted (adjusted for the gestational week, age, BMI and morning sickness) and maximally adjusted (minimally adjusted model plus ethnicity, physical activity, smoking, drinking, parity and mode of conception) multivariate LR models. When weight gain was included as a continuous variable, it was associated with a higher risk of fetal CHD. In the unadjusted LR model, the first-trimester weight gain showed a risk effect on CHD in crude (OR 1.04, 95% CI: 1.01 to 1.07), minimally adjusted (aOR 1.04, 95% CI: 1.01 to 1.08) and maximally adjusted (aOR 1.04, 95% CI: 1.01 to 1.08) LR models. After dividing first-trimester weight gain into four grades by the quartiles, the results showed that compared with weight gain in the first quartile (less than 0.0 kg), the fourth quartile (over 2.0 kg) was associated with a higher risk CHD in offspring (unadjusted model: 1.36 (1.08–1.72); minimally adjusted model: 1.29 (1.02–1.62); maximally adjusted model: 1.29 (1.02–1.63)).

Sensitivity analysis

Unadjusted and minimally adjusted models were used to evaluate further the association of the maternal weight change in early pregnancy with fetal CHD in various subgroups, including morning sickness, maternal BMI before pregnancy, FA and/or multivitamin supplementation, age, educational level, maternal physical activity, gestational week and mode of conception (figure 2, online supplemental appendix table A4). In the adjusted models, compared with weight gain less than 0.0 kg in early pregnancy, over 2.0 kg was associated with a higher risk of CHD in pregnant women who had morning sickness (aOR 1.37, 95% CI: 1.03 to 1.82), normal pre-pregnancy BMI (aOR 1.42, 95% CI: 1.08 to 1.88), moderate physical activity (aOR 1.46, 95% CI: 1.02 to 2.10), college/university level (aOR 1.41, 95% CI: 1.06 to 1.87), natural conception (aOR 1.32, 95% CI: 1.04 to 1.68) or with FA and/or multivitamin supplementation (aOR 1.28, 95% CI: 1.01 to 1.62) (figure 2). Besides, the sensitivity analysis in those unadjusted models showed similar results (online supplemental appendix table A4).

DISCUSSION

Main findings of this study

This study was based on the China birth cohort study. It included a large sample size of 114672 singleton pregnancies, allowing us to explore the potential association of maternal weight change in early pregnancy with fetal CHD in subgroups and adjusting for some potential confounders, including current pregnancy information, lifestyle behaviours and demographic characteristics. The association of maternal weight gain in early pregnancy with fetal CHD was similar to maternal BMI change at the normal level of maternal pre-pregnancy BMI. When regarding maternal weight gain as a continuous variable, it was associated with a higher risk of CHD in offspring.

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted model OR (95% CI)</th>
<th>Minimally adjusted model aOR (95% CI)</th>
<th>Maximally adjusted model aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (continuous)</td>
<td>1.04 (1.01 to 1.07)</td>
<td>1.04 (1.01 to 1.08)</td>
<td>1.04 (1.01 to 1.08)</td>
</tr>
</tbody>
</table>

Weight change

- Q1 (<0.0 kg): Ref
- Q2 (0.0–0.9 kg): 1.44 (1.14 to 1.83)
- Q3 (1.0–1.9 kg): 1.43 (1.11 to 1.83)
- Q4 (≥2.0 kg): 1.36 (1.08 to 1.72)

P for trend: 0.070

Unadjusted model: adjusted for none, the crude LR model. Minimally adjusted model: adjusted for the gestational week, age, body mass index and morning sickness. Maximally adjusted model: minimally adjusted factors plus ethnicity, physical activity, smoking, drinking, parity and mode of conception. aOR, adjusted OR; CHD, congenital heart disease; LR, logistic regression; Ref, reference.
After dividing it into four grades by the quartiles, the results showed that compared with a weight gain of less than 0.9 kg in early pregnancy, over 2.0 kg was associated with a higher risk of fetal CHD. Besides, the association was found in subgroups of women who had morning sickness, normal pre-pregnancy BMI, moderate physical activity, college/university level, natural conception or FA and/or multivitamin supplementation. However, it is uncertain whether it is an independent risk predictor, and the specific cause or mechanism of treatment still needs further study.

Possible reasons and comparison with previous studies

One reason may be that weight gain in early pregnancy, especially excessive weight gain, was a potential sign of impaired glucose metabolism or obesity in pregnant women. Maternal obesity can increase the risk of offspring developing cardiovascular diseases with deficient cardiac structure and function. Taylor et al.27 studied 232,990 offspring in Europe and found that maternal obesity and overweight were associated with a higher incidence of CHD. A systematic review and meta-analysis showed maternal obesity might predispose the offspring to CHD risk. Smith et al.18 studied 49 mothers and their 111 children and found that compared with their siblings born before maternal anti-obesity surgery, siblings born after maternal surgery had improved cardiometabolic markers. Besides, these studies showed that siblings born after maternal weight loss surgery are less obese, have lower fasting insulin levels, and lower blood pressure. Although the importance of maternal glucose metabolism and obesity as risk factors for CHD in the offspring is evident, the underlying mechanisms of these risk factors are unclear. Another reason may be that excessive weight gain during the first trimesters may affect the maternal intrauterine environment. As the fetal heart is unique in its dynamic development, the precisely choreographed embryology of the heart relies on a multilevel regulatory network and factors that change the intrauterine environment will impact fetal embryology and heart development.

Although the association has not been confirmed, the effect of pre-pregnancy or early-pregnancy BMI on CHD has been one of the focuses in previous studies. Based on our experience and literature review, few studies have been conducted to investigate the influence of first-trimester maternal weight gain on fetal CHD based on multiple factors. Still, there was no evidence for a causal intrauterine effect of obesity or overweight or higher maternal mean BMI in pre-pregnancy/early-pregnancy on the risk of fetal CHD. Previous studies have investigated the influence of maternal GWG on adverse neonatal or maternal outcomes, focusing on overall expected weight gain, weekly GWG or weight gain in the last two trimesters. A population-based birth cohort study, including 19,052 women, found significant associations between maternal pre-pregnancy BMI and adverse
perinatal outcomes. Besides, the pre-pregnancy BMI was more strongly associated with negative consequences than the amount of GWA, found by an individual participant-level meta-analysis. Senbanjo et al found that excess GWG, overweight and obesity had significant adverse consequences in Nigeria. According to IOM guidance, maternal weight gain varies with pre-pregnancy or early-pregnancy BMI. BMI is a widely recommended index to assess nutritional status in early pregnancy. Although the association of maternal BMI in early pregnancy with adverse consequences is controversial, it may be a sign of maternal health or potential fetal abnormalities, such as gestational diabetes, low birth weight, macrosomia, etc. Therefore, this study considered maternal BMI as a confounder in the adjusted LR models and did sensitivity analysis to explore and modify the association of maternal weight increase with CHD in offspring. This study found that in a subgroup of participants with a normal pre-pregnancy BMI, a weight gain of more than 2.0 kg in early pregnancy was associated with a higher risk of CHD compared with that of less than 0.0 kg. It suggests a concern about excessive weight gain in pregnant women with a normal BMI. Also, this study should not ignore the relatively high number of normal BMI cases (83488 cases, 72.8%).

Morning sickness is among women’s most common uncomfortable symptoms in early pregnancy. Besides, early pregnancy may be mistaken for weight gain because of temporary weight loss due to morning sickness or hyperemesis gravidarum, which may recover again by mid-pregnancy. Morning sickness from the questionnaire answered during early pregnancy was added into the LR model, still finding that over 2.0 kg was associated with a higher risk of CHD in offspring. After stratified analysis, there was still a similar association among pregnant women with morning sickness. It also suggests that excess weight gain may be a potential predictor for CHD in pregnant women with morning sickness. Unfortunately, this study did not obtain information on how many cases suffered from hyperemesis gravidarum and the information on the second and third trimesters, which limits the study.

Whether maternal periconceptional FA supplementation could reduce the risk for CHD in the offspring remains controversial. Wang et al found that maternal periconceptional supplementation with FA or multiple micronutrients containing FA seems to decrease the risk for CHD in offspring by analysing 63,969 cases drawn from two standardised network information systems. A published article using data from the CBCS suggested that there is no effect of FA and/or multivitamin supplementation on the fetal risk of CHD. The rate of participants without FA and/or multivitamin supplementation was only 2.8% in this study. In univariate analysis, FA and/or multivitamin supplementation was associated with weight gain but not CHD, so it was not considered a confounder in LR analysis. Among the pregnant women with FA and/or multivitamin supplementation, a weight gain over 2.0 kg in early pregnancy was still associated with a risk effect on CHD, compared with less than 0.0 kg. Furthermore, the results are similar in pregnant women with moderate physical activity, college/university level and natural conception moderate activity, indicating that the results were somewhat robust.

In a multicentre study that included 18 hospitals in the eastern or western region of China with 22765 consecutive infants born between 2011 and 2012, the overall prevalence of CHD was 8.98 per 1000 live births. The rate of CHD in the Wang et al study analysed data in Tongzhou district, Beijing, China, between 2013 and 2018, was 4.8% (308 cases), while this present study was 6.5% (749 cases). One reason may be that the research period and places were different. According to a population-based birth defect surveillance system in five counties in Shanxi province, China, a noteworthy increase in the prevalence of CHDs over time was found, and CHD ranked as the fifth most prevalent birth defect (8.63 per 10 000) between 2017 and 2022. Another reason may be that removing some cases according to the inclusion and exclusion criteria in this study to explore the association of weight gain in early pregnancy with CHD in the offspring may have led to a bias in calculating the proportion of CHD. The incidence or prevalence of CHD in China should be estimated in further study.

**Limitations**

Several limitations must be acknowledged. First, although we performed unadjusted and adjusted LR analyses as suggested by the Strengthening the Reporting of Observational Studies in Epidemiology statement, we did not include all confounders, which also play a significant role in the development of fetal heart disease. Many potential factors, such as genetic factors, may lead to CHD in the constantly changing process of pregnancy and some related influences on these unknown factors cannot be ruled out. Second, the number of CHD cases is relatively small, without information on specific subcategories, making it impossible to analyse particular CHD types further. In addition, the participants were included at 6–13+6 weeks of gestation, which was a relatively broad range. Although the gestational weeks were adjusted in the LR models and got similar results, the subdivision of gestational weeks for analysis is still needed with a more significant number of CHD in the future. Furthermore, this study only included weight changes during the first trimester, without data on maternal weight change in the second or third trimesters or other related factors, leading to biased estimates. All of those indicated the validation of our results is necessary, especially after adjustment of the disease incidence or validation in other large cohorts.

**CONCLUSIONS**

Although maternal weight change in early pregnancy was weakly associated with the risk of CHD in offspring, the excessive weight gain may be a potential predictor.
of CHD, especially among those with morning sickness and other conditions were routine, such as normal pre-pregnancy BMI, moderate physical activity, college/university level, natural conception or with FA and/or multivitamin supplementation. However, this study does not suggest weight gain during early pregnancy is better or worse than weight loss. This finding may be helpful for the prevention and early pregnancy screening of CHD in China and other countries.

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