ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Association of maternal weight gain in early pregnancy with congenital heart disease in offspring: a China birth cohort study</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Wang, Jingjing; Zhang, Simin; Li, Xiaofei; Han, Jijing; Sun, Lijuan; Wang, Li; Wu, Qingqing</td>
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VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Nagayasu, Yoko</th>
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<tr>
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<td>Osaka Medical and Pharmaceutical University</td>
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<td>07-Nov-2023</td>
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PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.
gain in early pregnancy and fetal risk for CHD based on the China birth cohort. It is an interesting topic. But the study has a few problems:

Title and abstract:
1. It said in title “birth cohort”, and “cross-sectional study” in abstract. How to explain the contradict between the title and abstract? Why the study design was thought as cross-sectional study?

Methods:
2. It was said a multicenter cohort study, but the information on the centers, and the quality control measures on data homogeneity was absent in the paper.
3. The weight change in early pregnancy was calculated with weight in early pregnancy minus pre-pregnancy weight. The weight change might not be comparable if the weight was not measured at same gestational week age. But the author did not provide the detail information on weight measurement, including the measuring gestational week age, the process, the clothes on while measuring, the precision of the scales, and quality control, etc.

Results:
4. What was the relationships for the table 2 with the objectives of the study? Suggest the authors to delete table 2. What was MBI in table 2?
5. For figure 2: What are the control group for estimate the OR(95%CI)? e.g. For the indication of maternal pre-pregnant BMI, which group was the reference group with OR=1?

Suggestion:
6. Please give the reasons for showing paternal information in table 1, the paternal information might be deleted if you had not enough evidence to maintain it.
7. Please give a description on the characteristic of the CHD and the subtype cases.
8. Please show the prevalence of CHD by weight gain in early pregnancy with a table or a figure.
9. Some pregnant women may weight loss in early pregnancy because of morning sickness. Suggest you to compare the fetal risk for CDH among those women with others.
10. To explore association of maternal weight gain in early pregnancy and risk for the subtypes of CHD which had enough cases.
11. A few studies show maternal periconceptional folic acid supplementation could reduce the fetal risk for CHD. Was the information collected in the cohort construction? Please contain the indication as a confounder in multiple variate LR if you could get the information.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Yoko Nagayasu, Osaka Medical and Pharmaceutical University
Comments to the Author:
This study is of great interest because it is a large cohort study of the association between early pregnancy weight gain and fetal heart disease. However, we suggest several modifications.
1. early pregnancy may be mistaken for weight gain because of temporary weight loss due to hyperemesis gravidarum, which recovers again by mid-pregnancy. This should be discussed. Reply: Thank you very much for your professional guidance; we fully agree. We have added information on morning sickness obtained from the questionnaire answered during early pregnancy into logistic regression analyses and sensitivity analysis, as well as to the discussion part.

In the methods part, Morning sickness, folic acid (FA) and/or multivitamin supplementation were divided into two levels: Yes or No.

In the results part, Besides, Table 2 shows the results of unadjusted (adjusted for none), minimally adjusted (adjusted for the gestational week, age, BMI, and morning sickness) …

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 (Table A4 in the Appendix and Figure 2).

In the discussion part, Morning sickness is among women’s most common uncomfortable symptoms in early pregnancy [38]. 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 [39]. 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.

2. this study only adjusted for maternal background. Indeed, external factors such as alcohol and tobacco are known to play a role in fetal heart disease. However, it is also true that genetic factors play a major role in the development of fetal heart disease. Therefore, we call for investigation and adjustment of the incidence of the disease in the same cohort. Reply: Your suggestion is excellent! We agree that genetic factors play a significant role in the development of fetal heart disease. Because of the limitations of the data we obtained, we would like to investigate and adjust the incidence of the disease in future research. We also added this in the limitation part.

In the discussion part, 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. All of those indicated the validation of our results is necessary, especially after adjustment of the disease incidence or validation in other large cohorts.

3. Why is maternal weight gain in early pregnancy a possible risk factor for fetal heart disease? Biochemical reasoning is needed. We suggest that these be added to the discussion. Reply: Thank you very much for your kind advice. We have added some possible explanations to the discussion by reviewing the literature and discussing with some specialists.

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 [16]. Taylor K et al. [17] studied 232,390 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 [18]. Smith J et al. [19] studied 49 mothers and their 111 children and found that compared to their siblings born before maternal antiobesity 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 [20], have lower fasting insulin levels [21], and lower blood pressure [21]. 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 [22]. 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 multi-level regulatory network [23], and factors that change the intrauterine environment will impact fetal embryology and heart development.

4. Overall, the discussion is poor. Suggest addressing other maternal backgrounds and sibling risks that may contribute to fetal heart disease.

Reply: We appreciate your valuable and helpful comments on our manuscript. Those comments are for revising and improving our paper and the essential guiding significance to our research. And we have modified and expanded the discussion section.

Reviewer: 2
Dr. Lei Jin, Peking University
Comments to the Author:
Potential impact of maternal weight gain in early pregnancy on fetal congenital heart disease: a multicenter study based on the China birth cohort (bmjopen-2023-079635)
Prevalence of CHD has increased in China and globally since last decades and the causes of CHD were not determined till today. The study aimed to explore the association of maternal weight gain in early pregnancy and fetal risk for CHD based on the China birth cohort. It is an interesting topic. But the study has a few problems:
Title and abstract:
1. It said in title “birth cohort”, and “cross-sectional study” in abstract. How to explain the contradict between the title and abstract? Why the study design was thought as cross-sectional study?
Reply: Thank you very much for your professional guidance. Concerning some similar published articles from the cohort, we previously considered this study to be a cross-sectional study. However, through your reminder and our discussion with the statistical experts, our study design is a cohort study, which has been revised.

Methods:
2. It was said a multicenter cohort study, but the information on the centers, and the quality control measures on data homogeneity was absent in the paper.
Reply: Thank you very much for your kind advice. We agree that the quality control measures on data homogeneity are very important in a multicenter cohort study. In the published paper, Yue et al. introduced the China birth cohort study (CBCS), including the study cohort, followed-up strategies, data collection, and data management. Because this study is part of the data obtained from the CBCS, no more corresponding information was obtained. However, we still added some summaries of CBCS in the methods part.
In the methods part,
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 centers in China [15]. The quality control measures on data homogeneity are essential in a multicenter cohort study.
study. The study cohort, followed-up strategies, data collection, and data management can be found in the published paper [14].

3. The weight change in early pregnancy was calculated with weight in early pregnancy minus pre-pregnancy weight. The weight change might not be comparable if the weight was not measured at same gestational week age. But the author did not provide the detail information on weight measurement, including the measuring gestational week age, the process, the clothes on while measuring, the precision of the scales, and quality control, etc.

Reply: Thank you very much for your professional guidance. In CBCS, women are enrolled in early pregnancy at 6–13+6 weeks of gestation. We supplemented the weight measurements and gestational week descriptions in the method part by referring to published articles from this cohort. In addition, we added analysis of weight gain at different gestational weeks, adjusted gestational weeks in models, and stratified our results for gestational weeks. We also added it in the limitation part.

In the methods part,

Weight was accurately measured using an electronic scale (BW-150; UWE, Beijing, China), with participants wearing light clothes, no shoes, and empty pockets [15].

In the results part,

Table A1 in the 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.

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...

In the discussion part,

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.

Results:

4. What was the relationships for the table 2 with the objectives of the study? Suggest the authors to delete table 2. What was MBI in table 2?

Reply: Thank you very much for your kind advice. Table 2 showed the association of maternal weight gain with CHD in offspring was similar to BMI in early pregnancy. We removed Table 2 from the manuscript and attached it to the Appendix. MBI is misspelled. It should be BMI.

5. For figure 2: What are the control group for estimate the OR(95%CI)? e.g. For the indication of maternal pre-pregnant BMI, which group was the reference group with OR=1?

Reply: Thank you very much for your kind advice. Figure 2 shows the effect of body weight as a continuous variable on CHD in the different subgroups, i.e., how much the risk of CHD in offspring increases with an increase of one unit (kg). We modified Figure 2 and added Table A4 in the Appendix. We have added to present the results that maternal weight gain as a rank variable (divided into four ranks by quantile) in the unadjusted (Table A4 in the Appendix ) and minimally adjusted (Figure 2) models, with the first rank (less than 0.0 kg) serving as the reference group to derive an OR or aOR for the other ranks.
Suggestion:
6. Please give the reasons for showing paternal information in table 1, the paternal information might be deleted if you had not enough evidence to maintain it.
Reply: Thank you for your kind advice. We deleted the paternal information.

7. Please give a description on the characteristic of the CHD and the subtype cases.
Reply: Thank you very much for your kind advice. Table A2 in the Appendix shows the characteristics of the CHD Group compared with the non-CHD Group. We are also aware that different subtypes of CHD may play different roles. However, we did not obtain specific subtypes of CHD. Still, concerning published articles using data from the CBCS, the three most common types were a ventricular septal defect, multiple CHD, and Tetralogy of Fallot. We both added those in the method and limitation part.

8. Please show the prevalence of CHD by weight gain in early pregnancy with a table or a figure.
Reply: Thank you very much for your kind advice. We added Figure A1 in the Appendix to show the prevalence of CHD by weight gain in early pregnancy.

9. Some pregnant women may weight loss in early pregnancy because of morning sickness. Suggest you to compare the fetal risk for CDH among those women with others.
Reply: Thank you very much for your professional guidance; we fully agree. We have added information on morning sickness obtained from the questionnaire answered during early pregnancy into the analysis (please see Table 1 and Table A2). Besides, it was also adjusted in the logistic regression analyses and added in the sensitivity analysis.

In the methods part,
Morning sickness, folic acid (FA) and/or multivitamin supplementation were divided into two levels: Yes or No.

In the results part,
Besides, Table 2 shows the results of unadjusted (adjusted for none), minimally adjusted (adjusted for the gestational week, age, BMI, and morning sickness) ...

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, ..., (Table A4 in the Appendix and Figure 2). 

In the discussion part,
Morning sickness is among women's most common uncomfortable symptoms in early pregnancy [38]. 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 [39]. 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.

10. To explore association of maternal weight gain in early pregnancy and risk for the subtypes of CHD which had enough cases.
Reply: Thank you for your kind advice. As mentioned above, we did not obtain specific subtypes of CHD. Still, concerning published articles using data from the CBCS, the three most common types
were a ventricular septal defect, multiple CHD, and Tetralogy of Fallot. We both added those in the method and limitation part.

In the methods part, we did not obtain specific subtypes of CHD. 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.

In the discussion part, second, the number of CHD cases is relatively small and without specific subcategories, making it impossible to analyze particular CHD types further.

In the methods part, we did not obtain specific subtypes of CHD. 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.

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In the discussion part, second, the number of CHD cases is relatively small and without specific subcategories, making it impossible to analyze particular CHD types further.

11. A few studies show maternal periconceptional folic acid supplementation could reduce the fetal risk for CHD. Was the information collected in the cohort construction? Please contain the indication as a confounder in multiple variate LR if you could get the information.

Reply: We appreciate your valuable and helpful comments on our manuscript. We add the FA and/or multivitamin supplementation in the revised version.

In the methods part, Morning sickness, folic acid (FA) and/or multivitamin supplementation were divided into two levels: Yes or No.

In the results part, Table 1 presents the significant differences in weight gain among… FA and/or multivitamin supplementation, and morning sickness.

The characteristics of the non-CHD and CHD group participants were shown in Table A2 in the Appendix.

In the adjusted models, compared to 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 … 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 (Table A4 in the Appendix).

In the discussion part, Whether maternal periconceptional FA supplementation could reduce the risk for CHD in the offspring remains controversial [40,41]. A published article [42] using data from the CBCS suggested that there is no effect of folic acid (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 to less than 0.0 kg.

Reviewer: 1
Competing interests of Reviewer: I have no COI.

Reviewer: 2
Competing interests of Reviewer: no.

VERSION 2 – REVIEW

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<td>REVIEW RETURNED</td>
<td>08-Feb-2024</td>
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<td>GENERAL COMMENTS</td>
<td>That weight gain in early pregnancy increases the risk of CHD and the specific numbers.</td>
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| REVIEW RETURNED | 14-Jan-2024 |

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<td>2. Please explain why you use the lowest weight gain as reference group? Is it better for less weight gain than more in early pregnancy? The optimal weight gain for whole gestational age is recommended by maternal pre-pregnant BMI.</td>
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<td>3. Please give the number of singleton births and CHD cases in each group of weight gain in early gestational age in table 3.</td>
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<td>4. Please add the discussion on the CHD incidence in the cohort. How about it compares to the previous publications in Chinese population and why?</td>
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**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 2
Dr. Lei Jin, Peking University

Comments to the Author:

Suggestions:

1. The data use in the study was abstracted from the CBCS, the cases of birth defect had detail description in the cohort, why you did not show the types of CHD and the cases?

Reply: Thank you very much for your kind advice; we fully agree that the types of CHD are important. The data used in the study was abstracted from the CBCS. Unfortunately, we only obtained information on the presence or absence of CHD in offspring without the specific subtypes, which are also added to the methods and limitations.

In the methods part,

…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 …

In the Limitations part,

…Second, the number of CHD cases is relatively small, without information on specific subcategories, making it impossible to analyze particular CHD types further…

2. Please explain why you use the lowest weight gain as reference group? Is it better for less weight gain than more in early pregnancy? The optimal weight gain for whole gestational age is recommended by maternal pre-pregnant BMI.
Reply: Thank you for your kind advice. We fully agree that the optimal weight gain for whole gestational age is recommended by maternal pre-pregnant BMI. As mentioned in the Limitations part, 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. Besides, the association of maternal weight gain with fetal CHD was similar to BMI in early pregnancy (Delong tests: $P = 0.091$). We analyzed the effect of maternal weight gain as a continuous variable and a rank variable (divided into four ranks by quantile) on CHD. We use the lowest weight gain as a reference group to analyze the effect of different levels of weight gain. In addition, the association seemed to exist in the women with a normal level of pre-pregnancy BMI (Table A3 in the Appendix). However, this study does not suggest that weight gain during early pregnancy is better than weight loss, which has been added in the Conclusions part.

3. Please give the number of singleton births and CHD cases in each group of weight gain in early gestational age in table 3.

Reply: Thank you very much for your professional guidance. We have added in the Result part,...After dividing first-trimester weight gain into four grades by the quartiles, the number and rate of CHD in the first quartile (Q1, <0.0kg) was 99(0.5%), 211(0.7%) in the second (Q2, 0.0-0.9 kg), 168(0.7%) in the third (Q3, 1.0-1.9kg), and 271 (0.7%) in the fourth (Q4, 2.0kg~) quartile (Figure A1 in the Appendix).... We did not give the number of singleton births as we excluded multiple pregnancies. We also excluded any abnormal conditions of the mother and fetus other than fetal CHD in the non-CHD group (including fetal malformation, miscarriage, pregnancy loss, premature birth, low birth weight, fetal macrosomia, etc.) and not within the range of 6 to 14 weeks of gestation to explore the association of weight gain in early pregnancy with CHD in the offspring. All of those were presented in the Methods part and Figure 1. Our study had some limitations, and your suggestion is excellent; we will focus on it in further research.

4. Please add the discussion on the CHD incidence in the cohort. How about it compares to the previous publications in Chinese population and why?

Reply: Thank you very much for your professional guidance, and we added in the Discussion part.

In the Discussion part, we added

...In a multicenter study [44] that included 18 hospitals in the eastern or western region of China with 22,765 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 [42] analyzed 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 [45]. 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.

In the References part, we added


5. Please clarify style of references, e.g. the format of reference number 13.

Reply: Thank you very much for your kind advice. We revised the style of the references. And the reference number 13 should be:


Reviewer: 1
Dr. Yoko Nagayasu, Osaka Medical and Pharmaceutical University
Comments to the Author:
That weight gain in early pregnancy increases the risk of CHD and the specific numbers. In your discussion, you have fully explained the points I have questioned.

Reviewer: 2
Competing interests of Reviewer: no.

Reviewer: 1
Competing interests of Reviewer: None