The association of maternal pre-pregnancy body mass index with macrosomia: a birth cohort study from China (#117489)

First submission

Guidance from your Editor

Please submit by **12 Jun 2025** for the benefit of the authors (and your token reward) .

Structure and Criteria
Please read the 'Structure and Criteria' page for guidance.

Custom checks
Make sure you include the custom checks shown below, in your review.

Author notes
Have you read the author notes on the guidance page?

Raw data check
Review the raw data.

Image check
Check that figures and images have not been inappropriately manipulated.

All review materials are strictly confidential. Uploading the manuscript to third-party tools such as Large Language Models is not allowed.
If this article is published your review will be made public. You can choose whether to sign your review. If uploading a PDF please remove any identifiable information (if you want to remain anonymous).

Files

Download and review all files from the materials page.

2 Figure file(s)
4 Table file(s)
1 Raw data file(s)
1 Other file(s)

Custom checks

Human participant/human tissue checks

- Have you checked the authors ethical approval statement?
- Does the study meet our article requirements?
- Has identifiable info been removed from all files?
- Were the experiments necessary and ethical?

Structure and Criteria

Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

You can also annotate this PDF and upload it as part of your review

When ready submit online.

Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your guidance page.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context. Literature well referenced & relevant.
- Structure conforms to PeerJ standards, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (see PeerJ policy).

EXPERIMENTAL DESIGN

- Original primary research within Scope of the journal.
- Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- **Impact and novelty is not assessed.** Meaningful replication encouraged where rationale & benefit to literature is clearly stated.
- All underlying data have been provided; they are robust, statistically sound, & controlled.
- Conclusions are well stated, linked to original research question & limited to supporting results.

Standout reviewing tips

The best reviewers use these techniques

Tip	*Example*
Support criticisms with evidence from the text or from other sources	*Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.*
Give specific suggestions on how to improve the manuscript	*Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).*
Comment on language and grammar issues	*The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult. I suggest you have a colleague who is proficient in English and familiar with the subject matter review your manuscript, or contact a professional editing service.*
Organize by importance of the issues, and number your points	*1. Your most important issue* *2. The next most important item* *3. …* *4. The least important points*
Please provide constructive criticism, and avoid personal opinions	*I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC*
Comment on strengths (as well as weaknesses) of the manuscript	*I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.*

The association of maternal pre-pregnancy body mass index with macrosomia: a birth cohort study from China

Mingxin Yan Equal first author, 1 , **Yunbo Zhang** Equal first author, 2 , **Doudou Zhao** 2, 3 , **Yan Zhao** 4 , **Danmeng Liu** 3 , **Li Shan** 3 , **Yang Mi** 3 , **Leilei Pei** Corresp., 2 , **Pengfei Qu** Corresp. 2, 3, 5

1 Institute for Hygiene of Ordnance Industry, Xi'an, China

2 Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi, China

3 Translational Medicine Center Northwest Women's and Children's Hospital, Xi'an, Shaanxi, China

4 The First Affiliated Hospital of Xi'an Jiaotong University Dermatology, Xi'an, Shaanxi, China

5 Central Laboratory, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China

Corresponding Authors: Leilei Pei, Pengfei Qu
Email address: pll_paper@126.com, xinxi3057@163.com

Objective: To investigate the association between pre-pregnancy body mass index (BMI) and the risk of macrosomia through a preconception-early pregnancy-birth cohort in China.

Methods: From July 2018 to December 2021, we recruited a total of 12,254 women of childbearing age from the Northwest Women's and Children's Hospital of China. We collected basic demographic characteristics and lifestyle behavior information of the subjects through questionnaires and practical measurements, and conducted further follow-up for pregnancy outcomes. The study assessed the association of pre-pregnancy BMI with macrosomia using logistic regression models, and performed a linear trend test. Moreover, we utilized restricted cubic splines and polynomial regression to investigate the non-linear relationship of pre-pregnancy BMI with macrosomia.

Results: A total of 11438 subjects were included in this study and the prevalence of macrosomia among all infants was 5.64 per cent. The results indicated that, when compared to the normal weight group, the risk of macrosomia was higher in the overweight and obesity groups (overweight: (OR =1.66 (1.35-2.01)); obesity: (OR =1.66 (1.13-2.45))), and the risk of macrosomia was lower in the underweight group (OR =0.55 (0.41-0.73)). Additionally, similar findings were observed concerning the relationship between pre-pregnancy BMI and grade 1 macrosomia. The use of restricted cubic splines revealed that the prevalence of macrosomia/grade 1 macrosomia increased with rising pre-pregnancy BMI. Furthermore, when we stratified the data by covariates, the nonlinear relationship between pre-pregnancy BMI and macrosomia/grade 1 macrosomia persisted. The results of the polynomial regression showed a gradual increase in fetal birth weight with increasing pre-pregnancy BMI levels.

Conclusions: Pre-pregnancy overweight and obesity were associated with higher risks of

macrosomia. Therefore, it indicates that it may be possible to decrease the risk of macrosomia through preconception weight regulation.
Keywords: Pre-pregnancy BMI; Macrosomia; Grade 1 macrosomia; Underweight; Overweight; Obesity; Birth weight

The association of maternal pre-pregnancy body mass index with macrosomia: a birth cohort study from China

Mingxin Yan [1,2†], Yunbo Zhang [2†], Doudou Zhao [2,3], Yan Zhao [4], Danmeng Liu [3], Li Shan [3], Yang Mi [3], Leilei Pei [2,*] and Pengfei Qu [2,3,5**]

[1] Institute for Hygiene of Ordnance Industry, Xi'an 710065, China

[2] Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an 710061, China

[3] Translational Medicine Center Northwest Women's and Children's Hospital, Xi'an 710061, China

[4] The First Affiliated Hospital of Xi'an Jiaotong University Dermatology, Xi'an 710061, China

[5] Central Laboratory, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Chaoyang, Beijing 100026, China.

*Corresponding author: Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an 710061, China.

**Corresponding author: Translational Medicine Center Northwest Women's and Children's Hospital, Xi'an 710061,China.

E-mail addresses: pll_paper@126.com (L. Pei), xinxi3057@163.com (P. Qu).

†These authors have contributed equally to this work

Abstract

Objective: To investigate the association between pre-pregnancy body mass index (BMI) and the risk of macrosomia through a preconception-early pregnancy-birth cohort in China.

Methods: From July 2018 to December 2021, we recruited a total of 12,254 women of childbearing age from the Northwest Women's and Children's Hospital of China. We collected basic demographic characteristics and lifestyle behavior information of the subjects through questionnaires and practical measurements, and conducted further follow-up for pregnancy outcomes. The study assessed the association of pre-pregnancy BMI with macrosomia using logistic regression models, and performed a linear trend test. Moreover, we utilized restricted cubic splines and polynomial regression to investigate the non-linear relationship of pre-pregnancy BMI with macrosomia.

Results: A total of 11438 subjects were included in this study and the prevalence of macrosomia among all infants was 5.64 per cent. The results indicated that, when compared to the normal weight group, the risk of macrosomia was higher in the overweight and obesity groups (overweight: (OR=1.66 (1.35-2.01)); obesity: (OR=1.66 (1.13-2.45))), and the risk of macrosomia was lower in the underweight group (OR=0.55 (0.41-0.73)). Additionally, similar findings were observed concerning the relationship between pre-pregnancy BMI and grade 1 macrosomia. The use of restricted cubic splines revealed that the prevalence of macrosomia/grade 1 macrosomia increased with rising pre-pregnancy BMI. Furthermore, when we stratified the data by covariates, the nonlinear relationship between pre-pregnancy BMI and macrosomia/grade 1 macrosomia persisted. The results of the polynomial regression showed a gradual increase in fetal birth weight with increasing pre-pregnancy BMI levels.

Conclusions: Pre-pregnancy overweight and obesity were associated with higher risks of macrosomia. Therefore, it indicates that it may be possible to decrease the risk of macrosomia through preconception weight regulation.

Keywords: Pre-pregnancy BMI; Macrosomia; Grade 1 macrosomia; Underweight; Overweight; Obesity; Birth weight

Introduction

Fetal macrosomia, defined as a birth weight of ≥4000g, is known to commonly prolong the labor process, increase the rate of cesarean section, postpartum hemorrhage and puerperal infections in mothers, and also lead to fetal injuries and asphyxia during delivery[1-3]. Studies have also shown long-term effects of macrosomia, including its influence on physical and intellectual development during childhood and adolescence, as well as an increased risk of chronic diseases such as hypertension and diabetes in adulthood[4-7]. Notably, developed countries have seen a rise of 15% to 25% in macrosomia prevalence over the past few decades[8,9]. Similarly, developing countries like China have also witnessed a rise in macrosomia due to improved living conditions and economic growth, with the prevalence increasing from 6.9% to 7.8% between 2007 and 2017[10-12]. Given the significant social and personal burden of macrosomia, it is crucial to identify its risk factors to develop primary prevention strategies.

This increase in macrosomia has coincided with changes in maternal pre-pregnancy BMI in modern society. The prevalence of pre-pregnancy obesity among women of childbearing age in the US has reached 22%, with a 69.3% increase over the past 10 years[13,14]. In China, data from the

2002 China Nutrition and Health Survey revealed that the rates of overweight and obesity among women of childbearing age reached 21.8% and 6.1%, respectively, and have been consistently increasing[15,16]. Some studies have suggested a potential association between elevated maternal pre-pregnancy BMI and excessive fetal birth weight[17-19].

For instance, a study from the ABCD Amsterdam cohort demonstrated a linear association between pre-pregnancy BMI and the child's weight and BMI at 14 months of age. A one-unit increase in pre-pregnancy BMI resulted in an increment of 29 g (95% CI 19 to 39) in weight and 0.041 kg/m^2 (95% CI 0.030 to 0.053) in BMI[20]. Similarly, a study from the Rotterdam cohort indicated that pre-pregnancy overweight or obesity resulted in a 1.30-fold and 1.74-fold increased risk of developing large sizes for gestational age[21]. However, these studies lacked a specific focus on the Chinese population and instead utilized international BMI standards. Even more importantly, their pre-pregnancy height and weight data were based on self-reporting in questionnaires. Another study in a Chinese population showed that women with pre-pregnancy overweight and obesity were associated with a 1.99-fold and 4.05-fold risk of macrosomia, respectively[17], while a cohort study in Taiwan, China, showed that a 6- to 46-fold increase in the risk of macrosomia for women with pre-pregnancy overweight and obesity[22]. Despite being conducted on a Chinese population, their differences were still relatively large. In addition, a meta-analysis highlighted inconsistent relationships between pre-pregnancy underweight and overweight/obesity in offspring, emphasizing the need for further research[19]. Therefore, focusing on the Chinese population, the effect of pre-pregnancy BMI on macrosomia needs to be further explored in a large data and more rigorous design.

To address these issues, we established a birth cohort in northwest China to explore the relationship between maternal pre-pregnancy BMI and macrosomia.

Methods

Study design and data sources

A total of 12,254 women of childbearing age were recruited into the preconception-early pregnancy-birth cohort at Northwest Women's and Children's Hospital of China from July 2018 to December 2021. To ensure uniformity and accuracy, a standardized and structured questionnaire was used to conduct a face-to-face survey of study subjects by investigators using uniform criteria and methods. Information on the birth of the newborn was collected according to the hospital medical record system. In addition to surveying the pregnant women themselves, the relatives in their family were also surveyed if necessary to enhance the accuracy of the information obtained. The questionnaire included various aspects of information, such as diagnosis of pregnancy outcome, sociodemographic characteristics, lifestyle, dietary nutrition and nutrient supplementation during pregnancy, and reproductive history and maternal health. The investigators, who are professionals ranging from front-line clinical and nursing staff to researchers or graduate students, are uniformly trained. The survey results are subjected to rigorous secondary quality control by professional auditors to ensure dual verification. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (Approval Number: 2018-KY-003-02). All research participants were fully informed about the study content prior to participation, obtained written consent, and signed informed consent forms.

Inclusion criteria: Women of childbearing age who underwent pre-pregnancy check-ups at the Northwest Women's and Children's Hospital of China from July 2018 to December 2021; voluntary enrolment in the preconception-early pregnancy-birth cohort after obtaining informed consent; and completeness of the relevant information. Exclusion criteria: Pre-pregnancy pre-existing underlying illnesses that may have an impact on neonatal birth outcomes; and psychiatric anomalies that hindered normal communication. Termination or withdrawal criteria: Request to be withdrawn from the cohort for various reasons; and loss of follow-up during the study period, serious illnesses, termination of pregnancy, or death. To ensure the final study's reliability and validity, we excluded 89 mothers with missing pre-pregnancy weight/height and 38 with missing covariates (parity、current GDM、fetal sex). Moreover, 624 participants were lost to follow-up, and 65 others underwent terminations/abortions. After applying these exclusion criteria, we included a total of 11,438 gestational mothers in the final study (Figure 1). (drop out rate...?)

Pre-pregnancy BMI assessment

The pre-pregnancy BMI of the mothers in this study was calculated from the height and weight values measured at the first antenatal visit (≤12 gestational weeks of pregnancy). We carefully measured height (accurate to 0.1 cm) and weight (accurate to 0.01 kg) of the mothers, who wore light clothing but no shoes. BMI was calculated as weight/height^2 (kg/m^2). In previous studies, it has been observed that pre-pregnancy height of pregnant women through questionnaires tends to be overestimated and weight tends to be underestimated, resulting in underestimation of BMI, which introduces information bias[20,23]. In addition, relevant studies have shown that height and weight measured at the first antenatal visit (≤12 gestational weeks of pregnancy) are highly

might lower than pre pregnancy weight because morning sickness?

consistent with pre-pregnancy height and weight[24]. Therefore, by utilizing measured height and weight in this study, we were able to minimize these biases and improve the accuracy of our findings.

According to Chinese standards, pre-pregnancy BMI of mothers was categorized as underweight (BMI < 18.5 kg/m^2), normal weight (18.5 ≤ BMI < 24.00 kg/m^2), overweight (24 ≤ BMI < 28.00 kg/m^2) and obesity (BMI ≥ 28 kg/m^2) [25]. Meanwhile, based on the World Health Organization (WHO) criteria, underweight (BMI < 18.5 kg/m^2), normal weight (18.5 ≤ BMI < 25.00 kg/m^2), overweight (25 ≤ BMI < 30.00 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were redefined[26].

Birth Outcomes

The primary outcome in this study was macrosomia, defined as infants with a birth weight ≥ 4000 g. Macrosomia was further classified into three grades[27], with Grade 1 representing infants weighing between 4000-4499g, Grade 2 between 4500-4999g, and Grade 3 being infants with a birth weight higher than 5000g[28].

Covariates

The main covariates in the study included sociodemographic characteristics, lifestyle behaviors and clinical characteristics of mothers during pregnancy, which might be associated with pregnancy outcomes[29,30]. Sociodemographic characteristics included fetal sex (male, female), parity (Nulliparous, Multiparous), maternal age (≤24 years, 25~29 years, 30~34 years, and ≥35 years), maternal education (high school or less, College/university and Postgraduate), maternal ethnicity (Han and Other), family socioeconomic status (Poor, Moderate and Rich). To measure the household economic level, we used principal component analysis, incorporating variables such as monthly household income, monthly expenditure, housing type, household appliances, and transportation, to construct a family wealth index and divided it into thirds as an indicator for poor, medium, and rich households[31].

Lifestyle behaviors included alcohol drinking before or during pregnancy (Yes, No), passive smoking before or during pregnancy (Yes, No). Alcohol drinking included a variety of alcoholic beverages (e.g. white wine, beer, red wine, etc.) before or during the whole pregnancy; Passive smoking was defined as inhaling smoke for more than 15 min per day and at least one day per week before or during pregnancy.

Clinical characteristics included cold/fever before or during pregnancy (Yes, No), folic acid supplementation before or during pregnancy (Yes, No), current gestational diabetes mellitus (GDM) (Yes, No). Folic acid supplementation before or during pregnancy means taking folic acid from the first 3 months of pregnancy to the time of conception. Current GDM is diagnosed in the middle of pregnancy according to Chinese criteria: Fasting plasma glucose (FPG) ≥5.1mmol/L is abnormal fasting glucose; 1-hour postprandial glucose ≥10.0moml/L is abnormal 1 hour glucose; 2-hour postprandial glucose ≥8.5mmol/L is abnormal 2-hour glucose. Those with at least one of the above indicators were diagnosed with GDM[32].

Statistical analyses

In univariate analysis, categorical variables were expressed as frequencies (n) and percentages (%) and compared between groups using the χ^2 test or Fisher's exact test. Quantitative variables were presented as median and interquartile range (IQR) when non-normally distributed.

In multivariate analysis, we initially employed logistic regression models to examine the correlation between pre-pregnancy BMI of mothers and macrosomia, accompanied by a linear trend test. Subsequently, we investigated this relationship in various subgroups, stratified by maternal age, maternal education, family wealth index, parity, current GDM, and fetal sex. Additionally, we explored the association between pre-pregnancy BMI and the three different grades of macrosomia. To ensure the robustness of the relationship between pre-pregnancy BMI and macrosomia, we conducted three sensitivity analyses. Firstly, we substituted the China BMI criteria with WHO BMI criteria to investigate the association between pre-pregnancy BMI and macrosomia, replicating all the analyses. Secondly, for further validation, we utilized restricted cubic splines with three knots to depict the potentially non-linear association between pre-pregnancy BMI and macrosomia. Finally, we applied polynomial regression to assess the linear relationship between pre-pregnancy BMI and birth weight. All statistical analyses were performed using SAS version 9.4 and R version 4.2.0, and two-sided $P< 0.05$ indicated a significant difference.

Results

Baseline characteristics

A total of 11438 subjects were included in this study, and pregnant women were divided into four groups based on Chinese BMI criteria: underweight (15.69%), normal weight (67.74%), overweight (13.59%) and obesity (2.98%) (Table 1). The subjects were predominantly aged 25-34 years (86.35%), college/university in education (75.88%), Han in ethnicity (98.61%), and moderate in family wealth index (64.74%).

The study showed significant differences between different pre-pregnancy BMI groups in age, education, wealth index, folic acid supplementation, parity, and current GDM, but no statistically significant differences in ethnicity, drinking, passive smoke, cold/fever, and fetal sex.

The association of pre-pregnancy BMI and macrosomia

Overall, a total of 645 (5.64%) cases of macrosomia were found in all infants, including 576 cases (89.30%) of grade 1 macrosomia, 50 cases (7.75%) of grade 2 macrosomia, and 19 cases (2.95%) of grade 3 macrosomia. Birth weight significantly differed among different pre-pregnancy BMI groups, with higher rates in the overweight and obesity groups (P <0.001). Among pre-pregnancy BMI subgroups, including underweight, normal weight, overweight, and obesity groups, stratified according to Chinese criteria, the incidence rates of macrosomia among infants were 3.12%, 5.37%, 9.14%, and 9.09%, respectively (P < 0.001) (Table 2). Notably, the overweight and obesity groups showed the highest prevalence of grade 1 macrosomia (Table 2).

After adjusting for all covariates using a logistic model, compared to the normal weight group, the underweight group had a 0.55-fold decreased risk of macrosomia (OR=0.55 (0.41-0.73)), while the overweight group (OR=1.66 (1.35-2.01)) and obesity group (OR=1.66 (1.13-2.45)) had a 1.66-fold increased risk of macrosomia. The linear trend tests were significant, indicating that the risk for macrosomia increased with the increment of pre-pregnancy BMI (Table 3). Similarly, compared to the normal weight group, the underweight group had a 0.57-fold decreased prevalence of grade 1 macrosomia (OR=0.57 (0.42-0.76)), while the overweight group (OR=1.62 (1.31-2.01)) and the obesity group (OR=1.55 (1.02-2.35)) had a 1.62-fold and 1.55-fold increased prevalence of grade 1 macrosomia, respectively. Furthermore, when compared to the normal weight group, the overweight group had a 2.80-fold increased prevalence of grade 2 macrosomia (OR=2.80 (1.47-5.32)), while the obesity group had a 3.46-fold increased risk of grade 2 macrosomia (OR=3.46 (1.19-10.10)). The linear trend test indicated a progressive increase in grade 1 and 2 macrosomia with increasing pre-pregnancy BMI (Supplementary Table S1). Consistently, in different subgroups stratified by baseline covariates, the relationship between pre-pregnancy BMI and macrosomia was directionally consistent, indicating good result stability (Supplementary Table S2).

Sensitivity analyses

According to the BMI criteria proposed by the WHO, the rate of macrosomia decreased by 0.53-fold in the underweight group (OR=0.53 (0.40-0.71)), increased by 1.72-fold in the overweight group (OR=1.72 (1.37-2.16)), and increased by 2.33-fold in the obesity group (OR=2.33 (1.44-3.78)), in comparison with the normal weight group. The linear trend test results were consistent with the results based on China criteria (P <0.001) (Table 4). Using the restricted cubic spline model, results suggested that BMI lower than 25 kg/m^2 was associated with a decreased risk of macrosomia/grade 1 macrosomia, while BMI higher than 25 kg/m^2 was associated with an increased risk of macrosomia or grade 1 macrosomia (Figure 2A and 2B). This correlation remains stable in different subgroups stratified by covariates (Supplementary Figures S1 and S2). Additionally, the results of the polynomial regression showed a gradual increase in fetal birth weight with increasing pre-pregnancy BMI levels (Supplementary Figure S3).

Discussion

According to this mother-infant cohort study in Northwest China, we found a prevalence of

5.64% of macrosomia in all infants. Pre-pregnancy underweight was associated with a decreased risk of macrosomia adjusting for all possible confounders by logistic regression, while pre-pregnancy overweight and obesity were associated with an increased risk of macrosomia. Moreover, we observed that the risk of macrosomia increased with quantitative pre-pregnancy BMI. Through a variety of sensitivity analysis, this relationship still persisted, suggesting that pre-pregnancy BMI is strongly associated with macrosomia.

In our cohort study, women with overweight and obesity had a 1.66-fold increased risk of macrosomia, compared to the normal weight group. A 2008 prospective cohort study in Iran by Sharifzadeh et al. confirmed that pre-pregnancy obesity was associated with an increased risk of macrosomia[33]. Clorado et al. based on the prenatal cohort found that for every 1 kg/m^2 increase in maternal BMI before pregnancy, there was a 5.21 g increase in neonatal adiposity, a 7.71 g increase in defatted weight, and a 0.12% increase in body fat percentage[34]. Previous studies suggested that pre-pregnancy overweight and obesity are important risk factors for pregnancy complications and adverse perinatal outcomes[35,36]. Our study results was consistent with some researches that also focused on Chinese. In a Chinese cohort study that included 20,321 mothers and infants, pre-pregnancy overweight and obesity increased the risk of macrosomia by 1.99-fold and 4.05-fold, respectively[17]. Similarly, in another Chinese cohort study, pre-pregnancy overweight and obesity increased the risk of macrosomia by 1.92-fold and 2.48-fold, respectively[30]. A meta-analysis, including 45 studies, showed that maternal pre-pregnancy overweight and obesity increased the risk of macrosomia by 1.67-fold and 3.23-fold, respectively among infants[19].

Several mechanisms have been proposed to explain the association between pre-pregnancy overweight and obesity and macrosomia. First, pre-pregnancy overweight and obesity may lead to the increased concentrations of glucose, amino acids and free fatty acids in the pregnant woman's body, thereby increasing the risk of abnormal birth weight in the baby[37]. Secondly, high pre-pregnancy BMI may lead to an abnormal distribution of adipose tissue, disrupting metabolic and immune functions, and affecting the intrauterine environment during pregnancy, resulting in fetal dysplasia and the development of macrosomia[38]. Additionally, studies confirm that adipose tissue is resistant to insulin function, further amplifying the risk of fetal macrosomia[39,40].

In our study, underweight mothers have a 0.55-fold decreased risk of macrosomia in offspring, compared to mothers with the normal weight group. Past findings on the association between pre-pregnancy underweight and macrosomia are inconclusive. Liu et al. systematically reviewed 60 related studies and reported a negative association between low pre-pregnancy BMI and macrosomia[41]. In a large cohort study of 105,768 mother-infant pairs, Li et al. demonstrated a correlation between pre-pregnancy underweight and the occurrence of macrosomia, which persisted after adjusting for covariates[29]. However, a recent cohort study that included 2,210 women found no significant association between pre-pregnancy underweight and macrosomia[22]. The discrepancy in the results may be due to the small sample size in this study. Our findings are consistent with most current studies suggesting that pre-pregnancy underweight is associated with a decreased risk of macrosomia. However, previous studies have shown that pre-pregnancy underweight increased the risk of small-for-gestational-age (SGA) and low birth weight (LBW)[19]. Therefore, it may be possible to decrease the risk of macrosomia by regulating weight before pregnancy, but it should be kept within a certain range to prevent an increased risk of other adverse pregnancy outcomes. Further studies should focus on the range of pre-pregnancy weight regulation that decreases the risk of macrosomia without increasing the risk of other adverse pregnancy outcomes.

Furthermore, we adopted restricted cubic splines to explore the association between pre-pregnancy BMI and macrosomia. The results showed that as pre-pregnancy BMI increased, the risk of macrosomia among infants progressively ascended. The results of the study remained stable in the subgroups stratified by covariates. Moreover, polynomial regression was further used to test the linear relationship between pre-pregnancy BMI and birth weight of infants. Maternal pre-pregnancy BMI was found to be linearly related to neonate birth weight. These results of restricted cubic splines and polynomial regression confirmed the effects of maternal pre-pregnancy body mass index on neonate macrosomia, and were consistent with the conclusion of logistic regression. From different perspectives, it was clear that the high correlation between pre-pregnancy BMI and macrosomia was confirmed separately.

The present study has the largest advantage of its birth cohort design. Data collection through follow-up interviews in conjunction with a hospital medical record system had a low rate of missing visits and provided strong evidence of causal association. Moreover, we conducted a comprehensive analysis using the Chinese and international standards of BMI respectively. In addition, we utilized different statistical models, including logistic regression, restricted cubic spline, and polynomial regression, to explore the relationship between the categorical and continuous BMI with macrosomia.

However, there are several limitations in our study that warrant discussion. Firstly, we did

→ Please add discuss about dietary intake, stress, physical activity, exercise and complications during pregnancy including the frequency of Antenatal care clinic ...

not measure the correlation between gestational weight gain and macrosomia in pregnant women. Previous studies have indicated that pre-pregnancy BMI, rather than gestational weight gain, is more closely correlated with neonatal birth weight[42]. Consequently, pre-pregnancy BMI has been proposed as an independent predictor of birth weight[43]. Secondly, even though we replaced the data from the questionnaire with actual height and weight measurements taken during the first antenatal visit (≤12 gestational weeks of pregnancy) to mitigate information bias, some discrepancies with the true pre-pregnancy measurements may still exist. Furthermore, in the stratified analysis, the sample size was insufficient in certain subgroups to thoroughly explore the association between pre-pregnancy BMI and macrosomia. Therefore, further research with a larger sample size is required to validate the findings. Finally, while we adjusted for numerous potential confounders, there may still be some residual effects associated with unknown factors.

Conclusions

In conclusion, our study indicates that pre-pregnancy overweight and obesity are risk factors for macrosomia, while pre-pregnancy underweight is also associated with macrosomia. Moreover, the results confirm a significant linear trend in the relationship between the continuous pre-pregnancy BMI and birth weight. These findings suggest that women may be able to potentially decrease the risk of macrosomia by managing their weight before conception.

Corresponding Authors: Leilei Pei, PhD (pll_paper@126.com) and Pengfei Qu, PhD (xinxi3057@163.com). Department of Epidemiology and Biostatistics, School of Public Health, Xi’an Jiaotong University Health Science Center, Xi’an, Shaanxi 710061, China; Translational Medicine Center Northwest Women's and Children's Hospital, Xi'an 710061, China.

Author Contributions: Drs Pei and Qu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MXY, YBZ: Writing – original draft. DDZ: Methodology, Investigation. YZ: Data curation, Investigation. DML: Conceptualization, Supervision. LS: Investigation. YM: Investigation. LLP: Funding acquisition, Supervision, Writing– review & editing. PFQ: Data curation, Writing– review & editing.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the National Natural Science Foundation of China (grant numbers 82103924 and 72174167);

Acknowledgments: We give sincerely thanks to Northwest Women's and Children's Hospital of China for their efforts in diagnosing macrosomia. Particularly, we are grateful to all participants and to the staff for their striving to collect data.

References

1. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. *Ann Nutr Metab.* 2015;66 Suppl 2:14-20.
2. Ouzounian JG. Shoulder Dystocia: Incidence and Risk Factors. *Clin Obstet Gynecol.* 2016;59(4):791-794.
3. Araujo Júnior E, Peixoto AB, Zamarian AC, Elito Júnior J, Tonni G. Macrosomia. *Best Pract Res Clin Obstet Gynaecol.* 2017;38:83-96.
4. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol.* 2007;196(4):322.e321-328.

5. Mu M, Wang SF, Sheng J, et al. Birth weight and subsequent blood pressure: a meta-analysis. *Arch Cardiovasc Dis.* 2012;105(2):99-113.

6. Azadbakht L, Kelishadi R, Saraf-Bank S, et al. The association of birth weight with cardiovascular risk factors and mental problems among Iranian school-aged children: the CASPIAN-III study. *Nutrition.* 2014;30(2):150-158.

7. Ezegwui HU, Ikeako LC, Egbuji C. Fetal macrosomia: obstetric outcome of 311 cases in UNTH, Enugu, Nigeria. *Niger J Clin Pract.* 2011;14(3):322-326.

8. Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet.* 2013;381(9865):476-483.

9. Salihu HM, Dongarwar D, King LM, Yusuf KK, Ibrahimi S, Salinas-Miranda AA. Trends in the incidence of fetal macrosomia and its phenotypes in the United States, 1971-2017. *Arch Gynecol Obstet.* 2020;301(2):415-426.

10. Zhao LJ, Li HT, Zhang YL, Zhou YB, Liu JM. [Mobile terminal-based survey on the birth characteristics for Chinese newborns]. *Beijing Da Xue Xue Bao Yi Xue Ban.* 2019;51(5):813-818.

11. Huang J, Lu QG, Ouyang JY, Yang B, Chu XW, Mao LM. Relationship between pre-pregnancy body mass index, pregnancy weight gain and neonatal birth weight and mode of delivery. China Maternal and Child Health. 2013;28(08):1235-1238.

12. Liang H, Zhang WY, Li XT. Reference range of maternal body mass gain during pregnancy in China based on the incidence of macrosomia - a multicenter cross-sectional study.

Chinese Journal of Obstetrics and Gynecology. 2017;52(03):147-152.

13. Kim SY, Dietz PM, England L, Morrow B, Callaghan WM. Trends in pre-pregnancy obesity in nine states, 1993-2003. *Obesity (Silver Spring).* 2007;15(4):986-993.

14. Chu SY, Kim SY, Bish CL. Prepregnancy obesity prevalence in the United States, 2004-2005. *Matern Child Health J.* 2009;13(5):614-620.

15. Ma GS, Li YP, Wu YF, et al. [The prevalence of body overweight and obesity and its changes among Chinese people during 1992 to 2002]. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2005;39(5):311-315.

16. Lai JQ, Yin SA. [The impact of experience in bearing child on the body mass index and obesity in women]. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2009;43(2):108-112.

17. Feng P, Wang XY, Long ZW, et al. [The association of pre-pregnancy body mass and weight gain during pregnancy with macrosomia: a cohort study]. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2019;53(11):1147-1151.

18. Ouzounian JG, Hernandez GD, Korst LM, et al. Pre-pregnancy weight and excess weight gain are risk factors for macrosomia in women with gestational diabetes. *J Perinatol.* 2011;31(11):717-721.

19. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PLoS One.* 2013;8(4):e61627.

20. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TG. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: results

from a multi-ethnic birth cohort study. *Arch Dis Child.* 2009;94(8):587-595.

21. Ay L, Kruithof CJ, Bakker R, et al. Maternal anthropometrics are associated with fetal size in different periods of pregnancy and at birth. The Generation R Study. *Bjog.* 2009;116(7):953-963.

22. Liang CC, Chao M, Chang SD, Chiu SY. Impact of prepregnancy body mass index on pregnancy outcomes, incidence of urinary incontinence and quality of life during pregnancy - An observational cohort study. *Biomed J.* 2020;43(6):476-483.

23. Stewart AW, Jackson RT, Ford MA, Beaglehole R. Underestimation of relative weight by use of self-reported height and weight. *Am J Epidemiol.* 1987;125(1):122-126.

24. Mamun AA, Callaway LK, O'Callaghan MJ, et al. Associations of maternal pre-pregnancy obesity and excess pregnancy weight gains with adverse pregnancy outcomes and length of hospital stay. *BMC Pregnancy Childbirth.* 2011;11:62.

25. Hua X, Shen M, Reddy UM, et al. Comparison of the INTERGROWTH-21st, National Institute of Child Health and Human Development, and WHO fetal growth standards. *Int J Gynaecol Obstet.* 2018;143(2):156-163.

26. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894:i-xii, 1-253.

27. Boulet SL, Salihu HM, Alexander GR. Mode of delivery and birth outcomes of macrosomic infants. *J Obstet Gynaecol.* 2004;24(6):622-629.

28. Boulet SL, Alexander GR, Salihu HM, Pass M. Macrosomic births in the united states: determinants, outcomes, and proposed grades of risk. *Am J Obstet Gynecol.*

2003;188(5):1372-1378.

29. Li G, Xing Y, Wang G, et al. Differential effect of pre-pregnancy low BMI on fetal macrosomia: a population-based cohort study. *BMC Med.* 2021;19(1):175.

30. Sun Y, Shen Z, Zhan Y, et al. Effects of pre-pregnancy body mass index and gestational weight gain on maternal and infant complications. *BMC Pregnancy Childbirth.* 2020;20(1):390.

31. Filmer D, Pritchett LH. Estimating wealth effects without expenditure data--or tears: an application to educational enrollments in states of India. *Demography.* 2001;38(1):115-132.

32. Ministry of Health of the People's Republic of China. People's Republic of China Health Industry Standard-Diagnosis of gestational diabetes: WS 331-2011 [S]. Beijing: Ministry of Health of the People's Republic of China, 2011.

33. Sharifzadeh F, Kashanian M, Jouhari S, Sheikhansari N. Relationship between pre-pregnancy maternal BMI with spontaneous preterm delivery and birth weight. *J Obstet Gynaecol.* 2015;35(4):354-357.

34. Starling AP, Brinton JT, Glueck DH, et al. Associations of maternal BMI and gestational weight gain with neonatal adiposity in the Healthy Start study. *Am J Clin Nutr.* 2015;101(2):302-309.

35. McDonald SD, Han Z, Mulla S, Beyene J. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. *Bmj.* 2010;341:c3428.

36. Dempsey JC, Ashiny Z, Qiu CF, Miller RS, Sorensen TK, Williams MA. Maternal pre-pregnancy overweight status and obesity as risk factors for cesarean delivery. *J Matern Fetal Neonatal Med.* 2005;17(3):179-185.

37. Hull HR, Thornton JC, Ji Y, et al. Higher infant body fat with excessive gestational weight gain in overweight women. *Am J Obstet Gynecol.* 2011;205(3):211.e211-217.

38. Alberico S, Montico M, Barresi V, et al. The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. *BMC Pregnancy Childbirth.* 2014;14:23.

39. Agha M, Agha RA, Sandall J. Interventions to reduce and prevent obesity in pre-conceptual and pregnant women: a systematic review and meta-analysis. *PLoS One.* 2014;9(5):e95132.

40. Vrachnis N, Belitsos P, Sifakis S, et al. Role of adipokines and other inflammatory mediators in gestational diabetes mellitus and previous gestational diabetes mellitus. *Int J Endocrinol.* 2012;2012:549748.

41. Liu P, Xu L, Wang Y, et al. Association between perinatal outcomes and maternal pre-pregnancy body mass index. *Obes Rev.* 2016;17(11):1091-1102.

42. Abdel Moety GA, Gaafar HM, Ahmed AH. Maternal prepregnancy BMI and gestational weight gain: which correlates more with neonatal birth weight? *Journal of Evidence-Based Women's Health Journal Society.* 2013;3(3):122-126.

43. Moore VM, Davies MJ, Willson KJ, Worsley A, Robinson JS. Dietary composition of pregnant women is related to size of the baby at birth. *J Nutr.* 2004;134(7):1820-1826.

Figure 1

Figure 1 Flow diagram for the study cohort selection

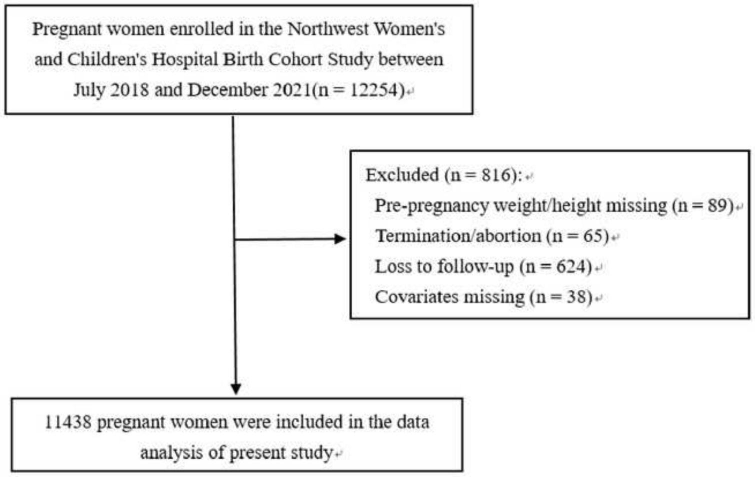

Figure 1 Flow diagram for the study cohort selection

Figure 2

Figure 2 Association of pre-pregnancy BMI with macrosomia (A) and Grade 1 macrosomia (B).

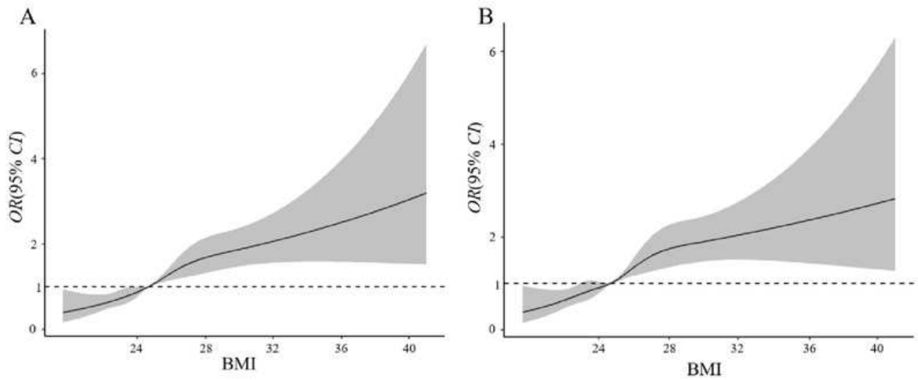

Figure 2 Association of pre-pregnancy BMI with macrosomia (A) and Grade 1 macrosomia (B). Adjusted for maternal age, education level, ethnicity, family financial situation, drinking before or during pregnancy, passive smoke before or during pregnancy, cold/fever before or during pregnancy, folic acid supplementation before or during pregnancy, parity, current GDM, fetal sex.

Table 1(on next page)

Table 1 Comparison of baseline characteristics between the four pre-pregnancy BMI groups.

1 **Table 1** Comparison of baseline characteristics between the four pre-pregnancy BMI groups.

Characteristics	N	Under weight	Normal weight	Overweight	Obesity	χ^2	*P* value
Patient number	11438	1795	7748	1554	341		
Maternal age group, years						174.342	<0.001
≤24	680	166(9.25)	403(5.20)	88(5.66)	23(6.74)		
25~29	5571	1010(56.27)	3773(48.70)	646(41.57)	142(41.64)		
30~34	4210	540(30.08)	2895(37.36)	630(40.54)	145(42.52)		
≥35	977	79(4.40)	677(8.74)	190(12.23)	31(9.09)		
Educational level						87.827	<0.001
Below high school	1298	185(10.31)	815(10.52)	231(14.86)	67(19.65)		
College/university	8345	1362(75.88)	5598(72.25)	1144(73.62)	241(70.67)		
Postgraduate	1795	248(13.82)	1335(17.23)	179(11.52)	33(9.68)		
Ethnicity						0.770	0.857
Han	11260	1770(98.61)	7623(98.39)	1532(98.58)	335(98.24)		
Other	178	25(1.39)	125(1.61)	22(1.42)	6(1.76)		
Family wealth index						64.902	<0.001
Poor	1374	215(11.98)	879(11.34)	206(13.26)	74(21.70)		
Moderate	7641	1162(64.74)	5154(66.52)	1092(70.27)	215(63.05)		
Rich	2449	418(23.29)	1715(22.13)	256(16.47)	52(15.25)		
Parity						79.455	<0.001
Nulliparous	8299	1437(80.06)	5590(72.15)	1042(67.05)	230(67.45)		
Multiparous	3139	358(19.94)	2158(27.85)	512(32.95)	111(32.55)		
Fetal sex						1.769	0.622
Male	5853	896(49.92)	3982(51.39)	805(51.80)	170(49.85)		
Female	5585	899(50.08)	3766(48.61)	749(48.20)	171(50.15)		
Drinking before or during pregnancy						1.908	0.592
Yes	371	62(3.45)	245(3.16)	49(3.15)	15(4.40)		
No	11067	1733(96.55)	7503(96.84)	1505(96.85)	326(95.60)		
Passive smoke before or during pregnancy						2.175	0.537
Yes	1771	291(16.21)	1173(15.14)	252(16.22)	55(16.13)		
No	9667	1504(83.79)	6575(84.86)	1302(83.78)	286(83.87)		
Cold/fever before or during pregnancy						0.729	0.866
Yes	2461	374(20.84)	1674(21.61)	341(21.94)	72(21.11)		
No	8977	1421(79.16)	6074(78.39)	1213(78.06)	269(78.89)		
Folic acid supplementation before or						273.051	<0.001[a]

during pregnancy							
Yes	11075	1795(100.00)	7385(95.31)	1554(100.00)	341(100.00)		
No	363	0(0.00)	363(4.69)	0(0.00)	0(0.00)		
Current GDM						270.862	<0.001
Yes	2796	285(15.88)	1789(23.09)	587(37.77)	135(39.59)		
No	8642	1510(84.12)	5959(76.91)	967(62.23)	206(60.41)		

[a] Fisher exact test.

Table 2(on next page)

Table 2 Relationship between macrosomia and pre-pregnancy BMI.

Table 2 Relationship between macrosomia and pre-pregnancy BMI.

Pregnancy outcomes	N	Under weight	Normal weight	Overweight	Obesity	χ^2/ F	P value
Macrosomia, n (%)						65.855	<0.001
No	10793	1739(96.88)	7332(94.63)	1412(90.86)	310(90.91)		
Yes	645	56(3.12)	416(5.37)	142(9.14)	31(9.09)		
Grade 1 macrosomia	576	52(2.90)	373(4.81)	125(8.04)	26(7.26)	69.821	<0.001[a]
Grade 2 macrosomia	50	3(0.17)	28(0.36)	15(0.97)	4(1.17)		
Grade 3 macrosomia	19	1(0.06)	15(0.19)	2(0.13)	1(0.29)		
Birth weight(g), Median (IQR)	11438	3230.00(3000.00,3500.00)	3330.00(3060.00,3600.00)	3400.00(3100.00,3700.00)	3340.00(3060.00,3670.00)	114.447	<0.001[b]

[a] Fisher exact test; [b] Kruskal–Wallis test.

IQR, interquartile range.

Table 3 (on next page)

Table 3 Association between pre-pregnancy BMI and macrosomia according to logistic regression analysis.

Table 3 Association between pre-pregnancy BMI and macrosomia according to logistic regression analysis.

Variable	Model 1	Model 2[a]	Model 3[b]
	OR (95%CI), *P*	*Adjusted OR (95%CI)*, *P*	*Adjusted OR (95%CI)*, *P*
Pre-pregnancy BMI			
Under weight	0.57(0.43~0.75), <0.001	0.56(0.42~0.75), <0.001	0.55(0.41~0.73), <0.001
Normal weight	1.00	1.00	1.00
Overweight	1.77(1.45~2.16), <0.001	1.79(1.47~2.19), <0.001	1.66(1.35~2.01), <0.001
Obesity	1.76(1.20~2.58), 0.004	1.80(1.22~2.64), 0.003	1.66(1.13~2.45), 0.010
P for trend	<0.001	<0.001	<0.001

[a] Model 2 used Model 1 and adjusted for maternal age, education level, ethnicity, and family financial situation. [b] Adjusted for Model 2 and drinking before or during pregnancy, passive smoke before or during pregnancy, cold/fever before or during pregnancy, folic acid supplementation before or during pregnancy, parity, current GDM, fetal sex.

Table 4(on next page)

Table 4 Effects of pre-pregnancy BMI on macrosomia based on the BMI criteria proposed by the WHO.

Table 4 Effects of pre-pregnancy BMI on macrosomia based on the BMI criteria proposed by the WHO.

Variable	Model 1	Model 2[a]	Model 3[b]
	OR (95%CI), P	*Adjusted OR (95%CI), P*	*Adjusted OR (95%CI), P*
Pre-pregnancy BMI			
Under weight	0.55(0.42~0.73), <0.001	0.55(0.41~0.73), <0.001	0.53(0.40~0.71), <0.001
Normal weight	1.00	1.00	1.00
Overweight	1.85(1.48~2.30), <0.001	1.87(1.50~2.33), <0.001	1.72(1.37~2.16), <0.001
Obesity	2.43(1.51~3.92), <0.001	2.48(1.54~4.02), <0.001	2.33(1.44~3.78), 0.001
P for trend	<0.001	<0.001	<0.001

[a] Model 2 used Model 1 and adjusted for maternal age, education level, ethnicity, and family financial situation. [b] Adjusted for Model 2 and drinking before or during pregnancy, passive smoke before or during pregnancy, cold/fever before or during pregnancy, folic acid supplementation before or during pregnancy, parity, current GDM, fetal sex.