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Preconception Paternal/Maternal Body Mass Index and Risk of Small/Large for Gestational Age Infant in over 4·7 Million Chinese Women Aged 20-49 Years: A Population-based Cohort Study in China

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Abstract

Evidence of couples' BMI and its influence on birth weight is limited and contradictory. Therefore, this study aims to assess the association between couple's preconception BMI and the risk of small for gestational age (SGA)/large for gestational age (LGA) infant, among over 4·7 million couples in a retrospective cohort study based on the National Free Pre-pregnancy Checkups Project (NFPCP) between December 1, 2013 and November 30, 2016 in China. Among the live births, 256,718 (5·44%) SGA events and 506,495 (10·73%) LGA events were documented, respectively. After adjusting for confounders, underweight men had significantly higher risk [OR 1·17 95%CI (1·15-1·19)] of SGA infants compared with men with normal BMI, while a significant and increased risk of LGA infants was obtained for overweight and obese men [OR 1·08 (95% CI: 1·06-1·09); OR 1·19 (95%CI 1·17-1·20)] respectively. The restricted cubic spline (RCS) result revealed a non-linearly decreasing dose-response relationship of paternal BMI (less than 22·64) with SGA. Meanwhile, a non-linearly increasing dose-response relationship of paternal BMI (more than 22·92) with LGA infants was observed. Moreover, similar results about the association between maternal preconception BMI and SGA/LGA infants were obtained. Abnormal preconception BMIs in either women or men were associated with increased risk of SGA/LGA infants, respectively. Overall, couple's abnormal weight before pregnancy may be an important preventable risk factor for SGA/LGA infants.

Keywords: Body mass index; Small-for-gestational age; Large-for-gestational age; Preconception; Cohort study.

Abbreviations: BMI, body mass index; SGA, small-for-gestational-age; LGA, large-for-gestational-age; NFPCP, National Free Pre-pregnancy Checkups Project

Shortened version of the title: Couples' Body Mass Index and Risk of Small/Large for Gestational Age Infant

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Introduction

Birth weight, as a major predictor of infant growth and survival, is associated with neonatal mortality and morbidity, cognitive ability, and metabolic disease including obesity, hypertension as well as type 2 diabetes mellitus during childhood or adult life[1-6]. Previous studies found that a high birth weight increases the risk of obesity in later life and may act as a mediator between prenatal influences and risk of disease in adults[7]. Magnus[8] reported that more than 50% of the total variance in birth weight result from variation of fetal genes, using the birth weights of offspring of twins. Besides fetal genes, multifactorial risk factors including socio-demographic factors (maternal age, ethnicity, educational level, economic status and paternal height), lifestyle (maternal diet, physical activity, smoking, drinking), nutritional status (preconception BMI, pregnancy weight gain, anemia), chronic disease (hypertension, diabetes) and antenatal care are associated with birth weight which is caused by the interaction of intrauterine, genetic and environmental factors[9-16].

An increasing number of studies have identified the association between maternal body mass index (BMI) and infant birth weight including small for gestational age (SGA), large for gestational age (LGA), macrosomia or low birth weight (LBW), which suggests that higher maternal preconception BMI is associated with an increased risk of LGA, while maternal preconception underweight is associated with an increased risk of SGA[17, 20]. The mechanism of the effect of maternal preconception BMI on birth weight has been unclear. Sharp and colleagues reported that both maternal underweight and obesity affect the neonatal epigenome via an intrauterine mechanism, and increased DNA methylation may mediate the associations of maternal underweight with lower offspring obesity and maternal obesity with greater offspring obesity[21]. Furthermore, studies have shown that insulin resistance which causes metabolic disorders and increases the availability of maternal nutrients to the fetus, leading to fetal growth acceleration, often occurs in women with high BMI or excessive weight gain during pregnancy[22-23].

However, less is known about the association between paternal BMI and risk of LGA/SGA, and the few previous studies have shown contradictory results. A study from Croatia found a significant association between paternal BMI and birth weight, while several other studies reported that paternal BMI was not directly associated with LGA/SGA[24-28]. However, paternal BMI in the few previous studies were almost collected from self-report rather than formal measurement. Previous evidence has shown that the mechanisms underlying a possible association between paternal BMI and SGA/LGA might involve affecting spermatozoa or genetic regulation, such as insulin-like growth factor-I (IGF-I) and insulin-like growth factor-II (IGF-II), which are expressed from the copy of the paternal gene[29-31].

Nowadays, consensus has been reached that low birth weight (LBW) is not an adequate measure of a ‘small baby’. Accumulating evidence suggests that the variable “SGA” is perceived as a more optimal measure than birth weight or LBW to assess fetal growth generally[32-34]. Therefore, this study aims to assess the association between preconception couple’s BMI and the risk of LGA/SGA, among over 4·7 million couples in a cohort study based on the National Free Pre-pregnancy Checkups Project (NFPCP) between 2013 and 2016.

Methods

Study Population and Design

Data for this national large population-based retrospective cohort study were extracted from the NFPCP, which is a national preconception free health service to provide free preconception health examinations and counselling for rural reproductive-aged couples throughout China. Since 2013, the NFPCP services were extended to both rural and urban married couples. The NFPCP has been supported by the National Health Commission and the Ministry of Finance of the People’s Republic of China. Detailed design, organization and implementation of NFPCP have been described in previously published articles[35-37].

In general, 5,709,510 Chinese women who were aged 20-49 years old at last menstrual period (LMP) participated in the NFPCP from January 1, 2013 to December 31, 2016 and successfully got pregnant and gave birth until December 31, 2017, were included. Then 134,258 women or their husbands with missing information on BMI data, 31,169 women who had multiparous pregnancy and 238,805 women who had other types of adverse pregnancy outcomes, such as fetal death, ectopic pregnancy, spontaneous abortion and medically-induced abortion, 585,465 women with missing information on birth weight or gestational week were excluded. Finally, a total of 4,719,813 women with singleton pregnancy were included in the analysis after considering the exclusion criteria in Figure 1.

This study was approved by the Institutional Research Review Board at the National Research Institute for Family Planning, Beijing, China. Written informed consent was obtained from all NFPCP participants. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection

The general NFPCP program consist of the three stages: preconception health examinations, early pregnancy follow-up, and pregnancy outcome follow-up. These stages were contained in the NFPCP to collect different types of data from all enrolled couples. Face-to-face interviews, medical examination and telephone interviews were conducted by qualified health staff using a standard questionnaire which includes a pre-pregnancy examination Chart (both husband and wife) to collect baseline information about demographic characteristics and several follow-up charts including the information of lifestyle or medical examination during early pregnancy, pregnancy outcome and infant condition in local family planning service agencies or maternal and child service centers.

In the first stage (preconception health examinations), couples who met the fertility policy and planned to conceive within 6 months, were advocated and encouraged by the domestic resident committee to participate in a preconception health examination. The basic information on family history, lifestyle, dietary nutrition, social-psychological factors, environmental poisons, physical examination and clinical examination were recorded in the pre-pregnancy examination chart for husband and wife, separately. The body weight and height of wives and their husbands wearing light, indoor clothing and no shoes were measured according to a standardized protocol. Next, BMI was calculated.

In the second stage (early pregnancy follow-up), the early pregnancy follow-up interview was conducted by trained healthcare staff using the telephone to obtain the conception status of women within 3 months after preconception health examinations. For the women who did not get pregnant at the first follow-up interview, repeated investigations were conducted subsequently every three months until up to one year after preconception examination. For pregnant women, information regarding the LMP, toxic or harmful substances exposure, and any lifestyle changes in the first trimester of pregnancy were collected.

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In the final stage (pregnancy outcome follow-up), women who had become pregnant during the early pregnancy follow-up were recontacted by trained research staff using telephone within 1 year to collect pregnancy outcome information. Adverse pregnancy outcomes including spontaneous abortion, low birth weight, induced labor, ectopic pregnancy, birth defects, preterm birth, and stillbirth were documented in the follow-up chart. Besides, information regarding puerpera's self-reported information on their delivery condition and fetal information such as the delivery date, birth weight and gender were self-reported and recorded during the interview. Women were encouraged to actively report their adverse pregnancy outcome events, if women had an abortion or other adverse pregnancy outcomes occurred in the early pregnancy period.

In the current study, the gestational week of women was initially calculated by the duration between the LMP and the time of delivery which were recorded in the early pregnancy follow-up and the pregnancy outcomes follow-up, respectively. Then, ultrasound examination adjusted gestational week was also collected in the pregnancy outcome follow-up survey. When the two gestational week records were different, the ultrasound examination adjusted gestational week was used.

Exposure and Outcome

The body weight and height were measured with wives and their husbands wearing light, indoor clothing and no shoes, respectively. Next, maternal/paternal own preconception weight and height were used to calculate the maternal/paternal preconception BMI [calculated as the weight (kg) in kilograms divided by height (m) in meters squared], which was further classified into four groups: 1) underweight (<18·5 kg/m^2), 2) normal weight (18·5–23·9 kg/m^2), 3) overweight (24·0–27·9 kg/m^2), and 4) obese (≥28·0 kg/m^2 or higher), respectively, according to the Chinese guidelines for the prevention and control of overweight and obesity in adults[38]. Couples were categorized into 9 groups according to their BMI levels (maternal BMI: paternal BMI),: 1. Underweight (wife): Underweight (husband); 2. Underweight (wife): Normal weight (husband); 3. Underweight (wife): Overweight & Obese (husband); 4. Normal weight (wife): Underweight (husband); 5. Normal weight (wife): Normal weight (husband); 6. Normal weight (wife): Overweight & Obese (husband); 7. Overweight & Obese (wife): Underweight (husband); 8. Overweight & Obese (wife): Normal weight (husband); 9. Overweight & Obese (wife): Overweight & Obese (husband).

SGA infant is defined as newborn birth weight by gestational age and gender below the 10th

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percentile (< 10th percentile); Appropriate for gestational age (AGA) infant is defined as newborn birth weight by gestational age and gender between the 10th percentile and 90th percentile (10^{th} to 90th percentile). LGA infant is identified as newborn birth weight by gestational age and gender beyond the 90th percentile (> 90th percentile) according to the Chinese national survey[39].

Covariates

The ages of women were calculated as the difference between the date of birth and the first day of the LMP of women; these ages were categorized into various age groups (20–24.9, 25–29.9, 30–34.9, 35–39.9, and ≥40 years). Higher education was categorized as levels of education of senior high school, college or higher. Ethnicity was categorised as Han nationality and Others(non-Han nationality). Diabetes mellitus was categorized as either self-reported diabetes or fasting blood glucose ≥7.0mmol/L. Physicians conducted seated blood pressure measurement in the right arm of the seated women/men using an automated blood pressure monitor, on a single occasion after women/men rested for 10 minutes or more. Hypertension was defined as self-reported hypertension or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Smoking was defined as smoking before or during early pregnancy (women/men who smoked at least 1 cigarette per day at least one year at the time of baseline examination). Alcohol drinking was defined as drinking once per week on average at the time of examination (regardless of the type of drinking, such as white wine, liquor, beer, red wine, yellow rice wine, etc. before or during early pregnancy.). Passive smoking was defined as exposure to environmental tobacco smoke before or during early pregnancy. History of adverse pregnancy outcomes was defined as the history of preterm birth (live birth between 28 and 36 completed weeks of pregnancy), later fetal death (stillbirth after 28 weeks of gestation or newborns who died within 7 days after birth) or spontaneous abortion (pregnancy loss occurring before the 28th week of gestation) in previous pregnancies.

Statistical analysis

Continuous variables with normal distribution were expressed as mean values (standard deviations), and non-normally distributed variables were expressed as median (inter-quartile range, IQR). Categorical variables were expressed as numbers (percentages) for baseline characteristics.

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The associations between the two categories of maternal/paternal preconception BMI levels (maternal/paternal preconception BMI levels, couple's BMI levels) and the risk of SGA or LGA were examined, respectively. The odds ratios (ORs) and their corresponding 95% CIs of SGA/LGA associated with BMI status of couples (9 groups), maternal/paternal preconception BMI levels (four groups) using age-adjusted and multivariate-adjusted multinomial logistic regression models, respectively, compared to appropriate for gestational age infant.

The OR and their corresponding 95% CI were estimated by age-adjusted and multivariate-adjusted multinomial logistic regression models separately, using normal weight (18·5–23·9 kg/m^2) as the reference group. Maternal and paternal age at last menstrual period (20-24·9, 25-29·9, 30-34·9, 35-39·9 and ≥ 40 years-old) as covariates were adjusted in all age-adjusted models. Covariates in the multivariate-adjusted regression models of BMI status of couples (9 groups) included maternal and paternal age at last menstrual period (20-24·9, 25-29·9, 30-34·9, 35-39·9 and ≥ 40 years-old), maternal and paternal height (continuous variables), maternal and paternal ethnic (Han, other ethnic), maternal and paternal education levels (senior high school, college or higher), parity (0, 1+), maternal and paternal area of residence (rural or urban), maternal hypertension (yes, no), maternal diabetes (yes, no), maternal and paternal alcohol drinking (yes, no), maternal and paternal smoking (yes, no), maternal and paternal passive smoking (yes, no), history of adverse pregnancy (yes, no). At meanwhile, in the multivariate-adjusted regression models of maternal/paternal preconception BMI levels (four groups) we additionally adjusted for paternal or maternal BMI levels (<18·5, 18·5–23·9, 24·0–27·9 and ≥28·0 kg/m^2). Besides, the individual and couple models after regrouping BMI levels using World Health Organization (WHO) criteria (underweight <18·5 kg/m^2, normal Weight 18·5–25·0 kg/m^2, overweight 25·0–30·0 kg/m^2 and Obese, 30·0 kg/m^2 or higher) were rerun [40].

Furthermore, the dose-response relationship of maternal/paternal preconception BMI levels and risk of SGA/LGA were assessed using restricted cubic spline (RCS), respectively, and five knots at the 5th, 25th, 50th, 75th and 95th percentiles of maternal/paternal preconception BMI levels were used in plotted smooth curves (the RCS with three, four or five knots was separately fitted, and the models with the lowest Akaike information criterion as the best model) were chosen, and Wald statistics was used to test the non-linearity of the

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dose-response[41-42]. Covariates were the same as the multivariate-adjusted regression models of maternal/paternal preconception BMI levels. Besides, the models after regrouping SGA/LGA using INTERGROWTH-21st criteria were rerun[43]. Additionally, sensitivity analysis was conducted after excluding couples with missing data on baseline characteristics.

Statistical analysis was performed using R software (V.3.5.0; https://www.r-project.org/) with the analysis packages 'epade (version 0.3.8)', 'forestplot (version 1.7.2)', 'rms (version 5.1–2)', 'ggplot2 (version 3.1.0)', 'reshape2 (version 1.4.3)' and 'speedglm (version 0.3–2)'. All statistical tests were 2-sided, and P values < 0·05 were considered statistically significant.

Results

Among all the 4,719,813 enrolled couples, 14·85% of women were overweight or obese (12·09% were overweight, 2·76% obese), and 13·53% were underweight, while 33·53% of men were overweight or obese (26·46% were overweight, 7·07% obese) and 4·10% were underweight (**Table 1**). Women who smoked cigarettes, were exposed to secondhand smoke, have pre-existing diabetes or history of adverse pregnancy outcomes were more likely with abnormal BMI. Women with BMI ≥25 kg/m^2 were more likely to be of Han nationality, aged and poor educated, from rural areas, and have higher blood pressure level than those women with BMI within 18·5–24·9 kg/m^2. Meanwhile, women with BMI <18·5 kg/m^2 were more likely to be parous and drink alcohol (**Supplemental table 2**). The husband with abnormal BMI was more likely to be of Han nationality, consume alcohol, smoke cigarettes or exposed to secondhand smoking. Besides, the husband with BMI ≥25 kg/m^2 were more likely to be older, living in the city and with more educational attainment (**Supplemental table 3**). Detailed descriptive characteristics of the study population by maternal/paternal preconception BMI are in **Table 1**, **Supplemental Table 2** and **Table 3**, respectively.

The final study population included 4,719,813 women (**Figure 1**) with a median birth weight of 3350 g (interquartile range 3100–3600) and median gestational age at birth of 39·71 weeks (interquartile range 38·57–40·43); 2,453,312 (51·98%) infants were male and 2,261,613 (47·92%) were female. Among the live births, 256,718 (5·44%) SGA events and 506,495 (10·73%) LGA events were documented, respectively. The incidence of SGA (7·61%) in the maternal preconception underweight group was significantly higher than that in normal-weight (5·28%), overweight (4·25%) or obese (4·06%) group, while the corresponding SGA incidence was 7·06%, 5·64%, 4·98% and 4·49%, respectively in paternal preconception underweight, normal, overweight or obese group. Meanwhile, the incidence of LGA was 8·70%, 10·48%, 13·46% and 15·26% for underweight, normal weight, overweight, and obese women, and the corresponding incidence for the husband was 9·32%, 10·24%, 11·47% and 13·09%, respectively (**Figure 2**).

After adjusted for maternal and paternal age at LMP, height, ethnicity, education, area of residence, alcohol drinking, smoking, passive smoking and maternal BMI, hypertension, diabetes, parity as well as the history of adverse pregnancy, it is shown that husbands who were underweight had significantly higher risk [OR 1·17 95%CI (1·15-1·19)] of SGA compared with the husband with normal BMI, while overweight or obese husband had lower risks with multivariable-adjusted OR of 0·92(95% CI: 0·90-0·93) and 0·87(95% CI: 0·85-0·88), respectively. In addition, a significant and increased risk of LGA was observed for overweight and obese men [OR 1·08 (95% CI: 1·06-1·09); OR 1·19 (95%CI 1·17-1·20)] respectively, but the negative association was identified with LGA for underweight men [OR 0·94 (95%CI 0·93-0·96)] (**Figure 2**). Reduced paternal BMI was associated with an increased risk of SGA when paternal BMI was less than 22·64 (*P* non-linear< 0·001). Meanwhile, increasing paternal BMI were associated with an increased risk of LGA when paternal BMI was more than 22·92 (*P* non-linear< 0·001). In our analysis, similar results about the association between maternal preconception BMI and SGA/LGA (BMI level was 20·71/20·96) were obtained and detailed multivariable-adjusted ORs (95% CI) and RCS result were described in **Figure 4** and **Supplemental Table 4**, respectively. Similar results were observed in the analysis according to WHO criteria of BMI (**Supplemental Table 7**). Moreover, similar results were observed in the analysis according to INTERGROWTH-21st criteria of SGA/LGA (**Supplemental Table 9**).

Further stratified analysis has shown that SGA infants rates was significantly higher among maternal underweight groups, compared with the reference group (couples with normal BMI), while overweight&obese women groups had significantly lower rates. Inversely, compared with couples with normal BMI, LGA infants rates were significantly lower among maternal underweight groups, while overweight&obese women groups had significantly higher rates

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of LGA infants (**Figure 3**). Detailed multivariable-adjusted ORs (95% CI) were described in **Supplemental Table 5**. Similar results were observed in the analysis according to WHO criteria of BMI (**Supplemental Table 8**). In sensitive analysis, similar results were obtained in analysis by excluding couples with missing data on baseline characteristics (**Supplemental Table 10**).

Discussion

In our large nationwide population-based retrospective cohort study of over 4·7 million couples in China, maternal/paternal abnormal preconception BMI levels were associated with increased risk of adverse SGA/LGA infants, respectively. A statistically significant decreased risk of SGA was identified both in females and males with the increasing of their BMI levels, and the higher the preconception BMI level is, the lower the risk of SGA is. Inversely, an increasing trend of the relative risk of LGA was found with the increasing of paternal or maternal BMI levels, preconception overweight and obesity were associated with increased risks of LGA both in men and women. Furthermore, we found significant non-linearly dose-response relationships that reduced paternal/maternal BMI were associated with an increased risk of SGA when paternal/maternal BMI were less than 22·64/20·71. Meanwhile, increasing paternal/maternal BMI was associated with an increased risk of LGA when paternal/maternal BMI was more than 22.92/20.96. After adjusted for couple's covariates including maternal BMI, we still found that higher paternal preconception BMI was associated with an increased risk of having an LGA infant, while lower paternal preconception BMI was associated with higher risks of SGA. To our knowledge, this is the first largest comprehensive study to explore an association for couple's preconception BMI with the risk of SGA/LGA in a Chinese population-based study.

In the present study, similar results about the association between maternal preconception BMI and SGA/LGA to previous studies which have consistently shown that maternal BMI is positively associated with birth weight of infants were obtained [17-20, 44]. However, previous studies of paternal BMI and its influence on birth weight showed contradictory results[24, 26-28, 45-47]. Although some studies have found that paternal body weight and height significantly correlated with the infant birth weight and length, a significant dose-response relationship was only identified in male infants[24, 26, 45]. Inversely, several other studies which were conducted in the third trimester of gestation or using paternal data collected from their wives, found no association between paternal preconception BMI and SGA/LGA, when certain paternal and maternal risk factors such as maternal height, BMI or paternal height were adjusted[25-28, 46, 48, 49]. In the current study, a positive, significant and independent non-linear dose-response relationship of paternal preconception BMI (less than 22.64) with LGA risk was observed, whereas a negative non-linear dose-response relationship between paternal preconception BMI (more than 22.92) and SGA risk was shown in this large cohort. Moreover, paternal data directly collected prior to pregnancy were used in our study which may effectively avoid information bias as well recalling bias.

In this study, compared with maternal/paternal normal BMI, a decreased risk of SGA for overweight and obese women/men was observed, but maternal/paternal overweight and obesity were associated with higher risks of LGA, respectively. Moreover, although maternal/paternal underweight was associated with lower risks of LGA, a significant and positive association of SGA was observed for underweight women/men, respectively. These findings imply that abnormal (both low and high) paternal/maternal BMI were associated with higher risks of SGA/LGA, respectively. Sufficient and consistently studies suggested that maternal pregnancy body mass index (BMI) and gestational weight gain (GWG) have been associated with SGA/LGA[44, 50]. we propose that couples' well weight management in the preconception period might be crucial for maternal and fetal health which might prevent the occurrence of SGA/LGA infant. Till now, the underlying mechanisms through which abnormal paternal BMI contributes to SGA/LGA still remain unknown. Evidence indicated that paternal obesity has been shown to increase DNA methylation near the transcription start locus of ARFGAP3 gene of germ cells, which was associated with lower offspring birth weight, increase the histone modification and modify the expression of sperm microRNAs[51-54]. Furthermore, the major growth factors in offspring gene, insulin-like growth factor-I (IGF-I) and insulin-like growth factor-II (IGF-II) which are associated with placental, fetal growth including skeletal length, and the expression from the copy of the paternal gene, but part results of these studies were obtained from animal experiments(29-31,55,56). All these studies indicated that the impact of paternal BMI on

SGA/LGA might be resulted from affecting spermatozoa or genetic regulation. Besides, the mechanism of the effect of maternal preconception BMI on birth weight has also been unclear. A Norwegian Research reported that more than 50% of the total population variance in birth weight result from fetal genes, and that less than 20% result from variation in maternal genes. The rest variance (20-30%) could be caused by random environmental effects[8]. A previous study has suggested that abnormal maternal BMI (both maternal underweight and obesity) affect the neonatal epigenome via an intrauterine mechanism, and increased DNA methylation might mediate the associations of maternal underweight with lower offspring obesity and maternal obesity with greater offspring obesity[21] . Furthermore, studies have shown that insulin resistance which leads to metabolic disorders and increases the availability of maternal nutrients to the fetus, causing to fetal growth acceleration, often occurs in women with high BMI[22, 23]. These studies suggested that epigenetics or other mechanism of couples' BMI may has potential to change that risk of SGA/LGA.

However, further randomized controlled trials lab research or cohort studies in other populations are still needed to comprehensively and deeply clarify the relationships between paternal/maternal preconception BMI and SGA/LGA infant or other adverse pregnancy outcomes, including miscarriage, preterm birth (PTB) and fetal death during the preconception period. These studies might provide more evidence to act against the overweight and obesity epidemic, which have become prevalent in women of reproductive age and cause a high disease burden in the present and future, as well as promote preconception health which is strongly associated with pregnancy outcome, and interventions during preconception period are urgently required to improve both maternal and child health[50, 57] .

A previous study found that maternal BMI during 14-16 weeks of gestation had a dominant influence on LGA, our results were consistent with this research[46]. In our analyses, the maternal-offspring SGA/LGA association is stronger than the paternal-offspring SGA/LGA association. These findings indicate that maintaining an optimal BMI level for couples prior to pregnancy might be the most beneficial condition for pregnancy preparation, although paternal preconception BMI showed a weaker effect on the risk of SGA/LGA. Interestingly, we also found that the women whose husbands were overweight or obese were more likely to

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be overweight or obese (**Supplemental Table 6**), which might be explained by couples having similar dietary or physical exercise models within one family unit or unfavorable lifestyles which result in obesity might affect each other in couples.

To our knowledge, this study is the largest comprehensive population-based cohort study to explore the association between the paternal and/or maternal preconception BMI and the risk of SGA/LGA in the study population of more than 4·7 million women, adjusting for numerous couple's confounders and covariates. Another strength is that dose-response relationship curves between paternal preconception BMI and risk of SGA/LGA infants were firstly assessed in our study. In addition, the maternal and paternal preconception weight and height data were measured objectively in this study. However, this analysis has some limitations. First, data on couples' socio-economic status, maternal gestational weight gain, and maternal complications, which have been associated with SGA/LGA infant, were not available in our study, so these factors could not be adjusted in our multivariable analysis. Another limitation is that data on infant birth weight was self-reported in this study, which could lead to inaccurate outcome calculation and the misclassification of SGA/LGA. Third, information on paternal dietary or physical exercise habits which might be shared with the mother wasn't collected in our study.

In conclusion, our study demonstrated that greater maternal/paternal preconception BMI was associated with an increased risk of having an LGA infant, while lower maternal/paternal preconception BMI was associated with higher risks of SGA, respectively. Although maternal-offspring SGA/LGA association is stronger than the paternal-offspring SGA/LGA association, with respect to the high prevalence of obesity worldwide, the importance of couple's weight management (couple's normal-BMI), should not be neglected during preconception examination or counselling. Our findings may have implications for managing and counseling in pregnancies to avoid adverse pregnancy outcomes. Future research studies are needed to clarify whether and how preconception counselling and interventions for couples with abnormal preconception BMI can reduce the risk of SGA/LGA.

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Ethics approval: The current study was approved by the Institutional Research Review Board at the National Research Institute for Family Planning, Beijing, China. Written informed consent was obtained from all NFPCP participants.

Conflicts of interest: none.

Authorship The corresponding author has full access to data in the study and takes responsibility for data integrity and the accuracy of data analysis. Tonglei Guo searched the literature, analysed the data, interpreted the results and drafted the manuscript. Jiajing JIA and Yuzhi DENG searched the literature and interpreted the results. Qiaomei Wang, Haiping Shen, and Donghai Yan led the data collection and laboratory testing. Yiping Zhang, Donghai Yan, Yuanyuan Wang, Hongguang Zhang, Zuoqi Peng, Jun Zhao, Yuan He, Ya Zhang, collected the data. Ying Yang and Xu Ma revised the manuscript.

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Figure Legend

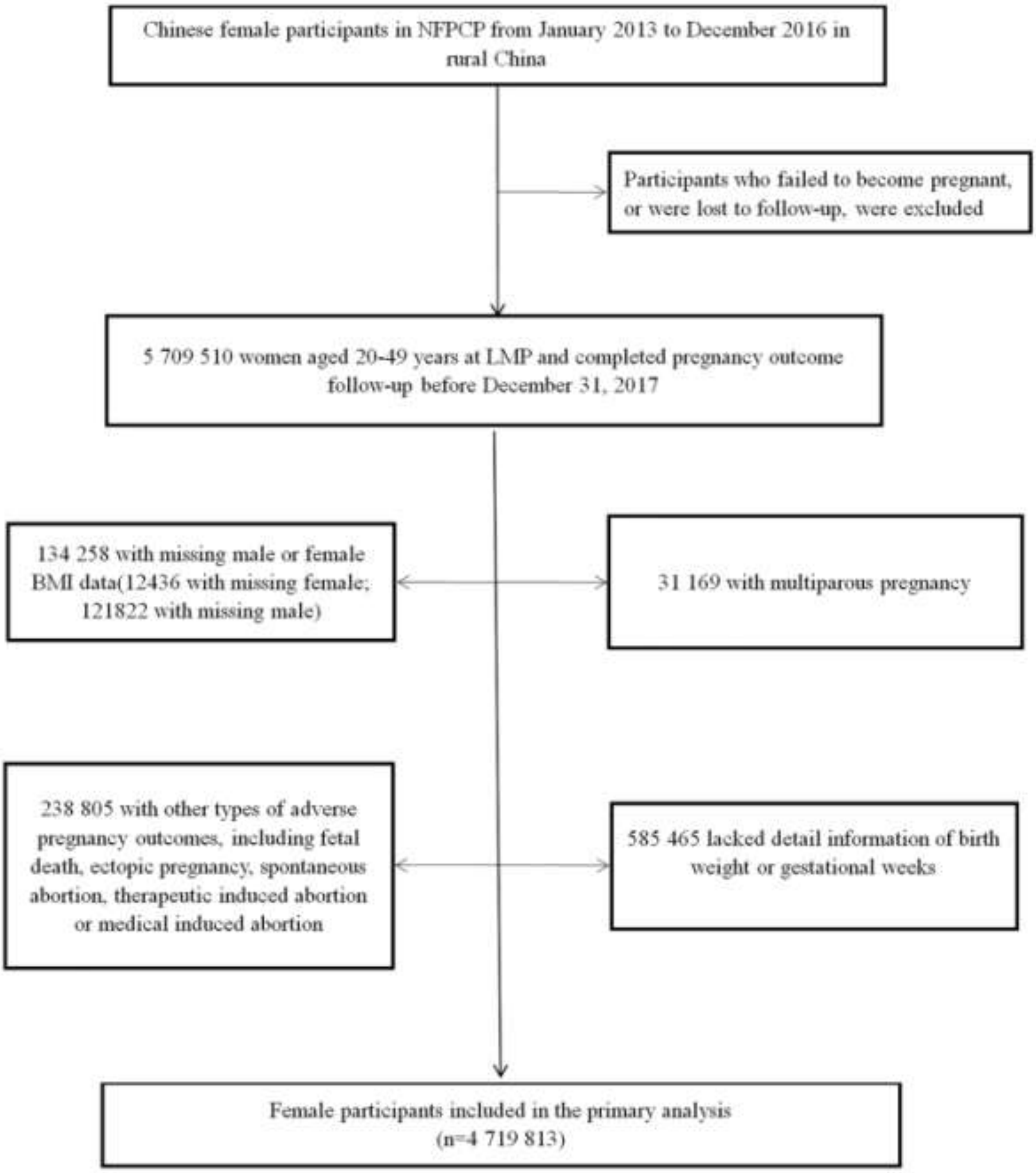

Figure 1. Flow Chart of the Study Population.

Abbreviations: NFPCP, National Free Pre-Pregnancy Checkups Project; BMI, body mass index; LMP, last menstrual period.

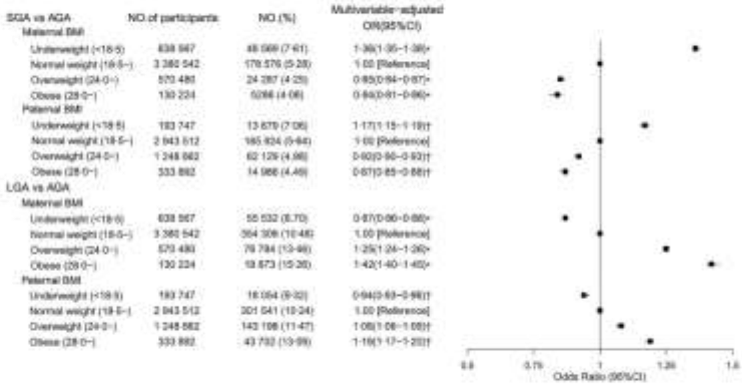

Figure 2. Associations between Maternal/ Paternal Preconception Body Mass Index and Risk of Small/Large for Gestational Age Infant (Odds Ratios and 95% Confidence Intervals).

Abbreviations: SGA, small for gestational age infant; AGA, appropriate for gestational age infant; LGA, large for gestational age infant; OR, odds ratios, BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared).

* Models were adjusted for maternal and paternal age at LMP, height, ethnic, education, area of residence, alcohol drinking, smoking, passive smoking and paternal BMI, maternal hypertension, diabetes, parity as well as history of adverse pregnancy.

† Models were adjusted for maternal and paternal age at LMP, height, ethnic, education, area of residence, alcohol drinking, smoking, passive smoking and maternal BMI, hypertension, diabetes, parity as well as history of adverse pregnancy.

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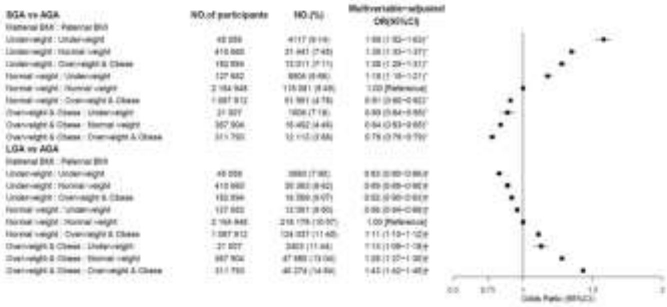

Figure 3. Adjusted ORs of Small/Large for Gestational Age Infant According to Body Mass Index of Couples.

Abbreviations: SGA, small for gestational age infant; AGA, appropriate for gestational age infant; LGA, large for gestational age infant; OR, odds ratios, BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared).

* † Multivariable-adjusted OR (95%CI) were adjusted for maternal and paternal age at LMP, height, ethnic, education, area of residence, alcohol drinking, smoking, passive smoking and maternal hypertension, diabetes, parity as well as history of adverse pregnancy.

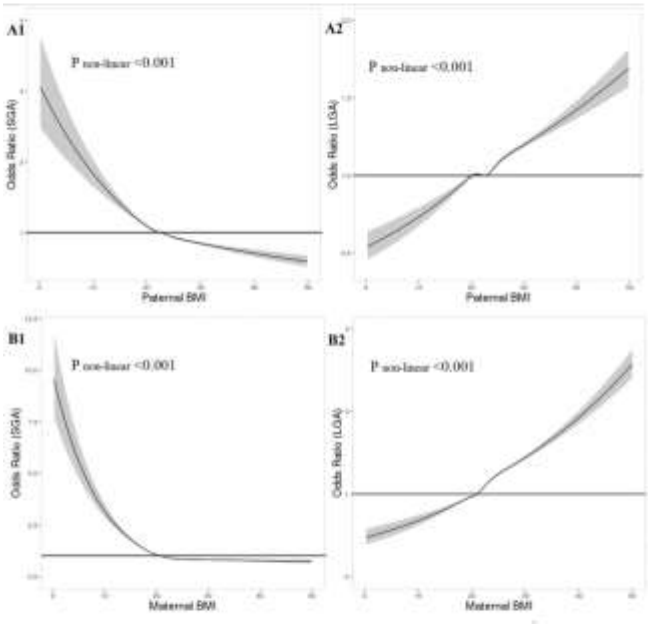

Figure 4. Dose-response Relationship between Maternal/ Paternal Preconception Body Mass Index and Risk of Small/Large for Gestational Age Infant.

Abbreviations: SGA, small for gestational age infant; LGA, large for gestational age infant; OR, odds ratios, BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared).

Graphs show the multivariable-adjusted OR of associations between paternal / maternal preconception body mass index and the risk of small for gestational age infant (A1, B1), large for gestational age infant (A2, B2), respectively. In the graph, black curves and shaded grey areas show predicted OR and 95 % CI, respectively.

A1, A2: Maternal and paternal age at LMP, height, ethnic, education, area of residence, alcohol drinking, smoking, passive smoking and maternal BMI, hypertension, diabetes, parity as well as history of adverse pregnancy were used in the analysis as covariates.

B1, B2: Maternal and paternal age at LMP, height, ethnic, education, area of residence, alcohol drinking, smoking, passive smoking, paternal BMI and maternal hypertension, diabetes, parity as well as history of adverse pregnancy were used in the analysis as covariates. The black lines represent the reference level.

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Table 1 Characteristics of the total study population.

characteristics	Maternal characteristics		Paternal characteristics	
	n	**%**	**n**	**%**
n	**4 719 813**		**4 719 813**	
Age at LMP (years)				
20-24·9	1 993 759	42·24	1 315 958	27·88
25-29·9	1 951 532	41·35	2 176 408	46·11
30-34·9	570 636	12·09	820 085	17·38
35-39·9	173 942	3·68	292 453	6·20
≥40	29 762	0·63	94 683	2·01
NA	-	-	20226	0·43
BMI (kg/m²)				
Underweight (<18·5)	638 567	13·53	193 747	4·10
Normal weight (18·5-)	3 380 542	71·62	2 943 512	62·36
Overweight (24·0-)	570 480	12·09	1 248 662	26·46
Obese (28·0-)	130 224	2·76	333 892	7·07
Height (cm)				
≤154·9	836 090	17·71	13 102	0·28
155-164·9	3 359 839	71·19	563 720	11·94
165-174·9	464 572	9·84	3 135 774	66·44
≥175	6790	0·14	954 673	20·23
NA	52 522	1·11	52 544	1·11
Parity				
0	2 891 375	61·26		-
1+	1 814 111	38·44		-
NA	14 327	0·30		-
Education				
High school or above	826 615	17·51	828 958	17·56
Primary school or below	3 759 853	79·66	3 762 879	79·73
NA	133 345	2·83	127 976	2·71
Ethnic (Han)				
Han	4 344 438	92·05	4 357 312	92·32

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Others	329 597	6·98	316 429	6·70
NA	45 778	0·97	46 072	0·98
Residence				
Rural	4 318 562	91·50	4 250 244	90·05
Urban	400 897	8·49	469 224	9·94
NA	354	0·01	345	0·01
Alcohol consumption				
Yes	127 794	2·71	1 328 359	28·14
No	4 571 665	96·86	3 376 538	71·54
NA	20 354	0·43	14 916	0·32
Smoking status				
Yes	9554	0·20	1 287 127	27·27
No	4 694 249	99·46	3 418 204	72·42
NA	16 010	0·34	14 482	0·31
Second-hand smoke				
Yes	522 844	11·08	1 106 179	23·44
No	4 180 555	88·57	3 596 297	76·20
NA	16 414	0·35	17 337	0·37
Hypertension			-	-
Yes	75 822	1·61	-	-
No	4 636 501	98·23	-	-
NA	7490	0·16	-	-
Diabetes mellitus			-	-
Yes	46 277	0·98	-	-
No	4 665 897	98·86	-	-
NA	7639	0·16	-	-
History of adverse pregnancy outcomes			-	-
Yes	753 274	15·96	-	-
No	3 952 209	83·74	-	-
NA	14 330	0·30	-	-
	Child characteristics			

	n/median	%/IQR		
Gestational age at birth, weeks	39·71	38·57-40·43	-	-
Birthweight, g	3350	3100-3600	-	-
SGA	256 718	5·44	-	-
LGA	506 495	10.73	-	-
Sex				
Female	2 261 613	47·92	-	-
Male	2 453 312	51·98	-	-
NA	4888	0·10	-	-

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared); LMP, last menstrual period; IQR, inter-quartile range; SGA, small for gestational age; LGA, large for gestational age; NA, missing data.