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Adverse pregnancy outcomes on the risk of overweight offspring: a population-based retrospective study in Xiamen, China

Yin-ling Chen¹, Li-li Han², Xiu-lin Shi¹, Wei-juan Su¹, Wei Liu¹, Li-ying Wang¹, Pei-ying Huang¹, Ming-zhu Lin¹, Hai-qu Song¹ & Xue-jun Li^{1*}

The growth trajectory of Chinese preschoolers still remains unclear. Our objective was to determine whether there was an association between adverse pregnancy outcomes and overweight offspring. We analyzed population-based retrospective cohort data from the Medical Birth Registry of Xiamen, which comprised 33,157 children examined from 1 to 6 years of age. Longitudinal analyses were used to evaluate the growth trajectories of offspring body mass index (BMI). Multivariate logistic regression was used to assess the effects of two adverse pregnancy outcomes, gestational diabetes mellitus (GDM) and being large-for-gestational age (LGA), on childhood overweight. Offspring of mothers with GDM and LGA has a higher annual BMI z-score from 1 to 6 years of age (all $P < 0.05$). But, a higher annual BMI z-score was only observed in children aged 1–5 years in models 1–3. Overall BMI z-score of offspring aged 1–6 who were born to mothers with GDM and LGA were also higher in models 1–3 (all $P < 0.05$). Additionally, offspring of mothers with GDM and LGA had a higher risk for overweight in model 1, from 1 to 6 years of age (odds ratio (OR), 1.814; 95% confidence interval (CI), 1.657–1.985; $P < 0.0001$). However, this association was attenuated after adjusting for maternal pre-pregnancy BMI (OR, 1.270; 95% CI, 0.961–1.679; $P = 0.0930$). Offspring of mothers with GDM and LGA had a higher BMI z-score and increased risk for overweight. Indeed, intrauterine exposure to maternal GDM and LGA could bias offspring to overweight, whereas maternal pre-pregnancy BMI may play a key role in offspring overweight for children born to mothers with GDM and LGA.

Worldwide, there are 155 million children aged 5–17 years who are overweight or obese¹. However, the prevalence of overweight among children in China aged 0–6 years increased from 6.5% in 2002 to 8.4% in 2013². Consequently, identifying risk factors is necessary for early intervention and prevention of childhood overweight or obesity. It has been reported that exposure to hyperglycaemia in utero may increase the risk for lifelong obesity due to gestational diabetes mellitus (GDM)³. GDM is characterised by impaired glucose intolerance with first recognition during pregnancy and is linked to substantial rates of perinatal or maternal complications. Indeed, GDM can affect many common pregnancy outcomes, and influencing 1–28 percent of pregnancies in 173 countries^{4,5}. The incidence of GDM is increasing worldwide, particularly in China⁶, and this is related to adverse pregnancy outcome such as large-for-gestational age (LGA) birth complications⁷. Compared with non-diabetic women, LGA infants born to women with GDM have distinctly elevated fat masses⁸. But, disproportionate intrauterine growth can lead to an increased abdominal perimeter⁹.

How GDM and LGA during pregnancy affects childhood growth is not well understood. Only three studies have examined the effects of both GDM and LGA on childhood overweight or obesity^{10–12}. In addition, to our knowledge, there are no data available on childhood body mass index (BMI) z-scores in the Chinese population. These data are necessary to understand the effect of GDM and LGA pregnancies on adverse childhood health outcomes including overweight or obesity, in this population.

Therefore, we conducted this study to track BMI z-score from infancy to early childhood (1–6 years) in a large population and to thereby determine the association between BMI z-score and offspring overweight with mother with GDM and LGA.

¹Department of Endocrinology and Diabetes, the First Affiliated Hospital of Xiamen University, Xiamen, China.

²Fujian Medical University, Fuzhou, China. *email: xmlixuejun@163.com

Variable	Available n	Exposed to m-nonGDM-AGA (n = 26379)	Exposed to m-GDM-AGA (n = 5179)	Exposed to m-GDM-LGA (n = 1599)	P value
Maternal characteristics					
Maternal age before pregnancy, mean(SD), y	32946	27.9 (3.8)	29.9 (4.3)	30.5 (4.4)	<0.0001
Gestational age at delivery, mean(SD), week	33105	39.0 (3.4)	38.5 (5.3)	38.6 (4.7)	0.5340
Pre-pregnancy BMI, mean(SD), kg/m ²	33082	20.6 (2.6)	21.8 (3.1)	23.0 (3.2)	<0.0001
Pre-pregnancy BMI category, n (%)	33082				<0.0001
<18.5		5649 (21.5)	663 (12.8)	75 (4.7)	
18.5–23.9		17922 (68.1)	3361 (65.1)	961 (60.1)	
24.0–27.9		2392 (9.1)	945 (18.3)	446 (27.9)	
≥28.0		351 (1.3)	201 (3.9)	116 (7.3)	
Gestational weight gain, mean(SD), kg	2378	1.8 (2.0)	2.7 (2.9)	2.5 (2.8)	<0.0001
Education, year (%)	30162				<0.0001
≤ 9		5237 (21.8)	1135 (24.1)	368 (24.9)	
> 9		18742 (78.2)	3572 (75.9)	1108 (75.1)	
Mean systolic pressure, mean(SD), mmHg	18907	107.1 (10.5)	109.6 (10.9)	109.9 (11.6)	<0.0001
Mean diastolic pressure, mean(SD), mmHg	18903	65.5 (7.8)	67.1 (8.2)	67.2 (8.3)	<0.0001
Fasting plasma glucose level, mean(SD), mmol/L	33157	4.4 (0.3)	4.8 (0.5)	5.0 (0.5)	<0.0001
1-h plasma glucose level, mean(SD), mmol/L	33157	7.4 (1.3)	9.9 (1.5)	10.0 (1.5)	<0.0001
2-h plasma glucose level, mean(SD), mmol/L	33157	6.3 (1.0)	8.4 (1.5)	8.5 (1.5)	<0.0001
Child characteristics					
Boy, %	17048	13393 (50.77)	2635 (50.88)	1020 (63.79)	<0.001
Birth weight, kg	33157	3.2 (0.3)	3.1 (0.4)	3.7 (0.3)	<0.001
Mode of infant feeding within the first 6 months, %	31409				0.0319
Exclusive formula feeding		3864 (15.48)	838 (17.02)	223 (14.60)	
Exclusive breastfeeding		2513 (10.07)	467 (9.48)	142 (9.30)	
Mixed breast and formula		18580 (74.45)	3620 (73.50)	1162 (76.10)	
BMI z-scores for age, mean (SD),					
1 year	32371	0.01 (0.91)	0.02 (0.92)	0.32 (0.93)	<0.0001
2 years	22743	−0.02 (0.87)	0.003 (0.89)	0.31 (0.87)	<0.0001
3 years	16317	−0.18 (0.92)	−0.15 (0.94)	0.13 (0.95)	<0.0001
4 years	7250	−0.18 (0.92)	−0.10 (0.95)	0.20 (0.93)	<0.0001
5 years	3271	−0.14 (0.93)	−0.05 (1.00)	0.23 (0.99)	<0.0001
6 years	345	−0.10 (1.03)	0.02 (1.04)	0.48 (0.98)	0.038

Table 1. Characteristics of mother exposed to LGA or GDM on child obesity. GDM, gestational diabetes mellitus; LGA, large for gestational age; AGA, appropriate for gestational age; m, mother; BMI, body mass index.

Results

Study participants characteristics. Our study population comprised 33,157 mother-child pairs, of which 26,379 mothers qualified as non-GDM and appropriate-for-gestational age (AGA) (m-nonGDM-AGA), 5,179 mothers qualified as GDM and AGA (m-GDM-AGA), and 1,599 mothers qualified as GDM and LGA (m-GDM-LGA) (Table 1). Offspring who were born from m-GDM-LGA pregnancies were more likely to have higher BMI z-score from 1–6 years of age (all $P < 0.05$) (Fig. 1). In addition, compared with m-nonGDM-AGA and m-GDM-AGA mothers, m-GDM-LGA mothers were more likely to have a higher pre-pregnancy BMI ($P < 0.001$). Although maternal age, blood pressure, and oral glucose tolerance test (OGTT) value among the three groups were all significantly different, the m-GDM-LGA group was slightly high compared to the other two groups. More than half of the babies were male in three groups (50.77%, 50.88%, and 63.79%, respectively). Most offspring were fed with a mixture of breast milk and formula within the first six months. The proportion of offspring that were exclusively breastfed was the least frequently used feeding method ($P = 0.0319$).

Effects of m-GDM-LGA on offspring BMI z-score. All pregnant women were divided into three groups according to maternal GDM and gestational age status, as shown in Table 2: m-nonGDM-AGA, m-GDM-AGA, and m-GDM-LGA. In models 1, 2, and 3, offspring who were born to m-GDM-LGA pregnancy were more likely to have higher BMI z-score from 1 to 5 years of age, compared with offspring who were born to m-nonGDM-AGA pregnancy or m-GDM-AGA pregnancy (all $P < 0.05$). However, no significant differences were observed for offspring BMI z-score at 6 years of age, even after adjusting for pre-pregnancy BMI and other covariates (all $P > 0.05$).

Our mixed model showed that offspring exposed to m-GDM-LGA pregnancy had the highest BMI Z-score trajectory compared with those exposed to m-GDM-AGA and m-nonGDM-AGA pregnancy in an unadjusted model (Fig. 2).

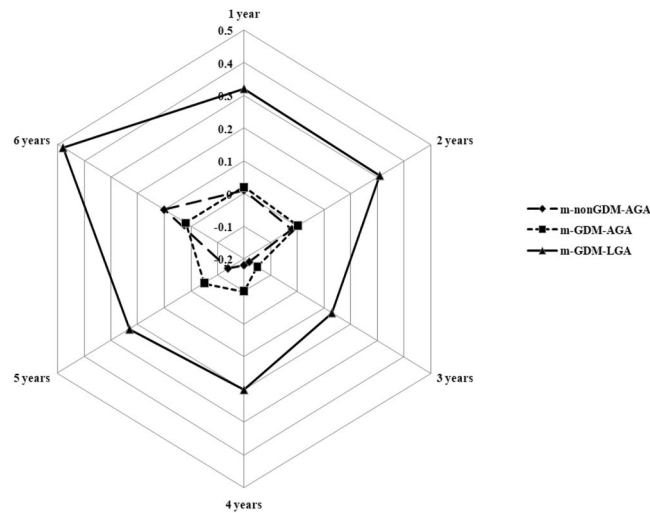


Figure 1. The annual BMI z-score for offspring who were born to m-nonGDM-AGA, m-GDM-AGA, and m-GDM-LGA pregnancy aged 1 to 6 years without adjustment for factors.

BMI z-score for age	Exposed to m-nonGDM-AGA	Exposed to m-GDM-AGA	Exposed to m-GDM-LGA	P value
Age 1 year				
Model 1	0.01 (0.01)	0.01 (0.02)	0.31 (0.03)	<0.0001
Model 2	0.15 (0.02)	0.16 (0.02)	0.45 (0.03)	<0.0001
Model 3	0.16 (0.02)	0.13 (0.02)	0.39 (0.03)	<0.0001
Age 2 year				
Model 1	-0.01 (0.01)	0.01 (0.02)	0.33 (0.03)	<0.0001
Model 2	0.06 (0.02)	0.08 (0.02)	0.40 (0.03)	<0.0001
Model 3	0.06 (0.02)	0.05 (0.02)	0.32 (0.03)	<0.0001
Age 3 year				
Model 1	-0.15 (0.01)	-0.12 (0.02)	0.16 (0.04)	<0.0001
Model 2	-0.11 (0.02)	-0.09 (0.03)	0.19 (0.04)	<0.0001
Model 3	-0.10 (0.02)	-0.12 (0.03)	0.09 (0.04)	<0.0001
Age 4 year				
Model 1	-0.15 (0.02)	-0.04 (0.04)	0.21 (0.06)	<0.0001
Model 2	-0.12 (0.03)	-0.02 (0.04)	0.23 (0.06)	<0.0001
Model 3	-0.12 (0.03)	-0.07 (0.04)	0.11 (0.06)	0.0002
Age 5 year				
Model 1	-0.11 (0.03)	0.03 (0.06)	0.18 (0.09)	0.0003
Model 2	-0.10 (0.03)	0.04 (0.06)	0.19 (0.09)	0.0003
Model 3	-0.10 (0.03)	-0.01 (0.06)	0.07 (0.09)	0.0447
Age 6 year				
Model 1	-0.07 (0.12)	0.02 (0.19)	0.24 (0.25)	0.4094
Model 2	-0.08 (0.13)	0.03 (0.20)	0.28 (0.26)	0.3165
Model 3	-0.11 (0.14)	0.02 (0.20)	0.21 (0.26)	0.3645

Table 2. Comparison of z-scores for BMI according to maternal GDM and LGA in different age. Data are showed as mean (SE). Model 1: adjusted for sex, maternal age, education, and infant feeding; Model 2: adjusted for covariates in Model 1 + maternal gestational weight gain; Model 3: adjusted for covariates in Model 2 + maternal pre-pregnancy body mass index. GDM, gestational diabetes mellitus; LGA, large for gestational age; AGA, appropriate for gestational age; m, mother; BMI, body mass index.

Effects of m-GDM-AGA on offspring BMI z-score and overweight. In this longitudinal analysis, m-GDM-AGA was significantly associated with a higher BMI z-score (models 1, 2, and 3) and overweight (models 2 and 3) across the time span of 1–6 years of age, even after adjusting for maternal pre-pregnancy BMI (Table 3). The offspring who were born to m-GDM-AGA pregnancy had 1.052-fold higher odds of becoming overweight from 1 to 6 years (OR, 1.052; 0.985–1.122; $P = 0.1292$) after adjusting for model 1 covariates,

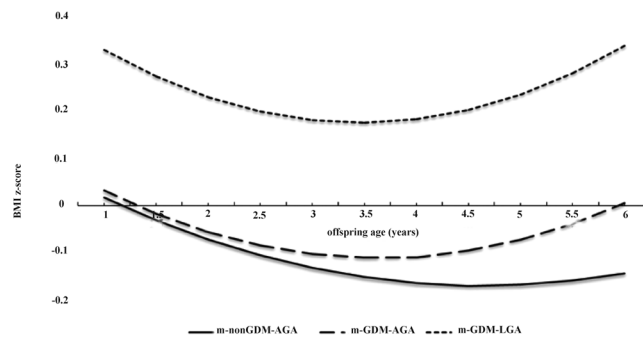


Figure 2. Growth trajectory of BMI z-score for offspring who were born to m-nonGDM-AGA, m-GDM-AGA, and m-GDM-LGA pregnancy aged 1 to 6 years with mixed model. LGA, large for gestational age; AGA, appropriate for gestational age; GDM, gestational diabetes mellitus; m, mother.

Outcome	m-GDM-AGA				m-GDM-LGA			
	BMI z-score		Overweight		BMI z-score		Overweight	
	Absolute changes in z-score estimate (95% CI)	P value	OR (95% CI)	P value	Absolute change in z-score estimate (95% CI)	P value	OR (95% CI)	P value
Model 1	0.023 (0.003–0.042)	0.0212	1.052 (0.985–1.122)	0.1292	0.315 (0.283–0.347)	<0.0001	1.814 (1.657–1.985)	<0.0001
Model 2	0.107 (0.049–0.164)	0.0003	1.528 (1.283–1.818)	<0.0001	0.253 (0.162–0.344)	<0.0001	1.366 (1.035–1.802)	0.0273
Model 3	0.087 (0.030–0.145)	0.0028	1.480 (1.243–1.764)	<0.0001	0.218 (0.128–0.309)	<0.0001	1.270 (0.961–1.679)	0.0930

Table 3. The joint effects of GDM and LGA on BMI z-score and risk of overweight. Model 1: adjusted for maternal age, education, and infant feeding, sex; Model 2: adjusted for covariates in Model 1 + maternal gestational weight gain; Model 3: adjusted for covariates in Model 2 + maternal pre-pregnancy body mass index. GDM, gestational diabetes mellitus; LGA, large for gestational age; AGA, appropriate for gestational age; m, mother; BMI, body mass index; OR, odds ratio; CI, confidence intervals.

1.528-fold higher odds after adjusting for model 2 (model 1 plus maternal gestational weight gain, $P < 0.0001$), and 1.480-fold higher odds after adjusting for model 3 covariates (model 2 plus pre-pregnancy BMI, $P < 0.0001$).

Effects of m-GDM-LGA on offspring BMI z-score and overweight. Offspring who were born to m-GDM-LGA pregnancy were more likely to have higher BMI z-score (models 1, 2, and 3) and become overweight (models 1 and 2) in early childhood (Table 3). After adjusting for model covariates, offspring who were born to m-GDM-LGA pregnancy had 1.814-fold higher odds of becoming overweight from 1 to 6 years of age (OR, 1.814; 1.657–1.985; $P < 0.0001$). 1.366-fold higher odds after adjusting for model 2 (model 1 plus maternal gestational weight gain) covariates ($P = 0.0273$), and 1.270-fold higher odds after adjusting for model 3 (model 2 plus pre-pregnancy BMI) covariates ($P = 0.0930$).

Discussion

To our knowledge, this is a large study to research association between GDM and LGA and preschool-aged children overweight after adjusting for covariates, and the first to associate BMI z-score with children overweight in preschool-aged children in China. We observed that offspring born to m-GDM-LGA pregnancy showed BMI z-score acceleration from 5 to 6 years of age compared with offspring born to m-GDM-AGA pregnancy. Meanwhile, annual BMI z-score had accelerated from 3 to 6 years of age. These results are consistent with a previous study that found BMI standard-deviation score increased with age, with particularly high acceleration during preschool years¹³. Several studies have also reported that a relationship exists between adolescent and adult overweight or obesity and high BMI during childhood^{14–16}. In addition, only 20 percent of young children who are overweight or obese will become a normal weight during adolescence. Previous studies have tracked BMI trajectories, found that high-growth BMI trajectory groups diverge from stable BMI trajectory groups starting at around 3 years of age^{17,18}. These results are consistent with our analysis.

Offspring born to m-GDM-LGA pregnancy retained higher BMI z-score during preschool years and had a higher risk of overweight compared with offspring born to m-GDM-AGA pregnancy after adjusting for covariates. However, the association between m-GDM-LGA pregnancy and offspring overweight was attenuated after adjusting for pre-pregnancy BMI. Several studies on offspring born to a GDM pregnancy have also observed similar results on overweight^{19,20}. In contrast, considering that pre-pregnancy BMI may significantly affect GDM²¹, offspring who were born to a GDM pregnancy cannot be directly compared to mother who have a higher pre-pregnancy BMI, on account of different methodology. Unexpectedly, there was no difference in BMI between LGA and non-LGA offspring born to GDM pregnancy in a study of 6 to 7-year-old infants¹¹.

With regard to childhood overweight or obesity, it is becoming increasingly clear that GDM can affect foetal metabolism and growth, which results in higher adiposity in the offspring¹. The ‘fetal programming theory’

emphasizes the significance of long term effect of suboptimal intrauterine exposure on offspring²². Hyperglycaemia in uterus can result in fetal overnutrition and elevated oxidative stress that induces pro-inflammatory response²³, methylation modifications²⁴, insulin secretion increasing²⁵, which can lead to hypothalamus epigenetic and neurohormonal changes²⁶, and high adiposity at birth³. Ultimately, these may lead to offspring overweight or obesity later in life⁴. A number of studies have investigated the association between GDM and offspring overweight or obesity^{27–29}, but have inconsistent results. A Swedish study suggested birth weight only played a minimal role in the relationship between GDM and offspring overweight or obesity. Overall, maternal GDM may predispose offspring to overweight or obesity later in life via mechanisms beyond excessive fetal growth, as illustrated by birth weight.

The major strength of this population-based study is a large sample size. Moreover, detailed information was obtained on pre-pregnancy BMI, which was not adequately adjusted for in previous studies. However, this study also has several limitations. Firstly, we did not have BMI z-score data for every offspring from 1 to 6 years of age. Secondly, study participants were all from the Chinese population, and therefore future studies among other ethnicities are needed. Thirdly, data on risk factors for offspring overweight or obesity such as maternal smoking or alcohol consumption would have improved the study.

In conclusion, this is a large population-based retrospective study on Chinese mother-child pairs. Offspring of mothers with GDM and LGA had a higher BMI z-score and increased risk of overweight from 1 to 6 years of age. However, the later association was attenuated after adjusting for maternal pre-pregnancy BMI, suggesting maternal pre-pregnancy BMI may play a key role in offspring overweight for children born to mothers with GDM and LGA. Therefore, we should focus on maternal pre-pregnancy weight to reduce the prevalence of childhood overweight or obesity. Further researches needed to expand these results to other populations, and to identify the underlying biological mechanisms.

Methods

Study design. We conducted a population-based retrospective study using the healthcare records data from the Medical Birth Registry in Xiamen (MBRX), China, between January 2011 and March 2018. This was a registration system established in 2007 in Xiamen based on a compulsory notification of all live and stillbirths from 12 weeks' gestation onward. This study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University (KYH2018–007) and conducted in accordance with the rules of the Declaration of Helsinki of 1975, revised in 2013. Informed consent was not required because this was a retrospective study.

Data sources of MBRX. All women in Xiamen are registered at their community health centres when they get pregnant, and were then referred to a secondary hospital or a tertiary hospital for healthcare from the 32nd gestational week till delivery. All children were given health examinations every year from birth (<3 days after birth) until the age of 6. Women and children were linked by individual record linkages to the Xiamen citizen health information system using the person-unique identification number assigned to each Xiamen citizen. Every child was also linked to his/her biological mother's maternal identification number.

Study population. A total of 33,157 mother-child pair healthcare records were available. All women over the age of 18 performed a 75-g OGTT between 24 and 28 weeks of gestational in this study. Eligibility criteria were as follows: (1) an OGTT was conducted between 24 and 28 weeks of gestation; (2) gestational age at delivery ≥ 37 weeks, with no major neonatal malformations or fetal/neonatal death; and (3) the offspring was followed-up through 6 years of age. Exclusion criteria included: (1) missing a mother's weight or height information at pre-pregnancy; (2) medical history of diabetes (diagnosed before the index pregnancy); and (3) fasting glucose level ≥ 7.0 mmol/L before 12 gestational weeks, as this could indicate an under-diagnosed diabetes cases prior to pregnancy.

Maternal and offspring characteristics. Information from MBRX on maternal factors included age, education, weight in 12 weeks before of pregnancy, occupation, first visit date, numbers of pregnancy/infants, last menstrual period, expected delivery date, smoking habits, drunk status, medical history, family history of disease, hypertension history, pregnancy reactions, as well as labour status. Furthermore, GDM, gestational weight gain, gestational age at delivery, height, weight, blood pressure, fasting glucose, gynaecological examinations, ultrasonography, gestational diabetes screening results, other lab tests results, complications during pregnancy, and pregnancy outcomes were also included in the MBRX system.

MBRX also included information from newborns to preschool-aged children on date of birth, sex, gestational week of birth, weight, Apgar score, names of the child and his/her parents, family history of diseases, feeding modalities (exclusive breast feeding, mixed breast and formula feeding, and exclusive formula feeding) during the first 6 months, date of examination, weight, height, number of teeth, and blood pressure.

Offspring measurements and data transformations. During each health examination, each child's height and weight was measured by a trained clinician. Body weight was measured in kilograms using regularly calibrated electronic scales.

Children were classified into three groups according to GDM and gestational age status during pregnancy: 1) children born to m-nonGDM-AGA; 2) children born to m-GDM-AGA; and 3) children born to m-GDM-LGA. Body mass index (BMI) was calculated as weight (kg) / height² (m²). BMI z-score for age was used to present the trajectory tracking of offspring BMI. We calculated sex-adjusted and age-adjusted z-score of childhood BMI referred to Chinese reference growth charts³⁰. Childhood overweight or obesity were also defined by age-specific and sex-specific Chinese criteria³⁰.

Variables definition. *Gestational diabetes mellitus.* GDM cases were identified between 24 and 28 weeks' gestation by conducting OGTT, which period is considered as the optimal period to make GDM diagnosis. According to the 2014 National Health and Family Planning Commission of the People's Republic of China criteria, after a 75 g glucose load, pregnant women would be considered to have GDM if one of the following plasma glucose values was met or exceeded: 0 hour, 5.1 mmol/L; 1 hour, 10.0 mmol/L; or 2 hours, 8.5 mmol/L⁶. Even if the test was performed after 28 weeks, it was still considered valid.

Large for gestational age. LGA was defined as birth weight was above 90 percentile for gestational age, according to gestational age and gender-specific intergrowth-21st curves³¹.

Statistical analysis. Mean±SD was showed for continuous variables, and discontinuous variables were presented as n (%). To evaluate our hypothesis that GDM and LGA were associated with offspring BMI growth trajectories, we performed several analysis. Firstly, mean BMI z-score were visually compared in yearly time intervals between m-nonGDM-AGA, m-GDM-AGA, and m-GDM-LGA. Secondly, the growth trajectories of offspring BMI were established by the longitudinal analyses that fitted flexible and smooth curves with a random-effects model³². The square model was used in BMI z-score points. The values of children from the GDM and LGA group and from children in the non-GDM and LGA group were modelled as shown below: $Y = \text{Intercept} + \beta_{0ij} + \beta_{1ij}(\text{age}) + \beta_{2ij}(\text{age})^2$. In addition, considering the previous studies and clinical relevance³³, we assessed the joint effect of GDM and pre-pregnancy BMI (a major risk factor for offspring overweight or obesity), using a model with a combination of GDM (yes, no) and BMI categories³⁴ (BMI < 23.9 kg/m², 24–27.9 kg/m², or ≥28 kg/m²) at 6 years of age. Thirdly, a logistic regression model was used to access the significance of offspring overweight between m-GDM-AGA and m-GDM-LGA groups. Three multivariable-adjusted models were included in this study. Model 1 adjusted for offspring sex, maternal age, education, and infant feeding; model 2 adjusted for the variables in model 1 plus maternal gestational weight gain; model 3 adjusted for the variables in model 2 plus maternal pre-pregnancy BMI. Statistical significance was two-tailed with a P-value < 0.05. All calculations were carried out using SAS 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Informed consent from participants

Informed consent of this retrospective study was waived by the ethics committee of the First Affiliated Hospital of Xiamen University (KYH2018–007).

Data availability

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

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Author contributions

C.Y.-L. and H.L.-L. collected and analyzed data, wrote the first draft, and created the table. S.X.-L., S.W.-J. and L.W. designed the statistical method and directed statistical analyses of the data. W.L.-Y., H.P.-Y., and L.M.-Z. analyzed and interpreted the data. S.H.-Q. and L.X.-J. designed the study, and revised the submission. All authors contributed to the discussion, and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to X.-j.L.

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