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June 2023 | HQ23DI00055

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Original Article
PEDIATRIC OBESITY

Obesity

What Links Maternal Prepregnancy BMI to Early Childhood BMI: A Serial Mediation Analysis

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Objective: The aim of this study was to explore the potential impact of maternal gestational weight gain (GWG), infant birth weight, and postnatal weight change (ΔWAZ) on the relationship between maternal prepregnancy BMI (ppBMI) and childhood BMI.

Methods: This retrospective cohort study analyzed a data set from Wuhan, China. The mediation effect of targeted mediators on the association between maternal BMI and childhood BMI at the age of 2 years was analyzed.

Results: In the mediation model comprising maternal GWG, infant birth weight, and the first-6-month ΔWAZ as mediators of the association between ppBMI and children's BMI, the per unit increase in ppBMI resulted in a 0.01-kg/m^2 increase in children's BMI, through all three mediators. For the model comprising infant birth weight and the first-6-month ΔWAZ as mediators but maternal GWG as a moderator, the indirect effects of the first-6-month ΔWAZ on the relationship between ppBMI and childhood BMI was 0.0018 higher when maternal GWG increased from average values to 1 SD above the average values.

Conclusions: Maternal GWG, infant birth weight, and the first-6-month ΔWAZ mediated the effects of maternal ppBMI on children's BMI. Interventions targeting these factors can mitigate the risk of childhood obesity.

Obesity (2021) **29**, 1164-1170.

Study importance

What is already known?

- Maternal prepregnancy BMI is known as one of the key determinants of childhood BMI.

What does this study add?

- Maternal gestational weight gain, infant birth weight, and postnatal 6-month weight gain mediate the association between maternal prepregnancy BMI and childhood BMI.

How might these results change the direction of research or the focus of clinical practice?

- Systematic interventions embedded in maternal and child health care targeting modifiable factors such as maternal prepregnancy BMI, gestational weight gain, infant birth weight, and postnatal weight change might mitigate the risk of childhood obesity and deliver public health benefits in China.

Introduction

The worldwide prevalence of childhood obesity, especially in developing economies, has been increasing rapidly (1,2). According to the national epidemiological survey data of nine cities in China, the childhood obesity rate has increased from 0.91% in 1989 to 4.2% in 2016 (3,4). Different parameters are used to assess childhood obesity, such as anthropometric equations, skinfold thickness, and bioelectrical impedance (5). BMI is one of the most common parameters used in epidemiological studies, owing to its ease of measurement, strong correction with body fat percentage, and acceptable accuracy in identifying individuals with overweight or obesity. Epidemiological studies have demonstrated positive associations between childhood obesity/BMI and metabolic morbidities in adulthood (6), such as obesity (7), diabetes (8), and cardiovascular disease (9), which have become public health concerns worldwide. Identifying risk factors related to early childhood BMI or BMI *z* score (BMI-Z) has important public health implications.

Maternal prepregnancy BMI (ppBMI) is a critical determinant of childhood obesity (10). A previous meta-analysis that comprised 162,129 mother–child pairs from 37 pregnancy and birth cohort studies identified a positive association between ppBMI and the risk of childhood overweight/obesity (11). However, factors linking maternal prepregnancy

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 Received: 26 July 2020; **Accepted:** 8 March 2021; **Published online 14 May 2021. doi:10.1002/oby.23176**

weight and children's obesity/BMI are not fully understood. Knowledge of these factors can enhance our understanding of the development of childhood obesity and guide clinical and public health practices by highlighting early life mechanisms linking maternal prepregnancy factors and child growth after birth. Exploring the mechanisms linking ppBMI and childhood obesity requires large sample sizes and comprehensive information on potential mediators. To our knowledge, the number of related studies is limited. Although some studies have examined the mediating role of birth weight (BW), their results have been inconsistent (12,13). Some pivotal confounding factors or mediators in the path/mediation analysis may have been unavailable in these studies, thereby rendering their results nongeneralizable or nonreproducible.

The identification and inclusion of potential mediating factors are essential to understand the mechanisms linking maternal ppBMI and childhood obesity. Mounting evidence has already demonstrated the positive effect of maternal gestational weight gain (GWG) on childhood BMI (14,15). Moreover, Heerman et al. revealed the impact of interaction between ppBMI and GWG on infant growth and found that GWG amplified the effect of ppBMI on the outcome (16). A study by Josey et al. reported that 8.1% of the effect of maternal obesity on childhood adiposity was mediated by GWG (17). These findings underscore the necessity of considering GWG to identify the link between ppBMI and childhood BMI. Infant postnatal weight change (ΔWAZ) should also be considered while assessing the association between maternal weight and childhood BMI. Rapid infant weight gain is influenced by maternal overweight/obesity or excessive GWG, and it also has been reported to increase childhood BMI and the risk of obesity (18-20). Furthermore, a previous study revealed an inverse relationship between infant postnatal weight gain and BW (21). Macrosomia and large-for-gestational-age infants often achieve lower postnatal ΔWAZ than low/normal-BW infants or small-for-gestational-age infants (22). Therefore, infant postnatal ΔWAZ, which has rarely been discussed in the past, should be included in an exploration of factors linking maternal weight status and childhood BMI.

In this study, we hypothesized that the effects of maternal ppBMI on childhood BMI might be the result of an interplay of linked factors, including maternal GWG, infant BW, and postnatal ΔWAZ. We assumed that maternal GWG moderated the indirect effects of infant BW and ΔWAZ in the maternal ppBMI–childhood BMI association. We undertook a serial mediation analysis to validate the hypothesized relationship.

Methods

Study design and participants

We used data from the Wuhan Maternal and Child Health Management Information System, which monitors pregnancies and early childhood health. Eligible mother–child pairs included in this study were registered in the system between 2009 and 2018 and consisted of primiparas aged ≥18 years who had a single live delivery with no congenital defects and who were between 28 and 42 weeks of gestation. We excluded participants with incomplete clinical and demographic information, such as maternal educational level, ppBMI, and GWG, as well as childhood weight, length, delivery type at birth, feeding patterns at 6 months, postnatal weight change during the first 6 months, and anthropometric follow-up data at the age of 2 years (±30 days). Finally, a total of 52,478 mother–child pairs were retained for analysis.

This study was approved by the Ethics Committee of Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, and Huazhong University of Science & Technology (No. 2020R025-E01). Because of this observational study's retrospective nature, the acquisition of informed consent from participants was waived.

Variable definition

The ppBMI was calculated as weight in kilograms divided by height in square meters. The GWG was the difference between maternal prepregnancy weight and weight before delivery. Gestational age (in weeks) was obtained by calculating the days between the date of birth and the mother's last menstrual date and dividing it by 7. The delivery type was classified as transvaginal or cesarean. Following the 2006 WHO Child Growth Standards (23), infant postnatal weight change was defined as the change in weight-for-age (ΔWAZ) during the first 6 months after birth. Feeding patterns were categorized as exclusive breastfeeding, mixed feeding, and artificial feeding (24). Maternal education was grouped into high school or below (≤12 years) and college or above (>12 years). Maternal childbearing age was calculated using the difference between the date of delivery and the mother's birth date divided by 365.

Statistical analysis

Mean and SD were used to describe continuous variables, and frequency and proportion were used for categorical variables. The Pearson correlation coefficients among ppBMI, GWG, BW, postnatal ΔWAZ, and BMI at the age of 2 years were calculated.

For the mediation analysis with GWG as a mediator (Figure 1A), the four regression equations used were as follows:

$$\text{Equation 1: } GWG \sim ppBMI;$$

$$\text{Equation 2: } BW \sim ppBMI + GWG;$$

$$\text{Equation 3: } \Delta WAZ \sim ppBMI + GWG + BW; \text{ and}$$

$$\text{Equation 4: } BMI \sim ppBMI + GWG + BW + \Delta WAZ.$$

Equations 1 and 2 were adjusted for maternal educational level, childbearing age, and infant sex and gestational age at birth as confounders. Equations 3 and 4 were further adjusted for two additional confounders, delivery type and feeding pattern.

For the mediation analysis with maternal GWG as a moderator (Figure 1B), we examined the interaction terms of independent variable and GWG in all the paths, including ppBMI → BW, ppBMI → ΔWAZ, ppBMI → BMI, BW → ΔWAZ, BW → BMI, and ΔWAZ → BMI. Significant effects of interaction between ppBMI and GWG on BW and ΔWAZ in the first 6 months were detected, indicating the possibility of two paths, i.e., ppBMI → BW and ppBMI → ΔWAZ, being moderated by maternal GWG. The three regression equations were included as follows:

$$\text{Equation 1: } BW \sim ppBMI + GWG + ppBMI{:}\ GWG;$$

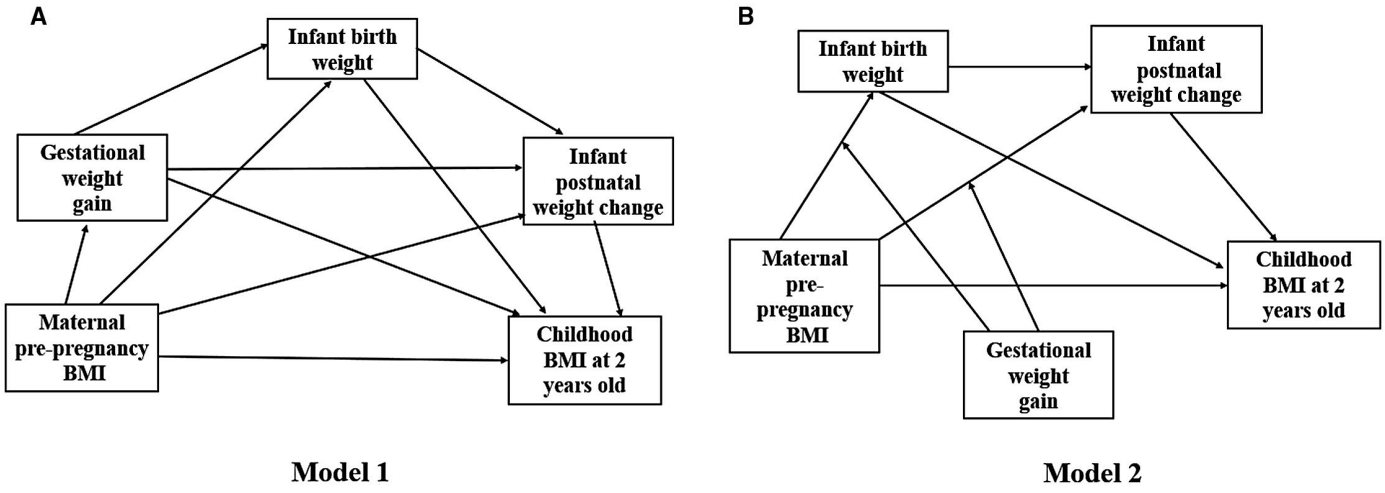

Figure 1 Mediation models with gestational weight gain as a mediator or moderator. Gestational weight gain and infant birth weight were adjusted for the confounders, maternal educational level, childbearing age, and infant sex and gestational age at birth. Infant postnatal weight change and childhood BMI at 2 years old were further adjusted for two additional confounders, delivery type and feeding pattern.

Equation 2: ΔWAZ ~ ppBMI + GWG + BW + ppBMI: GWG; and

Equation 3: BMI ~ ppBMI + GWG + BW + ΔWAZ.

We adjusted Equation 1 for the confounders maternal educational level, childbearing age, and infant sex and gestational age at birth and Equations 2 and 3 for two additional confounders, delivery type and feeding pattern.

All analyses were conducted using the R software (version 3.6, R Foundation for Statistical Computing, Vienna, Austria), and the serial mediation analysis was performed with the lavaan package. After mean-centering the continuous variables, indirect effects of the different paths were estimated using coefficient products and tested using the percentile bootstrap method (sample = 5,000). The standardized *z* scores of weight for children were calculated using the *anthro* package (25).

Results

We included 192,149 mother–child pairs initially, retaining 52,478 pairs for the mediation analysis after applying the exclusion criteria. Figure 2 shows the flowchart of the study. General characteristics of the study population are shown in Table 1. A total of 53% of children were boys, and 65% were born via cesarean delivery. The exclusive breastfeeding rate at 6 months was approximately 10%. The means of ppBMI and GWG were 20.5 kg/m^2 and 16.6 kg, respectively. The average BMI at the age of 2 years was 16.2 kg/m^2, and the average ΔWAZ in the first 6 months was 0.6.

Supporting Information Table S1 presents the Pearson correlation coefficients matrix of ppBMI, GWG, childhood weight at birth, ΔWAZ in the first 6 months, and BMI at the age of 2 years. The maternal ppBMI and GWG were negatively associated with infant postnatal ΔWAZ (r = −0.05, −0.09, respectively). Negative correlations were also found between ppBMI and GWG (r = −0.21) and between BW and postnatal ΔWAZ (r = −0.58). The coefficients and confidence intervals of the linear regression model are presented in Supporting Information Table S2, with all the estimates being statistically significant ($P < 0.001$).

For the mediation model with maternal GWG as a mediator and covariates adjusted for, the total effect of maternal ppBMI on offspring BMI was 0.0449 (bootstrap CI: 0.0408-0.0489), suggesting that for every unit (1 kg/m^2) increase in ppBMI, offspring BMI increased by 0.0449 kg/m^2. This effect rose to 0.0342 kg/m^2 (direct effect = 0.0342, bootstrap 95% CI: 0.0302-0.0382) when mediators such as maternal GWG, infant BW, and ΔWAZ were controlled for. The indirect effect of maternal ppBMI on offspring BMI through the three described variables was significant (indirect effect = 0.0107, bootstrap 95% CI: 0.0090-0.0125), accounting for 25% of the effect of maternal ppBMI on childhood BMI, suggesting that through all three mediators, for every unit (1 kg/m^2) increase in maternal ppBMI, offspring BMI increased by 0.01 kg/m^2. The indirect effects through BW, ΔWAZ, and GWG → BW → ΔWAZ were positive, and those for the other four paths (GWG, GWG → BW, GWG → ΔWAZ, and BW → ΔWAZ) were negative. All the indirect effects were statistically significant according to the bootstrapped CI (Table 2). We also performed an analysis using a supplementary mediation model with the corrected GWG (by subtracting BW from the total GWG), BW, and postnatal ΔWAZ. The results were almost identical to those obtained using GWG (Supporting Information Table S3).

For the mediation analysis with maternal GWG set as the moderator with covariates adjusted for, the indirect effects through BW, ΔWAZ, and BW → ΔWAZ were significant. The moderated effect of GWG was significant in the ppBMI → ΔWAZ → BMI path (index of moderation = 0.0018, bootstrap 95% CI: 0.0009-0.0028), suggesting that the indirect effects of ΔWAZ in the first 6 months between ppBMI and offspring BMI was 0.0018 higher when the maternal

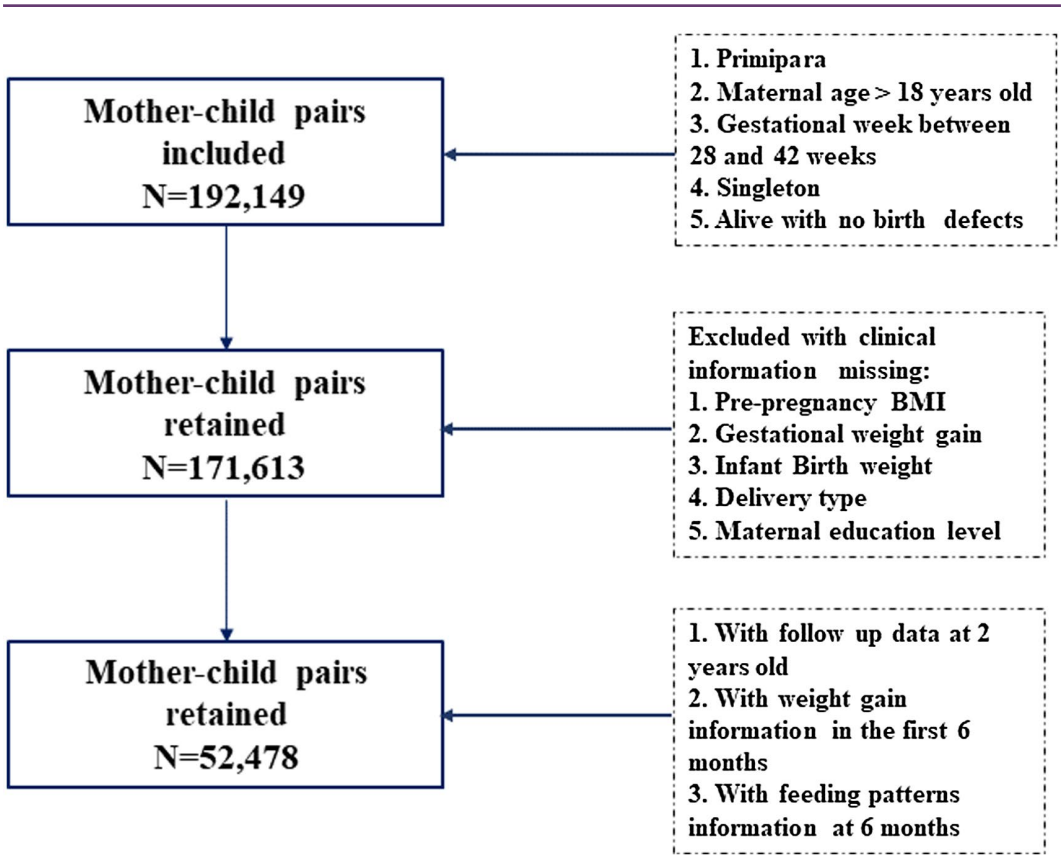

Figure 2 The flowchart of the current study. [Color figure can be viewed at wileyonlinelibrary.com]

GWG increased from the average values to 1 SD above the average values (Table 3).

Discussion

In this study, we explored the potential link between maternal ppBMI and BMI in early childhood. We demonstrated that approximately 25% of the significant association between maternal ppBMI and child BMI was mediated by several factors, including GWG, BW, and ΔWAZ in the first 6 months. Furthermore, we observed the moderated effect of GWG in this association through two other mediators.

Childhood growth is a complex multifactorial process. Independent effects of factors targeted in this study, such as ppBMI, GWG, BW, and postnatal ΔWAZ, have been widely examined previously and identified as risk factors for childhood obesity in the first 1,000 days of life (26). However, very few studies have explored their complicated interplay associated with child growth. Using a large sample from a Chinese birth cohort, we were able to confirm the association between maternal ppBMI and child BMI at the age of 2 years in the current analysis, and the potential roles of GWG, BW, and postnatal ΔWAZ could be identified using a multiple serial mediation approach.

Maternal ppBMI had a positive direct effect on child BMI in our study. A linear meta-analysis that included 46,703 children reported a similar result; an increase of maternal BMI by 1 kg/m^2 led to an increase in childhood BMI-Z by 0.09 kg/m^2 (10). Although in the current mediation analysis, the positive indirect effects of BW and postnatal ΔWAZ were both identified in the association between maternal ppBMI and child BMI, the results from previous studies have been inconclusive. Mesman et al. observed the negative effect of maternal ppBMI on child BMI after adjustment for BW and inferred that at least one third of the effect was mediated through BW (27). On the contrary, Adane et al. emphasized that the primary impact of prepregnancy obesity on child BMI appeared to be directly correlated, rather than being mediated by children's BW. However, the impact of GWG on the outcome variables was not accounted for in this study (13).

A negative association between ppBMI and GWG, which has been discussed in earlier literature (28,29), could have been a natural biological phenomenon or could have occurred because pregnant women with overweight or obesity were more likely to be advised for GWG control during prenatal checkups (30). Because of the inverse relationship between ppBMI and GWG, a negative indirect effect of GWG, with or without the involvement of BW in the mediation analysis, was reported in our study. A similar mediating role of GWG in the ppBMI–BW association was previously observed in Brazilian Birth Cohort

Studies (30). Our study also revealed a negative indirect effect through BW → ΔWAZ in the ppBMI–child BMI association, which was probably due to the negative effect of BW on postnatal 6-month ΔWAZ (31). Our mediation analysis showed that infants born to mothers with high BMI might achieve a higher BMI at the age of 2 years, especially when the high ppBMI was not followed by lower GWG or slower postnatal ΔWAZ in early infancy. As reported by Heerman et al., there may have been an interactive effect between ppBMI and GWG on infant growth (16). Therefore, we conducted a further mediation analysis with maternal GWG as a moderator and infant BW and postnatal ΔWAZ as mediators. The significant moderating effect of GWG was demonstrated in the ppBMI → ΔWAZ → BMI path.

The findings in our study point to GWG being a mediator and a moderator simultaneously in the association between maternal ppBMI and child BMI.

Evidence of potential biological mechanisms influencing the association between maternal ppBMI and child BMI, although far from clear, may offer some explanations regarding the dual role of GWG. Prepregnancy obesity is often characterized by circulating metabolomic and inflammatory changes, such as glucose-linked hypothalamic activation, insulin and leptin resistance, and inflammatory marker fluctuation (32,33). GWG may have affected the influence of prepregnancy obesity on these metabolomic changes; for example, the positive relationship between ppBMI and circadian cortisol in pregnant women was reported to be moderated by GWG (34). The combined effects of prepregnancy obesity and GWG may subsequently affect the placental size and transfer of nutrients (35), resulting in permanent metabolic adaptations in children, further impacting infant BW and postnatal growth. This may have eventually predisposed children to greater risks of obesity later in life (36).

Our study showed maternal obesity and childhood obesity are interrelated. China has established a comprehensive Three-tiered Maternal and Child Health Care Framework that consists of services such as maternal pregnancy health checks and weight gain monitoring, perinatal health care and child physical growth monitoring, and health checks embedded in it. Its role in preventing early childhood obesity should be endorsed, and relevant services such as the identification of high-risk children and the weight management of both mother and child should likewise be strengthened.

The strength of our study is the large sample size from a Chinese birth database. With comprehensive information on the risk factors

TABLE 1 Sample characteristics of the participants

Variable	Mean/*N*	SD/%
Birth weight (kg)	3.32	0.41
Maternal prepregnancy BMI (kg/m^2)	20.51	2.59
Gestational weight gain (kg)	16.58	5.59
Weight change of infants during the first 6 months	0.61	1.05
Childhood BMI at 2 years old	16.21	1.16
Gestational age (wk)	39.10	1.19
Childbearing age of mothers	27.11	3.69
Maternal educational level		
≤High school	32,518	61.97
>High school	19,960	38.03
Sex of infants		
Girl	24,536	46.75
Boy	27,942	53.25
Type of delivery		
Transvaginal	18,505	35.26
Cesarean	33,973	64.74
Feeding pattern at 6 months		
Exclusive breastfeeding	5,362	10.22
Not exclusive breastfeeding	47,116	80.41
Artificial feeding	4,920	9.38

TABLE 2 Indirect effects between maternal BMI and childhood BMI through different mediators

	Not adjusted		Adjusted	
Effects	Estimate	Bootstrap 95% CI	Estimate	Bootstrap 95% CI
ppBMI → GWG → BMI	−0.0051	(−0.0060 to −0.0043)	−0.0050	(−0.0058 to −0.0041)
ppBMI → BW → BMI	0.0318	(0.0301 to 0.0335)	0.0309	(0.0293 to 0.0326)
ppBMI → ΔWAZ → BMI	0.0078	(0.0067 to 0.0090)	0.0064	(0.0053 to 0.0076)
ppBMI → GWG → BW → BMI	−0.0070	(−0.0075 to −0.0066)	−0.0063	(−0.0068 to −0.0059)
ppBMI → GWG → ΔWAZ → BMI	−0.0009	(−0.0012 to −0.0007)	−0.0008	(−0.0011 to −0.0006)
ppBMI → BW → ΔWAZ → BMI	−0.0195	(−0.0205 to −0.0184)	−0.0182	(−0.0192 to −0.0173)
ppBMI → GWG → BW → ΔWAZ → BMI	0.0043	(0.0040 to 0.0046)	0.0037	(0.0035 to 0.0040)
Direct effect	0.0311	(0.0271 to 0.0350)	0.0342	(0.0302 to 0.0382)
Total indirect effect	0.0114	(0.0097 to 0.0132)	0.0107	(0.0090 to 0.0125)
Total effect	0.0425	(0.0386 to 0.0465)	0.0449	(0.0408 to 0.0489)

Feeding pattern is dichotomized into exclusive breastfeeding or not.
BMI, children's BMI at 2 years old; BW, infant birth weight; GWG, maternal gestational weight gain; ppBMI, maternal prepregnancy BMI; ΔWAZ, postnatal weight change of infants during the first 6 months.

TABLE 3 Moderated role of gestational weight gain in the indirect effects between maternal BMI and childhood BMI

		Without adjustment		With adjustment	
Effects	**GWG**	**Estimate**	**Bootstrap 95% CI**	**Estimate**	**Bootstrap 95% CI**
ppBMI → BW → BMI					
	Mean – SD	0.0343	(0.0323 to 0.0364)	0.0330	(0.0311 to 0.0349)
	Mean	0.0329	(0.0311 to 0.0346)	0.0320	(0.0303 to 0.0337)
	Mean + SD	0.0315	(0.0292 to 0.0338)	0.0310	(0.0288 to 0.0333)
	Index of moderation	–0.0014	(–0.0027 to –0.0001)	–0.0010	(–0.0022 to 0.0002)
ppBMI → ΔWAZ → BMI					
	Mean – SD	0.0062	(0.0048 to 0.0076)	0.0050	(0.0036 to 0.0064)
	Mean	0.0083	(0.0071 to 0.0095)	0.0068	(0.0056 to 0.0080)
	Mean + SD	0.0104	(0.0087 to 0.0121)	0.0086	(0.0070 to 0.0103)
	Index of moderation	0.0021	(0.0011 to 0.0031)	0.0018	(0.0009 to 0.0028)
ppBMI → BW → ΔWAZ → BMI					
	Mean – SD	–0.0202	(–0.0215 to –0.0190)	–0.0188	(–0.0199 to –0.0177)
	Mean	–0.0194	(–0.0205 to –0.0184)	–0.0182	(–0.0192 to –0.0172)
	Mean + SD	–0.0186	(–0.0200 to –0.0172)	–0.0177	(–0.0190 to –0.0164)
	Index of moderation	0.0008	(0.0000 to 0.0016)	0.0006	(–0.0001 to 0.0012)
Direct effect					
		0.0250	(0.0212 to 0.0288)	0.0281	(0.0242 to 0.0318)

Feeding pattern is dichotomized into exclusive breastfeeding or not.
BMI, children's BMI at 2 years old; BW, infant birth weight; GWG, maternal gestational weight gain; ppBMI, maternal prepregnancy BMI; ΔWAZ, postnatal weight change of infants during the first 6 months.

for childhood obesity, we were able to estimate a reliable direct effect of maternal ppBMI on child BMI and the indirect effects of the mediated variables. This study demonstrated that the positive impact of maternal ppBMI on child BMI at the age of 2 years was mediated by the causal links involving maternal GWG, infant BW, and postnatal ΔWAZ. Some limitations are also worth mentioning. First, previous studies have reported that the effects of maternal GWG on infant birth size and childhood obesity could also be trimester specific (37,38). However, in our study, we examined only the overall GWG. Second, we adopted a unidirectional (from maternal GWG to infant BW) hypothesis, as was done in previous studies (17,30,39). An inverse relationship may exist wherein fetal growth affects maternal weight gain. However, research on this topic is scarce. A nonrecursive model that can account for the bidirectional relationship between the two variables failed because of underidentification in the current study. Moreover, the results of the supplementary analysis using corrected GWG were almost identical to those using GWG. Third, we were not able to find an effective method to conduct a three-mediator serial mediation analysis involving the interaction term of exposure and the mediators. Therefore, we performed mediation analyses with GWG as a mediator and a moderator separately. Although this may have introduced bias in the indirect effects of the specific paths, the importance of the three targeted variables (maternal GWG, infant BW, and ΔWAZ between maternal ppBMI and child BMI) was similarly emphasized. Fourth, the proportion with missing data was comparatively large, and the distribution of covariates such as delivery type and feeding pattern was different between data retained for analysis and those excluded. The results of the mediation analysis were primarily identical, with or without the key covariates being adjusted. Finally, because of the nature of the cohort, we were unable to control the influence caused by other important child BMI-related variables, such as diet, sleep, and movement behavior (40). Nevertheless, previous studies have found that physical activity, diet, and sleep behavior had only minor effects on BMI-Z for children aged <5 years(41,42).

Conclusion

The two different mediation diagrams confirmed by the current study expand our knowledge regarding the development of childhood obesity, starting from maternal pregnancy weight status toward the serial paths that constitute infant BW and weight change in the first 6 months. Our findings can help develop intervention strategies/programs targeting maternal weight status and infant weight gain intended against the rapid rise in the epidemic of childhood obesity and related disorders.

Funding agencies: This study was funded by National Natural Science Foundation of China (81673182) and the Applied Frontier Project of Wuhan Municipal Science and Technology Bureau (2019020701011488).

Disclosure: The authors declared no conflict of interest.

Author contributions: YZ and HM designed the study, performed the statistical analysis, and drafted the initial manuscript. KX and CL prepared tables and figures. ZX and YT participated in data collection and extraction. SY and JZ revised the manuscript. All authors reviewed the manuscript and approved the final manuscript as submitted.

Supporting information: Additional Supporting Information may be found in the online version of this article.

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