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Gestational weight gain and neonatal outcomes in different zygosity twins: a cohort study in Wuhan, China

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ABSTRACT

Objective To evaluate whether twin zygosity influences the association between neonatal outcomes and gestational weight gain (GWG) based on the Chinese guidelines in twin-pregnancy women.

Design A retrospective cohort study. And it is not a clinical trial.

Setting Women with twin pregnancies living in Wuhan, China.

Participants A total of 5140 women who delivered live and non-malformed twins from 1 January 2011 to 31 August 2017 were included in this study.

Main outcome measure The primary neonatal outcomes included paired small for gestational age (SGA, <10 th percentile birth weight for gestational age and sex), low birth weight (LBW, <2500 g) and gestational age (<33 weeks and <37 weeks). The association between GWG and neonatal outcomes was examined by Logistic regression analyses.

Results A total of 5140 women were included, of whom 22.24%, 54.78% and 22.98% were below, within and above the Chinese guidelines, respectively. Among the including 10 280 infants, 26.28% of them were monozygotic (MZ) twins and 73.72% of them were dizygotic (DZ) twins. Women with low GWG had a significantly higher proportion of LBW/LBW and LBW/NBW infants, a greater likelihood of SGA/SGA and SGA/appropriate for gestational age (AGA) infants and a higher incidence of preterm birth. The associations persisted both in MZ and DZ twins, and twin zygosity influenced the degree of association between GWG and SGA, LBW and preterm birth. High GWG was associated with significant risk reductions in SGA/AGA pairs, LBW/LBW or LBW/NBW pairs, and less than 33 gestational weeks. However, high GWG was only associated with reduced risk of LBW/LBW pairs both in MZ and DZ twins.

Conclusions GWG below the Chinese recommendations increased the risk of SGA, LBW and preterm birth in both MZ and DZ twins. The effect was more pronounced in MZ twins than that in DZ twin pairs. A high GWG only reduced the risk of LBW/LBW pairs both in MZ and DZ twins.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present study is a cohort study enrolling a large population of 5140 twin-pregnancy women, including 601 underweight women.
⇒ To the best of our knowledge, this is the first study using stratified analyses by twin zygosity to assess the association between gestational weight gain and neonatal outcomes.
⇒ The history of twin pregnancies in previous pregnancies, and data on the chorionicity and amnionicity of twins were not collected; those are important factors that can potentially impact neonatal outcomes.

INTRODUCTION

The incidence of multiple births has dramatically risen in the past decade,[1] attributable to assisted reproductive techniques and older maternal age. Currently, 2%–4% of births are twin pregnancies worldwide.[2–4] As is well documented, twin pregnancies are at higher risk of perinatal and neonatal adverse outcomes compared with singleton pregnancies. In 2016, nearly 6 in 10 twins were born preterm in contrast with less than 1 in 10 singletons, and 55.47% of women with twin pregnancies delivered low birth weight (LBW) infants in the USA.[3] Those adverse outcomes confer increased risk for perinatal, childhood and adulthood complications, such as malnutrition and stunted growth in childhood,[5] as well as cardiovascular diseases,[6] poor neurodevelopmental outcomes and diabetes in adulthood.[7 8]

For twin pairs, gene, shared and non-shared environment influence the neonatal outcomes. Shared environment refers to intrauterine exposures, maternal factors and early environment.[9] The non-shared environment includes unequal distribution of blood supply and nutrients between twins in utero.[10] The potential impact from shared causes of fetal growth and complex diseases could be identified by evaluating associations within twin pairs. Dizygotic (DZ) twins share an average 50% of their gens, whereas monozygotic (MZ) twins share identical genes. Research on DZ and MZ twins has provided unique opportunities to distinguish between

environmental and genetic causes of phenotypic variations in human populations.

Gestational weight gain (GWG) treated as shared environment is important for monitoring and assessing the nutrition of pregnant women. Notably, excessive GWG is an increased risk for macrosomia[11] and childhood obesity.[12] Meanwhile, insufficient GWG is associated with an increased risk of preterm birth, LBW and small for gestational age (SGA) in singletons[11 13 14]; these outcomes are more likely to occur among twin pregnancies.[15 16] In 2009, the Institute of Medicine (IOM) suggested prepregnancy body mass index (BMI)-specific GWG recommendations in full-term twin pregnancies for normal prepregnancy BMI overweight women, and obese women, but did not provide guidelines for underweight women owing to insufficient data.[12] Our previous study provided the recommended GWG for all BMI categories. In order to reduce sample loss and provide more data, the following Chinese GWG recommendations were used: 18–26 kg for underweight women (<18.5 kg/m^2), 15–25 kg for normal prepregnancy BMI (18.5–23.9 kg/m^2), 12–21 kg for overweight women (24.0–27.9 kg/m^2) and 9–20 kg for obese women (≥28 kg/m^2).[17]

The relationship between the GWG and neonatal outcomes in twin-pregnancy women has been evaluated in several studies.[18–22] However, the majority of these studies were conducted in developed countries. Studies focusing on this issue in underdeveloped countries, including China, are limited. Although our prior study explored this association in the Chinese population,[17] there was no report on further within-pair stratification analysis based on zygosity in the study, neither did other studies conducted in developed countries. Additionally, the IOM did not provide recommendations for underweight women. Therefore, this study was conducted to investigate the relationship between neonatal outcomes and GWG according to the Chinese adult BMI categories and the Chinese recommendations and further to elucidate this association stratified by twin zygosity in a large population of twin-pregnant women in Wuhan, China.

MATERIALS AND METHODS

Study population

This cohort study was conducted in Wuhan, a central city in China. Participants' information was collected from the Wuhan Maternal and Child Health Management Information System (WMCHMIS), which was explained in detail in a previous study.[23] The data for the present study were collected in the WMCHMIS from 1 January 2011 to 31 August 2017. Initially, there were 723 249 records, with a total of 12 816 women with twin pregnancies. The exclusion criteria were identical to those in our previous study.[17] Additionally, women who delivered twins without a zygosity diagnosis were excluded (n=1785). Finally, a total of 5140 women and 10 280 infants were enrolled in this study.

Variables

Maternal demographic information consisting of age, gravidity, parity, level of education as well as prepregnancy weight and height were obtained via a questionnaire when they first visited community health centres for antenatal care. The gestational week was identified by the date of the last menstrual period and confirmed by B-ultrasound. Obstetric and newborn information was inputted into the WMCHMIS by midwives. Detailed quality control measures were outlined in our previous study.[17]

The total maternal GWG was the primary endpoint and was calculated by subtracting the delivery weight from the prepregnancy weight. Based on the 2009 IOM GWG guidelines for twin-pregnant women, recommended GWGs for normal, overweight and obese women are 17–25 kg, 14–23 kg and 11–19 kg, respectively.[12] Additionally, the total GWG was classified as below, within or above the IOM guidelines. Prepregnancy BMI was computed by weight (kg)/height squared (m^2), and participants were assigned to four groups according to the Chinese adult standards: underweight (<18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), overweight (24–27.9 kg/m^2) and obese (≥ 28 kg/m^2).[24]

Zygosity diagnosis of twins was performed by PCR-amplified short tandem repeat analysis with multiple unliked loci on a filter paper blood spot. Herein, nineteen polymorphic markers were used in accordance with our previous study[23] for the determination of twin zygosity, which was dichotomized into MZ and DZ twin.

Important covariates included: maternal delivery age (classified into five groups: <20, 20–24, 25–29, 30–34 and ≥35 years old), maternal level of education (treated as a substitute for socioeconomic status and categorised into three groups: less than high school, high school and college), parity (categorised into primiparous and multiparous), gravidity (categorised into <3 times and ≥3 times) and gestational weeks (divided into four groups: <28, 28–32, 33–36, ≥37).

The primary neonatal outcomes included paired SGA, birth weight (continuous outcome), LBW (<2500 g) and gestational weeks (<33 weeks and <37 weeks). SGA was defined as neonatal birth weight less than the 10th percentile while appropriate for gestational age (AGA) referred to birth weight at or above the 10th percentile for gestational age and sex[25] in accordance with birth weight curves in Chinese twins.[26]

Statistical analysis

Descriptive analysis, χ^2 tests and variance analysis were used to analyse categorical and continuous variables, respectively. Logistic regression models were performed to estimate the relationship between GWG and SGA/SGA pairs, SGA/AGA pairs, LBW/LBW pairs, LBW/NBW pairs, less than 33 gestational weeks and less than 37 gestational weeks. Confounding variables were selected based on earlier studies, including maternal delivery age (continuous), educational attainment, parity, gravidity,

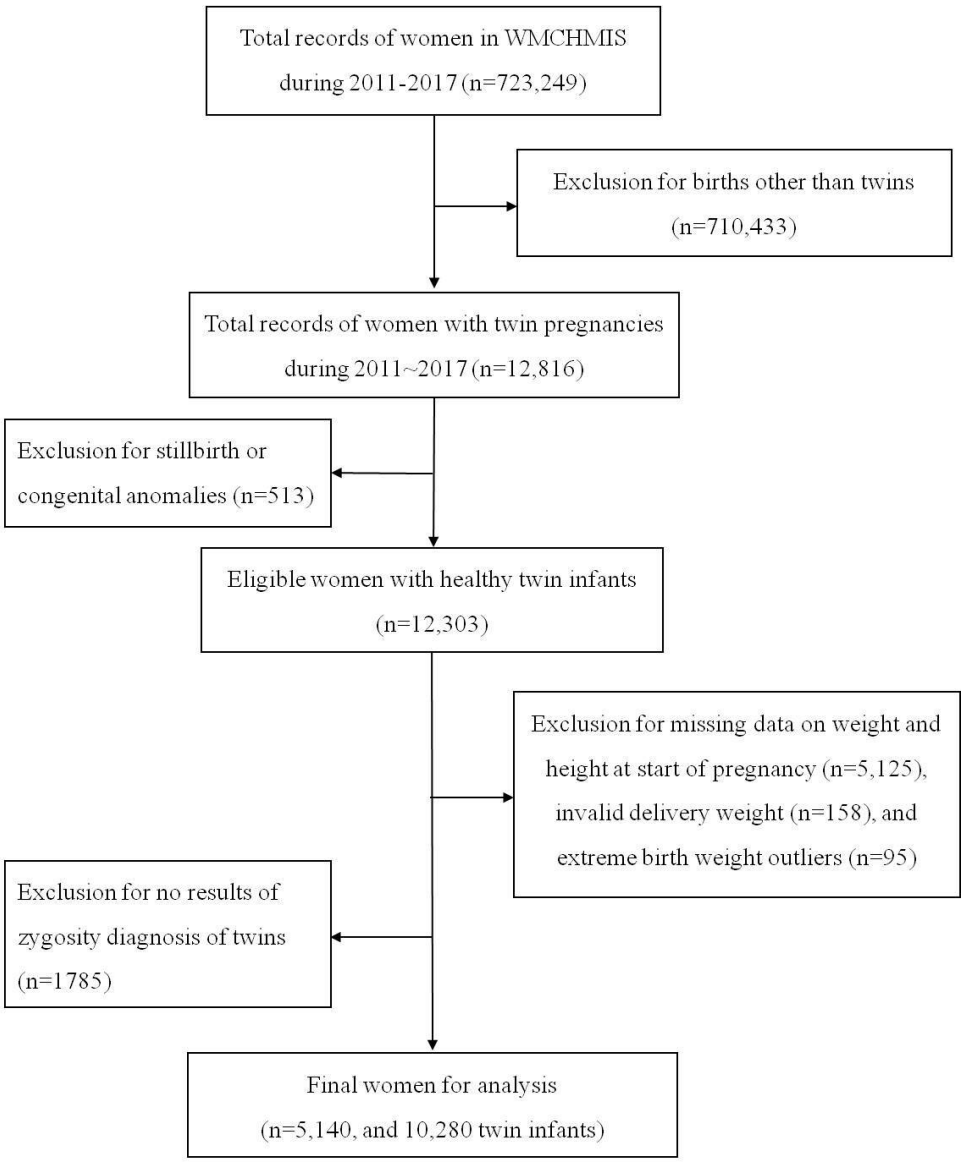

Figure 1 Flowchart of participant selection. WMCHMIS, Wuhan Maternal and Child Health Management Information System.

prepregnancy BMI, twin zygosity and gestational weeks. Strata-specific analyses by twin zygosity were also performed, and crude and adjusted ORs with 95% CIs were calculated. SAS V.9.2 (SAS Statistical Institute) was employed for the statistical analyses.

Patient and public involvement

None of the participants was involved in the questionnaire design or outcome measures; they were likewise not involved in the design, recruitment and implementation of the study. Furthermore, all participants were informed that their data would be used for research purposes.

RESULTS

Among the 5140 twin-pregnant women enrolled in our study (figure 1), three-quarters had a normal weight, 11.69% were underweight and 662 women (12.88%) were overweight or obese according to prepregnancy BMI based on the Chinese adult standards (table 1). The characteristics of the participants are listed in table 1. Besides, among the 5140 twin-pregnant women, 39.01% were 25–29 years old, and 55.02% had a college degree. Altogether, 77.76% of included women met or exceeded the Chinese GWG guidelines. Furthermore, 26.28% (1351) of the twins were MZ twin, 29.69% (1526) were DZ twins with the same sex and 44.03% (2263) were DZ twins with opposing genders.

Twin neonatal outcomes were assessed according to the Chinese-recommended GWG and presented in table 2. Eighty women delivered SGA/SGA pairs. The average gestational week was 36.22, and over half of the women had twins with ≥37 gestational weeks. The mean birth weight of the 5140 twin pairs was 4994.19 g, while 40.62% of the women delivered twins weighing ≥2500 g. Twin-pregnant women with normal or exceeding GWG were more likely to have twins that were heavier and had a longer gestational period.

Table 1 Characteristics of women and twin infants

	N (%)
Age at delivery	
≤ 19	16 (0.31)
20~24	517 (10.06)
25~29	2005 (39.01)
30~34	1913 (37.22)
≥35	689 (13.40)
Education level	
Less than high school	1186 (23.13)
High school	1120 (21.85)
College	2821 (55.02)
Parity	
Primiparous	3489 (67.88)
Multiparous	1651 (32.12)
Gravidity	
<3	4082 (79.42)
≥ 3	1058 (20.58)
Pre-pregnancy BMI (kg/m^2)	
Underweight(<18.5)	601 (11.69)
Normal (18.5~23.9)	3877 (75.43)
Overweight (24~27.9)	558 (10.86)
Obese (≥28)	104 (2.02)
Total	
Low	1143 (22.24)
Normal	2816 (54.78)
Exceeded	1181 (22.98)
Birth type	
Caesarean section	4916 (95.64)
Vaginal delivery	224 (4.36)
Twin zygosity	
Momozygotic twin	1351 (26.28)
Dizygotic twin	3789 (73.72)
Dizygotic twin with the same sex	1526 (29.69)
Dizygotic twin with different sex	2263 (44.03)
Apgar score 1 min	
≥7	9992 (97.20)
<7	288 (2.80)
Apgar score 5 min	
≥ 7	10215 (99.37)
<7	65 (0.63)
Gestational weeks	
<28	4 (0.08)
28~32	197 (3.83)
33~36	2355 (45.82)
≥37	2584 (50.27)

BMI, body mass index; GWG, gestational weight gain.

ORs for pregnancy outcomes by GWG and twin zygosity are presented in table 3. According to the Chinese guidelines, GWG below recommendations increased the risk for SGA/SGA pairs (OR=3.39, 95% CI 2.06 to 5.58), SGA/AGA pairs (OR=1.43, 95% CI 1.19 to 1.73), LBW/LBW pairs (OR=2.11, 95% CI 1.72 to 2.59), LBW/NBW pairs (OR=1.39, 95% CI 1.16 to 1.66), less than 33 gestational weeks (OR=2.44, 95% CI 1.81 to 3.30) and less than 37 gestational weeks (OR=1.52, 95% CI 1.32 to 1.75) after adjusting for confounding variables. GWG above recommendations was negatively associated with SGA/AGA pairs (OR=0.71, 95% CI 0.57 to 0.88), LBW/LBW pairs (OR=0.52, 95% CI 0.42 to 0.65), LBW/NBW pairs (OR=0.70, 95% CI 0.60 to 0.83), less than 33 gestational weeks (OR=0.45, 95% CI 0.27 to 0.74) but was not significant associated with SGA/SGA pairs (OR=0.99, 95% CI 0.53 to 1.89) and less than 37 gestational weeks (OR=0.93, 95% CI 0.81 to 1.06) after adjusting for confounding variables.

In the stratified analyses, twin zygosity adjusted the associations between GWG recommended by China and neonatal outcomes. Compared with participants with a normal GWG, those with a high GWG had a lower risk for SGA/SGA pairs in MZ twins (OR=0.80, 95% CI 0.31 to 2.09) but a higher risk for SGA/SGA pairs in DZ twins (OR=1.22, 95% CI 0.51 to 2.90). More importantly, high GWG was significantly associated with less than 33 gestational weeks in DZ twins (OR=0.45, 95% CI 0.26 to 0.77), but not in MD twins (OR=0.43, 95% CI 0.10 to 1.99). Meanwhile, low GWG was associated with a higher risk for SGA/SGA pairs, LBW/LBW pairs and less than 33 gestational weeks in MZ twins compared with DZ twins. There was a marginal difference in the association between low GWG and SGA/AGA pairs, NBW/LBW pairs and less than 37 gestational weeks between MZ and DZ twins based on the recommendations.

The associations between the IOM GWG recommendations and neonatal outcomes are provided in online supplemental tables S1 and S2.

DISCUSSION

Herein, we sought to explore the influence of GWG and zygosity in twin-pregnant women on neonatal outcomes in a large sample, which has not been evaluated in non-western industrialised nations. The present study demonstrated that GWG below the Chinese recommendation increased the risk for SGA/SGA pairs and SGA/AGA pairs, LBW/LBW pairs and LBW/NBW pairs, less than 33 gestational weeks and less than 37 gestational weeks. GWG above the IOM recommendation had an inverse relationship with SGA/AGA pairs, LBW/LBW pairs, LBW/NBW pairs and less than 33 gestational weeks.

Numerous studies have evaluated the associations between GWG and neonatal outcomes.[18 27 28] Lutsiv *et al* studied 1482 twins and 741 mothers and described that GWG below recommendations was significantly associated with SGA (OR=1.44, 95% CI 1.01 to 2.06), but GWG

Table 2 Twin neonatal outcomes by the Chinese recommended GWG

		IOM standard			
	Mean (SD)/N (%)	Low GWG	Normal GWG	Excess GWG	P
AGA/AGA pairs	4342 (84.47)	904 (17.59)	2394 (46.58)	1044 (20.31)	<0.0001
AGA/SGA pairs	718 (13.97)	205 (3.99)	390 (7.59)	123 (2.39)	
SGA/SGA pairs	80 (1.56)	34 (0.66)	32 (0.62)	14 (0.27)	
Larger twin birth weight (g)	2641.78 (381.42)	2503.26 (411.90)	2649.29 (359.02)	2757.93 (360.09)	<0.0001
Smaller twin birth weight (g)	2351.40 (382.34)	2231.73 (402.72)	2356.70 (368.45)	2458.96 (361.00)	<0.0001
Sum birth weight of twins	4994.19 (724.23)	4734.99 (781.74)	5005.99 (685.78)	5216.89 (675.20)	<0.0001
Both twins ≥2500 g	2088 (40.62)	318 (6.19)	1157 (22.51)	613 (11.93)	<0.0001
Both twins ≥1500 g and <2500 g	1340 (26.07)	422 (8.21)	704 (13.70)	214 (4.16)	
Both twins ≥1000 g and <1500 g	48 (0.93)	25 (0.49)	21 (0.41)	2 (0.04)	
Gestational weeks	36.22 (1.75)	35.80 (2.09)	36.30 (1.68)	36.48 (1.47)	<0.0001
≤32	201 (3.91)	90 (1.75)	93 (1.81)	18 (0.35)	<0.0001
33~36	2355 (45.82)	579 (11.26)	1254 (24.40)	522 (10.16)	
≥37	2584 (50.27)	474 (9.22)	1469 (28.58)	641 (12.47)	

AGA, appropriate for gestational age; GWG, gestational weight gain; IOM, Institute of Medicine; SGA, small for gestational age.

above guidelines was not significantly associated with SGA (OR=0.92, 95% CI 0.62 to 1.36),[29] which is consistent with our results; contrarily, Pettit *et al* reported that women with high GWG were less likely to deliver SGA neonates (p<0.01).[30] The results of LBW in this current study were comparable to another study (n=252) conducted by Liu *et al*, which implied that women at or above the IOM-recommended GWG were more likely to deliver infants with larger birth weights.[22] Nevertheless, Lutsiv *et al* found that the above association was not significant.[29] Our study also demonstrated that GWG below the recommendations increased the risk for pregnancies less than 33 and 37 weeks. This finding is consistent with an earlier study conducted by Gonzalez-Quintero *et al*,[18] but Liu *et al* reported that low GWG increased the risk of shorter than 37 gestational week, but did not increase the risk of less than 34 gestational weeks.[22] In comparison with previous reports, although there was no difference in the associations between low GWG and neonatal outcomes, the relationships between high GWG and neonatal outcomes were inconsistent. The disparity between these studies may be attributed to the study population, sample size and BMI classification criteria. Considering that the impact of GWG on twin neonatal outcomes may represent a modifiable risk factor and a high potential for intervention, it merits the attention of both patients and clinicians and warrants further investigation.

The stratified analyses by twin zygosity revealed that although GWG was associated with neonatal outcomes in both MZ and DZ twins, the magnitude of the associations varied between MZ and DZ twin pairs. The difference in these associations suggests that genetic mechanisms play a pivotal role in birth weight and gestational age in twin pregnancies. Prior twin studies have established the effect of heredity on neonatal outcomes.[31–33] A study using an Australian twin sample reported that the heritability estimates on birth weight were 23%.[34] Another study conducted in Sweden indicated that heritability estimates on gestational age were 31%.[31] Svensson *et al* indicated that over one-third of SGA births were attributable to genetic factors,[35] whereas Yoon-Mi Hur found that genetic factors accounted for 17% of the liability for birth weight.[33] The ORs of low GWG for SGA/SGA pairs, LBW/LBW pairs and pregnancies less than 33 weeks were larger in MZ twins than those in DZ twins. MZ twins share identical genes, and a previous study signalled that the maternal weight gain was lower in MZ pregnancies compared with DZ pregnancies.[36] Consequently, we speculate that GWG is a more significant measure for birth weight and gestation less than 33 weeks in twin pregnancies. On the other hand, high GWG was not significantly associated with a lower risk of SGA/SGA pairs, SGA/AGA pairs, LBW/NBW pairs, less than 33 gestational weeks or less than 37 gestational weeks in MZ twins, which indicated that high GWG was not helpful in improving the aforementioned neonatal outcomes in twin pregnancies.

The present study had several limitations that need to be taken into account. First, women who visited hospitals for antenatal care were not included in this study because they did not provide the relevant information to nurses in community health centres. Those women who received antenatal care in hospitals may have better economic conditions and gain more weight or control their weight more effectively. Thus, caution is warranted when interpreting these results. Second, the GWG recommendations were based on the assumption of a full-term delivery and may not be suitable for preterm births. We suggest that future studies focus on the impact of the rate of gain per trimester on neonatal outcomes. Third, key data on the history of previous twin pregnancies, as well as the

Table 3 ORs of pregnancy outcomes in relation to GWG and twin zygosity

	Number of women below recommendations	Adjusted OR (95% CI)	Number of women within recommendations (Reference)	Number of women above recommendations	Adjusted OR (95% CI)
SGA/SGA pairs	34/904	3.39 (2.06 to 5.58)*	32/2394	14/1044	0.99 (0.53 to 1.89)*
SGA/AGA pairs	205/904	1.43 (1.19 to 1.73)*	390/2394	123/1044	0.71 (0.57 to 0.88)*
LBW/LBW pairs	477/318	2.11 (1.72 to 2.59)*	763/1157	223/613	0.52 (0.42 to 0.65)*
LBW/NBW pairs	348/318	1.39 (1.16 to 1.66)*	896/1157	345/613	0.70 (0.60 to 0.83)*
Gestational week ≤32	90/1053	2.44 (1.81 to 3.30)†	93/2723	18/1163	0.45 (0.27 to 0.74)†
Gestational week ≤36	669/474	1.52 (1.32 to 1.75)†	1347/1469	540/641	0.93 (0.81 to 1.06)†
Monozygotic twin					
SGA/SGA pairs	20/202	4.11 (2.07 to 8.20)‡	17/611	6/261	0.80 (0.31 to 2.09)‡
SGA/AGA pairs	64/202	1.55 (1.10 to 2.18)‡	129/611	41/261	0.73 (0.50 to 1.07)‡
LBW/LBW pairs	151/70	2.78 (1.89 to 4.11)‡	253/289	72/145	0.58 (0.40 to 0.84)‡
LBW/NBW pairs	65/70	1.32 (0.90 to 1.95)‡	215/289	91/145	0.83 (0.60 to 1.14)‡
Gestational week≤32	18/268	4.67 (2.17 to 10.05)§	11/746	2/306	0.43 (0.10 to 1.99)§
Gestational week≤36	147/139	1.32 (1.00 to 1.74)§	333/424	123/185	0.87 (0.66 to 1.14)§
Dizygotic twin					
SGA/SGA pairs	14/702	3.03 (1.34 to 6.87)‡	15/1783	8/783	1.22 (0.51 to 2.90)‡
SGA/AGA pairs	141/702	1.38 (1.10 to 1.73)‡	261/1783	82/783	0.69 (0.53 to 0.90)‡
LBW/LBW pairs	326/248	1.88 (1.48 to 2.39)‡	510/868	151/468	0.50 (0.39 to 0.65)‡
LBW/NBW pairs	283/248	1.39 (1.14 to 1.70)‡	671/868	254/468	0.66 (0.55 to 0.80)‡
Gestational week≤32	72/785	2.16 (1.55 to 3.00)§	82/1977	16/857	0.45 (0.26 to 0.77)§
Gestational week≤36	522/335	1.60 (1.36 to 1.88)§	1014/1045	417/456	0.95 (0.81 to 1.11)§

*Adjusted for maternal delivery age (continuous), education level, parity, gravidity, pre-pregnancy BMI, twin zygosity, and gestational weeks.
†Adjusted for maternal delivery age (continuous), education level, parity, gravidity, pre-pregnancy BMI and twin zygosity.
‡Adjusted for maternal delivery age (continuous), education level, parity, gravidity, pre-pregnancy BMI and gestational weeks.
§Adjusted for maternal delivery age (continuous), education level, parity, gravidity and pre-pregnancy BMI.
BMI, body mass index; GWG, gestational weight gain; LBW, low birth weight, <2500 g; SGA, small for gestational age.

chorionicity and amnionicity of twins, were not acquired, which may affect neonatal outcomes.[37] However, there were some strengths in our study. This study included a large sample size of twin-pregnant women. To be best of our knowledge, this is the first study using stratified analyses by twin zygosity to assess the association between GWG and neonatal outcomes. MZ twins share identical genes; the associations between GWG and neonatal outcomes would be more accurate by excluding genetic factors. In addition, the study uncovered that low GWG increased the risk of LBW, SGA and preterm birth in twin-pregnant women after adjusting for twin zygosity. More studies are necessitated to further evaluate the impact of high GWG on neonatal outcomes.

In short, a GWG below the Chinese recommendation increased the risk for SGA, LBW and preterm birth. This association was observed in both MZ and DZ twin pairs. Additionally, the magnitude of the associations was higher in MZ twins than that in DZ twins, signifying that GWG plays an important role in these associations. Based on those findings, weight management should be included during antenatal care, and twin-pregnant women should maintain a healthy GWG.

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Patient consent for publication Consent obtained directly from patient(s).

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Data availability statement Data are available upon reasonable request. The datasets analysed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

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