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Research article

Birth weight discordance and adverse neonatal outcomes in appropriately grown premature twins

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ABSTRACT

Objective: This study aimed to analyze the clinical characteristics of birth weight discordant twins (BWDT) who were premature and appropriate-for-gestational-age or large-for-gestational-age. Additionally, it assessed the impact of birth weight discordance on the prognosis of appropriately grown premature twins, and investigated the effect of maternal factors on neonatal outcomes.

Study design: This retrospective cohort study included twins who were born alive after preterm labor at the Nanjing Drum Tower Hospital from January 2018 to December 2021, along with their mothers. Twins were arranged into discordant and concordant groups according to intertwin birth weight discordance, followed by the analysis of the clinical characteristics of mothers and the prognosis of neonates.

Results: A total of 585 mothers and 1170 neonates were included, with 47 mothers and 94 neonates in the discordant group. The incidence of birth weight discordance was 8.0% (94/1,170) in appropriately grown premature twins. The incidence of complications (43.2% vs. 21.8%) and transfer to the neonatal intensive care unit (NICU) (53.2% vs. 29.2%) was higher in the discordant group than in the concordant group ($p < 0.05$). Furthermore, the incidence of infectious diseases (36.7% vs. 19.4%), necrotizing enterocolitis (7.6% vs. 1.6%), and oxygen therapy rate (22.8% vs. 12.8%) were statistically significantly higher in the discordant group than in the concordant group ($p < 0.05$).

Conclusion: Birth weight discordance remains a high-risk factor for complications and transfer to the NICU in appropriately grown premature twins. It is important to pay attention to birth weight discordance when the outcomes of twins are assessed.

1. Introduction

Intertwin birth weight discordance refers to the difference in birth weight between twins, stemming from disparate intrauterine growth and development [1]. Its prevalence is approximately 16%, but exhibits significant geographic and demographic disparities.

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Intertwin birth weight discordance is a high-risk factor for adverse perinatal outcomes [2]. Several recent studies have demonstrated that birth weight discordance, not just low birth weight, is strongly associated with an increased risk of perinatal morbidity [3–5]. This discordance is usually attributed to fetal growth restriction (FGR) in the smaller fetus [6]. FGR is defined as a condition in which maternal, fetal, placental, and other pathological factors result in the failure of fetal growth to reach its genetic potential, often manifested as estimated fetal weight or abdominal circumference below the 10th percentile for the corresponding gestational age on ultrasound.

Up to 47% of twin pregnancies are associated with at least one small-for-gestational-age (SGA) fetus, defined as the twins whose birth weight percentile falls below the 10th percentile of their sex and gestational age. SGA is associated with significantly elevated adverse outcomes, which may account for the increasing morbidity of birth weight discordant twins (BWDT) [5,7,8]. While perinatal death risk is not increased in appropriately grown twins with discordant birth weight, this finding may underestimate the correlation of SGA with the morbidity of BWDT, due to a small number of cases [8]. Additionally, the incidence of complications in full-term infants is very low.

To eliminate the influence of SGA and full-term infants, this study analyzed the prognosis of premature twins with birth weight discordance who were appropriate for gestational age (AGA) or large for gestational age (LGA), aiming to provide guidance for perinatal consultation and neonatal management of twin pregnancies.

2. Materials and methods

2.1. The diagnostic criteria and definitions

The intertwin birth weight discordance was calculated using the following formula: (birth weight of the heavier twin - birth weight of the lighter twin)/birth weight of the heavier twin $\times$ 100% [9]. Twins with a birth weight difference of $\geq$20% were classified as the discordant group, while those with a difference of $<$20% were classified as the concordant group. Chorionicity was diagnosed using ultrasound examination in early pregnancy with reference to the "lambda sign," "T sign," placental number, and post-delivery placental examination [10]. The diagnostic criteria for complications were based on the relevant guidelines [11,12]. The composite neonatal morbidity was defined as the occurrence of any of the following conditions [3,5,13]: respiratory system diseases, including respiratory distress syndrome, transient tachypnea of the newborn, pulmonary hypertension, or bronchopulmonary dysplasia; infectious diseases, such as pneumonia, meningitis, and sepsis; necrotizing enterocolitis (NEC) (any grade); neurological diseases, including seizures and grade III or higher intraventricular hemorrhage; hypoglycemia (peripheral blood glucose $<$2.2 mmol/L); hypothermia (core body temperature $<$36.0 °C); retinopathy of prematurity (any grade). Twins were classified as AGA, LGA, and SGA when their birth weight percentile fell between the 10th and 90th percentiles, above the 90th percentile, and below the 10th percentile of sex and gestational age, respectively. Neonatal death referred to death within 28 days of birth.

2.2. Sample seize, the inclusion and exclusion criteria of study participants

We employed G*power 3.1.9.7 software to conduct a power analysis using t-tests with the parameters: Tail(s) = two, Effect size = 0.5, alpha = 0.05, and power = 0.80. This analysis led to the determination of a sample size of 585 mothers, which we consider adequate for this research.

The study enrolled preterm live birth ($<$37 weeks) twins delivered at the Nanjing Drum Tower Hospital from January 2018 to December 2021 and their mothers. The exclusion criteria were as follows: gestational age < 28 weeks; SGA in one of the twins; third or higher-order pregnancies; fetal demise, selective reduction, or stillbirth of one of the twins before delivery, which is defined as the loss of a pregnancy of $\geq$20 weeks or a fetal weight of $\geq$350g, with no signs of life such as breathing, heartbeat, umbilical cord pulsation, or voluntary muscle movements at the time of delivery [14]; monochorionic-monoamniotic pregnancies or other unique complications of monozygotic twins, such as twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence or twin reversed arterial perfusion sequence; fetal/newborn chromosomal abnormalities or severe structural abnormalities; maternal foreign ethnicity.

The participants were allocated into two groups based on intertwin birth weight discordance which was defined according to our previous study and two other studies [15–17].

2.3. Data collection of baseline characteristics and clinical outcomes

This retrospective cohort study was performed by conforming to the procedures outlined in the 2013 revised *Declaration of Helsinki* and was approved by the Ethics Committee of the Nanjing Drum Tower Hospital (Ethics Project No. 2020-264). The baseline characteristics and clinical outcomes of mothers and neonates were obtained from electronic medical records, including age, parity, history of cesarean section, mode of delivery, pre-pregnancy body mass index (BMI), chorionicity, assisted reproductive technology, gestational hypertension, and diabetes for mothers, as well as gender, gestational age, birth weight, 1-min and 5-min Apgar scores, transfer to the neonatal intensive care unit (NICU), use of respiratory support (including mechanical ventilation and non-invasive respiratory support for more than 24 h), oxygen therapy, use of pulmonary surfactant, occurrence of complications, and death for neonates.

2.4. Statistical analysis methods

The SPSS 22.0 and R 4.1.0 software were used for statistical analysis. Continuous data with normal distribution were expressed as mean ± standard deviation and compared using the he independent samples Student's *t*-test. Count data were summarized as numbers and percentages (%) and compared between the two groups with the Chi-squared or Fisher's exact test. The Chi-squared test was utilized when the expected counts in any cell of a 2x2 table were greater than 5, while Fisher's exact test was employed when the expected counts were less than 5. Three models were constructed based on baseline characteristics and clinical outcomes of participants to investigate influencing factors of neonatal outcomes, among which Model I was about birth weight discordance, Model II was adjusted for gestational age, birth weight, placental morphology, history of cesarean section, and assisted reproduction, and Model III was further adjusted for Model II plus gestational hypertension and gestational diabetes. Multivariate logistic regression analysis was used to investigate the effect of birth weight discordance on the composite neonatal morbidity and admission to NICU. The robustness of the results was assessed by constructing a propensity score model based on variables with statistical differences and clinical significance (gestational age, birth weight, placental morphology, and gestational hypertension) using logistic regression. Cases were weighted with the inverse probability of treatment weighting (IPTW) method based on the propensity score, where the weight was the reciprocal of the propensity score, to balance the distribution of potential confounding factors between the two groups. The subgroup analysis of the three models was performed according to gestational age and placental morphology. A difference was considered statistically significantly different at $p < 0.05$.

3. Results

From January 2018 to December 2021, 1,487 twins were delivered at the Nanjing Drum Tower Hospital, accounting for 10.7% (2,974/27,737) of all deliveries. After screening based on the inclusion and exclusion criteria, 585 mothers and 1,170 twin neonates were finally included in our study, with 47 mothers and 94 neonates in the discordant group and 538 mothers and 1,076 neonates in the concordant group. The results showed that the incidence of birth weight discordance was 8.0% (94/1,170) among appropriately grown premature twins (Fig. 1).

For mothers, no significant differences were observed in age, parity, mode of delivery, assisted reproduction, pre-pregnancy BMI, or gestational diabetes between the two groups. The discordant group had a higher proportion of mothers with a history of cesarean section (14.9% vs. 6.9%, $p = 0.006$) and gestational hypertension (36.2% vs. 24.7%, $p = 0.016$), as well as a lower proportion of mothers with monochorionic pregnancies (21.3% vs. 34.0%, $p = 0.013$) than the concordant group.

For neonates, the gestational age (34.0 ± 2.2 vs. 34.9 ± 2.0, $p < 0.001$) was smaller and the proportion of births at ≥ 34 weeks of gestation (57.4% vs. 77.0%, $p = 0.003$) was lower in the discordant group than in the concordant group, accompanied by a higher proportion of opposite-sex twins (48.9% vs. 28.1%, $p = 0.003$). The birth weight of neonates in the discordant group was lower than that in the concordant group (2175.3 ± 588.9 vs. 2295.1 ± 446.7, $p < 0.001$). Additionally, the birth weight of the lighter twin was markedly lower in the discordant group than in the concordant group (1877.9 ± 431.2 vs. 2206.2 ± 420.7, $p < 0.001$), while the birth weight of the heavier twin was not substantially different between the two groups (2472.7 ± 578.2 vs. 2383.9 ± 454.6, $p = 0.310$). All of these differences were statistically significant ($p < 0.05$) (Table 1).

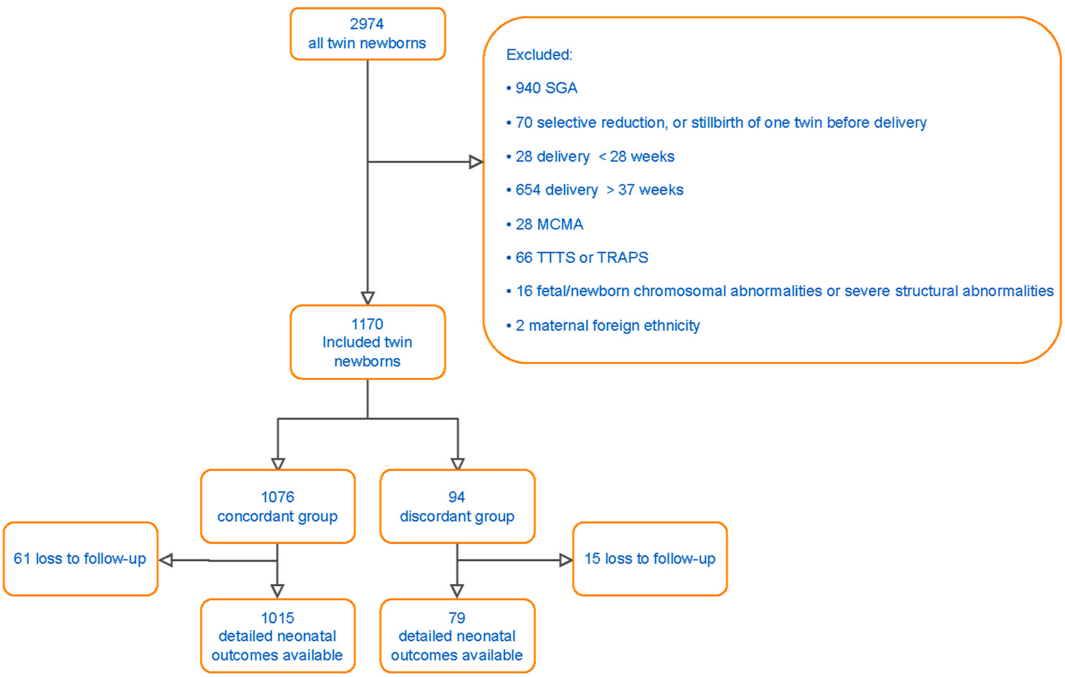

Fig. 1. Flow diagram SGA, small-for-gestational-age; MCMA, monochorionic monoamniotic; TTTS: twin-twin transfusion syndrome; TRAPS, twin reversed arterial perfusion sequence.

For neonates, the discordant group showed a statistically significantly higher rate of transfer to the NICU (53.2% vs. 29.2%, $p < 0.001$) and overall incidence of complications (43.2% vs. 21.8%, $p < 0.001$) and mortality (3.8% vs. 0.1%, $p < 0.001$) than the concordant group. Further analysis of diagnosis and treatment exhibited a statistically significantly higher incidence of infectious diseases (36.7% vs. 19.4%, $p < 0.001$), NEC (7.6% vs. 1.6%, $p < 0.001$), and oxygen therapy rate (22.8% vs. 12.8%, $p = 0.013$) in the discordant group than in the concordant group (Table 2).

Neonates in the discordant group were at a higher risk of transfer to the NICU (odds ratio [OR] = 2.76, 95% confidence interval [CI] = 1.80–4.22, $p < 0.001$) and had a higher overall incidence of morbidity (OR = 2.72, 95% CI = 1.71–4.33, $p < 0.001$) as compared with the concordant group. After the adjustment of covariates, the results remained consistent. After confounding factors were adjusted with the IPTW method, the results still suggested discordant birth weight as a risk factor for neonatal mortality and admission to the NICU. All differences were statistically significant ($p < 0.05$) (Table 3).

The effect of discordant birth weight on neonatal prognosis was not entirely consistent across chorionicity and gestational age groups. After adjustment for covariates, all three models elucidated discordant birth weight as a high-risk factor for the overall incidence of complications and neonatal transfer to the NICU in dichorionic twin pregnancies and premature infants at ≥ 34 weeks. All differences were statistically significant ($p < 0.05$) (Table 4).

4. Discussion

Intertwin birth weight discordance is a significant complication of twin pregnancies, influenced by various factors such as genetics and maternal and placental hemodynamics, leading to an increased risk of morbidity and mortality in perinatal infants [3,5,18–20]. Our previous study elaborated that intertwin birth weight discordance increased the overall incidence of complications and admission to the NICU in neonates and was positively correlated with the neonatal prognosis [9]. Additionally, it has been shown that FGR substantially elevated the risk of respiratory system diseases and infections after birth in low-birth-weight twins [21,22]. This study probed the impact of intertwin birth weight discordance on the prognosis of premature AGA infants by excluding the influence of SGA. Given the lower incidence of morbidity among full-term infants, our study specifically focused on premature infants for analysis. Our findings indicated that discordant birth weight significantly increased the overall incidence of complications and transfer to the NICU in AGA premature twins. This underscores the importance of discordant birth weight in the management of twin neonates by neonatologists.

The effect of discordant birth weight on normally growing fetuses is not yet clear. Intriguingly, Harper et al. analyzed the effects of discordant birth weight on appropriately grown twin pregnancies and observed that BWDT did not enhance the risk of adverse outcomes in dichorionic neonates [8]. Similarity, the research by D'Antonio et al. unraveled that discordant birth weight was independently correlated with the risk of diseases in twins born after 34 weeks regardless of whether they were SGA or not [3]. Our results manifested that premature AGA twins in the discordant group were at a higher risk of morbidity and transfer to the NICU, accompanied by a higher incidence of infectious diseases, NEC, and oxygen therapy, suggesting that appropriately grown premature twins with discordant birth weight might still be at risk of adverse perinatal outcomes. We hypothesize that preterm infants with a younger gestational age may inherently have a higher incidence of complications, while infants born after 34 weeks of gestation have a

Table 1
Baseline maternal characteristics in our cohort.

Characteristic	Discordant n = 47	Concordant n = 538	P-value[a]
Age (y ± SD)	31.0 ± 3.8	30.64 ± 4.0	0.223
Nulliparous, n (%)	36 (76.6)	435 (80.9)	0.480
Cesarean delivery	38 (80.9)	438 (81.4)	0.893
Monochorionic, n (%)	10 (21.3)	183 (34.0)	0.013
Assisted conception, n (%)	26 (55.3)	552 (64.3)	0.691
Prior cesarean delivery, n (%)	7 (14.9)	37 (6.9)	0.006
Prepregnancy BMI ≥28.0	3 (6.4)	21 (3.9)	0.250[b]
Hypertensive disorders of pregnancy, n (%)	17 (36.2)	133 (24.7)	0.016
Diabetes in prepregnancy, n (%)	12 (25.5)	114 (21.2)	0.327
Neonatal sex			
Male-male	11 (23.4)	203 (37.7)	0.050
Female-female	13 (27.7)	184 (34.2)	0.363
Male-female	23 (48.9)	151 (28.1)	0.003
Gestational age at birth (w ± SD)	34.0 ± 2.2	34.9 ± 2.0	< 0.001
<30	3 (4.4)	19 (3.5)	0.409[b]
30-33 + 6	17 (36.2)	105 (19.5)	0.007
≥34	27 (57.4)	414 (77.0)	0.003
Birth weight discordance (% ± SD)	23.9 ± 3.8	7.3 ± 5.2	< 0.001
Birth weight (g ± SD)			
Overall	2175.3 ± 588.9	2295.1 ± 446.7	< 0.001
Smaller twin	1877.9 ± 431.2	2206.2 ± 420.7	< 0.001
Larger twin	2472.7 ± 578.2	2383.9 ± 454.6	0.310

Abbreviations: BMI, body mass index; SD, standard deviation.
[a] Chi-square or Student's t-test.
[b] Fisher's exact test.

Table 2
Neonatal outcomes between the two groups.

Outcomes	Discordant n = 94[d]	Concordant n = 1076[d]	P-value[b]
Apgar at 1 min	8.6 ± 0.6	8.6 ± 0.6	0.218
Apgar at 5 min	9.5 ± 0.6	9.6 ± 0.7	0.328
Admission to NICU	50 (53.2)	314 (29.2)	< 0.001
Composite morbidity[a]	35 (43.2)	223 (21.8)	< 0.001
RDS/BPD[a]	7 (8.9)	109 (10.4)	0.670
Infectious diseases[a]	29 (36.7)	204 (19.4)	< 0.001
NEC[a]	6 (7.6)	17 (1.6)	< 0.001
Respiratory support[a]	12 (15.2)	119 (11.3)	0.300
PS use[a]	7 (8.9)	63 (6.0)	0.308
Oxygen therapy rate[a]	18 (22.8)	135 (12.8)	0.013
Neonatal death[a]	3 (3.8)	1 (0.1)	< 0.001[c]

Abbreviation: BPD, broncho pulmonary dysplasia; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PS, pulmonary surfactant; RDS, respiratory distress syndrome.
[a] Available for 1051 concordant dichorionic newborns and 79 discordant dichorionic newborns.
[b] Chi-square or Student's t-test.
[c] Fisher's exact test.
[d] Due to some of the newborns being lost to follow-up, their outcomes could not be tracked.

Table 3
Impact of birth weight discordance on neonatal complications and NICU admission.

Model	Neonatal morbidity			Admission to NICU		
	OR	95% *CI*	p-Value	OR	95% *CI*	p-Value
Model I	2.72	1.71-4.33	<0.001	2.76	1.80-4.22	<0.001
Model II	2.45	1.15-5.21	0.020	2.68	1.24-5.80	0.012
Model III	2.35	1.10-5.02	0.028	2.67	1.24-5.74	0.012
IPTW	2.27	1.65-3.13	<0.001	2.18	1.58-3.00	<0.001

Abbreviations: Model I was about birth weight discordance; Model II was adjusted for gestational age, birth weight, chorionicity, prior cesarean delivery, and assisted conception; Model III was adjusted for model II plus hypertensive disorders of pregnancy and pregestational diabetes; IPTW was adjusted for gestational age, birth weight, chorionicity, and hypertensive disorders of pregnancy.
CI, confidence interval; IPTW, inverse probability of treatment weighting; NICU, neonatal intensive care unit; OR, odds ratio.

Table 4
Association between birth weight discordance and neonatal outcomes in different chorionicity and gestational age groups.

	Model I			Model II			Model III		
Subgroup	OR	95% *CI*	p-Value	OR	95% *CI*	p-Value	OR	95% *CI*	p-Value
Composite morbidity									
Chorionicity									
MC	6.53	2.30-18.56	<0.001	2.20	0.24-20.44	0.489	2.32	0.23–23.36	0.476
DC	2.14	1.26-3.64	0.005	2.43	1.08-5.46	0.031	2.32	1.03–5.21	0.041
Gestational age at birth, w									
<34	2.34	0.53-10.36	0.265	1.00	0.17-5.87	0.997	0.70	0.11-4.48	0.708
≥34	2.81	1.30-6.04	0.008	3.13	1.37-7.17	0.007	3.05	1.33-6.99	0.009
Admission to NICU									
Chorionicity									
MC	6.04	2.26-16.14	<0.001	1.61	0.08–32.31	0.755	1.74	0.08–40.08	0.729
DC	2.23	1.37-3.61	0.001	2.66	1.21-5.85	0.015	2.64	1.21-5.78	0.015
Gestational age at birth, w									
<34	0.15	0.02-1.13	0.066	0.26	0.02–3.12	0.285	0.35	0.02–4.94	0.435
≥34	3.19	1.61-6.35	<0.001	3.82	1.75-8.31	<0.001	3.66	1.67-8.01	0.001

Abbreviations: Model I was about birth weight discordance; Model II was adjusted for gestational age, birth weight, chorionicity, prior cesarean delivery, and assisted conception; Model III was adjusted for model II plus hypertensive disorders of pregnancy and pregestational diabetes.
CI, confidence interval; DC, dichorionic; MC, monochorionic; NICU, neonatal intensive care unit; OR, odds ratio.

relatively lower incidence of complications, making the impact of birth weight discordance more pronounced in this context.

The systematic review of D'Antonio [3] showed that BWDT did not increase the risk of perinatal death in AGA infants. However, this author believed that the included observational studies in the review had some limitations, such as definition differences, different populations, estimation of the used fetal weight or birth weight, and lack of standardized measures of prenatal management. Our study, which had consistent inclusion criteria, demonstrated a significant difference in the mortality rate of twins between the concordant and discordant groups.

Chorionicity is a pivotal indicator for the prognosis of twin pregnancies. However, our previous study [9] of all twin neonates exhibited no correlation of chorionicity with the prognosis of BWDT, consistent with the results of D'Antonio [3]. Additionally, prior research on AGA twins unraveled that BWDT only elevated the rate of admission to the NICU for monochorionic infants, illustrating that discordant growth reflected differences in growth potential rather than differences in placental pathology. After the influence of SGA was excluded, our subgroup analysis of different models elucidated that the effect of birth weight discordance on the risk of morbidity in monochorionic infants was lost after adjustment for factors such as gestational age and birth weight, while it markedly enhanced the incidence of complications and transfer to the NICU in dichorionic infants. This result may be related to the low statistical analysis ability due to a few monochorionic cases and the exclusion of severe complications specific to TTTS and other monochorionic cases. Another cause is a generally higher risk of adverse perinatal outcomes in monochorionic pregnancies [23] which may be delivered at an earlier gestational age. Accordingly, the risk of neonatal morbidity is higher in monochorionic pregnancies regardless of birth weight discordance.

Moreover, our study identified a higher proportion of opposite-sex twins in the discordant group compared to the concordant group. This finding is consistent with the research of Burak Bayraktar et al. indicating that birth weight, head circumference, and body length in twin pregnancies are affected by the sex of the co-twin [24].

Our study has several advantages, including adjustment for various factors known to affect neonatal prognosis and the inclusion of a standardized population through IPTW, providing consistent and reliable results. Notably, the subgroup analysis unraveled that birth weight discordant remained a risk factor for morbidity in premature infants born after 34 weeks, emphasizing the importance of focusing on this population in clinical practice.

However, our study does have limitations. The lack of a recognized curve standard for twin birth weight and the definition of SGA based on singleton standards in China may lead to an underestimation of neonatal morbidity. The large difference in the size of study groups and the small sample size may limit the generalizability of the results. Additionally, further research is needed to examine the effects of a history of previous cesarean section or gestational hypertension on fetal weight discordance, the relationship between discordant birth weight and dizygotic twins, and the prognosis differences between lighter and heavier twins in birth weight discordance.

5. Conclusion

In summary, birth weight discordance is still associated with a high risk of adverse perinatal outcomes in premature twins, even as they grow normally. The results of the subgroup analysis unveiled that the effect of BWDT on late preterm infants may be of greater concern. Obstetricians and neonatologists should focus on the impact of birth weight discordance on premature twins and strengthen the perinatal management of BWDT in clinical practice.

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Ethical statement

The study was performed by conforming to the procedures outlined in the 2013 revised *Declaration of Helsinki* and was approved by the Ethics Committee of the Nanjing Drum Tower Hospital (Ethics Project No. 2020-264).

Consent for participate

Informed consent was obtained from all participants involved in the study.

Consent for publication

Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Ling Yang: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yan Zhou:** Writing – review & editing, Data curation. **Jie Qiu:** Writing – review & editing, Methodology, Formal analysis. **Nacheng Lin:** Writing – review & editing, Methodology. **Ning Gu:** Writing – review & editing, Formal analysis. **Yimin Dai:** Writing – review & editing, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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