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Birth Weight Discordance in Very Low Birth Weight Twins: Mortality, Morbidity, and Neurodevelopment

Nansi S. Boghossian, PhD[1], **Shampa Saha, PhD**[2], **Edward F. Bell, MD**[3], **Jane E. Brumbaugh, MD**[4], **Seetha Shankaran, MD**[5], **Waldemar A. Carlo, MD**[6], **Abhik Das, PhD**[7], **Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network**

[1]Department of Epidemiology & Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC

[2]Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

[3]Department of Pediatrics, University of Iowa, Iowa City, IA

[4]Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

[5]Department of Pediatrics, Wayne State University, Detroit, MI

[6]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

[7]Social, Statistical, and Environmental Sciences Unit, RTI International, Rockville, MD.

Abstract

Objective—Examine outcomes among birth weight concordant and discordant 401–1500 g twins.

Study Design—Twins (n=8,114) at NICHD Neonatal Research Network (1994–2011) were studied. Discordance (birth weight difference/larger twin birth weight × 100%) was categorized into: ≤14%, >14–20%, >20–30%, and >30%. Separate logistic regression models for the smaller and larger infants assessed the adjusted association between discordance and outcomes.

Results—Compared to the smaller twin with ≤14% discordance, mortality, necrotizing enterocolitis, severe retinopathy of prematurity, bronchopulmonary dysplasia, and neurodevelopmental impairment or death were highest among the smaller twins with discordance >30%. The larger twins with discordance >30% had higher odds of patent ductus arteriosus,

Corresponding Author: Edward F. Bell, MD, Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242. Telephone: 319-356-4006. Fax: 319-356-4685. edward-bell@uiowa.edu.

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moderate-to-severe cerebral palsy, blindness, cognitive and motor scores <70. Odds of cerebral palsy and blindness were also higher among the larger twins with discordance >14–20%.

Conclusion—Discordance >30% was associated with higher mortality in the smaller twin and higher morbidities among the smaller and larger twins.

Keywords

extremely preterm; small for gestational age

INTRODUCTION

Birth weight discordance (BWD) >20% is fairly common, affecting around 16% of twin pregnancies.[1] Few studies have examined neonatal morbidities, mortality beyond hospital discharge, and neurodevelopmental outcomes among preterm twins in relation to BWD.[2–5] Such studies had small sample sizes, used birth certificate data rather than medical charts, and failed to consider the impact of antepartum or intrapartum management.[1] The American College of Obstetricians and Gynecologists considers a 20% discrepancy in weight among twins to represent significant discordance.[6]

We used data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) Generic Database to examine BWD categories and their association with neonatal mortality, morbidities, and neurodevelopmental outcomes at 18–22 months' corrected age (CA) among very low birth weight (VLBW) preterm twins.

METHODS

Study Population

We studied preterm twins born or cared for at NRN hospitals January 1, 1994-December 31, 2011. The NRN is comprised of NICUs at academic and affiliated centers in the U.S. and a Data Coordinating Center. Between 1994 and 2007, all preterm VLBW infants (401–1500 g) born at or admitted to an NRN center within 14 days of birth were included in the NRN registry. In January 2008, eligibility criteria changed to include inborn infants with BW 401–1000 g or gestational age 22–28 weeks or infants enrolled in an NRN clinical trial. Trained research nurses abstracted maternal demographic, pregnancy, and delivery information and infant data collected from birth to hospital discharge, death, or 120 days. The institutional review board at each center approved data collection for the registry and follow-up study.

Surviving infants were eligible for a standardized comprehensive neurodevelopmental assessment at 18–22 months' CA by certified examiners if they weighed 401–1000 grams at birth (those whose follow-up window opened before January 1, 2008) or were born at 22–26 weeks or enrolled in an NRN study with follow-up (those whose follow-up window opened on or after January 1, 2008).

The study cohort included 8,322 twin infants born during the study period with both twins reported having no major congenital malformations. If one member of the set of twins died

due to twin-to-twin-transfusion syndrome (TTTS, n=23 twin pairs), both twin infants were excluded from the analysis. TTTS was only recorded if it was a cause of death. As our analyses were stratified by the smaller and larger infant in a pair, we further excluded 81 twin pairs (54 same-sex and 27 opposite-sex twin pairs) in which the infants within the twin pair had the same BW. This resulted in a total of 8,114 twin infants (4,057 pairs) for the current study. Of these, 4,377 infants were eligible for the follow-up at 18–22 months' CA of whom 3,767 (86.1%) infants had survival and follow-up data at 18–22 months' CA (Fig. 1).

Definitions

Birth weight discordance was calculated as:

$$[(\text{Larger twin BW} - \text{Smaller twin BW})/\text{Larger twin BW}] \times 100\%$$

and was categorized as discordance ≤14%, >14–20%, >20–30%, and >30%. Small for gestational age (SGA) was defined as sex-specific BW less than the 10th centile for gestational age.[7] Hospital death was defined as death before discharge or by 120 days for infants still hospitalized. Neonatal morbidities diagnosed during the hospital stay were recorded for infants surviving >12 hours and included patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), modified Bell's stage ≥IIA necrotizing enterocolitis (NEC),[8] severe intracranial hemorrhage (ICH) (grade 3 or 4) determined according to Papile's classification[9] or periventricular leukomalacia (PVL), early (EOS, onset at age ≤72 hours) and late-onset sepsis (LOS, >72 hours) defined by positive blood culture and intent to treat with antibiotics for ≥5 days, retinopathy of prematurity (ROP) defined for infants still hospitalized at 28 days, and bronchopulmonary dysplasia (BPD) defined as continuous use of supplemental oxygen at 36 weeks' postmenstrual age.

Neurodevelopmental impairment (NDI) was assessed at 18–22 months' CA. For the purpose of this analysis, from 1994–2005 NDI was defined as one or more of the following: Bayley-II Mental Developmental Index score <70, Bayley-II Psychomotor Developmental Index score <70, moderate or severe cerebral palsy, bilateral blindness, or hearing impairment with hearing aids in both ears. For infants born in 2006, NDI was defined as one or more of the following: Bayley-III cognitive composite score <70, Gross Motor Function Classification System level ≥2, blindness (some or no useful vision in either eye), or deafness (functional hearing impairment). Starting in 2010, the Bayley-III motor score was also collected, and a motor composite score <70 was added to the 2006 NDI definition. The World Health Organization Child Health Standards[10,11] were used to assess weight, length, and head circumference-for-age z-scores at 18–22 months' CA follow-up.

Statistical analysis

Maternal and infant demographic and clinical characteristics were compared between the BWD groups using Pearson's chi-square test for categorical outcomes and analysis of variance for continuous outcomes. Twins with a discordance of ≤14% formed the reference group. We examined the association of BWD with the in-hospital morbidities described above, death, and the composite of NDI or death before follow-up assessment. We first

tested for interaction terms between BWD group and size of the twin (larger vs. smaller twin) for mortality and all the major morbidities, using generalized estimating equations, which accounted for the twin correlated data. As the interaction terms were significant for the outcomes of mortality before and after hospital discharge, PDA, NEC, LOS, ROP, BPD, and NDI or death, we analyzed all the outcomes in the larger twin and in the smaller twin separately. Combined morbidity or death outcomes were also examined as secondary outcomes. Each composite outcome was recorded as "yes" if the infant had the morbidity or died before being assessed for the outcome (for PDA and NEC, death within 12 hours; for EOS and LOS death within 3 days; for ICH and PVL, death before sonography; for ROP, death in the first 28 days; for BPD, death before 36 weeks' postmenstrual age) and "no" if the infant survived until evaluation and did not have the morbidity. We adjusted for birth year, study center included as a random effect, maternal ethnicity/race, any course of antenatal steroid use, gestational age, and infant sex in the primary models. In the secondary models, we also adjusted for SGA. For outcomes evaluated at 18–22 months, we additionally adjusted for maternal education, while for models examining NDI, we also included a cohort effect to indicate Bayley II vs. Bayley III. Logistic regression models treating the center effect as a random effect were used for all the primary and secondary analyses. We report the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from these models. No adjustments were made for multiple comparisons. A p-value <0.05 was considered for statistical significance. Analyses were conducted using SAS (SAS Institute, Cary, NC).

Sensitivity Analyses

We conducted several sensitivity analyses:

1. We re-ran all the models restricting the study period to 2006–2011 to adjust for chronic hypertension and diabetes mellitus, as these data were first collected starting in 2006.
2. We analyzed the outcomes stratifying by same-sex versus opposite-sex twins, as a surrogate for chorionicity.
3. As the BW eligibility criteria (401–1000 g) for follow-up assessment might exclude the larger twin from analyses if the BW was above 1000 g, we re-ran the models of neurodevelopmental outcomes restricting the data to infants for whom both twins were assessed at follow-up.

RESULTS

Study Population

Among the 8,114 VLBW twin infants, BWD rates of ≤14%, >14–20%, >20–30%, and >30% were 69% (n=5,606), 13% (n=1,094), 10% (n=848), and 7% (n=566), respectively. Mothers who were older, married, white, educated beyond high school, and with history of diabetes and/or hypertension were more likely to have twins with higher BWD (Table 1). Antenatal steroid use and C-section were more common among mothers with more discordant twins. Same-sex twins were more likely to have higher discordance levels. Twins with higher discordance were, on average, of higher gestational age. Among the smaller

twins in each pair, higher BWD was associated with a lower mean BW and a higher rate of SGA, while among the larger twins in each pair, higher BWD was associated with a higher mean BW (Table 1).

In-hospital Mortality and Morbidities

Smaller twins—Among the smaller twins in each pair, the OR of in-hospital mortality was higher with increasing levels of discordance. Smaller twins with the highest discordance level (>30%) had increased odds of mortality (OR=7.9; 95% CI 5.6–11.3), NEC, LOS, severe ICH or PVL, severe ROP, and BPD than smaller twins with the lowest discordance level (≤14%) (Table 2). Twins with discordance levels of >20–30% also had higher odds of mortality and BPD while twins with discordance levels of >14–20% had higher odds of BPD only compared to twins who were not discordant (≤14%). Twins with discordance levels of >14–20% also had lower odds of PDA. Early-onset sepsis did not differ significantly among the groups.

Adjustment for SGA, a proxy for fetal growth restriction, reduced the ORs for each discordance group with the biggest reductions observed for those with the largest discordance (Table 2). After adjustment for SGA, only mortality (OR=3.2; 95% CI 2.1–4.8), NEC (OR=2.1; 95% CI 1.3–3.4), severe ROP (OR=2.4; 95% CI 1.1–5.4), and BPD (OR=2.3; 95% CI 1.6–3.6) remained significantly higher among twins with the highest discordance level, while differences were no longer significant for LOS and ICH/PVL. For those with discordance of >20–30%, only BPD remained significantly increased (OR=1.6; 95% CI 1.2–2.1) following adjustment for SGA status, while the decreased odds of PDA for those with discordance >14–20% remained significant (OR=0.75; 95% CI 0.60–0.93).

Larger twins—Among the larger twins, only PDA was significantly different between groups, with the highest level of discordance associated with increased odds of PDA (OR=1.5; 95% CI 1.1–1.9) (Table 2). Adjusting for SGA did not change this association significantly.

Composite outcomes of each morbidity or death among smaller and larger twins—When examining the composite outcomes of each morbidity or death, all the results remained the same as for the morbidities alone except for the composite outcome of EOS or death among twins >30% discordant, the composite of severe ROP or death among twins >20–30% discordant among the smaller twins, and the composite of BPD or death among the larger twins >30% discordant (Supplementary Table 1). With additional adjustment for SGA among the smaller twins, the odds of the composite outcome of EOS or death were higher among infants with discordance >30%, and the odds of severe ROP or death were higher among infants with discordance of >20–30%; among the larger twins with discordance >30%, the composite outcome of BPD or death was increased (Supplementary Table 1).

Neurodevelopmental Outcomes at 18 to 22 Months' Corrected Age

Smaller twins—Among the smaller twins at the 18–22-month follow-up, those with the highest discordance level had increased odds of mortality, NDI, and the composite outcome

of NDI or death compared to those with discordance ≤14% (Table 3). Of the individual components of NDI, the odds of blindness and cognitive composite score <70 were significantly higher among the smaller twins with the greatest discordance. Twins with discordance >20–30% also had increased odds of mortality before follow-up.

After adjusting for SGA, only death before follow-up (OR=3.1; 95% CI 1.9–5.1) and the composite outcome of NDI or death (OR=2.2; 95% CI 1.3–3.6) remained significantly higher among those with the greatest discordance (Table 3).

At 18–22 months' CA, smaller twins with the highest discordance level had significantly lower weight and smaller head circumference for age compared to those with discordance ≤14%.

Larger twins—Larger twins with the greatest discordance had higher odds of moderate-to-severe cerebral palsy, blindness, and a cognitive and motor score <70 but did not have higher odds of NDI. Twins with discordance of >14–20% also had higher odds of cerebral palsy and blindness, while those with discordance of >20–30% did not.

After adjusting for SGA, the results did not change, and the odds of moderate-to-severe cerebral palsy (OR=3.6; 95% CI 1.7–7.7), blindness (OR=13.3; 95% CI 1.8–100), and cognitive (OR=4.8; 95% CI 1.3–18.1) and motor scores <70 (OR=6.6; 95% CI 1.2–36.7) remained significantly higher among the larger twins with the highest discordance level. Similarly, adjusting for SGA did not change the results among the larger twins with discordance level of >14–20%; the odds of cerebral palsy (OR=1.9; 95% CI 1.0–3.5) and blindness (OR=8.1; 95% CI 1.9–34.4) remained higher compared to twins with discordance level ≤14% (Table 3).

Sensitivity Analyses

The ORs were overall very similar after restricting the study cohort to infants born 2006–2011 and adjusting for chronic hypertension and diabetes mellitus (results not shown). When examining same-sex twins, the results for in-hospital outcomes (Supplementary Table 2) and most of the outcomes at 18–22 months' CA (Supplementary Table 3) did not change. However, when examining opposite-sex twins for in-hospital outcomes (Supplementary Table 4) and outcomes at 18–22 months' CA (Supplementary Table 5), several estimates lost statistical significance; however, the differences remained in the same direction except for NEC and severe ROP among the smaller twins with the highest discordance. The loss of statistical significance might be explained by inadequate power; of the most highly discordant twins, opposite-sex twins constituted only 21%. When examining the neurodevelopmental outcomes, restricting the data to both twin infants meeting the eligibility criteria (401–1000 g) for follow-up assessment did not change any results (data not shown).

DISCUSSION

We examined the associations between BWD and VLBW preterm twin outcomes and found that most adverse outcomes including mortality, NEC, severe ROP, and BPD, were more

common among the smaller twins with the highest BWD level (>30%). The larger twins with the highest discordance level had increased odds of PDA, moderate-to-severe cerebral palsy, blindness, and cognitive and motor scores <70. After adjusting for SGA, several estimates diminished, consistent with the close link between fetal growth and twin BWD.

Our study limitations include lack of data on chorionicity and incomplete data on TTTS. We attempted to account for this by stratifying by same-sex and opposite-sex twins. To define SGA among twins, we used singleton specific charts. However, compared to singletons, twin fetuses show decreased growth velocity starting at 32 weeks' gestation, which should not affect our very preterm population.[12] Strengths of our study include a large sample size with rich data on in-hospital and follow-up outcomes.

Different cutoffs have been used to define BWD with the most common being 15%,[13–15] 20%,[3,16,17] and 25%.[18–22] The American College of Obstetricians and Gynecologists acknowledges a 20% weight discrepancy between twins as significant discordance.[6] Our discordance rates are similar to those reported in a U.S. population-based study that did not exclude congenital malformations; approximately 25% of twin deliveries experienced discordance ≥15%, and around 5% had discordance ≥30%.[23] Twins with malformations are known to have higher BWD rates.[3,16,21,24] Although we excluded twins with major malformations, our high discordance rates are, at least in part, the result of using BW rather than gestational age as the main eligibility criterion for our database in the early study years (1994–2007), resulting in an excess of SGA infants.

BWD has been examined previously as a contributor to perinatal and neonatal mortality. In a Canadian study (n=7,821 twin pairs), BWD ≥30% was the optimal threshold for perinatal mortality irrespective of chorionicity.[25] In a U.S. study (n=128,168 twin pairs) using National Center for Health Statistics data, after adjusting for gestational age and BW for gestational age, compared to the non-discordant smaller twins (<15%), highly discordant smaller twins 25–29% (OR=2.02; 95% CI 1.58–2.60) and ≥30% (OR=2.05; 95% CI 1.66–2.51) had increased mortality odds.[23] In that study, only larger twins with discordance ≥30% (OR=2.25; 95% CI 1.71–2.96) had increased mortality odds compared to the larger twin in non-discordant pairs.[23] We found higher mortality odds only in the smaller highly discordant (>30%) twin in a pair but not in the larger highly discordant twin.

Few studies have investigated in-hospital morbidities among preterm discordant twins.[2–5] In a cohort of 335 twin pairs <37 weeks that excluded infants with malformations, BWD >20% was a predictor of a composite outcome of neonatal mortality or major morbidity.[2] In one of the larger U.S. studies (n=1,318 twin pairs of ≥24 weeks' gestation), discordance ≥20% was not associated with NEC or RDS, but was associated with a nonsignificant trend toward higher IVH rates.[3] Two other smaller studies, one conducted in in Turkey (n=136 twin pairs) and one in the U.S. (n=119 twin pairs), failed to find an association between discordance and the morbidities we examined (BPD, PDA, sepsis, IVH/PVL, and NEC) when comparing discordant (≥15% and ≥20%) with concordant preterm twins.[4,5] The small samples and smaller BWD threshold definitions in previous studies may have precluded detecting such associations.

Few studies have examined neurodevelopmental outcomes in relation to BWD. One study showed that the BW distribution was similar between twin infants with and without cerebral palsy or mental retardation (n=115 infants).[26] Another study found that both monochorionic and dichorionic infants with discordance ≥30% (n=18 twins) had higher incidence of cerebral white matter lesions compared to those with <30% discordance (n=124 twins).[27] In a study of 71 monozygotic twins, a BW difference of 340 g or more was associated with a decrease in verbal IQ in the smaller twin, while a difference less than 340 g was associated with a lower verbal IQ score in the larger compared to the smaller twin.[28] None of the above studies adjusted for growth restriction. Without adjusting for SGA, several of our adverse neurodevelopmental outcomes occurred more often among the smaller twins with large BWD. Adjusting for SGA diminished these differences, illustrating the difficulty of separating the contributions of fetal growth restriction and twin BWD. Our observation that the larger but not the smaller discordant twin was more likely to have moderate or severe cerebral palsy and delayed motor and cognitive composite scores is interesting but hard to explain. Confounding by an unknown variable might be a potential explanation. Additional research exploring mechanisms that affect fetal brain development in twins is needed.

In conclusion, we found that large BWD was associated with higher odds of mortality in the smaller twin and higher odds of morbidities among both twins. Larger discordance should trigger heightened fetal surveillance among VLBW twins; however, decisions about the timing of delivery must balance the risks of prematurity against the risks of increasing BWD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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See Supplement B.

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ABBREVIATIONS

BPD	bronchopulmonary dysplasia
BWD	birth weight discordance
CA	corrected age
CI	confidence interval
EOS	early-onset sepsis
ICH	intracranial hemorrhage
LOS	late-onset sepsis
MDI	mental developmental Index

NDI	neurodevelopmental impairment
NEC	necrotizing enterocolitis
NRN	Neonatal Research Network
OR	odds ratio
PDA	patent ductus arteriosus
PDI	psychomotor developmental index
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
TTTS	twin-to-twin-transfusion syndrome
VLBW	very low birth weight

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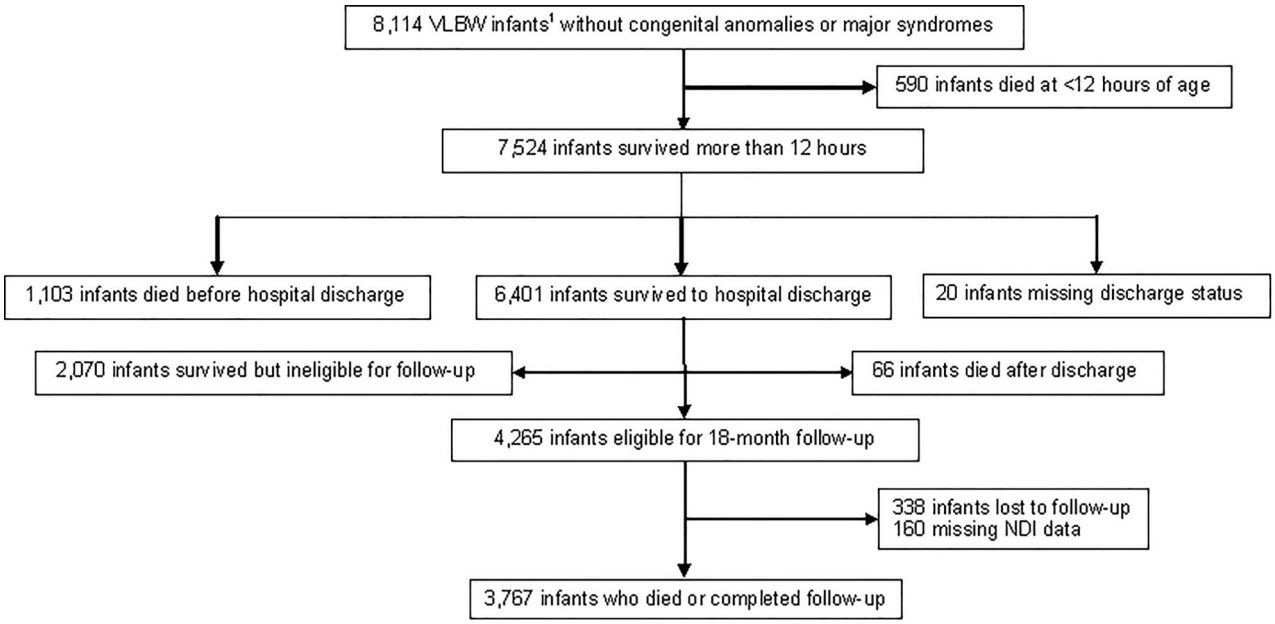

[1] Excludes 23 twin pairs (46 infants) in which one or both twin infants died due to twin-twin transfusion syndrome and 81 twin pairs (162 infants) who had twin infants with the same birthweight.

FIGURE 1.

Study population of VLBW infants in NICHD Neonatal Research Network born 1994–2011

TABLE 1.

Infant and maternal characteristics of twin births by percentage of birth weight discordance

	Birth Weight Discordance (%)				P-value[1]
	≤14	>14–20	>20–30	>30	
Overall	***N=5606***	***N=1094***	***N=848***	***N=566***	
Maternal age ≤19 y	652/5550 (11.7)	122/1086 (11.2)	80/838 (9.6)	54/562 (9.6)	0.15
Maternal age ≥35 y	774/5550 (13.9)	168/1086 (15.5)	142/838 (16.9)	124/562 (22.1)	<0.001
Mother not married	2604/5452 (47.8)	514/1078 (47.7)	360/836 (43.1)	196/554 (35.4)	<0.001
Hispanic	678/5328 (12.7)	118/1050 (11.2)	110/804 (13.7)	58/526 (11.0)	0.28
Race					
White	3144/5458 (57.6)	622/1082 (57.5)	508/824 (61.7)	342/558 (61.3)	0.065
Black	2040/5458 (37.4)	406/1082 (37.5)	276/824 (33.5)	166/558 (29.7)	<0.001
Other	274/5458 (5.0)	54/1082 (5.0)	40/824 (4.9)	50/558 (9.0)	0.001
Mother <high school	274/4492 (6.1)	68/866 (7.9)	46/656 (7.0)	12/450 (2.7)	0.002
Diabetes	188/5558 (3.4)	40/1090 (3.7)	38/844 (4.5)	32/564 (5.7)	0.026
Preeclampsia/Hypertension	564/5558 (10.1)	164/1092 (15.0)	178/842 (21.1)	162/560 (28.9)	<0.001
Antenatal steroids	4345/5596 (77.6)	858/1093 (78.5)	705/843 (83.6)	490/566 (86.6)	<0.001
C-section	3524/5600 (62.9)	740/1094 (67.6)	584/848 (68.9)	505/565 (89.4)	<0.001
Gestational age mean ± SD, wk	26.9 ± 2.6	26.8 ± 2.6	27.1 ± 2.4	27.8 ± 2.1	<0.001
Same sex	3750/5604 (66.9)	696/1094 (63.6)	568/848 (67.0)	448/566 (79.2)	<0.001
Both male	2046/5604 (36.5)	374/1094 (34.2)	298/848 (35.1)	234/566 (41.3)	0.031
Both female	1704/5604 (30.4)	322/1094 (29.4)	270/848 (31.8)	214/566 (37.8)	0.002
Smaller Twin	***N=2803***	***N=547***	***N=424***	***N=283***	
Birth weight mean ± SD, g	941 ± 282	841 ± 242	791 ± 209	668 ± 160	<0.001
SGA	229/2803 (8.17)	91/547 (16.6)	14¾24 (33.7)	229/283 (80.9)	<0.001
Apgar at 5-minute ≤3	315/2780 (11.3)	70/544 (12.9)	4¾20 (10.2)	32/279 (11.5)	0.63
Delivery room resuscitation[2]	2608/2737 (95.3)	509/530 (96.0)	400/418 (95.7)	276/281 (98.2)	0.14
Mechanical ventilation	2058/2577 (79.9)	412/502 (82.1)	320/398 (80.4)	225/265 (84.9)	0.19
Surfactant	1877/2797 (67.1)	392/546 (71.8)	282/424 (66.5)	195/283 (68.9)	0.17

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	Birth Weight Discordance (%)				P-value[1]
	≤14	>14–20	>20–30	>30	
Early indomethacin in the first 24 h of life	716/2572 (27.8)	14¼97 (28.4)	119/398 (29.9)	81/264 (30.7)	0.68
Larger Twin	***N=2803***	***N=547***	***N=424***	***N=283***	
Birth weight mean ± SD g	1005 ± 299	1010 ± 290	1044 ± 274	1129 ± 240	<0.001
SGA	137/2802 (4.9)	27/547 (4.9)	20/424 (4.7)	15/283 (5.3)	0.99
Apgar at 5-minute ≤3	303/2780 (10.9)	71/545 (13.0)	38/423 (9.0)	22/282 (7.8)	0.074
Delivery room resuscitation[2]	2612/2741 (95.3)	517/534 (96.8)	405/416 (97.4)	271/282 (96.1)	0.13
Mechanical ventilation	2086/2587 (80.6)	424/505 (84.0)	329/406 (81.0)	227/271 (83.8)	0.24
Surfactant	1937/2796 (69.3)	414/547 (75.7)	295/424 (69.6)	216/282 (76.6)	0.003
Early indomethacin in the first 24 h of life	720/2582 (27.9)	139/504 (27.6)	112/406 (27.6)	63/272 (23.2)	0.43

Figures are N/total (%), unless otherwise stated.

[1] P-values have been obtained using Pearson's chi-square test for categorical outcomes and analysis of variance for continuous outcomes.

[2] Delivery room resuscitation is defined if the infant received any of: oxygen, bag and mask ventilation, chest compression, intubation or medicine such as epinephrine.

TABLE 2.

Odds ratios (95% CI)[1] of smaller and larger twin in-hospital outcomes for VLBW twins by birth weight discordance

Smaller Twin	Birth Weight Discordance (%)			
	≤14	**>14–20**	**>20–30**	**>30**
	N=2803	***N=547***	***N=424***	***N=283***
In-hospital death				
N/Total (%)	573/2797 (20.5)	126/546 (23.1)	102/423 (24.1)	93/283 (32.9)
OR				
Model 1	REF	1.25 (0.94–1.65)	**1.82 (1.33–2.48)**	**7.93 (5.57–11.3)**
Model 1 + SGA	REF	1.11 (0.83–1.48)	1.34 (0.96–1.86)	**3.18 (2.09–4.84)**
PDA				
N/Total (%)	1044/2580 (40.5)	176/502 (35.1)	139/398 (34.9)	96/264 (36.4)
OR				
Model 1	REF	**0.73 (0.59–0.91)**	0.81 (0.64–1.04)	0.98 (0.73–1.30)
Model 1 + SGA	REF	**0.75 (0.60–0.93)**	0.86 (0.67–1.11)	1.15 (0.81–1.62)
NEC				
N/Total (%)	213/2582 (8.25)	32/502 (6.37)	29/399 (7.27)	39/264 (14.8)
OR				
Model 1	REF	0.73 (0.50–1.09)	0.83 (0.55–1.27)	**2.31 (1.58–3.38)**
Model 1 + SGA	REF	0.73 (0.49–1.07)	0.81 (0.53–1.24)	**2.11 (1.32–3.39)**
EOS				
N/Total (%)	38/2580 (1.47)	4/502 (0.80)	7/399 (1.75)	5/264 (1.89)
OR				
Model 1	REF	0.53 (0.19–1.51)	1.23 (0.54–2.79)	1.53 (0.59–3.96)
Model 1 + SGA	REF	0.51 (0.18–1.46)	1.12 (0.47–2.65)	1.21 (0.39–3.79)
LOS				
N/Total (%)	634/2475 (25.6)	132/478 (27.6)	98/377 (26.0)	73/249 (29.3)
OR				
Model 1	REF	1.08 (0.86–1.37)	1.06 (0.81–1.38)	**1.72 (1.26–2.35)**

Model 1 + SGA	REF	1.05 (0.82–1.33)	0.96 (0.73–1.27)	1.29 (0.89–1.88)	
Severe ICH/PVL					
N/Total (%)	369/2328 (15.9)	62/451 (13.7)	59/368 (16.0)	42/248 (16.9)	
OR					
Model 1	REF	0.84 (0.62–1.15)	1.11 (0.80–1.53)	**1.73 (1.19–2.51)**	
Model 1 + SGA	REF	0.83 (0.61–1.13)	1.05 (0.75–1.46)	1.48 (0.94–2.33)	
Severe ROP					
N/Total (%)	127/1932 (6.57)	29/384 (7.55)	23/301 (7.64)	15/200 (7.50)	
OR					
Model 1	REF	1.22 (0.76–1.96)	1.49 (0.88–2.52)	**3.50 (1.86–6.58)**	
Model 1 + SGA	REF	1.16 (0.72–1.88)	1.35 (0.78–2.33)	**2.42 (1.09–5.39)**	
BPD					
N/Total (%)	683/2184 (31.3)	146/397 (36.8)	125/312 (40.1)	97/205 (47.3)	
OR					
Model 1	REF	**1.34 (1.03–1.74)**	**1.89 (1.41–2.53)**	**4.11 (2.91–5.80)**	
Model 1 + SGA	REF	1.27 (0.97–1.65)	**1.59 (1.18–2.14)**	**2.34 (1.55–3.55)**	
Larger Twin		**Birth Weight Discordance (%)**			
	≤14	**14–20**	**20–30**	**>30**	
	N=2803	***N=547***	***N=424***	***N=283***	
In-hospital death					
N/Total (%)	569/2794 (20.4)	118/546 (21.6)	77/423 (18.2)	35/282 (12.4)	
OR					
Model 1	REF	1.05 (0.79–1.41)	1.11 (0.80–1.57)	1.45 (0.92–2.27)	
Model 1 + SGA	REF	1.07 (0.80–1.43)	1.14 (0.81–1.61)	1.47 (0.93–2.32)	
PDA					
N/Total (%)	1099/2589 (42.4)	223/506 (44.1)	170/407 (41.8)	126/272 (46.3)	
OR					
Model 1	REF	1.03 (0.83–1.27)	1.01 (0.80–1.28)	**1.45 (1.10–1.91)**	
Model 1 + SGA	REF	1.03 (0.83–1.27)	1.01 (0.79–1.28)	**1.45 (1.10–1.92)**	
NEC					

N/Total (%)	228/2589 (8.81)	41/506 (8.10)	3¾06 (8.13)	14/271 (5.17)
OR				
Model 1	REF	0.87 (0.61–1.24)	0.89 (0.60–1.32)	0.62 (0.35–1.10)
Model 1 + SGA	REF	0.87 (0.61–1.24)	0.89 (0.60–1.32)	0.62 (0.34–1.10)
EOS[2]				
N/Total (%)	35/2589 (1.35)	8/506 (1.58)	¼06 (0.25)	1/271 (0.37)
OR				
Model 1	REF	1.20 (0.55–2.62)	0.19 (0.03–1.37)	0.36 (0.05–2.67)
Model 1 + SGA	REF	1.19 (0.54–2.60)	0.19 (0.03–1.37)	0.36 (0.05–2.65)
LOS				
N/Total (%)	634/2489 (25.5)	134/485 (27.6)	93/393 (23.7)	51/262 (19.5)
OR				
Model 1	REF	1.11 (0.88–1.41)	0.93 (0.71–1.22)	1.00 (0.71–1.41)
Model 1 + SGA	REF	1.11 (0.88–1.41)	0.93 (0.71–1.22)	1.00 (0.71–1.41)
Severe ICH/PVL				
N/Total (%)	394/2344 (16.8)	78/467 (16.7)	75/367 (20.4)	30/254 (11.8)
OR				
Model 1	REF	0.99 (0.74–1.31)	1.34 (0.99–1.81)	0.95 (0.62–1.45)
Model 1 + SGA	REF	0.99 (0.74–1.31)	1.35 (0.99–1.83)	0.96 (0.63–1.47)
Severe ROP				
N/Total (%)	109/1929 (5.65)	26/383 (6.79)	18/311 (5.79)	8/219 (3.65)
OR				
Model 1	REF	1.16 (0.70–1.87)	1.03 (0.58–1.83)	1.11 (0.50–2.46)
Model 1 + SGA	REF	1.15 (0.70–1.88)	1.03 (0.58–1.83)	1.11 (0.50–2.46)
BPD				
N/Total (%)	666/2192 (30.4)	147/417 (35.3)	109/343 (31.8)	69/244 (28.3)
OR				
Model 1	REF	1.19 (0.91–1.54)	1.16 (0.86–1.55)	1.31 (0.94–1.87)
Model 1 + SGA	REF	1.17 (0.90–1.53)	1.15 (0.86–1.54)	1.34 (0.94–1.90)

Abbreviations: BPD, bronchopulmonary dysplasia; EOS, early-onset sepsis; ICH, intracranial hemorrhage; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SGA, small for gestational age.

Model 1 adjusted for birth year, study center, maternal ethnicity/race, antenatal steroids, gestational age, and sex.

Model 1 + SGA adjusted for the variables in model 1 and SGA; reference level is ≤14% birth weight discordant group.

Bolded figures indicate significance.

[1]The adjusted odds ratio (95% CI) were obtained using logistic regression models treating the center effect as random.

[2]Due to model convergence issues, center was not included in the model.

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TABLE 3.

Odds ratios (95% CI)[1] of smaller and larger twin outcomes by 18 to 22 months' corrected age for VLBW twins by birth weight discordance

Smaller Twin	**Birth Weight Discordance (%)**			
	≤14	**>14–20**	**>20–30**	**>30**
	N=1315	***N=293***	***N=268***	***N=183***
Death before follow-up				
N/Total (%)	556/1315 (42.3)	120/293 (41.0)	104/268 (38.8)	87/183 (47.5)
OR				
Model 1	REF	1.13 (0.83–1.56)	**1.73 (1.23–2.46)**	**6.67 (4.33–10.3)**
Model 1 + SGA	REF	1.05 (0.74–1.46)	1.33 (0.91–1.90)	**3.08 (1.88–5.09)**
NDI				
N/Total (%)	270/759 (35.6)	49/173 (28.3)	47/164 (28.7)	34/96 (35.4)
OR				
Model 1	REF	0.79 (0.53–1.17)	0.94 (0.63–1.42)	**2.11 (1.25–3.56)**
Model 1 + SGA	REF	0.74 (0.50–1.11)	0.81 (0.52–1.24)	1.34 (0.72–2.48)
NDI or Death				
N/Total (%)	826/1315 (62.8)	169/293 (57.7)	151/268 (56.3)	121/183 (66.1)
OR				
Model 1	REF	0.91 (0.67–1.23)	1.34 (0.97–1.85)	**4.68 (3.08–7.12)**
Model 1 + SGA	REF	0.84 (0.62–1.14)	1.04 (0.74–1.46)	**2.19 (1.34–3.57)**
MDI<70				
N/Total (%)	199/508 (39.2)	33/118 (28.0)	33/123 (26.8)	21/76 (27.6)
OR				
Model 1	REF	0.68 (0.42–1.09)	0.76 (0.47–1.22)	1.27 (0.68–2.35)
Model 1 + SGA	REF	0.65 (0.40–1.06)	0.68 (0.42–1.13)	0.96 (0.47–1.97)
PDI<70				
N/Total (%)	130/504 (25.8)	22/118 (18.6)	22/122 (18.0)	13/74 (17.6)
OR				
Model 1	REF	0.73 (0.43–1.25)	0.84 (0.49–1.45)	1.42 (0.70–2.89)

Model 1 + SGA	REF	0.67 (0.39–1.16)	0.69 (0.39–1.22)	0.84 (0.37–1.92)
Moderate to severe cerebral palsy[2]				
N/Total (%)	63/759 (8.30)	8/170 (4.71)	9/164 (5.49)	5/96 (5.21)
OR				
Model 1	REF	0.68 (0.31–1.48)	0.94 (0.45–2.00)	1.50 (0.55–4.09)
Model 1 + SGA	REF	0.66 (0.30–1.44)	0.85 (0.39–1.87)	1.11 (0.33–3.75)
Blindness[2]				
N/Total (%)	7/759 (0.92)	2/172 (1.16)	1/164 (0.61)	2/96 (2.08)
OR				
Model 1	REF	1.49 (0.29–7.77)	1.32 (0.14–12.1)	**12.7 (1.84–87.6)**
Model 1 + SGA	REF	1.31 (0.24–7.15)	0.83 (0.07–9.79)	3.60 (0.21–61.3)
Deafness[2]				
N/Total (%)	20/757 (2.64)	2/171 (1.17)	3/164 (1.83)	3/96 (3.13)
OR				
Model 1	REF	0.52 (0.12–2.29)	1.05 (0.30–3.69)	2.81 (0.72–11.00)
Model 1 + SGA	REF	0.44 (0.10–1.98)	0.69 (0.17–2.77)	0.97 (0.17–5.69)
Cognitive composite score <70[2]				
N/Total (%)	24/243 (9.88)	5/52 (9.62)	2/40 (5.00)	6/20 (30.0)
OR				
Model 1	REF	0.82 (0.26–2.58)	0.72 (0.16–3.34)	**9.16 (2.54–33.0)**
Model 1 + SGA	REF	0.71 (0.22–2.34)	0.45 (0.08–2.50)	3.22 (0.53–19.4)
Motor composite score <70[2]				
N/Total (%)	14/136 (10.3)	1/29 (3.45)	2/20 (10.0)	2/6 (33.3)
OR				
Model 1	REF	0.24 (0.03–1.94)	1.11 (0.21–5.76)	4.61 (0.64–33.0)
Model 1 + SGA	REF	0.24 (0.03–1.96)	1.13 (0.21–5.95)	*—4*
Z-score[3]				
Weight for age	−0.51 (1.07)	−0.65 (1.02)	**−0.82 (1.08)**	**−1.29 (1.16)**

Length for age	−0.97 (1.38)	−1.04 (1.09)	−1.17 (1.05)	−1.58 (1.41)	
Head circumference for age	−0.20 (1.32)	−0.12 (1.11)	−0.35 (1.32)	**−0.77 (1.31)**	
Larger Twin	**Birth Weight Discordance (%)**				
	≤14	**>14–20**	**>20–30**	**>30**	
	N=1225	***N=233***	***N=176***	***N=74***	
Death before follow-up					
N/Total (%)	538/1225 (43.9)	111/233 (47.6)	67/176 (38.1)	23/74 (31.1)	
OR					
Model 1	REF	1.09 (0.76–1.55)	0.89 (0.59–1.34)	0.94 (0.51–1.74)	
Model 1 + SGA	REF	1.11 (0.78–1.58)	0.90 (0.60–1.37)	0.97 (0.52–1.79)	
NDI					
N/Total (%)	241/687 (35.1)	41/122 (33.6)	29/109 (26.6)	18/51 (35.3)	
OR					
Model 1	REF	0.87 (0.54–1.39)	0.66 (0.40–1.11)	1.38 (0.70–2.72)	
Model 1 + SGA	REF	0.85 (0.53–1.37)	0.67 (0.40–1.12)	1.39 (0.70–2.76)	
NDI or Death					
N/Total (%)	779/1225 (63.6)	152/233 (65.2)	96/176 (54.5)	41/74 (55.4)	
OR					
Model 1	REF	0.97 (0.69–1.38)	0.73 (0.49–1.07)	1.15 (0.66–1.99)	
Model 1 + SGA	REF	0.96 (0.67–1.37)	0.71 (0.48–1.05)	1.20 (0.68–2.10)	
MDI<70					
N/Total (%)	176/436 (40.4)	26/68 (38.2)	22/67 (32.8)	9/28 (32.1)	
OR					
Model 1	REF	0.73 (0.41–1.30)	0.68 (0.38–1.22)	0.67 (0.27–1.61)	
Model 1 + SGA	REF	0.72 (0.40–1.29)	0.69 (0.39–1.24)	0.66 (0.27–1.61)	
PDI<70					
N/Total (%)	114/430 (26.5)	24/69 (34.8)	11/67 (16.4)	9/28 (32.1)	
OR					
Model 1	REF	1.43 (0.80–2.54)	0.53 (0.26–1.08)	1.39 (0.59–3.29)	
Model 1 + SGA	REF	1.38 (0.78–2.47)	0.55 (0.27–1.11)	1.39 (0.57–3.35)	

Moderate to severe cerebral palsy				
N/Total (%)	59/687(8.59)	18/121 (14.9)	6/108 (5.56)	11/51 (21.6)
OR				
Model 1	REF	**1.94 (1.07–3.51)**	0.69 (0.29–1.66)	**3.55 (1.67–7.58)**
Model 1 + SGA	REF	**1.90 (1.04–3.45)**	0.69 (0.29–1.68)	**3.56 (1.65–7.65)**
Blindness[2]				
N/Total (%)	4/685(0.58)	5/122 (4.10)	1/109 (0.92)	2/51 (3.92)
OR				
Model 1	REF	**6.96 (1.71–28.3)**	1.41 (0.14–13.78)	**14.3 (2.03–100.1)**
Model 1 + SGA	REF	**8.07 (1.89–34.4)**	1.59 (0.16–16.41)	**13.3 (1.79–100.1)**
Deafness[2]				
N/Total (%)	20/685 (2.92)	3/121 (2.48)	4/108 (3.70)	1/51 (1.96)
OR				
Model 1	REF	0.81 (0.23–2.78)	1.36 (0.45–4.12)	0.71 (0.09–5.53)
Model 1 + SGA	REF	0.81 (0.23–2.79)	1.35 (0.45–4.08)	0.71 (0.09–5.55)
Cognitive composite score <70[2]				
N/Total (%)	22/246 (8.94)	6/50 (12.0)	¾2 (7.14)	4/22 (18.2)
OR				
Model 1	REF	1.61 (0.58–4.46)	0.74 (0.16–3.53)	**4.90 (1.31–18.3)**
Model 1 + SGA	REF	1.59 (0.58–4.41)	0.76 (0.16–3.63)	**4.84 (1.30–18.1)**
Motor composite score <70[2]				
N/Total (%)	14/143 (9.79)	4/31 (12.9)	2/24 (8.33)	3/14 (21.4)
OR				
Model 1	REF	1.57 (0.42–5.93)	1.22 (0.20–7.38)	**6.66 (1.19–37.4)**
Model 1 + SGA	REF	1.55 (0.41–5.85)	1.21 (0.20–7.28)	**6.55 (1.17–36.7)**
Z-score[3]				
Weight for age	−0.41 (1.13)	−0.35 (1.12)	−0.53 (1.04)	−0.40 (1.19)
Length for age	−0.88 (1.33)	−0.83 (1.35)	−0.88 (1.15)	−0.88 (1.45)
Head circumference for age	−0.09 (1.38)	−0.13 (1.40)	−0.19 (1.42)	−0.21 (1.58)

Abbreviations: MDI, Bayley-II Mental Developmental Index; NDI, neurodevelopmental impairment; PDI, Bayley-II Psychomotor Developmental Index; SGA, small for gestational age.

Model 1 adjusted for birth year, study center, maternal ethnicity/race, antenatal steroids, gestational age, and sex.

Model 1 + SGA adjusted for variables in model 1 and SGA; reference level is ≤14% birth weight discordant group.

For all NDI or Death and NDI only models, a cohort effect was included in the model to indicate Bayley II vs Bayley III.

Bolded figures indicate significance.

[1]The adjusted odds ratio (95% CI) were obtained using logistic regression models treating the center effect as random.

[2]Due to model convergence issues, center was not included in the model.

[3]Z-scores determined based on WHO Child Health Standards.

[4]Not reported due to the small sample size n=6.