Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Early growth outcomes in very low birth weight infants with bronchopulmonary dysplasia or fetal growth restriction

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BACKGROUND: To assess the growth outcomes at 18 months corrected age in very low birth weight (VLBW) infants compared to standardized norms, and in VLBW infants with and without bronchopulmonary dysplasia (BPD) or fetal growth restriction (FGR).
METHODS: In all, 1149 VLBW infants completed anthropometrics at 18 months corrected age. To derive weight, height, and body mass index (BMI) percentiles and *z*-scores at 18 months, we used the SAS macro from the Centers for Disease Control and Prevention (CDC). *z*-scores for a child's sex and age are based on the World Health Organization's growth charts for children <24 months of age.
RESULTS: Female and male VLBW infants had higher body-mass-index (BMI)-for-age *z*-scores compared to normative data (0.82 and 1.77 respectively). No significant difference was found in BMI-for-age *z*-scores in BPD and non-BPD (1.76 vs. 2.3; $p = 0.4$), nor in FGR and non-FGR (1.24 vs. 2.16; $p = 0.2$).
CONCLUSIONS: At 18 months corrected age, VLBW infants, including those with BPD or FGR, had BMI-for-age *z*-scores higher than reference standards. No significant difference was seen comparing BMI-for-age *z*-scores in the BPD/non-BPD and FGR/non-FGR groups.

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INTRODUCTION

Very low birth weight (VLBW; ≤1500 g) infants are at risk for poor growth during infancy and throughout childhood.[1] Despite efforts to improve neonatal nutrition[2] and reduce the severity of neonatal illnesses,[3] the prevalence of postnatal growth failure (defined as weight <10% for postmenstrual age) at NICU discharge remains around 50%[4] and persistent low body weight (defined as 2 standard deviations below normal for corrected age) is in excess of 16% by 2 years of age among VLBW children.[5] Conversely, excessive "catch-up" growth throughout childhood into adolescence (defined as upward centile crossing[6]) could lead to obesity,[7] increasing the risk of cardiovascular,[8,9] metabolic,[10] and other adverse health outcomes.[11–13] Though many studies focus on weight as a long-term outcome measure, it is important to incorporate the impact of height as VLBWs are known to be shorter than their term counterparts.[14] Furthermore, many VLBWs are affected by significant neonatal morbidities, like bronchopulmonary dysplasia (BPD) or fetal growth restriction (FGR), that influence weight gain.[15,16]

BPD, which affects approximately 30% of VLBW infants, is associated with increased energy expenditure contributing to early growth failure and higher nutritional demands.[17] Thus, catch-up growth is an important component of care for infants with BPD, as well as for infants with low weight-for-age as a result of FGR. In population-based studies, catch-up growth after FGR is associated with decreased hospital admissions, lower mortality rate,[18] and improved cognition.[19] However, accelerated growth during the first 3 months of life may increase the risk of later metabolic dysregulation.[20] Additionally, though both BPD and FGR infants have weight outcomes lower than those infants without BPD or FGR, they also have height outcomes that are lower than their unaffected counterparts,[21,22] impacting BMI-for-age *z*-scores in these two populations. Evaluation of BMI is important, since BMI is more strongly associated with cardiovascular outcomes than weight or height alone.[23] By examining growth patterns specific to infants with BPD or FGR, the impact of these morbidities on early growth can be better understood.

The primary objectives of this study are (1) to describe the frequency of poor and excessive growth among VLBW infants in the first years of life and (2) to evaluate whether BPD or FGR influence growth outcomes. We hypothesized that: (1) VLBW infants, as compared to normative data, have delayed weight and length growth and (2) VLBW infants with BPD or FGR have greater delay in growth than VLBW infants without these conditions.

METHODS

Study participants

Inclusion criteria for the current analysis were: (1) birth in either of two level 3 neonatal intensive care units (NICU) in Winston-Salem, North Carolina, (2) date of birth between January 2002 and December 2011, (3) very low birth weight (birth weight less than 1500 g), and (4) survival to 18 months corrected age. Of 1792 infants who met the inclusion criteria, 1206 (67%) were seen for follow-up evaluations at 18 months corrected age and 1149 infants had complete anthropometric measurements documented

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Table 1. Maternal and infant characteristics of the VLBW cohort ($N = 1149$).

	Total $N = 1149$	BPD $N = 290$	Non-BPD $N = 854$	$p^{§}$	FGR $N = 255$	Non-FGR $N = 894$	$p^{§}$
Gestational age (weeks) Mean (SD)	27.4 (2.5)	25.6 (1.8)	28.0 (2.5)	<0.01	29.1 (3.1)	26.9 (2.1)	<0.01
Birth weight (g) Mean (SD)	943 (257)	758 (209)	1005 (241)	<0.01	878 (312)	961 (236)	<0.01
Female *n* (%)	573 (50%)	119 (41%)	454 (53%)	<0.01	141 (55%)	432 (48%)	0.05
Race *n* (%)							
Caucasian	607 (53%)	155 (26%)	448 (74%)	0.01	155 (25%)	452 (75%)	<0.01
African American	396 (35%)	86 (22%)	310 (78%)		83 (21%)	313 (79%)	
Other	131 (11%)	45 (35%)	85 (65%)		16 (12%)	115 (88%)	
Unknown	15 (1%)	4 (27%)	11 (73%)		1 (7%)	14 (93%)	
Maternal age (years) Mean (SD)	27.3 (6.2)	26.8 (6.0)	27.5 (6.3)	<0.01	27.1 (6.1)	27.4 (6.3)	<0.01
Marital status *n* (%)							
Married	539 (47%)	138 (26%)	398 (74%)	0.81	117 (22%)	422 (78%)	0.64
Not married	599 (52%)	150 (25%)	447 (75%)		137 (23%)	462 (77%)	
Unknown	11 (1%)	2 (18%)	9 (82%)		1 (9%)	10 (91%)	

[§]*p* values are derived from Student's two-sample *t* test for continuous variables and chi-square test for categorical variables.

in our follow-up clinic database and were therefore included in the analysis.

Measurements

During the follow-up visits, weight and height measurements were obtained by physicians, pediatric nurse practitioners, or a nurse with special expertise in neonatal follow-up. Weights were obtained using a calibrated scale with the infant undressed; lengths were obtained supine with the infant's head held in place against the head board by the parent or an assistant, the legs fully extended at the knee, and the ankle in a neutral position against the recumbent length board.

Clinical data

Data were collected prospectively in an electronic clinical database and retrieved for the current analysis. Clinically significant BPD was defined as supplemental oxygen requirement at 36 weeks corrected age in those infants <32 weeks at birth.[24] FGR was defined as birth weight <10% for gestational age based on Fenton growth curves.[25]

Statistical analyses

Fenton growth charts for anthropometric parameters at birth were used to calculate fetal growth restriction for gestational age and sex.[25] To derive weight, height, and body mass index (BMI) percentiles and *z*-scores at 18 months corrected age, we used the SAS macro from the Centers for Disease Control and Prevention.[26] *z*-scores for a child's sex and age are based on the World Health Organization's growth charts for children <24 months of age.

For group comparisons, chi-square tests for categorical variables and Student's two-sample *t* test for continuous variables were used. Linear mixed model regression was used to evaluate the associations between BPD and growth outcomes, adjusting for fetal growth restriction, gestational age, twin status, maternal age, child sex, and race. This model was also used to evaluate the associations between FGR and growth outcomes, adjusting for BPD, gestational age, twin status, maternal age, child sex, and race. Additionally, logistic regression was used for group comparisons for *z*-score >2 at 18 months corrected age. SAS version 9.4 (SAS Institute, Inc, Cary, NC) was used to perform the statistical analyses.

Table 2. Average anthropometric *z*-scores at 18 months corrected age for VLBW infants by gender.

	Females ($N = 573$)	Males ($N = 576$)
Weight *z*-score mean (SD)	−0.30 (1.15)	−0.39 (1.22)
Length *z*-score mean (SD)	−0.81 (2.54)	−1.27 (3.52)
BMI *z*-score mean (SD)	0.82 (6.05)	1.77 (9.48)

RESULTS

Demographic data are presented in Table 1. The mean (±SD) gestational age (GA) for the total cohort was 27.4 (±2.5) weeks and mean birth weight was 943 (±257) g. Fifty percent were female. On average, infants with BPD had lower GA and birth weight, were more likely to be male, and had younger mothers. Infants with FGR, on average, had lower birth weight and higher GA, were more likely to be female, and had younger mothers.

As shown in Table 2, females and males had similar means for weight-for-age *z*-score at 18 months corrected age; however, males had lower mean length-for-age *z*-score and higher mean BMI-for-age *z*-score as compared to females at 18 months corrected age.

Table 3 provides a comparison of anthropometric data by BPD and FGR. Weight was lower in BPD infants at 18 months corrected age with an average weight-for-age *z*-score of −0.73 as compared to an average weight-for-age *z*-score of −0.45 in those VLBW infants without BPD ($p = 0.19$). BMI-for-age *z*-scores were not different among infants with and without BPD (1.76 vs. 2.3; $p = 0.4$) nor did the groups differ in the proportion with weight-for-age and BMI-for-age *z*-scores >2.

Comparing infants with and without fetal growth restriction, weight-for-age *z*-score at 18 months corrected age was lower among those with FGR (−1.36 vs. −0.48; $p < 0.01$) as was average height-for-age *z*-score (−2.37 vs. −1.63; $p < 0.01$). However, BMI-for-age *z*-scores were not significantly different between the two groups (1.24 vs. 2.16; $p = 0.2$). No FGR infants had weight-for-age *z*-score >2, whereas 3.5% of non-FGR infants had weight-for-age *z*-score >2. No differences were found between the two groups in the proportion with BMI-for-age *z*-score >2.

Table 3. Results for BPD and FGR predicting adjusted mean weight, height and BMI-for-age *z*-scores at 18 months corrected age.

	BPD	Non-BPD	Diff between means	$p^{\S}$	FGR	Non-FGR	Diff between means	$p^{£}$
N	290	854			255	894		
Weight								
kg (CL)[a]	9.98 (9.43, 10.54)	10.26 (9.71, 10.81)	0.28 (0.08, 0.49)	0.34	9.18 (8.63, 9.72)	10.25 (9.74, 10.77)	1.08 (0.88, 1.28)	<0.01
z-score (CL)[a]	−0.73 (−1.17, −0.28)	−0.45 (−0.90, −0.01)	0.28 (0.10, 0.44)	0.19	−1.36 (−1.80, −0.91)	−0.48 (−0.90, −0.06)	0.87 (0.71, 1.04)	<0.01
z-score > 2, *n* (%)	6 (2%)	24 (3%)	–	0.49	0 (0%)	30 (3.5%)	–	<0.01
Height								
cm (CL)[a]	77.16 (73.96, 80.36)	77.59 (74.42, 80.76)	0.43 (−0.75, 1.60)	0.91	75.34 (72.05, 78.63)	77.65 (74.54, 80.76)	2.31 (1.11, 3.50)	<0.01
z-score (CL)[a]	−1.83 (−2.98, −0.69)	−1.62 (−2.75, −0.48)	0.21 (−0.21, 0.64)	0.91	−2.37 (−3.55, −1.12)	−1.63 (−2.75, −0.52)	0.73 (0.30, 1.17)	<0.01
z-score>2, *n* (%)	2 (0.7%)	25 (3%)	–	0.03	1 (0.4%)	26 (3%)	–	0.02
BMI								
BMI (CL)[a]	19.14 (13.96, 24.31)	20.13 (14.99, 25.26)	0.99 (−0.90, 2.90)	0.45	18.54 (13.19, 23.89)	19.83 (14.77, 24.90)	1.30 (−0.65, 3.24)	0.26
z-score (CL)[a]	1.76 (−1.20, 4.72)	2.3 (−0.63, 5.24)	0.54 (−0.57, 1.66)	0.40	1.24 (−1.82, 4.30)	2.16 (−0.73, 5.05)	0.92 (−0.21, 2.05)	0.20
z-score > 2, *n* (%)	20 (7%)	59 (7%)	–	0.99	13 (5%)	66 (8%)	–	0.20

[§]*p* values are derived from linear mixed model regression analyses adjusting for fetal growth restriction, gestational age, twin status, maternal age, infant sex, and infant race.
[£]*p* values are derived from linear mixed model regression analyses adjusting for BPD, gestational age, twin status, maternal age, infant sex, and infant race.
[a]95% confidence intervals are reported.

DISCUSSION

At 18 months corrected age, VLBW infants have weight and length-for-age *z*-scores lower than the reference standards and BMI-for-age *z*-scores higher than the reference standards. The relatively high BMI-for-age *z*-scores among VLBW infants are attributable in large part to heights that are lower than the reference standards. Weight-for-age *z*-scores were significantly lower among FGR children, as compared to non-FGR children, but weight-for-age *z*-scores were not significantly lower among BPD children, as compared to those without BPD. Group differences (BPD vs. non-BPD or FGR vs. non-FGR) were not found for BMI-for-age *z*-scores. This is one of the few studies of growth in the VLBW infants to characterize growth in subgroups of VLBW infants with BPD or FGR and one of the few studies to focus on BMI *z*-scores in early childhood.

The lower weight-for-age *z*-score at 18 months observed among infants with BPD may be attributed to several factors, including respiratory illnesses, which can worsen nutritional status,[27] and increased caloric expenditure with increased work of breathing. Studies by others suggest that chronic respiratory disease can impact early childhood growth in these infants.[21] Other factors that might contribute to decreased weight-for-age *z*-scores among VLBW infants include disordered feeding that affects many preterm infants, as well as factors associated with preterm birth, such as maternal age, race, and socioeconomic status (SES).[28,29] SES and race are known correlates of growth in full-term children.[30]

Studies in other cohorts suggest that despite advances in nutrition over the past quarter century that have led to more rapid catch-up growth among individuals born VLBW,[31,32] VLBW infants remain shorter than their term counterparts at all ages from early infancy, throughout childhood and even into adulthood.[33–35] However, during adolescence and adulthood, premature infants are at risk for becoming overweight or obese and consequently developing cardiovascular and metabolic derangements.[36–38] One longitudinal population-based study of extremely low gestational age infants showed a decline in weight-for-age *z*-scores through age 3 years, and then a significant catch-up from age 3 years through adolescence with BMI-for-age *z*-scores also increasing from age 3 years through adulthood.[20] In another study, by 14 years of age, extremely low birth weight infants had similar rates of obesity as their term normal birth weight controls.[7] Additionally, a cohort of FGR children continued to gain excess abdominal fat from 2 to 4 years of age after completion of catch-up weight gain.[39]

The potential clinical implication of our finding that VLBW infants have lower than normal length-for-age *z*-scores at 18 months is that BMI may be an early indicator in predicting long-term growth and subsequent cardiometabolic outcomes. Though catch-up growth is associated with positive short- and long-term benefits, potential long-term adverse health outcomes must also be considered.[40] Our data suggest that high BMI-for-age *z*-score can manifest as early as 18 months corrected age, not only in the VLBW cohort as a whole but additionally in the subset of infants with BPD and FGR.

Despite its large size, the study sample was derived from a two-NICU single-center study, potentially limiting generalizability. Follow-up ended at 18 months adjusted age, and measurements of growth derived later in childhood would further enhance knowledge regarding growth trajectories in VLBW infants, both with and without BPD and/or FGR. Another limitation is the unavailability of the nutritional information such as proportions of breastmilk and formula feedings, caloric density of feeds, and oral feedings vs. gastrostomy feedings, which may further characterize differences in growth. Strengths of this study include its relatively large sample of VLBW infants and consideration of two neonatal factors (BPD and FGR) that appear to influence growth outcomes.

Although VLBW infants have weight and height-for-age *z*-scores behind term reference standards at 18 months corrected age, BMI-for-age *z*-scores are above zero in both male and female VLBW infants, including those with BPD and FGR, perhaps indicating early signs of accelerated weight gain with lagging linear growth. With shorter stature in premature infants than term counterparts as they age, BMI-for-age *z*-scores may be an early predictor of long-term unhealthy weight gain in VLBW infants.

AUTHOR CONTRIBUTIONS

J.C. made substantial contributions to this manuscript, including the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the initial manuscript and revising it, and has given final approval of the version to be published. E.J. made substantial contributions to the analysis and interpretation of data, reviewed and edited the manuscript, and has given final approval of the version to be published. J.S. made substantial contributions to the design of the study, analysis and interpretation of data, reviewed and edited the manuscript, and has given final approval of the version to be published. W.T.A. made substantial contributions to the design of the study, formal analysis and interpretation of data, reviewed and edited the manuscript, and has given final approval of the version to be published. T.M.O. made substantial contributions to the design of the study,

acquisition of data, analysis and interpretation of the data, reviewed and edited the manuscript, and has given final approval of the version to be published.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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