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Contemporary definitions of infant growth failure and neurodevelopmental and behavioral outcomes in extremely premature infants at two years of age

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BACKGROUND: Associations of 2-year neurodevelopmental and behavioral outcomes with growth trajectories of preterm infants are unknown.

METHODS: This secondary analysis of a preterm cohort examined in-hospital and discharge to 2-year changes in anthropometric z-scores. Two-year follow-up included Bayley Scales of Infant Development (BSID-III) and Child Behavior Checklist.

RESULTS: Among 590 infants, adjusted in-hospital growth was not associated with any BSID-III subscale. Occipitofrontal

circumference (OFC) growth failure (GF) in-hospital was associated with increased adjusted odds of attention problems (aOR 1.65 [1.03, 2.65]), aggressive behavior (aOR 2.34 [1.12, 4.89]), and attention-deficit-hyperactivity symptoms (aOR 1.86 [1.05, 3.30]). Infants with OFC GF at 2 years had lower adjusted BSID-III language scores (-4.0 [-8.0, -0.1]), increased odds of attention problems (aOR 2.29 [1.11, 4.74]), aggressive behavior (aOR 3.09 [1.00, 9.56]), and externalizing problems (aOR 3.01 [1.07, 8.45]) compared to normal OFC growth cohort.

CONCLUSION: Infants with OFC GF are at risk for neurodevelopmental and behavioral impairment.

CLINICAL TRIAL REGISTRATION: This study is a secondary analysis of pre-existing data from the PENUT Trial Registration: NCT01378273.

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INTRODUCTION

Providing adequate nutrition to the premature infant for the first two years is essential for neurodevelopment, the gut microbiome, bone health, and metabolism [1–4]. The most common markers of adequate nutritional status are serial measurements of anthropometrics (weight, length, and occipitofrontal circumference (OFC)). However, the definition of inadequate growth, or "growth failure," (GF) during neonatal intensive care unit (NICU) admission is varied [5]. Furthermore, there is limited information on what constitutes optimal growth after NICU discharge.

Extremely preterm infants are at substantial risk for both GF and neurodevelopmental impairment. Early studies examining GF in extremely low birth weight (ELBW) infants defined GF based on changes in growth velocity and small for gestational age status at 36 weeks postmenstrual age (PMA) [6–8]. Greater weight gain was associated with improved Bayley Scales of Infant Development (BSID)-II mental and psychomotor subscales at 18 months [6, 8] and at 22 months [6]. Similar findings were found for OFC growth [6, 8]. However, increased weight gain or "catch-up growth" in infancy has also been associated with lower lean body mass, increased total body fat in adolescence, and increased risk for metabolic diseases later in life [9, 10]. Studies utilizing growth velocity and small for gestational age status at 36 weeks are difficult to interpret because they are not standardized and did not account for the infant's initial growth percentiles [11].

To address this concern, many groups now consider changes in weight, length, or OFC z-score as a better measure for adequate growth [2, 12–17]. Studies of the relationship between changes in z-score during the initial hospitalization of ELBWs and neurode-velopmental outcomes show mixed results [8, 16, 17], and there has been minimal research evaluating the association of z-score changes after discharge with neurodevelopment [18].

The objective of this study was to examine changes in weight, length, and OFC z-scores from birth to discharge and from discharge to 2 years corrected age and their potential associations with neurodevelopmental and behavioral outcomes. We hypothesized that poor linear growth would be associated with adverse neurodevelopmental and behavioral outcomes at 2 years of age.

METHODS

Patient population

This is a secondary analysis of the Preterm Erythropoietin Neuroprotection (PENUT) Trial (NCT #01378273) [19]. PENUT was a randomized, doubleblinded, placebo-controlled trial of erythropoietin for neuroprotection in infants born 24 through 27 completed weeks of gestation. The study was

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conducted at 19 sites and 30 NICUs in the United States between December 2013 and September 2016 [19]. Infants with known chromosomal differences or congenital anomalies known to affect neurodevelopmental outcomes were excluded from enrollment. All infants enrolled in the PENUT Trial who survived and were assessed for long-term developmental outcomes were eligible for this analysis except those requiring invasive mechanical ventilation at discharge (N = 17), and those with hydrocephalus/ventriculomegaly on cranial ultrasound at 36 weeks postmenstrual age (PMA) (N = 39) as these entities are known to affect growth and OFC parameters. The PENUT Trial was approved by an institutional review board at each site. Informed parental consent was obtained before infant enrollment. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines.

We collected data about maternal characteristics, pregnancy, and delivery, as well as infant characteristics including anthropometric measurements, time to regain birth weight, exposure to medications, and comorbidities during their NICU stay [19]. Severe NEC was defined as Bell's stage 2b to 3. Severe ICH was defined as grade III or IV either unilateral or bilateral, according to Papile staging. Bronchopulmonary dysplasia (BPD) was defined as requiring nasal cannula or higher levels of respiratory support at 36 weeks PMA. Severe sepsis was defined as cultureproven bacterial or fungal sepsis resulting in blood-pressure support or substantive new respiratory support. Feeding status at discharge was defined as the method the infant was being fed (orally, gavage, or parenteral nutrition dependent). At 20 to 33 months CA, infants were evaluated by certified examiners who assessed cognitive, motor, and language development with BSID-III. All BSID-III subscales were based on the corrected age at the time of the assessment. Child Behavior Checklist (CBCL) for ages 1-5 years was administered, and T scores for emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behavior problems, depressive problems, anxiety problems, autism spectrum problems, attention deficit/ hyperactivity problems, oppositional defiant problems, and total problem score were collected. Infants were also screened by the Modified Checklist for Autism in Toddlers (M-CHAT-R), and the total score was collected.

Growth parameters analyzed

Weight, length, and OFC measurements were collected at birth, 14 days, discharge, and 2 years corrected age. Body mass index (BMI) was calculated at 2 years corrected age. Fenton growth curves were utilized to calculate weight, length, and OFC z-scores for growth parameters during the NICU hospitalization [20]. Weight, length, OFC, and BMI z-scores were calculated using Centers for Disease Control and Prevention growth curves at 2 years corrected age [21]. Weight, length, and OFC GF during hospitalization were defined as: z-score discharge – z-score birth \leq -0.8, as defined by the Academy of Nutrition and Dietetics [14]. Weight, length, or OFC accelerated growth during hospitalization was defined as: z-score discharge – z-score birth ≥0.8 for weight or length. Normal growth during hospitalization was defined as a z-score change of -0.799 to 0.799. Weight, length, or OFC GF from discharge to follow-up were defined as: z-score 2 years – z-score discharge \leq –0.8. Weight or length accelerated growth from discharge to follow-up was defined as: z-score 2 years – z-score discharge ≥0.8. Normal growth from discharge to follow-up was defined as a z-score change of -0.799 to 0.799. If z-score changes were >3 or <-3, they were truncated to 3 or -3 to avoid bias in likely input errors. 53 (9%) infants had one or more z-score change truncated between birth and discharge, and 80 (13.6%) infants had one or more z-score change truncated between discharge and follow-up.

Statistical analyses

Because this study was a post-hoc analysis of a randomized control trial, it was not powered. Summary demographic variables are presented as mean and standard deviation (SD) except for days to regain birthweight which is presented as median with interquartile range (IQR). Outcome data (BSID-III, CBCL, and M-CHAT-R) were assumed to have an underlying normal (BSID-III, M-CHT) or binomial (CBCL) distribution given sample size. Z-score calculations were completed using the peditools library in R, and the cohorts were divided into GF, normal growth, and accelerated growth for weight, length, and OFC. The associations between change in z-scores from birth to discharge and BSID-III scores were visually compared using locally estimated scatter plot smoothing (IDES) plot. For all inferential analyses, generalized estimating equations (GEE) with robust standard

errors were used to appropriately account for potential correlation of outcomes for same-birth siblings [22]. Baseline and demographic factors were compared across growth trajectory groups using a multivariate Wald test.

GEE linear regression models adjusted for gestational age, sex, maternal education, >14 days of dexamethasone, length z-score at birth, pregnancy induced hypertension, grade III or IV intracranial hemorrhage (severe ICH), BPD, erythropoietin use, and feeding status at discharge were used to compare growth categories to neurodevelopmental and behavioral scores (BSID-III and M-CHAT-R). GEE logistic regression models were used to determine adjusted odds ratios (aOR) for having a borderline/clinical score in CBCL sub-parameters based on post-discharge growth trajectory, adjusting for gestational age, sex, maternal education, >14 days of dexamethasone, length z-score at birth, pregnancy induced hypertension, severe ICH, BPD, erythropoietin use, and feeding status at discharge. Maternal race was adjusted for in both GEE linear and logistic regression models examining growth categories from discharge to 2 years. Model outputs are presented as adjusted mean difference or aOR with 95% confidence intervals (CI). All analyses were conducted using R statistical package (Version 4.1.2, Foundation for Statistical Computing, Vienna, Austria). A p < 0.05 was considered statistically significant.

RESULTS

Growth from birth to NICU discharge

Of the original 941 infants enrolled in the trial, 692 survived and had at least one BSID-III subscale score assessed at 2-year followup. After excluding infants who had mechanical ventilation at discharge (n = 17), ventriculomegaly (n = 39), and missing followup body measurement data (n = 46), n = 590 infants met the criteria for this secondary analysis. Maternal and child characteristics for infants with length growth cohorts are shown in Table 1, weight growth cohorts in Supplementary Table 1, and OFC growth cohorts in Table 2. Growth velocities and common co-morbidities of prematurity including necrotizing enterocolitis, severe ICH, BPD, symptomatic culture-positive sepsis, and length of stay are included. BMI z-score at 2 years did not differ between those with weight or length accelerated, normal growth, or GF during their initial hospitalization. Birth to discharge weight z-score change was positively associated with length z-score change $(r^2 = 0.16, p < 0.001, Supplementary Fig. 1A)$ and OFC z-score change ($r^2 = 0.21$, p < 0.001, Supplementary Fig. 1C). Birth to discharge OFC z-score change was positively associated with length z-score change ($r^2 = 0.09$, p < 0.001, Supplementary Fig. 1B).

After adjustments for comorbidities, changes in length, weight, and OFC z-score were not associated with BSID-III cognitive, motor, or language scores, either when dichotomized by GF/ accelerated growth or as continuous variables (Fig. 1A–I).

When examining behavioral characteristics at 2 years, infants with accelerated linear growth had a significantly lower adjusted total M-CHAT-R score compared to those with normal linear growth (-0.82 [-1.27, -0.37], p = 0.0004). Weight and OFC growth were not associated with total M-CHAT-R score, though there was a trend towards a lower MCHAT-R score in infants with accelerated OFC growth compared to normal OFC growth (-0.481 [-0.97, 0.01], p = 0.054). Compared to infants with normal OFC growth, infants who experienced OFC GF had increased adjusted odds of borderline or clinical CBCL scores for attention problems (aOR 1.65 [1.03, 2.65]; p = 0.038), aggressive behavior (aOR 2.34 [1.12, 4.89]; p = 0.024), and attention-deficit-hyperactivity symptoms (aOR 1.86 [1.05, 3.30]; p = 0.032) (Fig. 2). There were no significant differences in CBCL by weight or length growth cohorts.

Growth from discharge to 2 years

Cohort characteristics are described for weight in Table 2, length in Supplementary Table 2, and OFC in Supplementary Table 3. Discharge to 2-year weight z-score change was positively associated with length z-score change ($r^2 = 0.21$, p < 0.001,

	Length GF, n (%)	Normal Length Growth, n (%)	Accelerated Length Growth, n (%)	<i>p</i> -value
Included infants ($n = 590$)	353	208	29	-
Maternal Characteristics				
Maternal age, years	28.6 (6.1)	29.8 (6.3)	30.7 (5.7)	0.071
Maternal education				
High School or less	123 (34.8)	53 (25.5)	7 (24.1)	0.06
Some College	98 (27.8)	74 (35.6)	10 (34.5)	
Bachelor's or greater	83 (23.5)	63 (30.3)	9 (31.0)	
Not reported	49 (13.9)	18 (8.7)	3 (10.3)	-
Maternal race				
White	232 (65.7)	143 (68.8)	22 (75.9)	0.80
Black	84 (23.8)	44 (21.2)	4 (13.8)	
Other	24 (6.8)	16 (7.7)	2 (6.9)	
Not reported	13 (3.7)	5 (2.4)	1 (3.4)	-
Hispanic maternal ethnicity	72 (20.4)	52 (25.0)	9 (31.0)	0.30
Pregnancy induced hypertension	31 (8.8)	16 (7.7)	1 (3.4)	0.54
Infant Characteristics				
Small for gestational age	48 (13.6)	27 (13.0)	3 (10.3)	0.91
Male sex	181 (51.3)	105 (50.5)	14 (48.3)	0.92
Gestational age, weeks	25.5. (1.1)	25.8 (1.1)	26.0 (1.0)	0.99
Birth weight z-score	-0.03 (0.85)	-0.12 (0.87)	-0.16 (0.97)	0.45
Birth length z-score	-0.20 (0.94)	-0.59 (0.92)	-1.48 (1.59)	<0.0001
Birth OFC z-score	-0.25 (0.85)	-0.25 (0.95)	-0.13 (2.65)	0.97
Time to regain birth weight, days	9.0 (4.5)	8.6 (4.5)	9.0 (3.3)	0.69
Discharge weight z-score	-1.04 (0.82)	-0.73 (0.81)	-0.40 (0.95)	<0.0001
Discharge length z-score	-2.08 (1.22)	-0.91 (0.99)	0.26 (1.32)	<0.0001
Discharge OFC z-score	-0.91 (1.24)	-0.60 (0.91)	-0.24 (0.91)	<0.0001
Severe necrotizing enterocolitis	16 (4.5)	7 (3.4)	0 (0.0)	1.0
Severe intracranial hemorrhage	27 (7.6)	11 (5.3)	4 (13.8)	0.14
Bronchopulmonary dysplasia	209 (59.2)	132 (63.5)	21 (72.4)	0.090
Severe sepsis	22 (6.2)	9 (4.3)	1 (3.4)	0.64
>14 days of dexamethasone	24 (6.8)	15 (7.2)	1 (3.4)	0.64
Length of stay, days	102 (32)	101 (30)	99 (20)	0.72
Weight growth velocity, g/day	21.1 (4.3)	22.8 (4.5)	25.9 (4.0)	<0.0001
Length growth velocity, cm/day	0.10 (0.03)	0.20 (0.02)	0.21 (0.04)	<0.0001
OFC growth velocity, cm/day	0.10 (0.02)	0.11 (0.02)	0.11 (0.04)	0.022

Table 1. Cohort subject characteristics during the timeframe of birth to hospital discharge.

GF and accelerated growth are defined as having length GF or accelerated length growth at discharge. Categorical variables are represented by n (%). Continuous variables are represented with mean (SD) except for time to regain birth weight which is median (IQR). *P*-values were calculated using a multivariate Wald test adjusting for treatment group except for maternal education and race, which were compared using a Chi-square test. *P*-values <0.05 are highlighted in bold.

Supplementary Fig. 1D) and OFC z-score change ($r^2 = 0.24$, p < 0.001, Supplementary Fig. 1F). Discharge to 2-year length z-score change was negatively associated with OFC z-score change ($r^2 = 0.11$, p < 0.001, Supplementary Fig. 1E).

After adjustments for comorbidities, OFC GF at follow-up was associated with significantly lower language scores (-4.0 [-8.0, -0.1], p = 0.046) but not cognitive scores (-3.0 [-6.8, 0.7], p = 0.11) or motor scores (-3.8 [-8.4, 0.9], p = 0.11). There were no differences in BSID-III cognitive, motor, and language scores with changes in length or weight z-score.

Infants with accelerated weight growth at 2 years had increased adjusted odds of borderline or clinical withdrawn behavior (aOR 2.07 [1.10, 3.88], p = 0.024) and a trend toward greater odds of total behavioral problems (aOR 1.82 [0.97, 3.39], p = 0.061) compared to those with normal weight growth (Fig. 3). Infants with OFC GF at 2 years had increased odds of attention problems

(aOR 2.29 [1.11, 4.74], p = 0.025), aggressive behavior (aOR 3.09 [1.00, 9.56], p = 0.049), and externalizing problems (aOR 3.01 [1.07, 8.45], p = 0.037), as well as a trend towards a greater odds of total problems (aOR 2.38 [0.96, 5.89], p = 0.10) compared to those with normal OFC growth (Fig. 3). Behavioral outcomes on the CBCL did not differ by linear growth cohorts. There were no significant differences in M-CHAT-R scores across any growth groups between discharge and 2-year follow-up.

DISCUSSION

This large, multi-center post-hoc study examined the association between growth parameter z-score changes to 2-year neurodevelopmental and behavioral outcomes among extremely premature infants. Utilizing contemporary definitions of GF currently endorsed by the Academy of Nutrition and Dietetics [14], we did

Table 2.	Cohort subject	characteristics during	the timeframe of birth	to hospital	discharge

	OFC GF, n (%)	Normal OFC Growth, n (%)	Accelerated OFC Growth, n (%)	<i>p</i> -value
Included Infants ($n = 590$)	208	335	47	-
Maternal Characteristics				
Maternal age, years	28.2 (6.4)	29.6 (6.1)	30.8 (5.3)	0.051
Maternal education				
High School or less	62 (29.8)	108 (32.2)	13 (27.7)	0.80
Some College	64 (30.8)	99 (29.6)	19 (40.4)	
Bachelor's or greater	52 (25.0)	91 (27.2)	12 (25.5)	
Not reported	30 (14.4)	37 (11.0)	3 (6.4)	-
Maternal race				
White	146 (70.2)	222 (66.3)	29 (61.7)	0.40
Black	45 (21.6)	77 (23.0)	10 (21.3)	
Other	14 (6.7)	22 (6.7)	6 (12.8)	
Not reported	3 (1.4)	14 (4.2)	2 (4.3)	-
Hispanic maternal ethnicity	51 (24.5)	72 (21.5)	10 (21.3)	0.56
Pregnancy induced hypertension	17 (8.2)	25 (7.5)	6 (12.8)	0.50
Infant Characteristics				
Small for gestational age	19 (9.1)	51 (15.2)	8 (17.0)	0.075
Male sex	105 (50.5)	173 (51.6)	22 (46.8)	0.80
Gestational age, weeks	25.3 (1.1)	25.8 (1.1)	26.1 (1.0)	0.96
Birth weight z-score	0.14 (0.83)	-0.15 (0.82)	-0.36 (1.09)	<0.0001
Birth length z-score	-0.26 (1.02)	-0.42 (0.94)	-0.75 (1.39)	0.037
Birth OFC z-score	0.19 (1.26)	-0.42 (0.72)	-0.90 (1.17)	<0.0001
Time to regain birth weight, days	9.6 (4.3)	8.4 (4.4)	8.2 (4.5)	0.005
Discharge weight z-score	-1.12 (0.74)	-0.83 (0.86)	-0.46 (0.86)	<0.0001
Discharge length z-score	-1.83 (1.30)	-1.38 (1.23)	-1.56 (1.97)	0.0008
Discharge OFC z-score	-1.43 (0.88)	-0.58 (0.76)	0.82 (2.00)	<0.0001
Severe necrotizing enterocolitis	15 (7.2)	7 (2.1)	1 (2.1)	0.034
Severe Intracranial Hemorrhage	19 (9.1)	19 (5.7)	4 (8.5)	0.47
Bronchopulmonary Dysplasia	129 (62.0)	204 (60.9)	29 (61.7)	0.64
Severe Sepsis	13 (6.3)	15 (4.5)	4 (8.5)	0.41
>14 days of dexamethasone	22 (10.6)	17 (5.1)	1 (2.1)	0.24
Length of stay, days	107 (27)	100 (34)	98 (22)	0.034
Weight Growth Velocity, g/day	20.2 (4.4)	22.6 (4.2)	24.9 (4.7)	<0.0001
Length Growth Velocity, cm/day	0.10 (0.04)	0.10 (0.03)	0.15 (0.05)	0.0001
OFC Growth Velocity, cm/day	0.09 (0.02)	0.10 (0.01)	0.14 (0.03)	<0.0001

GF and accelerated growth are defined as having occipitofrontal circumference (OFC) GF or accelerated OFC growth at discharge. Categorical variables are represented by n (%). Continuous variables are represented with mean (SD) except for time to regain birth weight which is median (IQR). *P*-values were calculated using a multivariate Wald test adjusting for treatment group except for maternal education and race, which were compared using a Chi-square test. *P*-values <0.05 are highlighted in bold.

not find significant differences in BSID-III scores based on growth parameters obtained during hospital stay. However, OFC GF during NICU hospital stay was associated with attention problems, aggressive behavior, and ADHD symptoms. Accelerated length growth during hospitalization was associated with improved M-CHAT-R score. OFC GF from discharge to 2-year follow-up was associated with modestly decreased language score, increased attention problems, increased aggressive behavior, and increased externalizing problems. Accelerated weight z-score gain was associated with increased withdrawn behavioral problems. These findings suggest infants with OFC growth faltering during and post-hospitalization are at risk for neurodevelopmental and behavioral problems.

Studies examining growth during the NICU hospitalization and subsequent neurodevelopment are heterogeneous and conflicting. Different metrics (velocities vs. changes in z-scores vs.

complex multivariate modeling of expected to observed), differing time points of evaluation (birth vs. nadir, 36 weeks PMA vs. discharge or post-discharge age), and different growth curves (Fenton vs. INTERGROWTH) have been used [2, 6-8, 12-17, 23-28]. In this study, we utilized changes in z-scores utilizing the GF definition applied by Goldberg et al. using the Fenton growth curve from birth to discharge [14, 20]. Brinkis et al. examining ELBW and very preterm infants utilizing these definitions did not find differences in neurodevelopmental outcomes on the BSID-II at 12 months [1]. In contrast, Rohsiswatmo et al. found a decline in weight z-score >1.2 to be associated with increased days to oral feeding [24], a known strong predictor of neurodevelopmental outcomes, and Yitayew et al. found a weight z-score change >1 to be associated with lower BSID-III scores [25]. Other studies identify poor linear growth as detrimental to cognitive and language outcomes [8, 15, 17, 26]. Yet another study found an association



Fig. 1 Z-score change from birth to hospital discharge for weight, length, and OFC and Bayley Scales of Infant Development (BSID-III) scores. Z-score change from birth to discharge for length (A–C), weight (D–F), and OFC (G–I) and Bayley Scales of Infant Development III (BSID-III) scores. The black line represents the local average determined using locally-estimates scatterplot smoothing (loess), and the shading represents the 95% confidence intervals.

between a small OFC at birth and discharge with lower intelligence and motor scores in very preterm infants [27]. These results call for a standardized approach for evaluating growth in the clinical and research arenas.

This study found OFC GF from discharge to 2 years corrected age was associated with lower BSID-III language scores. There is less known about growth following NICU discharge in extremely preterm infants, but studies have found OFC to be associated with neurodevelopment. Many studies examining premature infant OFC growth following NICU discharge to various time points found an association with increased OFC growth with improved mental processing composite score intelligence quotient at 8 years [26], reading scores, lower odds of executive dysfunction, and lower odds of poor motor function at 8 years [29]. Also, increased weight velocity following discharge decreased the odds of neurodevelopmental impairment in a non-linear fashion [30]. Furthermore, a study examining growth from discharge to 2 years found gains in weight/length z-score was associated with decreased odds of cognitive impairment at 10 years old [18]. These studies suggest that growth following NICU discharge should be closely monitored by the pediatrician and the optimal growth trajectory requires further refinement.

Clinicians provide anticipatory guidance to parents on the potential developmental trajectory of their preterm infant, but the

	n (%)	aOR by OFC Growth (95%CI)					
Attention Problems							
Growth Failure	46 (22%)	1.65 (1.03-2.65)			-		
Normal Growth	47 (14%)	Reference			+		
Accelerated Growth	7 (15%)	1.07 (0.41-2.77)		-			
Aggressive Behavior							
Growth Failure	19 (9%)	2.34 (1.12-4.89)			-		
Normal Growth	15 (4%)	Reference			÷.		
Accelerated Growth	2 (4%)	0.77 (0.15-3.99)			-		_
Attention Deficit Problems							
Growth Failure	26 (11%)	1.86 (1.05-3.30)			-		_
Normal Growth	28 (8%)	Reference			÷.		
Accelerated Growth	5 (11%)	0.86 (0.25-3.02)	_		-		-
			0.25	0.50	1.0	2.0	4.0

Fig. 2 Forest plots of adjusted odds of borderline/clinical Child Behavior Checklist problem scores by in-hospital occipitofrontal circumference (OFC) growth cohorts. Adjusted odds ratio (aOR) and 95% confidence intervals (CI) for borderline/clinical score compared to those with normal growth is shown.

	n (9/)	aOR by Weight Growth (95% CI)	
Withdrawn Robavior	(/0)	acit by meight Growth (35%Cl)	
Growth Eailure	4 (49/)	0 57 (0 22 1 40)	
Normal Growth	4 (470)	0.57 (0.22-1.49)	
Assoluted Crowth	23 (0 %)	2.07 (1.10.2.99)	Ī
Total Drablema	29 (10%)	2.07 (1.10-3.88)	
Total Problems	7 (00/)	0.00.00.05.4.05	
Growth Failure	7 (6%)	0.68 (0.25-1.85)	
Normal Growth	24 (9%)	Reference	
Accelerated Growth	28 (16%)	1.82 (0.97-3.39)	
	n (%)	aOR by OFC Growth (95%CI)	
Attention Problems			
Growth Failure	16 (28%)	2.29 (1.11-4.74)	
Normal Growth	49 (17%)	Reference	• ·
Accelerated Growth	32 (15%)	0.83 (0.50-1.38)	
Aggressive Behavior			
Growth Failure	7 (12%)	3.09 (1.00-9.56)	
Normal Growth	14 (5%)	Reference	+
Accelerated Growth	15 (7%)	1.38 (0.61-3.14)	
Externalizing Problems			
Growth Failure	8 (14%)	3.01 (1.07-8.45)	
Normal Growth	17 (6%)	Reference	+
Accelerated Growth	19 (9%)	1.52 (0.73-3.17)	
Total Problems			
Growth Failure	10 (17%)	2.38 (0.96-5.89)	
Normal Growth	26 (9%)	Reference	÷
Accelerated Growth	23 (11%)	1.31 (0.68-2.52)	
		, , , , , , , , , , , , , , , , , , , ,	
			0.25 0.50 1.0 2.0 4.0 8.0

Fig. 3 Forest plots of adjusted odds of borderline/clinical Child Behavior Checklist problem scores by discharge to 2-year followup occipitofrontal circumference (OFC) and weight growth cohorts. Adjusted odds ratio (aOR) and 95% confidence intervals (CI) for borderline/clinical score compared to those with normal growth is shown.

trajectory is complex and dependent on the post-discharge environment. Recent studies have guestioned if the BSID-III underestimates longer-term neurodevelopmental impairment rates [31, 32]. More accurate assessments of cognitive development, executive function, psychiatric symptoms, and social function are possible as children age. A meta-analysis showed positive predictive values of evaluations performed using either the BSID or Griffiths Mental Development Scales between 1 and 3 years ranged from 20% to 89%, and negative predictive values ranged from 48% to 95% when children were assessed after 5 vears of age [33]. One study examined children born at less than 32 weeks completed both a BSID-II and a BSID-III at 2 years followed by a Wechsler Preschool and Primary Scale of Intelligence Fourth Edition and found the BSID-II underestimated intelligence quotient where the BSID-III overestimated intelligence quotient [31]. A recent study published by the Neonatal Research Network assessed extremely preterm infants and healthy term reference infants' BSID-III scores, and found using a term reference-based threshold showed higher impairment in extremely preterm infants compared to BSID-III norm-based thresholds, suggesting this may be a preferred methodology [32]. Our study found no differences in continuous BSID-III scores with in-hospital growth but found differences in OFC growth cohorts after

Although there are multiple studies showing preterm infants are at risk for behavioral and psychiatric problems [34-36], our study is of few examining behavioral outcomes and growth trajectories during and after hospitalization. In our study, poor OFC growth during NICU hospital stay and from discharge to 2 years was associated with attention problems and aggression problems. We also found there were increased withdrawn behavioral problems with accelerated weight growth after discharge. Furthermore, we identified a small (<1 point) decrease in M-CHAT-R score with accelerated linear growth compared to those with normal linear growth during hospitalization. We also noted a trend of a small decreased M-CHAT-R score with accelerated OFC growth compared to normal OFC growth. While the original M-CHAT in ELBW infants has shown poor sensitivity and positive predictive value for autism [37], the M-CHAT-R has recently been shown to be associated with neurobehavioral and CBCL outcomes, suggesting the M-CHAT-R may have utility as a developmental screen [38].

One potential reason we did not appreciate substantial differences in neurodevelopmental outcomes in infants with weight GF during NICU hospitalization is due to the methodology of examining birth weight z-score rather than weight nadir z-score. The use of weight at birth versus nadir weight is currently controversial. Weight nadir z-score may better reflect expected physiologic weight loss [39]. A study examining weight gain velocity calculations recommended the utilization of the weight nadir or day seven weight rather than birth weight [40]. Day 7 was deemed not to be significantly different than the nadir and less laborious for clinicians and researchers [40]. Our study chose to use birth weight z-score as described in Goldberg et al. as this information is standardly available in the majority of NICUs and thus is more generalizable.

We anticipated that linear growth would affect neurodevelopment and behavioral outcomes due to differences in lean body mass (bone, muscle, water). Compared to weight and OFC, length is believed to be the anthropometric measure best associated with lean body mass/fat-free mass [41]. Increased fat-free mass has been associated with improved neurodevelopmental outcomes including full-scale IQ [42], improved vocabulary, cognitive flexibility, and general cognitive function at pre-school age [43] and larger brain size at term [44]. However, studies examining the relationship between length and body composition have had small sample sizes. In contrast, in this large study of preterm infants with prospectively collected data, we did not find significant differences in BSID-III scores between in-hospital and post-discharge length cohorts. We did find a modest improvement in the M-CHAT-R score in the accelerated linear growth cohort compared to those with normal linear growth. Further large, prospective studies exploring lean mass and developmental outcomes are required.

The strength of this secondary analysis is the utilization of a large, contemporary cohort of extremely premature infants across 30 NICUs in the United States [19]. This study included a battery of developmental tests, including not only the use of BSID-III scores, but also CBCL and MCHAT-R scores [19]. This allows for a more comprehensive developmental assessment. We also applied the use of anthropometric z-score assessments which are being adopted by many quality improvement networks in the United States; thus, our results are relevant to current clinical practice. Accounting for all of these factors, we believe these results are generalizable to other US-based NICUs.

This study also has limitations. Growth was not a primary aim of the PENUT Trial, and length measurements were performed per unit protocol. Thus, we cannot be sure all length measurements were obtained on a length board which is more accurate measures of an infant's length [45–47]. Furthermore, there was a lack of serial growth measurements during the hospital stay and post-discharge. Because of the multi-center nature of the PENUT Trial, sites followed their own nutrition protocols and we do not have information on dietary intake such as parental nutrition components, proportion of parent's own milk, donor milk, and formula during hospital stay or after discharge.

In conclusion, extremely preterm infant growth trajectories during hospitalization showed associations with behavioral outcomes, and growth trajectories after NICU hospitalization showed associations with neurodevelopmental and behavioral outcomes. Normal OFC growth appeared to be the most neuroprotective. These findings suggest that our current nutritional definitions of weight and length GF during NICU hospitalization may not be associated with neurodevelopmental outcomes. Furthermore, nutritional studies exploring how to improve OFC growth during NICU hospitalization are imperative to optimize neonatal nutrition in preterm infants. Importantly, further research is required to determine optimal growth trajectories after NICU hospitalization, which may be most important for neurodevelopmental outcomes.

DATA AVAILABILITY

De-identified individual participant data is available through the NINDSData Archive under "Clinical Research Datasets". The data is de-identified and a limited access data set is available through a request form on that page. Data dictionaries, in addition to study protocol, the statistical analysis plan, and the informed consent form will be included. The data will be made available upon publication of all PENUT Trial related manuscripts to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal.

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AUTHOR CONTRIBUTIONS

KMS conceptualized the design of the secondary analysis, interpreted the data, and composed the initial draft of the manuscript. TRW performed the statistical analysis. TRW, GCV, KG, DTH, JBL, SK, BAC, PJH, DEM, and SEJ were involved in the revisions of the manuscript, and all agreed to the final draft of the manuscript being submitted.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The PENUT Trial was approved by the institutional review board at each participating site and was registered with the Food and Drug Administration. Each participant participated with informed consent. The study was performed in accordance with Declaration of Helsinki.

ADDITIONAL INFORMATION

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