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Postnatal Growth of Preterm Infants 24 to 26 Weeks of Gestation and Cognitive Outcomes at 2 Years of Age

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Abstract

Background: Weight z scores at 36 weeks of postmenstrual age (PMA) define postnatal growth failure (PGF) and malnutrition. This study aimed to determine weight z scores at 36 weeks PMA that are associated with adverse cognitive outcomes at 2 years of age.

Methods: In this retrospective cohort study, 350 infants 24 to 26 weeks of gestation born between 2006 and 2014 and followed at 2 years were included. Weight z scores at birth and at 36 weeks PMA were calculated using the INTERGROWTH-21st growth curves. The primary outcome was cognitive delay at 2 years of age (Bayley-III cognitive score < 85).

Results: Neither the traditional definition of PGF (z score below -1.3) nor the recently proposed definition of malnutrition (z score decline of 1.2 or greater) was associated with cognitive delay. Both a weight z score below -1.0 at 36 weeks PMA (RR: 1.65; 95% CI: 1.10 - 2.49; p < 0.05) and a decline below -1.0 in weight z score from birth to 36 weeks PMA (RR: 1.40; 95% CI: 1.00 - 1.94; p < 0.05) were associated with a higher risk of cognitive delay.

Conclusion: With optimal cutoffs, INTERGROWTH-21st weight z scores can predict the risk of cognitive delay.

INTRODUCTION

Postnatal growth failure (PGF) defined as weight <10th percentile at 36 weeks of postmenstrual age (PMA) (1) affects up to 60% of extremely preterm infants (2–4). To prevent PGF, clinicians often prescribe diets that favor postnatal growth consistent with fetal

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Authors' contributions: Dr Salas conceptualized and designed the study, supervised data collection, performed the statistical analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Bhatia assisted with the study design, designed the data collection instruments, collected data, and reviewed and revised the manuscript. Prof. Carlo assisted with the study design and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Patient consent was not required to analyze the clinical data included in this retrospective cohort study

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Category of study: Clinical.

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growth (5) and assume that by reducing PGF, the risk of adverse neurodevelopmental outcomes is also being reduced. This assumption might explain the recent uptrend observed in the reporting of PGF (6), but it is not consistently supported by clinical evidence from observational studies (7).

The current operational definition of PGF suggests that weight at a single time point during the postnatal period (i.e., 36 weeks PMA) (8, 9) is more important than growth rate, length, and head growth to predict the risk of adverse neurodevelopment (7). Since the AAP and ESPGHAN consensus guidelines recommend comparable growth rates – not comparable weights – between extremely preterm infants and normal fetuses of the same PMA (10, 11), alternative approaches have been proposed to redefine optimal growth in this population (5, 9, 12–15).

Some experts recommend using z score values from the INTERGROWTH-21st growth curves (14) instead of those from the Fenton growth curves – the current international standard generated with cross-sectional data (9, 16) – because the INTERGROWTH-21st growth curves were generated with longitudinal data from mother-infant dyads who had reliable gestational ages and proper nutrition (14). Regardless of the type of growth curves used, other experts consider critical to calculate not only weight z scores at 36 weeks PMA (i.e., PGF) but also changes in weight z scores from birth to 36 weeks PMA (i.e., neonatal malnutrition) (12). These two alternative approaches have robust scientific frameworks, but they need validation in studies that correlate postnatal growth and adverse neurodevelopment, undeniably one of the most critical outcomes of neonatal care.

The purpose of this study was to evaluate the association between postnatal growth and cognitive scores. We hypothesized that, in extremely preterm infants, alternative definitions of postnatal growth alterations using weight-for-age z scores at birth and weight-for-age z scores at 36 weeks PMA of the INTERGROWTH-21st growth curves would predict cognitive delay at 2 years of age.

METHODS

In this retrospective cohort study, extremely preterm infants 24^{0/7} to 26^{6/7} weeks of gestation admitted to the neonatal intensive care unit at the University of Alabama at Birmingham (UAB) Hospital between 2006 and 2014 were included. Infants with major congenital anomalies or missing follow-up data were excluded. The study protocol was approved by the UAB Institutional Review Board.

With the INTERGROWTH-21st growth curves (14), the following current and alternative definitions of growth outcomes between birth and 36 weeks PMA were examined: (A) PGF defined as weight z score below -1.3 or 10th percentile at 36 weeks PMA (i.e., usual definition of PGF) (1); (B) Moderate to severe malnutrition defined as a decline or change in weight z score below -1.2 from birth to 36 weeks PMA (i.e., current definition of moderate to severe malnutrition) (12); (C) PGF defined as weight z score below -1.0 at 36 weeks PMA (i.e., alternative definition of PGF created with a classification tree method that dichotomized weight z score data at 36 weeks PMA based on the probability of cognitive

delay); (D) Moderate to severe malnutrition defined as a decline in weight z score below – 1.0 from birth and 36 weeks PMA (i.e., alternative definition of moderate to severe malnutrition created with a classification tree method that dichotomized weight z score data from birth to 36 weeks PMA based on the probability of cognitive delay). The usual definition of PGF has been previously validated, but it relies on weight at a single time point. The current definition of neonatal malnutrition has not yet been validated, but it could have a stronger association with cognitive outcomes because it relies on weight at two time points.

The primary outcome of the study was the cognitive composite score of the Bayley Scales of Infant and Toddler Development, Third Edition (CCS BSID-III) at 2 years of corrected age. This score was determined by trained and certified examiners. Cognitive delay was defined as a CCS BSID-III < 85, and severe cognitive delay was defined as a CCS BSID-III < 70. Secondary outcomes included growth rates from birth to 36 weeks PMA calculated with the exponential method(16, 17) and other critical anthropometric measurements at 36 weeks PMA.

Statistical analyses

Prior data indicated that the proportion of extremely preterm infants with a CCS BSID-III < 85 was approximately 35%(18). Assuming a hypothetical risk ratio (RR) for cognitive delay in exposed infants relative to unexposed infants of 1.5 (least extreme RR to be detected), we planned a study with a minimum of 94 exposed infants and at least 187 unexposed infants (1:2 ratio of exposed to unexposed infants) for a power of 80% and a 0.05 using a χ^2 test.

Baseline characteristics of the study population were summarized as means \pm SDs, medians and interquartile ranges (IQRs), and frequencies and proportions. The linear correlation of weight z scores from birth to 36 weeks PMA and weight-for-age z score at 36 weeks PMA with growth rate was measured with the Pearson correlation coefficient. The association between growth outcomes at 36 weeks PMA or hospital discharge (whichever occurred first) and cognitive outcomes at 2 years of age was analyzed with unadjusted and adjusted generalized linear models that included CCS BSID-III < 85 as the outcome variable. With these linear models assuming a Poisson distribution, risk ratios (RRs) and 95% confidence intervals (CIs) for the association between several definitions of PGF and the outcome of cognitive delay were estimated. Adjusted risk ratios (aRRs) were estimated with adjusted models that included gestational age, corrected age at follow-up assessment, and major in-hospital morbidities associated with adverse neurodevelopmental outcomes as covariates. The major in-hospital comorbidities included in the adjusted models were intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), meningitis, bronchopulmonary dysplasia (BPD) treated with postnatal steroids, and necrotizing enterocolitis (NEC) stage 2 or greater.

For comparison purposes, the diagnostic accuracy of the Fenton growth curves to predict cognitive outcomes was also assessed using a similar approach. All statistical analyses were performed using JMP Pro 14.0 (SAS Institute, Cary, NC).

RESULTS

Between 2006 and 2014, 558 extremely preterm infants with gestational ages between 24 and 26 weeks were admitted to the neonatal unit at the University of Alabama at Birmingham Hospital. Approximately 20% of them died during their hospitalization and 1% of them had congenital anomalies. Of 432 infants eligible for follow-up assessments, 350 returned for neurodevelopmental assessment at 2 years of age (81%). Baseline characteristics of these infants, including major in-hospital comorbidities, are summarized in Table 1.

Using the INTERGROWTH-21st growth curves, we documented that PGF (i.e., weight z score below -1.28 or weight $< 10^{\text{th}}$ percentile at 36 weeks PMA) occurred in 152 of 350 infants (43%). Cognitive delay (i.e., CCS BSID-III < 85) occurred in 101 of 350 infants (29%) and severe cognitive delay (i.e., CCS BSID-III < 70) occurred in 35 of 350 (10%).

The usual definition of PGF (i.e., weight z score below -1.28) was not associated with a higher risk of cognitive delay in unadjusted and adjusted analyses (Table 2). Similarly, the current definition of moderate to severe malnutrition based on declines in weight z scores from birth to 36 weeks PMA (i.e., change in weight z score below -1.2) was not associated with a higher risk of cognitive delay in unadjusted and adjusted analyses.

The alternative definition of PGF (i.e., weight z score below -1.0) and the alternative definition of moderate to severe malnutrition (i.e., change in weight z score below -1.0) were both associated with a higher risk of cognitive delay at 2 years in unadjusted analyses (Table 2). The association between the alternative definition of PGF and the diagnosis of cognitive delay was independent of gestational age at birth, age at follow-up assessment, and five in-hospital morbidities associated with adverse neurodevelopmental outcomes (IVH grade 3 or 4, PVL, meningitis, BPD, and NEC stage 2 or greater). Both the alternative PGF definition and the alternative malnutrition definition were associated with lower cognitive scores, slower growth rates, and more significant negative differences in length and head circumferences between measurements at birth and measurements at 36 weeks PMA (Table 3). Most infants with PGF or moderate to severe malnutrition had growth rates from birth to 36 weeks PMA below 13 g/kg/day. The linear correlation between slower growth rates and higher declines in weight z scores between birth and 36 weeks PMA was stronger ($r=0.94$; $p < 0.05$) than the linear correlation between slow growth rates and weight-for-age z score at 36 weeks PMA ($r=0.61$; $p < 0.05$) (Figure 1).

Using the Fenton growth curves, we documented that PGF (i.e., weight z score below -1.28 or weight $< 10^{\text{th}}$ percentile at 36 weeks PMA) occurred in 235 of 350 infants (67%). Unlike the usual definition of PGF (i.e., weight z score below -1.28), the alternative definition of PGF using the Fenton growth curves (i.e., weight z score below -1.87) was associated with a higher risk of cognitive delay in an unadjusted analysis. The current and alternative definitions of moderate to severe malnutrition based on declines in weight z scores from birth to 36 weeks PMA using the Fenton growth curves were not associated with a higher risk of cognitive delay in unadjusted and adjusted analyses (Supplementary Material).

DISCUSSION

In this cohort study, we identified growth outcomes of extremely preterm infants 24 to 26 weeks of gestation associated with a higher risk of adverse cognitive outcomes at 2 years of age. Using the INTERGROWTH-21st growth curves, we determined that neither the usual definition of PGF nor the recently proposed definition of malnutrition was associated with lower cognitive scores at 2 years of age. We established that PGF defined as a weight-for-age z score of -1.0 or lower at 36 weeks PMA and moderate to severe malnutrition defined as a decline or change in weight-for-age z score of 1.0 or higher from birth to 36 weeks were both associated with a higher risk of cognitive delay (i.e., CCS BSID-III < 85). The association between the alternative definition of PGF and cognitive delay was independent of in-hospital comorbidities. Both alternative definitions were significantly associated with lower cognitive scores, slower growth rates, and more substantial declines in length and head circumference z scores from birth to 36 weeks PMA.

This is one of the first observational studies that uses the INTERGROWTH-21st growth curves to evaluate the association between traditional outcomes of growth (i.e., PGF and malnutrition) and adverse neurodevelopmental outcomes among extremely preterm infants. We chose weight instead of head circumference to assess the association between postnatal growth and cognitive outcomes (7) because extremely preterm infants have a higher risk of developing severe IVH. When extremely preterm infants develop post-hemorrhagic hydrocephalus due to severe IVH, head circumference is not associated with favorable neurodevelopmental outcomes.

Many support the use of the INTERGROWTH-21st growth curves because they were developed using longitudinal data from mother-infant dyads of geographically diverse backgrounds who had reliable gestational ages, proper nutrition, and good medical care (14). Others question the validity of these curves for assessing infants less than 30 weeks because the number of preterm infants that contributed to the development of the INTERGROWTH-21st growth curves was limited (19). Our comparative analysis showed that the INTERGROWTH-21st growth curves were more predictive of cognitive outcomes than the Fenton growth curves. It also demonstrated that, unlike usual and current definitions, alternative definitions of growth alterations with the INTERGROWTH-21st growth curves were less prevalent and more accurate to predict adverse neurodevelopmental outcomes. Redefining short-term outcomes in neonatal research is challenging, but it could be justified if these redefined short-term outcomes are highly predictive of adverse long-term outcomes. For instance, a recent observational study demonstrated that an alternative definition of BPD had a higher diagnostic accuracy in predicting neurodevelopmental impairment (NDI) (20).

In the absence of large randomized trials targeting specific growth rates to reduce cognitive deficits, a sufficiently powered cohort study is a reliable source of clinical evidence to guide clinical practice regarding optimal growth rates. Regardless of the definition used, PGF and moderate to severe malnutrition among extremely preterm infants were consistently associated with growth rates below 13 g/kg/day. Our finding that growth rates are strongly correlated with declines in weight z scores indicates that analyzing changes in weight z

scores (i.e., malnutrition) instead of analyzing single-time weight z scores (i.e., PGF) (19) or calculating growth rates (21) could be justified. Without using the term “malnutrition”, other studies have analyzed the association between changes in weight z scores from birth to 36 weeks PMA and neurodevelopment (22, 23). Our finding that changes or declines in weight z scores were not associated with cognitive outcomes after adjustment for in-hospital comorbidities confirms that changes in weight z scores and growth rates are markers of inadequate nutrition and illness severity. Previous studies have shown that growth rates are often confounded by illness severity and comorbidities associated with extreme prematurity (24, 25). We confirmed that reductions of 25% or more on growth rates have a negative impact on weight, length, and head circumferences at 36 weeks PMA, but we did not observe growth rate declines in the ranges proposed to define malnutrition in preterm infants – up to 75% reductions in growth rates (12). These results underscore the importance of redefining or validating a definition of malnutrition that predicts adverse neurodevelopmental outcomes in extremely preterm infants who survive to discharge.

The main strengths of this study were the report of risk ratios, the assessment of cognitive outcomes with standardized methods, and the sufficient power to detect true differences in longitudinal growth data between groups. We calculated risk ratios instead of odds ratios to avoid overestimation of risk. We selected cognitive delay as the primary outcome of the study because cognitive scores define most of the variability in the outcome of NDI (18, 26–29). Cognitive outcomes at 2 years of age have some limitations (26), but overall they are good predictors of cognitive function in early adulthood (30). To increase the external validity of our study, we chose the INTERGROWTH-21st growth curves to assess the postnatal growth of extremely preterm infants (15) and we included analysis of declines in z scores in view of recent evidence (12, 15, 19).

One of the main limitations is the single-center study design. Our findings need validation with larger datasets that include longitudinal growth data and allow analyses of variations in practice. Another limitation is that we only included infants who survived through 2 years of age and underwent neurodevelopmental assessments. This approach systematically excluded critically ill infants with inadequate nutritional support or growth failure who died from severe comorbidities. We attempted to overcome this limitation with a generalized linear model that accounted for in-hospital comorbidities but establishing the mechanisms by which severity of illness affects nutritional practices, growth, and survival without a disability is complex (25). We did not include infants < 24 weeks of gestation because the INTERGROWTH-21st growth curves do not have weight z scores at birth for this population. Only growth curves generated with cross-sectional data (Fenton, Olsen, and other growth curves) (9, 31) provide weight z scores at birth for infants < 24 weeks of gestation. For this high-risk population, if analyses of declines in weight z scores from birth to 36 weeks PMA are proposed, an adjustment of the weight z score at birth to account for weight loss due to postnatal extracellular fluid contraction during the first weeks after birth might be needed. Subtracting -0.8 z score units from the weight z score at birth generated with cross-sectional data seems a reasonable approach (5, 9, 13, 32).

In conclusion, in this single-center retrospective cohort, the association between postnatal growth defined by weight-for-age z scores calculated with the INTERGROWTH 21st growth

curves and higher cognitive scores at 2 years of age was independent of in-hospital comorbidities that predict adverse neurodevelopmental outcomes of extremely preterm infants. We conclude that in order to establish the association between the risk of cognitive delay and insufficient nutrition in extremely preterm infants 24 to 26 weeks, clinicians should prevent declines in weight z scores higher than -1.0 and weight z scores at 36 weeks PMA less than -1.0 in the INTEGROWTH-21st growth curves. Future observational studies should generate more longitudinal data to define normal postnatal growth of “healthy” preterm infants and future interventional studies that target ideal growth rates during the neonatal period should consider the use of the INTEGROWTH-21st growth curves to improve the detection of PGF and improve the prediction of cognitive outcomes in extremely preterm infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact:

- New growth curves generated with longitudinal data could overcome some limitations of traditional growth curves generated with cross-sectional data. When these new growth curves are used to assess the growth of preterm infants, alternative definitions for postnatal growth alterations may be needed.
- This study examines the association between postnatal growth alterations defined by the INTERGROWTH-21st growth curves and adverse cognitive outcomes at 2 years of age.
- With alternative definitions of postnatal growth failure and malnutrition, the INTERGROWTH-21st growth curves can help establish the association between postnatal growth of extremely preterm infants and adverse neurodevelopmental outcomes in early childhood.

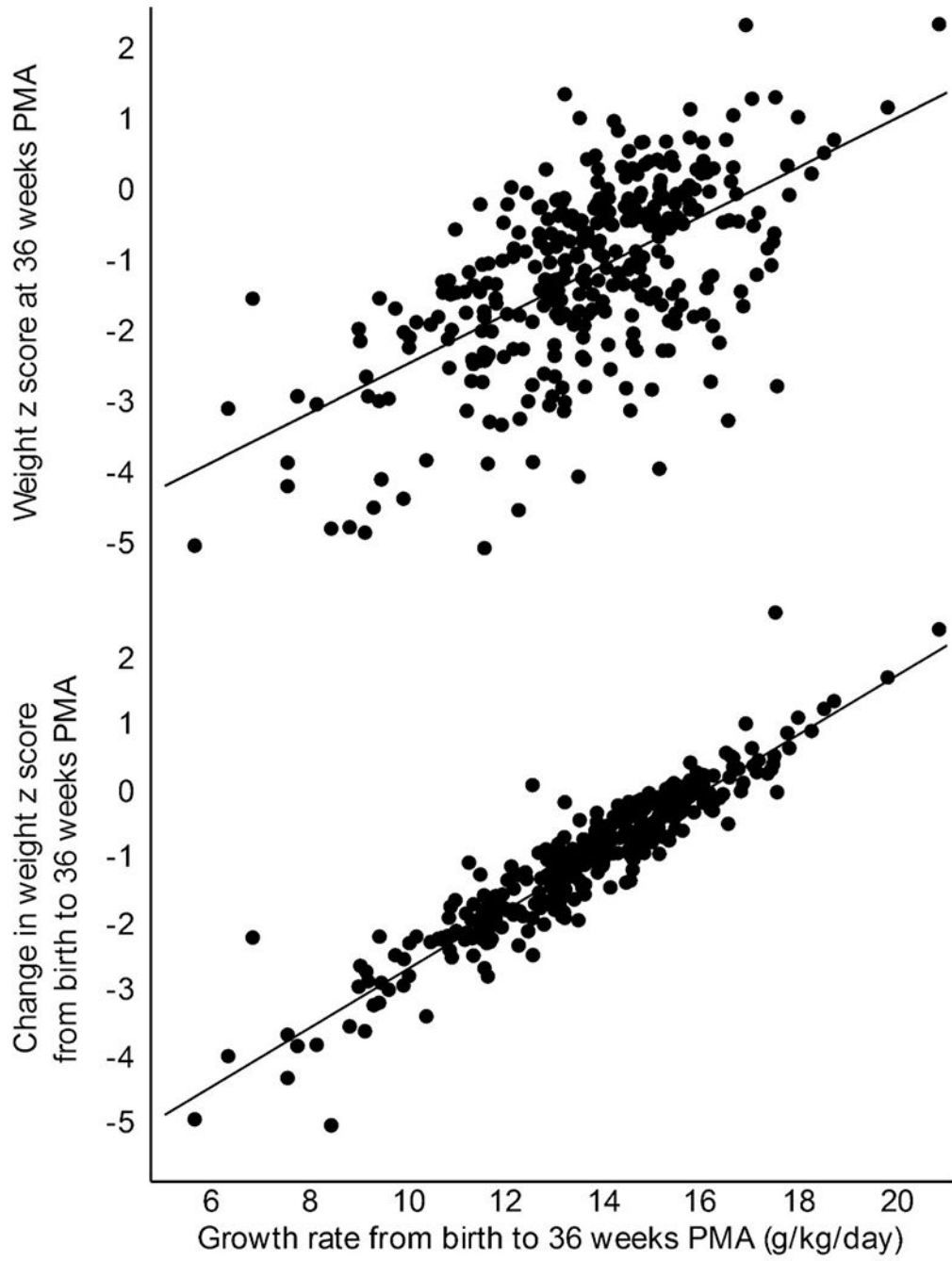


Figure 1. Linear correlation of weight z score at 36 weeks PMA and changes in weight z score from birth to 36 weeks PMA with growth rate.

Table 1:

Infant demographics and clinical characteristics

Variables	n=350
Birth weight in grams, mean (SD)	750 (138)
Gestational age in weeks, median (IQR)	25 (24 – 26)
Weight z score at birth, mean (SD)	0 (0.8)
Male sex, %	48
Black race, %	53
Antenatal steroids, %	95
Multiple gestation, %	25
Corrected age at follow-up in months, median (IQR)	24 (22 – 26)
Cognitive score, mean (SD)	93 (15)
Postnatal age at initiation of enteral feeding, median (IQR)	3 (2 – 3)
Time to full enteral feeding, median (IQR)	15 (12 – 22)
Duration of parenteral nutrition, median (IQR)	14 (11 – 24)
Growth rate in g/kg/day ^(a) , median (IQR)	14 (13 – 15)
IVH grade 3 or 4, %	13
PVL, %	2
Meningitis, %	10
NEC stage 2 or greater, %	4
BPD, %	14
ROP stage 3 or greater, %	11

^(a) calculated with the exponential method. Patel et al. (17)

Table 2.

Growth outcomes at 36 weeks PMA in extremely preterm infants 24 to 26 weeks of gestation and cognitive outcomes at 2 years of age

Growth outcome	z score cutoff	CCS BSID-III < 70	CCS BSID-III < 85	Risk Ratio (RR) and adjusted Risk Ratio (aRR) ^(a) for CCS BSID-III < 85
Usual definition of PGF ^(b)				
Weight z score at 36 weeks PMA				
	-1.3	17/198 (9) 18/152 (12)	53/198 (27) 48/152 (32)	RR: 1.17; 95% CI: 0.80 – 1.74; p=0.41 aRR: 1.13; 95% CI: 0.76 – 1.68; p=0.54
Current definition of malnutrition ^(c)				
Decline in weight z score from birth to 36 weeks PMA				
None	< 0.8	13/151 (9)	38/151 (25)	RR: 1.26 ^(d) ; 95% CI: 0.85 – 1.87; p=0.24 aRR: 1.13; 95% CI: (0.76 – 1.68); p=0.53
Mild	-0.8 to 1.2	8/63 (13)	18/63 (29)	
Moderate to severe	>1.2	14/136 (10)	45/136 (33)	
Alternative definition of PGF ^(e)				
Weight z score at 36 weeks PMA				
	-1.0	10/171 (6) 25/179 (14)	37/171 (22) 64/179 (36)	RR: 1.65; 95% CI: 1.10 – 2.49* aRR: 1.53; 95% CI: 1.02 – 2.34*
Alternative definition of malnutrition ^(f)				
Decline in weight z score from birth to 36 weeks PMA				
	- 1.0	16/192 (8) 19/158 (12)	47/192 (25) 54/158 (34)	RR: 1.40; 95% CI: 1.00 – 1.94* aRR: 1.21; 95% CI: 0.81 – 1.82; p=0.34

^(a) Adjusted for gestational age at birth, age at follow-up, and the following in-hospital comorbidities: PVL, meningitis, IVH grade 3 or 4, BPD treated with postnatal steroids, proven NEC (stage 2 or greater).

^(b) As usually defined according to birth percentiles (< 10th percentile), Fenton et al. (1)

^(c) As recently proposed in a consensus statement, Goldberg et al. (12)

^(d) None or mild vs. moderate or severe

^(e) As determined by a classification tree method that dichotomized weight z score data at 36 weeks PMA based on the probability of cognitive delay.

^(f) As determined by a classification tree method that dichotomized weight z score data from birth to 36 weeks PMA based on the probability of cognitive delay.

* p < 0.05

Table 3.

Other outcomes associated with growth alterations at 36 weeks PMA

CCS BSID-III	Growth rates from birth to 36 weeks PMA (g/kg/day)	Length z score at 36 weeks PMA	Length z score difference between birth and 36 weeks PMA	Head circumference z score at 36 weeks PMA	Head circumference z score difference between birth and 36 weeks PMA	Difference between actual and ideal weight at 36 weeks PMA (g) ^(a)
PGF defined with INTERGROWTH-21 st weight-for-age z score at 36 weeks PMA below -1.28						
No	95 ± 15*	14.6 ± 1.7	-1.3 ± 1.3	-1.0 ± 1.2	-0.9 ± 1.4	-84 ± 270
Yes	92 ± 15	12.5 ± 2.3	-3.0 ± 1.3	-2.1 ± 1.3	-2.8 ± 1.4	-418 ± 281
Moderate or severe malnutrition defined with INTERGROWTH-21 st declines in weight z scores below -1.2						
No	94 ± 15*	15.0 ± 1.4	-1.7 ± 1.4	-1.1 ± 1.2	-1.1 ± 1.5	-48 ± 231
Yes	92 ± 15	11.7 ± 1.7	-2.8 ± 1.4	-2.1 ± 1.3	-2.6 ± 1.5	-514 ± 216
PGF defined with INTERGROWTH-21 st weight-for-age z score at 36 weeks PMA below -1.0						
No	96 ± 14	14.8 ± 1.7	-1.2 ± 1.2	-0.9 ± 1.2	-0.8 ± 1.4	-60 ± 272
Yes	90 ± 16	12.7 ± 2.3	-2.9 ± 1.4	-2.0 ± 1.3	-2.6 ± 1.4	-390 ± 278
Moderate or severe malnutrition defined with INTERGROWTH-21 st declines in weight z scores below -1.0						
No	95 ± 15	15.2 ± 1.4	-1.7 ± 1.5	-1.0 ± 1.3	-1.0 ± 1.6	-22 ± 229
Yes	92 ± 16	11.9 ± 1.7	-2.6 ± 1.4	-2.0 ± 1.3	-2.5 ± 1.5	-481 ± 218

* NS

^(a) According to www.growthcalculator.org. Landau-Crangle, et al. (13)