Association of Poor Postnatal Growth with Neurodevelopmental Impairment in Infancy and Childhood: Comparing the Fetus and the Healthy Preterm Infant References

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Objectives To compare the classification of preterm postnatal poor growth using healthy preterm vs fetal growth references and to examine associations with neurodevelopmental impairment in infancy and childhood.

Study design We included 613 infants born at <33 weeks of gestation. Using the INTERGROWTH-21st (healthy-preterm growth) reference and the Fenton and Olsen (fetal growth) references, we classified poor growth as a decline in z-score from birth to term-equivalent >0.8 SD (weight), >1 SD (head), and >2 SD (length). We used generalized estimating equations to estimate aOR for neurodevelopmental impairment at 18 months and 7 years of corrected age, comparing infants with and without poor growth by each reference, accounting for multiple births and covariates.

Results The prevalence of poor growth was higher with INTERGROWTH-21st than with fetal references for all measurements. Agreement was higher between the Fenton and Olsen (fetal) growth references (0.72-0.81) than between INTERGROWTH-21st and fetal references (0.41-0.59). Poor growth by fetal references (but not by INTERGROWTH-21st) was associated with low neurodevelopmental scores in infancy and childhood. Poor weight gain using the Fenton reference was associated with 18-month Mental Developmental Index <85 (aOR 1.6, 95%CI: 1.1, 2.4) whereas poor weight gain by the INTERGROWTH-21st reference was not (aOR 1.0, 95%CI: 0.6, 1.7). Poor linear growth by the Olsen reference, but not INTERGROWTH-21st, was associated with 7-year verbal intelligence quotient <70 (aOR 3.5, 95%CI: 1.1, 12.7).

Conclusions Poor neonatal growth categorized using fetal references showed stronger associations with long term neurodevelopment than poor growth categorized using the INTERGROWTH-21st standards. *(J Pediatr 2020;225:37-43)*.

The classification of preterm infants with poor postnatal growth in the neonatal intensive care unit (NICU) can serve as a risk indicator for future neurodevelopmental impairment.[1,2] The American Academy of Pediatrics recommends that preterm infants' growth approximates the growth of the healthy fetus.[3] Therefore, fetal growth references such as those developed by Olsen and Fenton are commonly used for monitoring postnatal growth.[4,5] Recently, the INTERGROWTH-21st project challenged this approach, arguing that matching fetal growth is unattainable for hospitalized preterm infants, and will inevitably lead to overfeeding.[6] The INTERGROWTH-21st preterm postnatal growth charts were developed using the healthy preterm infant (instead of the fetus) as the reference.[7] These longitudinal growth charts were constructed from an international cohort of 201 healthy preterm infants, but only a small number (n = 12) were born <32 weeks of gestation.[7] This small sample size has led to concerns about their use as standards for preterm growth.

Single-center studies in Turkey and India showed that cross-sectional classifications of extrauterine growth restriction (weight <10th percentile at hospital discharge) were different when using Fenton vs INTERGROWTH-21st growth charts.[8,9] Importantly, no study to date has evaluated the impact of the different growth classifications on long-term outcomes such as neurodevelopment, which is relevant to the clinical performance of any preterm growth chart. Therefore, the aims of this study were to compare the classification of preterm postnatal poor growth in weight, length, and head circumference from birth to term equivalent age between fetal references (Fenton and Olsen) and a healthy preterm growth reference (INTERGROWTH-21st); and to examine the association of poor growth classifications by each reference with adverse neurodevelopmental outcomes in infancy and childhood.

BSID-II	Bayley Scales of Infant Development, 2nd edition
MDI	Mental development index
NICU	Neonatal intensive care unit
PDI	Psychomotor development index

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Methods

We performed a secondary analysis of data from the Docosahexaenoic acid for the Improvement of Neurodevelopmental Outcomes study, a randomized controlled trial of docosahexaenoic acid supplementation for preterm infants born at <33 weeks of gestation.[10] Infants in this trial were recruited from 5 Australian perinatal centers from April 2001 to October 2005. Details of the recruitment and follow-up have been reported elsewhere.[10,11] The trial intervention had minimal effect on our outcomes of interest. Therefore, we combined both randomization groups into one cohort for the current analyses. For our analysis to address aim 2, we included the children enrolled in the primary trial (n = 657) who completed neurodevelopmental assessments at 18 months (n = 613, 93%) and 7 years (n = 582, 89%) corrected age.

Trained research staff measured and recorded infants' weight, length, and head circumference weekly to discharge home and at term equivalent age (40 weeks of postmenstrual age). According to standardized procedures, weight was measured with a calibrated electronic scale, head circumference with a nonstretchable tape measure, and length with a recumbent length board.

We calculated weight, head circumference, and length z-scores for gestational age at birth and week 1 of postmenstrual age, and at term equivalent age using 2 fetal growth references (Fenton and Olsen) and a healthy preterm growth reference (INTERGROWTH-21st).[4,5,7] Following recent recommendations for the identification of malnutrition in preterm infants, we assessed growth longitudinally by evaluating the z-score change over time.[12] We selected a priori cut-offs for weight, head circumference, and linear growth from birth to term equivalent age based on the best available published literature: poor weight gain as a z-score decline of >0.8 SD, poor head growth as a decline of >1 SD, and poor linear growth as a decline of >2 SD.[13-15]

At 18 months of corrected age, neurodevelopment was assessed using the Bayley Scales of Infant Development, 2nd edition (BSID-II). The BSID-II consists of 2 subscales: the mental development index (MDI), which assesses language and cognition, and the psychomotor development index (PDI), which assesses fine and gross motor skills. The test is age-standardized to a mean of 100 and SD of 15. Children unable to be tested owing to severe impairment were assigned a score of 40. At 7 years of corrected age, neurodevelopment was assessed using the Wechsler Abbreviated Scale of Intelligence and the Wide Range Achievement Test, fourth edition. The Wechsler Abbreviated Scale of Intelligence comprises 4 subtests (vocabulary, similarities, block design, and matrix reasoning). These subtests yield a verbal IQ, a performance IQ, and a full scale IQ, which provide a reliable estimate of a child's intellectual functioning that is age standardized to a mean of 100 ± 15.[16] We administered 3 of the 4 Wide Range Achievement Test subtests (word reading, spelling, math computation), which are also age-standardized to a mean of 100 ± 15. We categorized neurodevelopmental impairment as mild to severe for a given test if the score was <85 (1 SD below the mean), and as moderate to severe if the score was <70 (2 SD below the mean).

We considered variables associated with both postnatal growth and neurodevelopment including gestational age, size at birth, sex, maternal education (categorized by tertiary education or not), and comorbidities of prematurity including necrotizing enterocolitis (Bell stage ≥II), sepsis (positive blood culture), intraventricular hemorrhage grade 3 or 4, and chronic lung disease (supplemental oxygen administration at 36 weeks of postmenstrual age).

Statistical Analyses

To address aim 1, we used proportions of agreement to measure the interobserver agreement of categorical classifications of poor growth between the 2 fetal references (Fenton and Olsen) and between the healthy preterm reference and each of the fetal references.[17] Then, we used Bland-Altman analyses to quantify the systematic bias between the mean difference in the z-scores calculated using each growth reference.[18] To address aim 2, we estimated unadjusted and aOR of low neurodevelopmental scores at 18 months and 7 years of corrected age among infants with vs without poor growth in weight, head circumference, and length as classified by each of the 3 growth references. We used generalized estimating equations models to account for intrafamilial correlation (multiple births). We adjusted models for potential explanatory variables associated with both poor growth and neurodevelopmental impairment, so that the OR would indicate the extent to which poor growth was associated with the outcome independently of these factors. For each growth reference, we calculated diagnostic performance and discriminatory ability using sensitivity, specificity, and area under the receiving operating curve. We used SAS version 9.3 (SAS Institute Inc, Cary, North Carolina) and SPSS version 24 (IBM Corp, Armonk, New York) for statistical analyses.

Results

The characteristics of study participants and their mothers are shown in **Table I**. Compared with the 613 infants included in our analysis for aim 2, the 44 excluded infants (no neurodevelopmental data) had a slightly lower mean gestational age (28.2 weeks vs 29.2 weeks; P = .006) and birth weight (1181 g vs 1318 g; P = .015). Compared with the 613 infants assessed at 18 months of corrected age, the subset of 582 infants who were followed up at 7 years of corrected age had similar mean gestational age (29.1 weeks vs 29.2 weeks; P = .60) and similar birth weight (1315 g vs 1318 g; P = .88).

Table II shows the prevalence of poor growth as classified by each reference and the proportions of agreement in the classification of poor growth between the 3 growth references. For weight, head circumference, and length, more infants were classified by INTERGROWTH-21st as

Table I. Demographic and clinical characteristics of 613 infants and their mothers enrolled in the DHA for the Improvement of Neurodevelopmental Outcomes (DINO) study

Characteristics	Median (range) or number (%)
Infants and children	
Gestational age, weeks	30 (23-33)
Birth weight, kg	1.34 (0.32-2.62)
Singleton	404 (66)
Male sex	328 (54)
Term equivalent age, weeks	39 (37-48)
Chronic lung disease*	131 (21)
Intraventricular hemorrhage (grade 3 or 4)	20 (3)
Sepsis	98 (16)
Necrotizing enterocolitis	20 (3)
Comorbidities of prematurity†	190 (31)
Postnatal steroid treatment	56 (9)
BSID-II at 18 months‡ (n = 613)§	
MDI <85	157 (26)
PDI <85	131 (21)
MDI <70	50 (8)
PDI <70	53 (9)
Wechsler Abbreviated Scale of Intelligence at 7 years of age‡ (n = 582)	
Verbal IQ <85	94 (16)
Performance IQ <85	68 (12)
Full scale IQ <85	88 (15)
Verbal IQ <70	13 (2)
Performance IQ <70	8 (1)
Full scale IQ <70	10 (2)
Wide Range Achievement Test at 7 years of age‡ (n = 582)	
Word Reading <85	90 (15)
Spelling <85	122 (21)
Math <85	190 (33)
Word Reading <70	29 (5)
Spelling <70	23 (4)
Math <70	55 (10)
Mothers	Mean (SD) or number (%)
Age, y	30.6 (5.5)
Received antenatal steroids	540 (88)
Smoked in pregnancy	152 (25)
Tertiary education	306 (50)
Race/ethnicity	
White	558 (91)
Asian	26 (4)
Aboriginal or other	29 (5)

DHA, docosahexaenoic acid.
*Supplemental oxygen at 36 weeks of postmenstrual age.
†Any of the following diagnoses during NICU hospitalization: chronic lung disease, intraventricular hemorrhage grade 3 or 4, sepsis, or necrotizing enterocolitis.
‡Scaled scores according to corrected age.
§In the DINO trial, 614 infants were evaluated using BSID-II: 611 infants had both MDI and PDI results, 2 infants had MDI results only, and 1 infant had subtests of BSID-II only (eg, no MDI or PDI).

Table II. Prevalence of poor growth by INTERGROWTH 21st, Fenton 2013, and Olsen 2010 and agreement in the classification of poor growth between references

Studies	Weight* (n = 651)	Head circumference† (n = 622)	Length‡ (n = 606)
Prevalence of poor growth z-score in-hospital decline			
INTERGROWTH-21st	442 (68)	142 (23)	191 (32)
Olsen 2010	299 (46)	81 (13)	113 (19)
Fenton 2013	260 (40)	62 (10)	89 (15)
Agreement in the classification of poor growth between references			
Fenton vs Olsen	0.81 (0.77-0.85)	0.72 (0.63-0.81)	0.79 (0.72-0.86)
INTERGROWTH vs Olsen	0.54 (0.50-0.58)	0.53 (0.45-0.61)	0.59 (0.52-0.66)
INTERGROWTH vs Fenton	0.56 (0.52-0.60)	0.41 (0.33-0.49)	0.47 (0.40-0.54)

Values are number (%) or proportions of agreement for poor growth, 95% CI.
*Decline in weight z -score >0.8 SD from birth to term equivalent age.
†Decline in head circumference z-score >1 SD from week 1 to term equivalent age.
‡Decline in length z-score >2 SD from week 1 to term equivalent age.

having poor growth compared with Fenton and Olsen. The proportions of agreement for poor growth classifications was moderately high (0.72-0.81) between the 2 fetal references for all measurements. Agreement between fetal and healthy-preterm references was lower (0.53-0.59 with Olsen; 0.41-0.56 with Fenton).

The **Figure** (available at www.jpeds.com) illustrates the mean z-scores in weight, head circumference, and length from birth to term equivalent age. Over time, mean z-scores for weight and length declined, whereas mean z-scores for head circumference increased. When growth was assessed cross-sectionally, at each time point, the same measurement represented a higher z-score with INTERGROWTH-21st compared with fetal references. When growth was assessed longitudinally, for the same absolute change in weight and length, the change in z-score was greater when plotted on INTERGROWTH-21st growth reference compared with plotting on fetal growth references, with the greatest differences observed at younger gestational ages. The Bland-Altman analyses for weight demonstrated that, on average, the weight z-scores determined by INTERGROWTH-21st were 0.41 units higher (95% CI, 0.39-0.43) than the weight z-scores determined by Fenton and 0.38 units higher (95% CI, 0.36-0.40) than the weight z-scores determined by Olsen. The head z-scores determined by INTERGROWTH-21st were, on average, higher than the head z-scores determined by Fenton (mean 0.35 units higher; 95% CI, 0.31-0.39) or Olsen (mean 0.25 units; 95% CI, 0.20-0.30). Similarly, the average length z-scores by INTERGROWTH-21st were higher than Fenton (mean 0.20 units; 95% CI, 0.15-0.25) or Olsen (mean 0.14 units; 95% CI, 0.10-0.18).

Table III (available at www.jpeds.com) and **Table IV** (available at www.jpeds.com) show the prevalence of adverse neurodevelopmental outcomes at 18 months and at 7 years corrected age in infants with and without poor growth as classified by each reference.

Table V displays the unadjusted and aOR for adverse neurodevelopmental outcomes at 18 months corrected age comparing infants with vs without poor growth in weight, head circumference, and length classified using the 3 growth references. When fetal references were used to assess growth, poor weight gain from birth to term equivalent age was associated with a higher odds of delayed development at 18 months. In contrast, infants classified as

Table V. Odds of low neurodevelopmental scores at 18 months corrected age in infants with poor growth as classified by INTERGROWTH-21st, Olsen 2010, and Fenton 2013

	INTERGROWTH	INTERGROWTH	Olsen	Olsen	Fenton	Fenton
Outcome measures	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
BSID-II						
Weight						
MDI <85	1.1 (0.7-1.7)	1.0 (0.6-1.7)	1.6* (1.1-2.1)	1.5* (1.01-2.3)	1.7* (1.2-2.5)	1.6* (1.1-2.4)
PDI <85	1.4 (0.9-2.6)	1.4 (0.8-2.5)	1.7* (1.2-2.3)	1.6* (1.1-2.4)	1.8* (1.2-2.7)	1.5* (1.1-2.4)
MDI <70	1.5 (0.7-3.1)	1.2 (0.5-2.7)	2.2* (1.1-3.7)	2.0* (1.2-4.1)	2.1* (1.2-4.1)	2.0* (1.1-3.8)
PDI <70	2.3* (1.4-9.3)	1.9* (1.2-8.5)	2.5* (1.3-4.1)	2.2* (1.2-4.2)	2.6* (1.4-5.1)	2.3* (1.2-4.5)
Head circumference						
MDI <85	1.7 (0.9-3.6)	1.0 (0.6-3.7)	1.8 (0.9-3.2)	1.7 (0.8-3.6)	2.2* (1.3-3.2)	2.1* (1.3-3.5)
PDI <85	2.5* (1.6-5.7)	1.4 (0.8-2.5)	3.1* (1.6-5.7)	2.9* (1.4-5.9)	3.0* (1.6-4.1)	2.3* (1.4-3.9)
MDI <70	2.0 (0.8-5.1)	1.6 (0.6-4.4)	2.4* (1.2-5.5)	2.4* (1.1-6.2)	3.4* (1.7-5.9)	3.5* (1.8-6.8)
PDI <70	2.7* (1.1-7.2)	2.5 (0.9-7.0)	3.5* (1.5-7.9)	2.9* (1.1-7.6)	3.1* (1.5-5.8)	2.7* (1.3-5.7)
Length						
MDI <85	1.2 (0.5-1.7)	0.8 (0.3-2.1)	2.6* (1.1-5.5)	2.0 (0.7-4.1)	2.1 (1.0-4.3)	1.2 (0.5-3.0)
PDI <85	1.4 (0.7-2.5)	1.1 (0.5-2.3)	3.1* (1.4-7.3)	2.5* (1.1-5.4)	2.3* (1.1-5.0)	1.8* (1.1-3.6)
MDI <70	1.3 (0.5-1.7)	0.9 (0.4-1.4)	1.9 (1.0-3.1)	1.7 (0.8-3.4)	1.6 (0.8-2.4)	1.2 (0.6-2.0)
PDI <70	1.3 (0.6-2.2)	1.1 (0.5-2.3)	2.0* (1.1-3.7)	1.7 (0.9-2.9)	1.9* (1.1-3.1)	1.3 (0.9-2.4)

For each of the 3 growth references, the first column shows OR adjusted only for intra-familial correlation and second column shows aOR for gestational age at birth, sex, maternal education, and clinical complications (intraventricular hemorrhage grade 3 or 4, sepsis, necrotizing enterocolitis, or chronic lung disease).
*$P < .05$.

having poor weight gain by INTERGROWTH-21st did not have significantly higher odds of MDI <85 compared with infants without poor weight gain by this reference. Even after adjusting for explanatory variables, infants with poor weight gain by the fetal references had twice the odds of moderate to severe cognitive delay (MDI <70) at 18 months. Poor weight growth by all 3 references was associated with moderate to severe motor delay (PDI <70) at 18 months in both unadjusted and adjusted models.

With fetal references, but not with the healthy preterm growth reference, poor head growth to term equivalent age was associated with adverse neurodevelopmental outcomes after adjustment for covariates. Similarly, we found statistically significant associations between poor linear growth by fetal references with low BSID-II scores at 18 months corrected age. Compared with infants without stunting by fetal references, stunted infants had significantly greater odds of PDI <85 and PDI of <70. In contrast, stunting by INTERGROWTH-21st was not associated with PDI <85 or PDI <70.

Table VI shows the unadjusted and aOR of adverse neurodevelopmental outcomes at 7 years corrected age in infants with vs without poor growth in weight, head circumference and length classified using the 3 growth references. By classifying growth using fetal references, poor growth in head or length during the NICU hospitalization was associated with adverse neurodevelopmental outcomes at school age. For instance, poor head growth by fetal references was associated with a full IQ score of <70 at 7 years, even after adjustment for covariates, whereas poor head growth as classified by INTERGROWTH-21st was not.

With regard to length assessments, infants with neonatal stunting by fetal references had a higher odds of a performance IQ of <85 than infants without stunting by fetal references. Poor linear growth as classified by fetal references was also significantly associated with low academic achievement scores, even after adjustment for covariates. In contrast, when using the healthy preterm reference to categorize stunting, we found no significant associations with neurodevelopmental impairment at school age.

Table VII (available at www.jpeds.com) shows measures of diagnostic performance of each growth reference for prediction of neurodevelopmental impairment in infancy. Poor growth by the healthy preterm reference had greater sensitivity than the fetal references for identifying infants with neurodevelopmental impairment; whereas fetal references had greater specificity. The fetal references had moderate but higher discriminatory ability for predicting neurodevelopmental impairment than the healthy preterm reference. Similarly, for adverse outcomes at school age, poor growth by the healthy preterm reference had the greatest sensitivity, and fetal references the greatest specificity (data not shown). Notably, area under the receiving operating curve values and CIs showed that none of the 3 growth references had high accuracy for prediction of later neurodevelopment.

Discussion

The INTERGROWTH-21st preterm postnatal growth standards were developed from a cohort of healthy preterm infants based on the theory that this select group of infants provide a standard for how all preterm infants should grow postnatally. The conceptual framework of INTERGROWTH-21st contrasts with the reference fetus concept that underpins the current American Academy of Pediatrics nutritional recommendations and the preterm growth references in common clinical use (Fenton and Olsen).[3] We examined not just the differential classification, but also the implications for long-term clinical outcomes of using the healthy preterm reference rather than the fetal reference to

Table VI. Odds of low neurodevelopmental scores at 7 years corrected age in infants with poor growth as classified by INTERGROWTH-21st, Olsen 2010, and Fenton 2013

Outcome measures	INTERGROWTH OR (95% CI)	INTERGROWTH aOR (95% CI)	Olsen OR (95% CI)	Olsen aOR (95% CI)	Fenton OR (95% CI)	Fenton aOR (95% CI)
Weight						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ <85	1.3 (0.8-2.6)	1.0 (0.2-2.0)	1.1 (0.7-1.7)	0.9 (0.6-1.6)	1.4 (0.9-2.2)	1.2 (0.7-2.0)
Performance IQ <85	1.6 (1.0-4.5)	1.5 (0.6-4.1)	1.6 (0.9-2.6)	1.7 (0.9-3.0)	1.5 (0.8-2.4)	1.2 (0.7-2.1)
Full IQ <85	1.5 (0.9 -3.4)	1.2 (0.6-2.6)	1.4 (0.8-1.9)	1.2 (0.8-2.0)	1.3 (0.8-2.1)	1.1 (0.7-1.9)
Verbal IQ <70	1.7 (0.4-8.8)	1.1 (0.2-7.4)	2.8 (0.8-7.6)	2.4 (0.7-8.7)	2.4 (0.8-11.0)	2.3 (0.6-8.8)
Performance IQ <70	1.6 (0.4-23)	1.8 (0.3-37)	1.5 (0.4-6.0)	1.8 (0.5-7.2)	1.5 (0.3-6.2)	1.5 (0.3-7.0)
Full IQ <70	2.1 (0.4-26.4)	3.1 (0.3-49.9)	2.9 (0.6-8.1)	3.2 (0.8-13.6)	3.5 (0.8-16.0)	3.4 (0.8-17)
Wide Range Achievement Test						
Word Reading <85	1.1 (0.6-2.0)	1.0 (0.6-1.9)	1.0 (0.6-1.5)	0.9 (0.5-1.4)	1.1 (0.7-1.7)	1.0 (0.6-1.6)
Spelling <85	1.4 (0.9-2.5)	1.3 (0.8-2.5)	1.6* (1.1-2.3)	1.5 (0.9-2.4)	1.4 (1.0-2.1)	1.3 (0.8-2.0)
Math <85	1.2 (0.8-2.0)	1.1 (0.7-1.8)	1.2 (0.8-1.5)	1.0 (0.7-1.5)	1.2 (0.8-1.7)	1.1 (0.7-1.5)
Word Reading <70	2.6 (0.8-18.4)	1.8 (0.7-17.4)	2.4 (1.0-4.1)	1.4 (0.6-3.6)	3.4* (1.2-6.8)	2.2 (0.9-5.6)
Spelling <70	1.9 (0.6-7.1)	2.0 (0.5-7.9)	1.6 (0.6-3.3)	1.5 (0.6-3.9)	2.3 (0.8-5.1)	1.8 (0.7-4.7)
Math <70	1.3 (0.7-3.2)	1.1 (0.5-3.2)	1.3 (0.7-2.1)	1.1 (0.6-2.1)	1.6 (0.8-2.7)	1.3 (0.7-2.4)
Head circumference						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ <85	1.3 (0.6-3.2)	1.0 (0.4-2.7)	1.9 (0.9-3.9)	1.5 (0.6-3.6)	1.7 (1.0-2.9)	1.6 (0.9-3.0)
Performance IQ <85	2.0 (0.8-5.8)	1.8 (0.6-5.1)	2.6* (1.2-5.7)	2.4* (1.1-6.1)	2.0* (1.1-3.5)	1.8* (1.1-3.7)
Full IQ <85	1.9 (0.9 -4.8)	1.7 (0.6-4.4)	2.2* (1.1-4.7)	1.9* (1.01-4.8)	2.1* (1.2-3.7)	2.1* (1.1-3.9)
Verbal IQ <70	3.8 (1.0-15.3)	3.1 (0.6-15.6)	5.9* (1.4-27.4)	5.5* (1.3-23.6)	5.4* (1.4-15.8)	4.6* (1.2-17.8)
Performance IQ <70	3.2 (0.8-21.9)	4.1 (0.5-51.0)	6.7 (0.9-29)	5.2 (0.9-27.9)	5.1* (1.2-23.5)	7.7* (1.9-31.1)
Full IQ <70	3.2 (0.6-14.5)	3.3 (0.4-27.2)	6.8* (1.7-36.9)	8.3* (1.8-38.9)	5.7* (1.3-18.6)	6.5* (1.4-31.3)
Wide Range Achievement Test						
Word Reading <85	0.8 (0.3-2.1)	0.6 (0.2-1.8)	1.3 (0.6-3.0)	1.2 (0.5-2.9)	1.1 (0.4-1.5)	0.9 (0.3-1.3)
Spelling <85	1.2 (0.5-2.7)	1.1 (0.4-2.5)	1.6 (1.0-3.3)	1.5 (0.7-3.3)	1.4 (0.9-2.5)	1.4 (0.8-2.6)
Math <85	0.9 (0.4-1.9)	0.7 (0.3-1.6)	1.5* (1.0-2.9)	1.2 (0.7-2.4)	1.4 (0.9-2.2)	1.2 (0.7-2.0)
Word Reading <70	2.1 (0.6-8.7)	1.7 (0.4-6.9)	2.7* (1.1-8.6)	1.9 (0.6-6.5)	2.9* (1.2-6.2)	2.1 (0.9-5.4)
Spelling <70	2.5 (0.8-11.6)	2.3 (0.6-10.3)	2.4 (0.7-7.5)	1.9 (0.6-8.6)	3.1* (1.3-8.1)	3.3* (1.2-9.8)
Math <70	1.8 (0.7-5.8)	1.7 (0.6-5.5)	2.8* (1.2-6.3)	2.5* (1.1-7.0)	2.0 (1.0-3.8)	1.8 (0.8-3.9)
Length						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ <85	1.2 (0.8-2.9)	1.1 (0.5-2.5)	1.7 (0.8-3.3)	1.3 (0.6-2.8)	1.8 (0.9-3.0)	1.3 (0.7-2.6)
Performance IQ <85	1.7 (0.8-4.6)	1.4 (0.7-4.0)	2.3* (1.1-5.0)	1.3 (0.6-3.0)	2.1* (1.1-4.5)	1.3 (0.7-2.8)
Full IQ <85	1.3 (0.7 -3.0)	1.0 (0.4-2.3)	1.8* (1.1-3.8)	1.2 (0.6-2.6)	1.6 (0.9-3.3)	1.2 (0.6-2.5)
Verbal IQ <70	2.2 (0.5-13.2)	2.0 (0.5-9.9)	4.2* (1.6-18.1)	3.5* (1.1-12.7)	3.9* (1.1-12.6)	2.1 (0.6-8.2)
Performance IQ <70	1.3 (0.3-10.6)	0.9 (0.2-4.2)	2.4 (0.5-12.9)	2.1 (0.6-7.5)	1.7 (0.3-9.1)	1.3 (0.3-4.9)
Full IQ <70	1.7 (0.3-10.6)	0.9 (0.2-4.2)	3.1 (0.7-12.8)	1.3 (0.4-4.3)	2.7 (0.5-9.0)	1.4 (0.4-5.1)
Wide Range Achievement Test						
Word Reading <85	1.5 (0.9-3.2)	1.4 (0.7-3.1)	2.2* (1.2-4.0)	1.7* (1.0-3.6)	1.9* (1.1-3.3)	1.4* (1.0-2.9)
Spelling <85	1.3 (0.7-2.4)	1.2 (0.6-2.3)	1.8 (1.0-3.5)	1.7 (0.8-3.4)	1.5 (0.9-2.6)	1.2 (0.6-2.4)
Math <85	1.6 (0.9-2.8)	1.3 (0.7-2.4)	2.1* (1.1-3.6)	1.7 (0.9-3.3)	1.7 (1.0-2.8)	1.3 (0.8-2.4)
Word Reading <70	2.0 (0.7-6.0)	1.5 (0.5-4.3)	4.1* (1.6-10.4)	3.3* (1.3-8.5)	3.4* (1.3-7.3)	2.2 (0.9-5.4)
Spelling <70	2.7 (0.7-9.4)	1.5 (0.4-5.7)	4.3* (1.4-12.4)	2.2 (0.7-6.8)	3.9* (1.5-11.1)	2.5* (1.1-6.0)
Math <70	1.9 (1.0-6.1)	2.0 (0.8-5.0)	2.3* (1.1-5.3)	1.5 (0.6-3.8)	2.1 (1.0-4.6)	1.5 (0.9-3.9)

For each of the 3 growth references, first column shows OR adjusted only for intra-familial correlation and second column shows aOR for gestational age at birth, sex, maternal education, and clinical complications (intraventricular hemorrhage grade 3 or 4, sepsis, necrotizing enterocolitis, or chronic lung disease).
*$P < .05$.

assess and monitor the postnatal growth of preterm infants. We found that by using change in z-score definitions of poor growth, a greater number of infants were classified as having poor postnatal growth using the healthy preterm reference compared with the fetal references. Further, our results suggest that classifying poor growth using the fetal reference was more effective in identifying infants at the greatest risk for adverse neurodevelopmental outcomes in infancy and childhood compared with the healthy preterm reference.

With regard to the classification of poor growth, we found that the agreement was high between the 2 fetal references; meaning that, in general, infants classified as having poor growth by Olsen were also classified as poorly grown by Fenton. In contrast, the agreement was lower between the fetal and healthy preterm references. We also found that the diagnosis of growth alterations (ie, poor growth) was affected by the selection of the categorization method (cross-sectional vs longitudinal) and of the growth reference (fetal vs healthy preterm). For instance, cross-sectionally, the same weight appeared as a higher z-score with INTERGROWTH-21st compared with both Olsen and Fenton. In contrast, when growth was assessed longitudinally, the pattern of classification was reversed; that is, the same absolute difference in weight represented a greater change in z-score for INTERGROWTH-21st compared with fetal

references. As a result, with longitudinal growth assessments, more infants were classified as having poor growth by INTERGROWTH-21st than by fetal references.

In relation to the association of growth with neurodevelopmental outcomes, we found that poor growth as classified by the fetal references was more highly associated with adverse neurodevelopmental outcomes than poor growth classified by the healthy preterm reference. Growth treated as a trajectory (change in z-score) has been shown to have better predictive ability for long-term outcomes than cross-sectional assessments of growth.[19,20] Our findings further support the need to update our traditional cross-sectional extrauterine growth restriction definition (weight <10th percentile at 36 weeks postmenstrual age) with longitudinal growth assessments that may be more useful indicators of long-term health.

Our results are in agreement with previous studies that reported significant associations of categorical classifications of poor weight growth and poor head growth during the NICU hospitalization with adverse neurodevelopmental outcomes at 18-24 months corrected age in preterm infants. Among these studies, various fetal growth references were used. Some authors determined growth categories using local references, whereas others used the Fenton reference.[14,19-22] Adding to this body of evidence, we found that categorical classifications of poor linear growth by fetal references also were associated with adverse neurodevelopmental outcomes at school age. Globally, childhood stunting is widely recognized as a malnutrition indicator.[23] However, less is known about neonatal stunting in the preterm population. We showed that neonatal stunting by fetal references was associated with low developmental scores across several domains at 7 years of corrected age. These findings improve our understanding of growth alterations beyond the limited evaluation of weight gain alone. We hypothesize that linear growth during the NICU hospitalization indexes brain growth and a number of clinical factors that affect higher level cognitive functions that become more evident later in childhood.[15]

A novel aspect of our study is that we examined neurodevelopmental outcomes beyond infancy. A previous study examined the association between change in head z-score from birth to NICU discharge and IQ at 8 years.[21] They reported that poor head growth from birth to discharge was not associated with IQ, but was associated with minor motor impairment at 8 years. We did not evaluate motor outcomes at school age, but did find a positive association of poor head growth from birth to term equivalent age with IQ at 7 years. The authors of the prior study did not report the cut-off selected to define impaired growth.[21] A different cut-off may explain the different results. Additionally, in their study, social class was strongly correlated with IQ at 8 years. It is possible that our covariate of maternal education failed to incorporate additional socioeconomic determinants of IQ at school age.

Overall, the better performance of the fetal references compared with the healthy preterm reference in assessing later neurodevelopmental risk is likely related to the differential categorization of poor growth. Using longitudinal assessments of growth, the Olsen and Fenton references identified a group of more severely growth restricted infants than INTERGROWTH-21st, whereas the healthy preterm reference overclassified infants with poor growth compared with fetal references. Poor growth in the NICU is a known risk indicator of adverse neurodevelopmental outcomes and the severity of growth restriction increases the risk of morbidity.[24] Our results from this cohort of infants born at <33 weeks of gestation suggest that the fetal reference may be preferable to the healthy preterm reference for identifying infants at an increased risk of adverse neurodevelopmental outcome in this population. However, before discarding the healthy preterm concept, we recommend further evaluation with healthy preterm standards derived from larger samples.

Strengths of our study include the large multicenter sample of preterm infants with standardized weight, head, and length measurements as well as detailed research-quality neurodevelopmental outcomes. We also examined neurodevelopment beyond infancy and into later childhood across multiple neurodevelopmental domains, and showed important associations of categorical classifications of poor postnatal growth in the NICU with long-term neurodevelopmental outcomes. A limitation of our study is that we relied on growth assessment tools that are inherently imperfect to assess the growth of infants born very preterm. Despite the greater precision and power related to the strict methodology and longitudinal design of the INTERGROWTH-21st growth charts, the small number of very preterm infants that contributed to their development likely explains the greatest differences between INTERGROWTH-21st and the fetal references that we observed at these lower gestational ages. However, although a greater number of very preterm infants were included in the construction of the fetal references, these charts are also limited at the lowest gestational ages because they use size at birth as a proxy for fetal size. Not surprisingly, the more prematurely an infant is born, the more likely it is that the size at birth systematically deviates from the healthy fetal size. Further, a number of clinical factors other than growth contribute to neurodevelopment. As a consequence, none of the preterm growth charts available to date exhibit strong sensitivity or specificity to accurately predict neurodevelopmental impairment. There is a need to further examine growth assessment tools complementary to anthropometry (ie, biomarkers, body composition, brain imaging) that improve the predictive ability for long-term neurodevelopment and could be used to counsel families and to target interventions. Nonetheless, the finding of associations of poor longitudinal growth during the critical period of the NICU hospitalization with adverse neurodevelopment later in life, even after adjusting for birth characteristics, comorbidities related to prematurity, and maternal education, is clinically relevant. These findings underscore the importance of promoting not only weight gain but also linear growth and head growth, aiming for the fetal target, to optimize long-term health in very preterm infants. We were also limited by the lack of consensus for the best definitions of poor growth in the NICU. Future studies could be designed to

identify optimal cut-offs for each growth reference using clinically meaningful short and long-term outcomes. Finally, generalizability of our findings may be limited by the characteristics of the cohort with predominantly white mothers of relatively high socioeconomic status.

Compared with the fetal references Fenton and Olsen, the INTERGROWTH-21st preterm postnatal growth standards categorize a greater number of infants as having poor growth. With longitudinal assessments of growth and at the thresholds used in our study, the fetal references performed better than the healthy preterm reference to identify infants at risk of long-term neurodevelopmental impairment. Our results support the use of existing fetal references to inform clinical decision making and for population-level surveillance and quality improvement work relating to the postnatal growth of very preterm infants. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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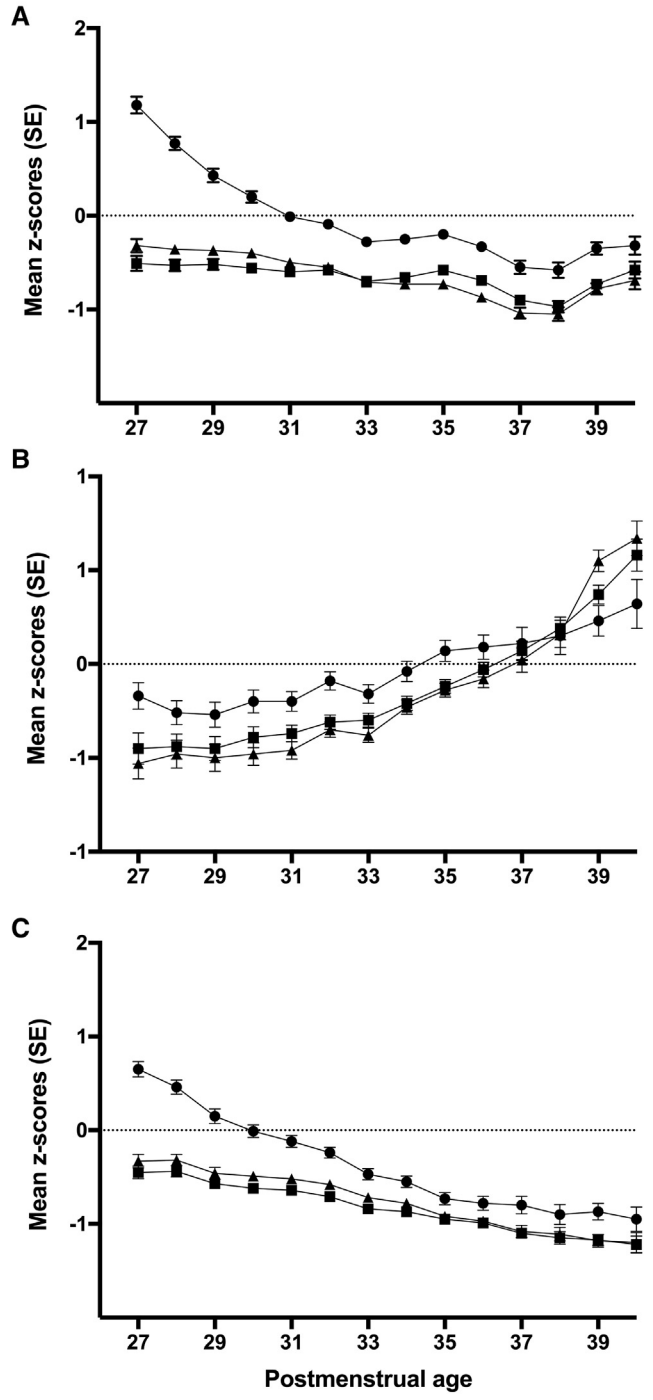

Figure. The mean z-scores for **A,** weight, **B,** head circumference, and **C,** length, plotted on the INTERGROWTH-21st (circles), Olsen 2010 (triangles), and Fenton 2013 (squares).

Table III. Prevalence of adverse neurodevelopmental outcomes at 18 months corrected age in infants with and without poor growth, classified using INTERGROWTH-21st, Olsen 2010, and Fenton 2013

Classifications	INTERGROWTH		Olsen		Fenton	
BSID-II	Poor growth (n = 423)	Not poor growth (n = 190)	Poor growth (n = 281)	Not poor growth (n = 332)	Poor growth (n = 251)	Not poor growth (n = 362)
Weight						
MDI <85	110 (26.0)	47 (24.7)	85 (30.2)	72 (21.7)	79 (31.5)	78 (21.5)
PDI <85	97 (22.9)	34 (17.9)	73 (26.0)	58 (17.5)	69 (27.5)	62 (17.1)
MDI <70	38 (9.0)	12 (6.3)	32 (11.4)	18 (5.4)	29 (11.6)	21 (5.8)
PDI <70	44 (10.4)	9 (4.7)	35 (12.5)	18 (5.4)	33 (13.1)	20 (5.5)
BSID-II	Poor growth (n = 142)	Not poor growth (n = 465)	Poor growth (n = 85)	Not poor growth (n = 522)	Poor growth (n = 67)	Not poor growth (n = 540)
Head circumference						
MDI <85	47 (33.1)	105 (22.6)	30 (35.3)	122 (23.4)	27 (40.3)	125 (23.1)
PDI <85	48 (33.8)	79 (17.0)	34 (40.0)	93 (17.8)	27 (40.3)	100 (18.5)
MDI <70	18 (12.7)	31 (6.7)	13 (15.3)	36 (6.9)	13 (19.4)	36 (6.7)
PDI <70	22 (15.5)	30 (6.5)	17 (20.0)	35 (6.7)	13 (19.4)	39 (7.2)
BSID-II	Poor growth (n = 192)	Not poor growth (n = 407)	Poor growth (n = 120)	Not poor growth (n = 479)	Poor growth (n = 96)	Not poor growth (n = 503)
Length						
MDI <85	53 (27.6)	98 (24.1)	49 (40.8)	102 (21.3)	37 (38.5)	114 (22.7)
PDI <85	48 (25.0)	78 (19.2)	46 (38.3)	80 (16.7)	33 (34.4)	93 (18.5)
MDI <70	18 (9.4)	31 (7.6)	15 (12.5)	34 (7.1)	11 (11.5)	38 (7.6)
PDI <70	20 (10.5)	31 (7.6)	16 (13.3)	35 (7.3)	13 (13.5)	38 (7.6)

Results are shown as number (%) for infants with data on both growth and developmental outcomes, weight (n = 613), head circumference (n = 607), and length (n = 599).

Table IV. Prevalence of adverse neurodevelopmental outcomes at 7 years corrected age in infants with and without poor growth, classified using INTERGROWTH-21st, Olsen 2010, and Fenton 2013

	INTERGROWTH		Olsen		Fenton	
Classifications	**Poor growth (n = 384)**	**Not poor growth (n = 198)**	**Poor growth (n = 262)**	**Not poor growth (n = 320)**	**Poor growth (n = 237)**	**Not poor growth (n = 345)**
Weight						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ <85	67 (17.4)	27 (13.6)	45 (17.2)	49 (15.3)	45 (19.0)	49 (14.2)
Performance IQ <85	51 (13.3)	17 (8.6)	38 (14.5)	30 (9.4)	34 (14.3)	34 (9.9)
Full IQ <85	64 (16.7)	24 (12.1)	46 (17.6)	42 (13.1)	41 (17.3)	47 (13.6)
Verbal IQ <70	10 (2.6)	3 (1.5)	9 (3.4)	4 (1.3)	8 (3.4)	5 (1.4)
Performance IQ <70	6 (1.6)	2 (1.0)	5 (1.9)	3 (0.9)	4 (1.7)	4 (1.2)
Full IQ <70	8 (2.1)	2 (1.0)	7 (2.7)	3 (0.9)	7 (3.0)	3 (0.9)
Wide Range Achievement Test						
Word reading <85	61 (15.9)	29 (14.6)	40 (15.3)	50 (15.6)	39 (16.5)	51 (14.8)
Spelling <85	88 (22.9)	34 (17.2)	66 (25.2)	56 (17.5)	57 (24.1)	65 (18.8)
Math <85	131 (34.1)	59 (29.8)	92 (35.1)	98 (30.6)	83 (35.0)	107 (31.0)
Word reading <70	24 (6.3)	5 (2.5)	19 (7.3)	10 (3.1)	20 (8.4)	9 (2.6)
Spelling <70	18 (4.7)	5 (2.5)	13 (5.0)	10 (3.1)	14 (5.9)	9 (2.6)
Math <70	39 (10.2)	16 (8.1)	28 (10.7)	27 (8.4)	28 (11.8)	27 (7.8)
	Poor growth (n = 140)	Not poor growth (n = 436)	Poor growth (n = 78)	Not poor growth (n = 498)	Poor growth (n = 63)	Not poor growth (n = 513)
Head circumference						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ <85	26 (18.6)	65 (14.9)	19 (24.4)	72 (14.5)	14 (22.2)	77 (15.0)
Performance IQ <85	25 (17.9)	41 (9.4)	17 (21.8)	49 (9.8)	12 (19.0)	54 (10.5)
Full IQ <85	31 (22.1)	57 (13.1)	20 (25.6)	68 (13.7)	16 (25.4)	72 (14.0)
Verbal IQ <70	7 (5.0)	6 (1.4)	6 (7.7)	7 (1.4)	5 (7.9)	8 (1.6)
Performance IQ <70	4 (2.9)	4 (0.9)	4 (5.1)	4 (0.8)	4 (6.3)	4 (0.8)
Full IQ <70	5 (3.6)	5 (1.1)	6 (7.7)	4 (0.8)	4 (6.3)	6 (1.2)
Wide Range Achievement Test						
Word reading <85	18 (12.9)	70 (16.1)	14 (17.9)	74 (14.9)	10 (15.9)	78 (15.2)
Spelling <85	31 (22.1)	88 (20.2)	22 (28.2)	97 (19.5)	16 (25.4)	103 (20.1)
Math <85	42 (30.0)	144 (33.0)	32 (41.0)	154 (30.9)	25 (39.7)	161 (31.4)
Word reading <70	11 (7.9)	17 (3.9)	8 (10.3)	20 (4.0)	7 (11.1)	21 (4.1)
Spelling <70	10 (7.1)	13 (3.0)	6 (7.7)	17 (3.4)	6 (9.5)	17 (3.3)
Math <70	19 (13.6)	35 (8.0)	15 (19.2)	39 (7.8)	10 (15.9)	44 (8.6)
	Poor growth (n = 182)	Not poor growth (n = 388)	Poor growth (n = 114)	Not poor growth (n = 456)	Poor growth (n = 91)	Not poor growth (n = 479)
Length						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ <85	32 (17.6)	58 (14.9)	25 (21.9)	65 (14.3)	21 (23.1)	69 (14.4)
Performance IQ <85	28 (15.4)	37 (9.5)	22 (19.3)	43 (9.4)	17 (18.7)	48 (10.0)
Full IQ <85	32 (17.6)	54 (13.9)	25 (21.9)	61 (13.4)	19 (20.9)	67 (14.0)
Verbal IQ <70	6 (3.3)	6 (1.5)	6 (5.3)	6 (1.3)	5 (5.5)	7 (1.5)
Performance IQ <70	3 (1.6)	5 (1.3)	3 (2.6)	5 (1.1)	2 (2.2)	6 (1.3)
Full IQ <70	4 (2.2)	5 (1.3)	4 (3.5)	5 (1.1)	3 (3.3)	6 (1.3)
Wide Range Achievement Test						
Word reading <85	35 (19.2)	52 (13.4)	28 (24.6)	59 (12.9)	21 (23.1)	66 (13.8)
Spelling <85	44 (24.2)	74 (19.1)	32 (28.1)	86 (18.9)	24 (26.4)	94 (19.6)
Math <85	71 (39.0)	113 (29.1)	52 (45.6)	132 (28.9)	39 (42.9)	145 (30.3)
Word reading <70	13 (7.1)	14 (3.6)	13 (11.4)	14 (3.1)	10 (11.0)	17 (3.5)

(*continued*)

Table IV. Continued

Classifications	INTERGROWTH		Olsen		Fenton	
	Poor growth (n = 384)	Not poor growth (n = 198)	Poor growth (n = 262)	Not poor growth (n = 320)	Poor growth (n = 237)	Not poor growth (n = 345)
Spelling <70	12 (6.6)	10 (2.6)	11 (9.6)	11 (2.4)	9 (9.9)	13 (2.7)
Math <70	24 (13.2)	29 (7.5)	18 (15.8)	35 (7.7)	14 (15.4)	39 (8.1)

Results are shown as number (%) for infants with data on both growth and developmental outcomes, weight (n = 582), head circumference (n = 576), and length (n = 570).

Table VII. Diagnostic performance of poor growth as classified by INTERGROWTH-21st, Fenton 2013, and Olsen 2010 for neurodevelopmental impairment in infancy

	INTERGROWTH			Olsen			Fenton		
Measures	**Sn**	**Sp**	**AUC (95% CI)**	**Sn**	**Sp**	**AUC (95% CI)**	**Sn**	**Sp**	**AUC (95% CI)**
Poor weight growth									
MDI <85	0.70	0.31	0.50 (0.45-0.55)	0.54	0.57	0.59 (0.55-0.63)	0.50	0.62	0.61 (0.57-0.65)
PDI <85	0.74	0.32	0.53 (0.48-0.58)	0.56	0.57	0.61 (0.56-0.66)	0.53	0.62	0.63 (0.58-0.68)
MDI <70	0.76	0.31	0.53 (0.46-0.61)	0.64	0.56	0.65 (0.58-0.72)	0.58	0.61	0.66 (0.59-0.73)
PDI <70	0.83	0.32	0.60 (0.55-0.65)	0.66	0.56	0.67 (0.61-0.73)	0.62	0.61	0.68 (0.62-0.74)
Poor head growth									
MDI <85	0.31	0.79	0.56 (0.51-0.61)	0.22	0.88	0.57 (0.52-0.62)	0.20	0.91	0.60 (0.55-0.65)
PDI <85	0.38	0.80	0.60 (0.55-0.65)	0.28	0.89	0.61 (0.56-0.66)	0.22	0.92	0.64 (0.59-0.69)
MDI <70	0.37	0.77	0.59 (0.52-0.66)	0.30	0.87	0.63 (0.56-0.70)	0.27	0.90	0.66 (0.59-0.73)
PDI <70	0.41	0.78	0.62 (0.55-0.69)	0.33	0.88	0.64 (0.56-0.72)	0.26	0.90	0.67 (0.61-0.74)
Poor linear growth									
MDI <85	0.35	0.70	0.51 (0.46-0.56)	0.32	0.85	0.61 (0.56-0.66)	0.26	0.87	0.57 (0.52-0.62)
PDI <85	0.38	0.71	0.54 (0.49-0.59)	0.37	0.84	0.61 (0.56-0.66)	0.28	0.87	0.59 (0.54-0.64)
MDI <70	0.37	0.72	0.58 (0.52-0.64)	0.31	0.81	0.59 (0.53-0.65)	0.24	0.85	0.59 (0.53-0.65)
PDI <70	0.39	0.70	0.55 (0.49-0.61)	0.31	0.83	0.61 (0.54-0.68)	0.27	0.85	0.61 (0.55-0.67)

AUC, area under the receiving operating curve; *Sn*, sensitivity; *Sp*, specificity.