

BMI Curves for Preterm Infants

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abstract

BACKGROUND AND OBJECTIVES: Preterm infants experience disproportionate growth failure postnatally and may be large weight for length despite being small weight for age by hospital discharge. The objective of this study was to create and validate intrauterine weight-for-length growth curves using the contemporary, large, racially diverse US birth parameters sample used to create the Olsen weight-, length-, and head-circumference-for-age curves.

METHODS: Data from 391 681 US infants (Pediatrix Medical Group) born at 22 to 42 weeks' gestational age (born in 1998–2006) included birth weight, length, and head circumference, estimated gestational age, and gender. Separate subsamples were used to create and validate curves. Established methods were used to determine the weight-for-length ratio that was most highly correlated with weight and uncorrelated with length. Final smoothed percentile curves (3rd to 97th) were created by the Lambda Mu Sigma (LMS) method. The validation sample was used to confirm results.

RESULTS: The final sample included 254 454 singleton infants (57.2% male) who survived to discharge. BMI was the best overall weight-for-length ratio for both genders and a majority of gestational ages. Gender-specific BMI-for-age curves were created ($n = 127\,446$) and successfully validated ($n = 126\,988$). Mean z scores for the validation sample were ~ 0 (~ 1 SD).

CONCLUSIONS: BMI was different across gender and gestational age. We provide a set of validated reference curves (gender-specific) to track changes in BMI for prematurely born infants cared for in the NICU for use with weight-, length-, and head-circumference-for-age intrauterine growth curves.

WHAT'S KNOWN ON THIS SUBJECT: Preterm infants experience disproportionate growth failure postnatally and may be large weight for length despite being small weight for age by hospital discharge. There is no routinely used measure to quantify and monitor disproportionate growth in the NICU.

WHAT THIS STUDY ADDS: BMI differs across gender and gestational age. We provide a set of validated reference curves to track changes in BMI for prematurely born infants for use with weight-, length-, and head-circumference-for-age intrauterine growth curves.

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Prematurity is the only period during the life cycle for which there is no routinely used measure of body proportionality, like BMI, to assess growth, nutritional status, and associated risk. Elevated BMI in children and adults is correlated with higher body fatness^{1,2} and risk of later related diseases,^{3,4} so BMI is an important part of clinical assessment at later ages. In preterm infants, concern about rapid postnatal growth, fat accumulation, and their potential adverse effects has increased interest in the composition and proportionality of postnatal growth.^{5–12} Because there is no routine clinical measurement of body composition in the NICU setting, a proxy such as BMI could be a useful clinical tool for preterm infants.

Growth assessment in preterm infants focuses on size for age. Intrauterine size-for-age growth curves^{13,14} compare the weight, length, and head circumference of an infant with those of reference fetuses of the same gestational age and evaluate how an infant is growing compared with fetuses of the same age, as recommended.¹⁵ However, size for age does not identify growth that is disproportionate or weight gain that might be too low or high for an infant's length. There is evidence that preterm infants experience poor growth postnatally,^{9,16–21} and upon closer look this growth failure is disproportionate between growth measures^{9,20,22}: head growth is best, weight growth is slower and the focus of concern, but gain in length is slowest.⁹ Currently there is no way to quantify and monitor disproportionate growth in the NICU. An infant's weight-for-age and length-for-age percentiles may be compared, but a weight-for-length ratio provides a simple, objective, and more accurate method of identifying, quantifying, and tracking disproportionate growth by comparing weight relative to length in 1 parameter.

A growth curve for the assessment of weight relative to length in preterm infants has been available for decades from Lubchenco et al²³ but is based on a small, geographically limited sample. Olsen et al found that Lubchenco's ponderal index (or weight/length³) provided different information about weight growth status in preterm infants than weight for age alone²²; for example, most of the infants categorized as small weight for age were appropriate weight for length at birth and hospital discharge. Others also have described variation in growth status assessed by weight for age versus body fat or its proxies (ie, weight-for-length ratios).^{24–27}

The ideal measure of body proportionality as an indicator of growth and nutritional status in preterm infants of all gestational ages lacks agreement.^{23,25,26,28–30} Weight-for-length ratios are good candidates because these measurements are routinely performed in the NICU. The goals for this study were to identify the weight-for-length ratio most highly correlated with weight and uncorrelated with length for infants born between 22 and 42 weeks' gestation, create and validate a set of growth curves, and show how the selected ratio differs across gender and gestational age.

METHODS

Infant data used in this study were previously used to create and validate our published weight-, length-, and head-circumference-for-age intrauterine growth curves.¹³ A deidentified sample of 391 681 infants was collected between 1998 and 2006 from 248 US hospitals in 33 states by Pediatrix Medical Group, Inc. Estimated gestational age was the best estimate of the neonatologist of gestational age, based on obstetric history, obstetric examinations, prenatal ultrasound, and postnatal physical examinations.

This best estimate was recorded to the closest completed week. We included infants of estimated gestational age between 22 and 42 weeks for whom data were available on birth weight (measured on an electronic scale, in grams) and length (measured by measuring tape or length board, in millimeters).

Exclusion criteria included gender not specified and factors with a known or suspected negative impact on intrauterine growth (eg, multiple births, congenital anomalies, mortality before discharge). We excluded extreme outliers for any of the growth measures (weight, length, or head circumference), defining these as infants with values >2 times the interquartile range above the 75th percentile or below the 25th percentile for each gestational age.¹³ The samples were divided by gender for curve creation, given birth size differences, so that our curves would be consistent with the World Health Organization (WHO) growth standards and Centers for Disease Control and Prevention 2000 growth charts.^{31,32} We used the SAS SURVEYSELECT procedure (SAS Institute, Inc, Cary, NC) to split each gender-specific sample into 2 random samples stratified by gestational age, race, and birth hospital state to produce the curve creation samples and curve validation samples.

Identification of the Ideal Weight-for-Length Ratio

The ideal weight-for-length ratio has been defined as that most highly correlated with weight and uncorrelated (or $r \approx 0$) with length/height.³³ Using established methods^{28,33} we tested 6 weight-for-length ratios for these relationships: weight/length, weight/length² (BMI), weight/length^{1/2}, weight/natural log of length, weight/length³, and weight/lengthⁿ, where "n" is Benn's index, a gestational age-specific regression coefficient designed to

have a low correlation with length. BMI was selected as the best overall ratio (see Results).

Curve Creation

We created gender-specific BMI-for-age growth curves by using LMSchartmaker Pro (version 2.3, 2006; Cole and Green³⁴), creating smoothed percentile curves for the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles. The Lambda Mu Sigma (LMS) method estimates 3 equivalent degrees of freedom (EDF) parameters: a Box-Cox power transformation of skewness (l), median (m), and coefficient of variation (s). Instructions for using the methods and additional details can be found in the LMSchartmaker user's guide.³⁵

The LMS BMI curves developed according to the methods suggested by Pan and Cole³⁵ showed some evidence of kurtosis and lack of fit, so we used 2 techniques to improve fit. First, we used Loess regression in SAS to identify influential outliers, limiting the data for constructing the curves to individuals with residuals from the Loess model that were within the middle 98% of the sample ($n = 54\,585$ girls, $n = 72\,881$ boys).

Next, we used the Generalized Additive Models for Location, Scale and Shape (GAMLSS) R package by Stasinopoulos and Rigby,³⁶ which allowed us to model kurtosis directly and has an automated algorithm suggesting EDF for 4 parameters (l, m, s, and kurtosis, abbreviated t). We created BMI curves by using the Box-Cox Power Exponential (BCPE) Distribution within GAMLSS for both the full and Loess limited data sets. The limited data sets produced better-fitting curves. From several candidate models for each gender, we selected models with the lowest generalized Akaike information criterion; both chosen models also had the lowest EDF (l, m, s, t = 7.6, 10.1, 11.5, 2.0 for girls and 2.0, 15.4, 11.6, 2.4 for boys, respectively).

The l, m, s EDF suggested by the BCPE algorithm in the GAMLSS R program were quite different from those found by using the Pan and Cole suggested methods for the LMSchartmaker program and produced better-fitting curves. However, the BCPE model is equivalent to the LMS model when $t = 2$,³⁷ so we used the suggested l, m, s EDF from the BCPE models in new LMS models.

Finally, using methods from the WHO Child Growth Standards,³⁸ we compared the values of the BMI curve percentiles from the full BCPE model with a simpler LMS model by

using the same l, m, s EDF values selected by the BCPE modeling process in both models. The BMI percentiles from the best BCPE models differed little from those of the LMS models. The largest difference was 0.2 of a BMI point.

We chose the final curves between the BCPE and LMS models by using the full curve creation data set because the full data set represented the actual distribution of infants; the candidate curve percentiles were used to classify all infants (≤ 3 rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles). We then determined which curve came closer

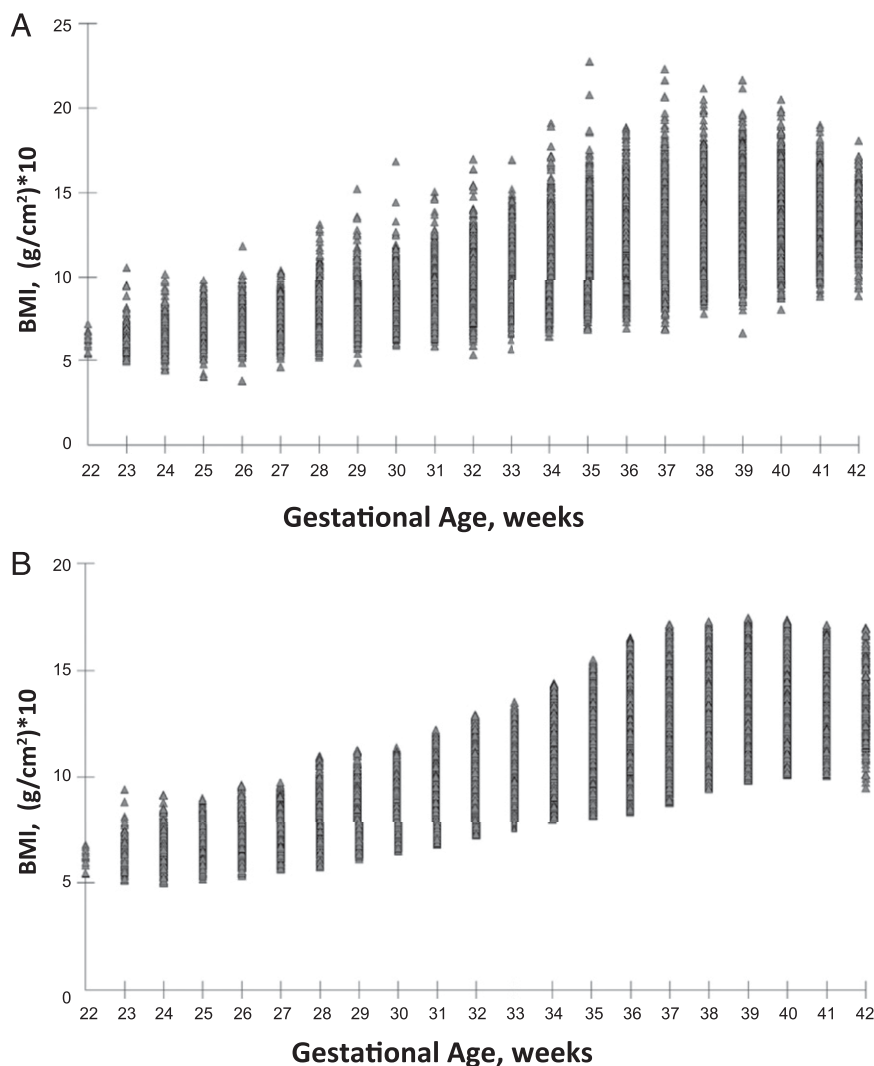


FIGURE 1 Plots of (A) the full curve data set and (B) the Loess limited data set for girls.

to the expected value (eg, closer to classifying 3% of the sample \leq 3rd percentile) at each gestational age for each classification and declared the superior curve at each age as that which came closest to the target percentile. In a tie, we selected the simpler LMS model.

The LMS curves were better for both genders, being superior in 33 of 42 size for gestational age comparisons for girls and 37 of 42 for boys. By definition, ~10% of a population should be below the 10th percentile (small for gestational age [SGA]), ~80% at or between the 10th and 90th percentiles (appropriate for gestational age [AGA]), and ~10% above the 90th percentile (large for gestational age [LGA]). In addition, the more complex BCPE model was never superior to the LMS model for 19 gestational-age-specific percentile classifications for girls and was

superior only for 23- and 26-week boys. Thus, we selected the LMS models for both genders. Although overall curve fit was better when all gestational ages were used to create the curves, fit at the individual gestational ages 22, 23, and 42 weeks was sufficiently poor that we do not include these points in the final curve and percentile results below.

Curve Validation

We validated the curves with the randomly generated validation samples by using infants born at 24 to 41 weeks only. We calculated z scores by using the l, m, s parameters, and we computed standard deviations and confidence intervals for each age and gender group. Validation was initially done in SAS 9.3 and confirmed in R 3.1.0. Mean z scores were expected to be 0 and mean standard deviations to be 1.

Using an adjusted α of .003 for 18 comparisons within each gender, we plotted means and confidence intervals to visualize any deviation from expected values. Next we examined the percentage of infants whose growth measurements fell within the distribution typically used in NICUs for classifying infant size: SGA, AGA, or LGA.

RESULTS

Identification of the Ideal Weight-for-Length Ratio³³

Weight/length³ was moderately correlated with both weight and length, but correlation with length was always negative and usually less than -0.3 , indicating that it overcorrected for length.²⁸ Weight/length², or BMI, and weight/length¹ were both correlated with weight and uncorrelated with length. For each

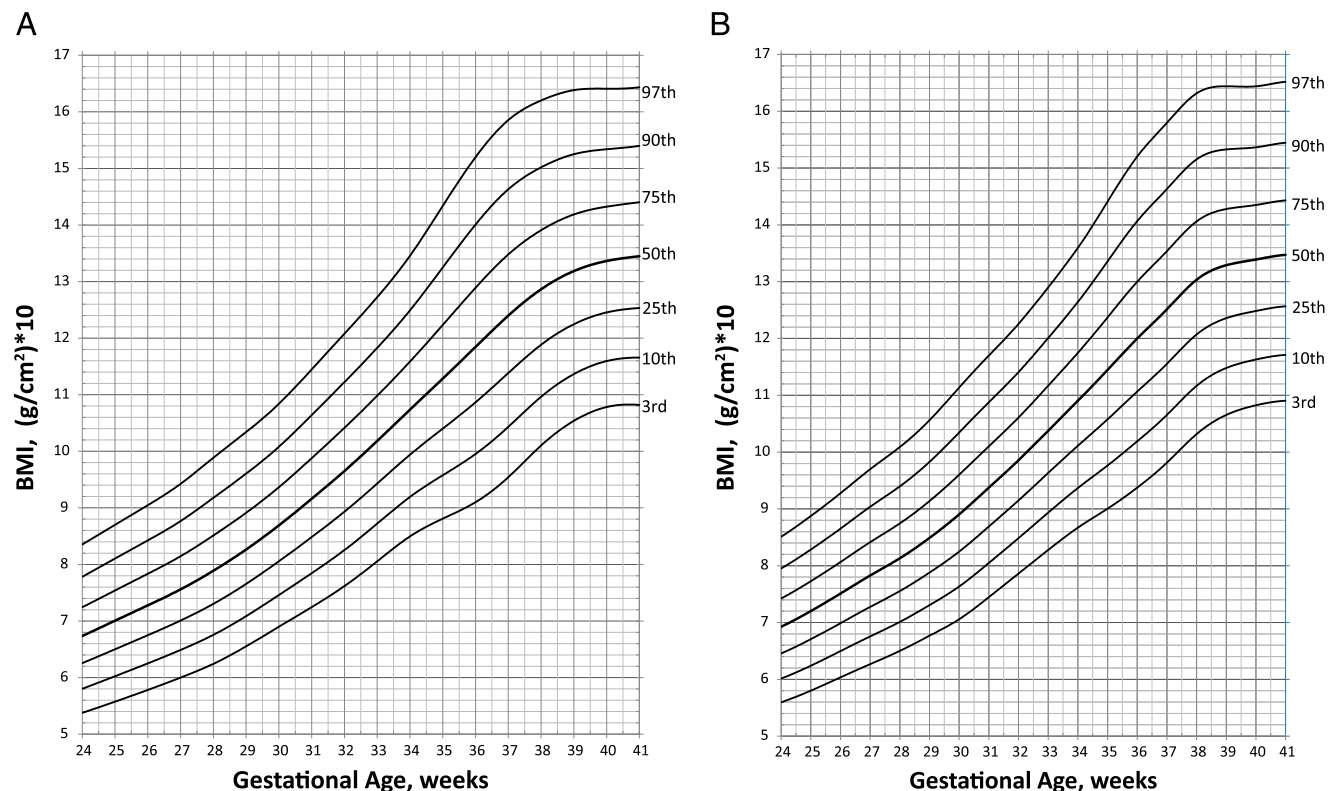


FIGURE 2

BMI-for-age intrauterine growth curves. A, Girls; B, Boys. ©2014 Olsen IE, Lawson ML, Ferguson AN, Cantrell R, Grabich SC, Zemel BS, Clark RH. All rights reserved. Reprinted with permission. The authors specifically grant to any health care provider or related entity a perpetual, royalty-free license to use and reproduce Fig 2 as part of a treatment and care protocol.

TABLE 1 LMS Values and Percentiles for Female BMI-for-Age [(g/cm²)*10] Growth Curves

Gestational Age (wk)	n	Mean	Median	L	M	S	Percentiles						
							3rd	10th	25th	50th	75th	90th	97th
24	428	6.73	6.69	0.20436	6.734847	0.109993	5.38	5.80	6.26	6.73	7.24	7.78	8.35
25	589	7.06	6.98	0.240113	7.005395	0.111203	5.57	6.02	6.50	7.01	7.54	8.10	8.70
26	757	7.33	7.30	0.244235	7.276484	0.111862	5.78	6.25	6.75	7.28	7.83	8.42	9.05
27	946	7.57	7.57	0.207293	7.559349	0.112801	6.00	6.49	7.01	7.56	8.15	8.77	9.42
28	1163	7.94	7.89	0.152314	7.887805	0.114883	6.24	6.76	7.30	7.89	8.51	9.18	9.89
29	1228	8.30	8.27	0.157302	8.263847	0.113994	6.55	7.09	7.66	8.26	8.91	9.60	10.34
30	1572	8.72	8.70	0.196138	8.690219	0.112902	6.90	7.46	8.06	8.69	9.36	10.08	10.84
31	2002	9.22	9.17	0.220911	9.159153	0.11425	7.24	7.84	8.48	9.16	9.88	10.64	11.45
32	2945	9.69	9.64	0.234645	9.651788	0.115124	7.62	8.25	8.93	9.65	10.41	11.22	12.08
33	4102	10.23	10.20	0.22088	10.18235	0.1142	8.05	8.72	9.43	10.18	10.98	11.83	12.72
34	5816	10.81	10.76	0.156873	10.73633	0.114924	8.50	9.19	9.94	10.74	11.59	12.49	13.46
35	4980	11.35	11.25	0.13732	11.28477	0.121735	8.81	9.58	10.40	11.28	12.23	13.25	14.34
36	4596	11.90	11.84	0.214643	11.84423	0.128108	9.10	9.95	10.87	11.84	12.89	14.01	15.20
37	4284	12.49	12.44	0.247743	12.39839	0.126778	9.54	10.43	11.38	12.40	13.48	14.63	15.86
38	5639	12.95	12.88	0.196413	12.86351	0.117996	10.10	10.96	11.88	12.86	13.91	15.02	16.20
39	5858	13.26	13.16	0.141546	13.18563	0.110283	10.54	11.36	12.25	13.19	14.19	15.25	16.38
40	5417	13.43	13.34	0.211803	13.36399	0.10492	10.78	11.59	12.45	13.36	14.32	15.34	16.41
41	1866	13.45	13.44	0.388779	13.44849	0.104309	10.82	11.66	12.53	13.45	14.40	15.40	16.44

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gestational age, we determined which measure had the highest correlation and scored the measures based on this correlation. BMI was the best measure for girls (12 of the 22 highest correlations), and weight/lengthⁿ was the best measure for boys (also 12 of the 22 highest correlations). The Benn index values rounded to 2 except for 23-week boys and 23- and 24-week

girls, so we selected BMI as most appropriate measure. For ease of clinical use, we selected 1 ratio for which growth curves were created and validated. The mean correlation between BMI and weight was 0.71 for girls and 0.68 for boys, and the mean correlation between BMI and length was −0.03 for girls and −0.07 for boys.

Evaluation of Outliers and Final Curve Generation

Plots of the full curve data set and the Loess limited data set for girls are shown for comparison in Fig 1. The figure shows how removal of outliers improves the curve fit. Final BMI curves are presented in Fig 2. Average BMI for the full curve data set was 11.4 (SD = 2.3)

TABLE 2 LMS Values and Percentiles for Male BMI-for-Age [(g/cm²)*10] Growth Curves

Gestational Age (wk)	n	Mean	Median	L	M	S	Percentiles						
							3rd	10th	25th	50th	75th	90th	97th
24	441	6.95	6.90	0.162649	6.925844	0.104742	5.60	6.01	6.46	6.93	7.42	7.95	8.51
25	705	7.24	7.17	0.163671	7.20182	0.106296	5.80	6.24	6.71	7.20	7.73	8.29	8.88
26	863	7.54	7.52	0.164706	7.510527	0.107421	6.03	6.50	6.99	7.51	8.06	8.65	9.28
27	1008	7.88	7.84	0.165763	7.827689	0.109134	6.27	6.76	7.28	7.83	8.41	9.04	9.70
28	1255	8.16	8.11	0.166843	8.131427	0.109847	6.50	7.01	7.55	8.13	8.75	9.40	10.09
29	1473	8.54	8.51	0.167922	8.489882	0.111159	6.77	7.31	7.88	8.49	9.14	9.83	10.56
30	1952	8.95	8.90	0.168978	8.904723	0.113935	7.06	7.63	8.25	8.90	9.60	10.35	11.14
31	2410	9.43	9.41	0.169983	9.375006	0.112906	7.45	8.05	8.69	9.38	10.10	10.88	11.70
32	3603	9.90	9.85	0.170912	9.857181	0.110895	7.86	8.49	9.15	9.86	10.61	11.41	12.25
33	4912	10.43	10.37	0.171754	10.37792	0.110858	8.28	8.93	9.63	10.38	11.17	12.01	12.90
34	7145	10.96	10.92	0.172493	10.90406	0.112346	8.67	9.37	10.11	10.90	11.75	12.64	13.59
35	6812	11.51	11.44	0.173106	11.44493	0.117447	9.00	9.76	10.58	11.44	12.37	13.36	14.41
36	6869	12.08	12.01	0.173621	11.99975	0.120805	9.38	10.19	11.06	12.00	13.00	14.07	15.20
37	6558	12.56	12.51	0.174061	12.51268	0.118914	9.81	10.65	11.55	12.51	13.54	14.63	15.80
38	8610	13.12	13.05	0.174445	13.03349	0.114496	10.32	11.16	12.07	13.03	14.06	15.15	16.31
39	8156	13.35	13.30	0.174802	13.28914	0.108389	10.65	11.48	12.36	13.29	14.28	15.33	16.44
40	7089	13.44	13.38	0.175141	13.39009	0.104435	10.82	11.63	12.48	13.39	14.35	15.37	16.44
41	2486	13.56	13.51	0.175463	13.47175	0.103808	10.90	11.71	12.57	13.47	14.43	15.45	16.52

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for girls and 11.7 (SD = 2.3) for boys, whereas average BMI for the limited data set was 11.4 (SD = 2.3) for girls and 11.7 (SD = 2.2) for boys. BMI is reported in the following units: (g/cm²)*10. Tables 1 and 2 contain the LMS values by gestational age and gender, along with percentiles.

Evaluation of Curves' Performance for the Validation Data Set

Figure 3 contains z scores with confidence intervals for each gestational age. For the validation samples (girls $n = 54\,257$, boys $n = 72\,731$), BMI

z scores calculated from the curves had a mean of -0.00 (SD = 1.08) for girls and 0.00 (SD = 1.09) for boys. The overall SGA, AGA, and LGA percentages were 9.6, 80.6, and 9.8, respectively. Size classification by gender and gestational age is shown in Fig 4.

DISCUSSION

In a large, racially diverse, contemporary set of birth data from infants admitted to US NICUs, we captured the relationship between weight and length overall in infants 24 to 41 weeks' gestational age at

birth best with weight/length², or BMI. Then, combining our previously reported methods¹³ with those used for the WHO curves and Loess regression, we created and successfully validated gender-specific BMI-for-age percentile tables and intrauterine growth curves. We showed that BMI changes across gender and gestational age, as revealed by the different shape of the curves and values of the percentiles for the different genders and ages (see Fig 2 and Tables 1 and 2).

These gender-specific BMI-for-age growth curves help to fill a gap in neonatal nutritional assessment methods. There are no clinical tools for the assessment of weight relative to length in preterm infants more recent than those published by Lubchenco et al²³ and Miller and Hassanein.³⁹ Our BMI-for-age curves were created from the same large, recent, racially diverse US sample of infants reported by Olsen et al.¹³ The 4 gender-specific curves (weight, length, head circumference, and BMI) allow a more complete assessment of preterm infant growth status at specific postmenstrual age after birth. A measure of weight relative to length provides important information about the growth status of preterm infants that is currently not quantified in the NICU. As an infant grows and is plotted on curves for weight, length, and head circumference, there is no quantification of proportionality of growth. It can be estimated visually but not easily calculated. We believe that quantifying disproportionate growth will provide information to individualize and better target nutritional care. For example, a preterm infant whose weight is considered small for age but large for length²² would probably benefit from a different nutrition care plan than an infant whose weight is considered small for age and length.

Careful evaluation of growth in preterm infants is important

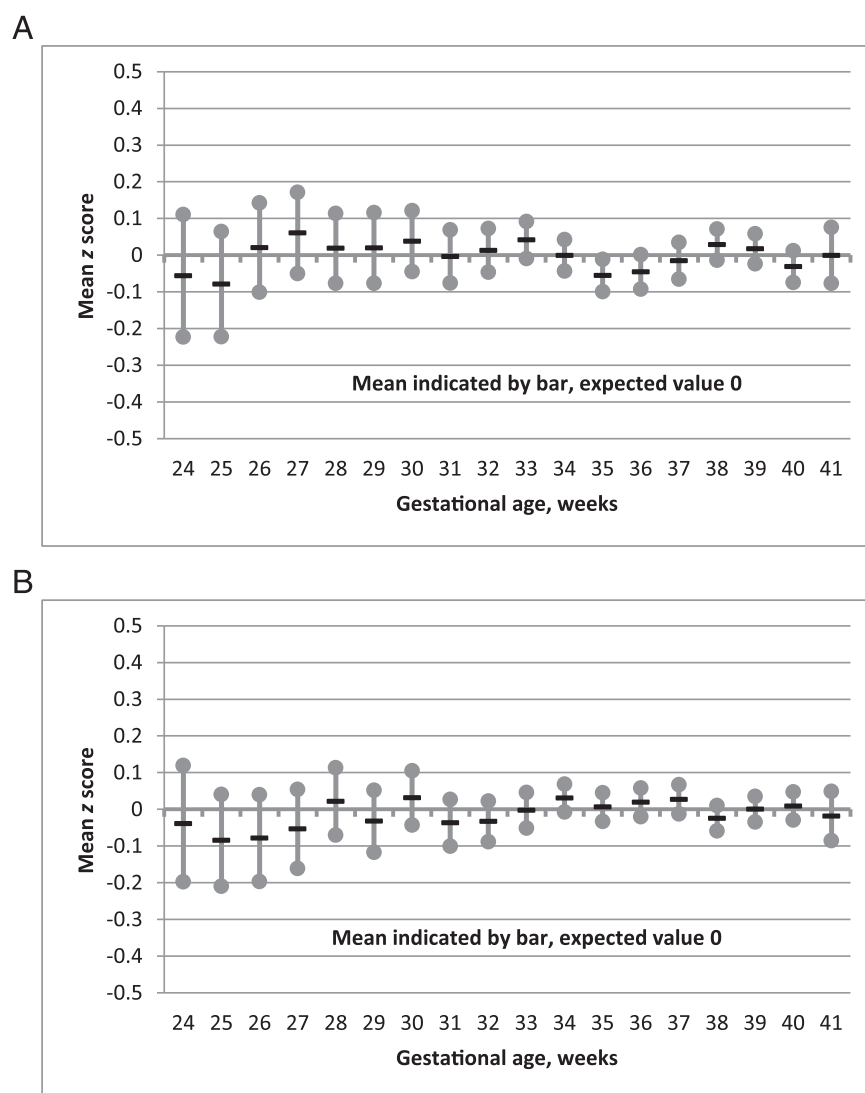


FIGURE 3 Birth BMI mean z scores and 99.7% CIs (with an adjusted α of .003 for 18 comparisons) in validation sample by gestational age. A, Girls ($n = 54\,257$); B, Boys ($n = 72\,731$).

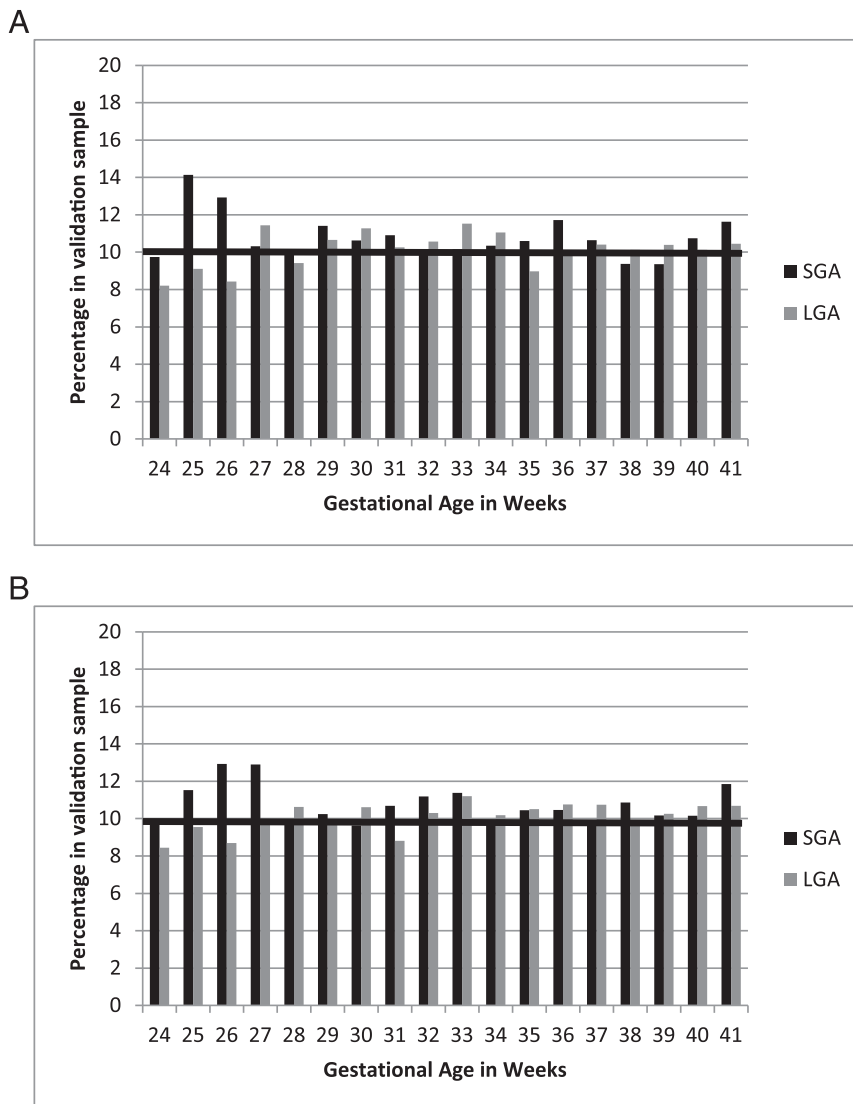


FIGURE 4
Classification as SGA or LGA by BMI for age in validation samples. A, Girls ($n = 54\,257$); B, Boys ($n = 72\,731$). Expected percentage of SGA and LGA is $\sim 10\%$.

because postnatal or extrauterine growth restriction, defined as the decline in growth status from birth percentiles often to <10 th percentile weight-for-age by hospital discharge, remains a substantial problem,^{16,17,40} has a negative impact on outcomes,^{9,41–43} is modifiable,^{18,20,44–49} and may not be identified without the appropriate assessment tools.^{13,22} Although extrauterine growth restriction usually refers to weight growth restriction, it also affects head and especially length growth.^{9,16,19,20}

Poor growth in weight, length, or head circumference is associated with poor neurodevelopmental outcomes.^{21,41–43} The relationships between poor growth and poor neurodevelopment are well documented for weight and head circumference,^{9,21,41–43} and recently a study of AGA, very low birth weight (<1500 g at birth) infants by Ramel et al⁹ found a significant relationship between poor linear growth and poor neurodevelopment scores at 24 months. Early disproportionate poor growth was statistically worse for length than

weight z score ($P = .004$), but the disproportionality was not quantified. Our BMI-for-age growth curves could be used to quantify and track the degree of weight growth relative to length growth over time by plotting BMI for age or calculating BMI-for-age z scores.

Given the associations between BMI, body fatness, and adverse health outcomes in other age groups,^{1–4} one might expect similar associations in preterm infants. When measured at hospital discharge (37 ± 1.2 weeks' gestational age), BMI was correlated with overall fat mass ($r = 0.69$) and central fat mass ($r = 0.57$) in a study of 149 preterm infants (≤ 34 weeks' gestation, ≤ 1750 g at birth).⁵⁰ Data are not available in preterm infants at earlier postnatal ages because measuring the body composition of small infants is difficult,^{51–53} particularly because of the high acuity of preterm infants in the clinical setting. New methods are promising^{12,54} but not easily accessible. The first step to understanding these associations in preterm infants is to define a population reference for calculation of BMI percentiles and z scores.

For infants born at 24 to 41 weeks' postmenstrual age, BMI adequately meets the criteria proposed by Benn³³ and later Cole and colleagues^{28,55} for a ratio of relative size that is most correlated with weight and least with length. This ratio is easy to calculate and use in the NICU. Using a smaller, more mature sample, Cole et al²⁸ indicated that "ponderal index is slightly better than BMI," but they recommended using the Benn index. The Benn indexes in their sample were much closer to 3 than 2. Our largest Benn index (in 36-week girls) was 2.39. The samples are clearly from different populations.

Despite the benefits of including BMI growth curves in the assessment of preterm infants, there are limitations. Preterm birth is not a normal event,

and even when we try to create a “normal” sample of preterm infants there will be some selection bias, which is described in detail in a recent review.⁵⁶ As a result of this limitation, growth curves based on birth data sets do not represent a precise estimate of ideal growth but remain the best available estimate for assessing infant size at birth and postnatally.^{57,58}

Another limitation of BMI is that it quantifies disproportionality between weight and length. As a result, growth restriction or excess resulting in stunted or excessive weight and length will not be identified by BMI or other weight-for-length ratios. Therefore, our new BMI curves are intended as adjunct measures of growth, not replacements for the size-for-age

growth curves. Finally, BMI does not distinguish between body fat mass and fat-free mass. When body composition of former preterm infants at corrected full-term age is compared with that of full-term infants, fat mass is equivalent or greater and fat-free mass is less in former preterm infants, resulting in higher body fat percentage estimates.^{10,50,59} As body composition data for preterm infants become available, relationships between weight-for-length ratios, body composition, and outcomes must be explored.

CONCLUSIONS

Because the postnatal growth fluctuations commonly experienced

by preterm infants are disproportionate (in particular, length growth is slower than weight growth), infants may be large weight for length despite being small weight for age at hospital discharge. The gender-specific BMI-for-age percentile tables and growth curves will help reveal disproportionate growth failure in infants that is not detected by current size-for-age methods. Used in conjunction with weight-, length-, and head-circumference-for-age growth curves, these BMI-for-age tools will provide a more complete assessment of preterm infant size, helping individualize nutritional care to optimize growth and other health outcomes in preterm infants.

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