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Growth of Preterm and Full-Term Children Aged 0-4 Years: Integrating Median Growth and Variability in Growth Charts

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Objectives To assess the distribution of height, weight, and head circumference (HC) in preterm infants for ages 0-4 years, by gestational age (GA) and sex, and to construct growth reference charts for preterm-born children, again by GA and sex, for monitoring growth in clinical practice.

Study design The community-based cohort study covered a quarter of The Netherlands. 1690 preterm infants (GA, 25-35^{+6} weeks) and a random sample of 634 full-term control infants (GA 38-41^{+6}), who were followed from birth to 4 years of age. Height, weight, and HC were regularly assessed during routine well-child visits and data were retrospectively collected.

Results At all ages, the median height and weight of preterm children were lower compared with full-term children. Growth depended on the child's GA. Increase in HC showed an early catch-up and was similar to full-term children by the age of 1. Height, weight, and HC were more variable in boys, particularly in the very preterm children.

Conclusions At 0 to 4 years, the growth of preterm children differed from that of full-term children and depended on their GA. The greater variability of growth in boys suggests that they are more vulnerable to the complications of preterm birth that influence growth. These growth charts are the most precise tools currently available for monitoring growth in preterm children. *(J Pediatr 2012;161:460-5)*.

During the past decade, the neurodevelopmental outcomes and social implications of preterm birth have been studied widely.[1-3] Nevertheless, the consequences of preterm birth for growth are not fully understood. Early preterm-born children (early preterms, gestational age [GA] <32 weeks) are known for their ability to catch up on growth. Nevertheless, they have relatively high rates of growth restraint of <−2 SDs (10%-20%) for long-term growth.[4,5]

More recently, moderately preterm born children (moderate preterms, GA 32-36 weeks) were also found to differ from full-term children for growth.[6] Although the prevalence of growth restraint was less than for early preterms (~5%), former moderate preterms were, on average, shorter and weighed less than full-term children.[6] Growth within the normal full-term range may have both a favorable effect on neurodevelopmental outcomes and on the prevention of metabolic syndrome in preterms.[7,8]

Our knowledge of the normal ranges of growth across the entire range of preterm GAs is incomplete. Ideally, growth in preterms should be comparable with that in full-terms if prenatal and postnatal feeding is adequate. However, "normal" feeding, based on feeding practices in full-term children, may not be achieved in preterm children. The "normal ranges," derived from the growth charts for full-term children, are likely to be poor substitutes for monitoring growth in preterms. The usefulness of other growth charts currently available, such as those of Guo et al,[9-11] is also limited. First, the specific preterm growth charts are often based on cross-sectional birth data. Second, consensus is lacking on the correction for prematurity. In practice, preterms' calendar age is often adjusted for GA. For example, a preterm-born child at a GA of 32 weeks and a calendar age of 8 weeks is treated as a newly born full-term child for anthropometric and neurodevelopmental data. This adjustment depends on untested assumptions. Moreover, growth until term age is then derived from intrauterine growth.[9-13] Adequate growth charts for early and moderate preterms are needed, because poor growth is an indication for interventions such as specific feeding strategies or growth hormone therapy. Also, without adequate growth charts, excessive weight gain might go unnoticed.

CV	Coefficient of variation
GA	Gestational age
HC	Head circumference
Lollipop	Longitudinal Preterm Outcome Project
NICU	Neonatal intensive care unit
P50	50th percentile
PCHCs	Preventive child healthcare centers

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Our aim was to assess the median (P50) growth and the variation around the P50 for height, weight, and head circumference (HC) of preterms for ages 0 to 4 years, by GA and sex. Our second aim was to construct growth reference charts, again by GA and sex, for monitoring growth of preterms.

Methods

This study was part of Longitudinal Preterm Outcome Project (Lollipop), a study of growth, development, and the general well-being of preterm children (registered with controlled-trials.com: ISRCTN80622320).[6,14] The Lollipop cohort consists of a community-based sample of early and moderately preterm children born before 36 weeks of gestation and randomly selected full-term controls seen at preventive child healthcare centers (PCHCs) to 4 years of age. Attendance at this age was 97%. The sample comprised children born in northern, central, eastern, and southern regions of the Netherlands. Thirteen PCHCs participated, covering ~25% of the population. Oversampling of early preterm infants was done by 5 tertiary neonatal intensive care units (NICUs) covering a larger portion of The Netherlands. These NICUs sampled all early preterm infants, discharged alive from their unit. The sampling was done for children born between January 1, 2002, and December 31, 2003.

The cohort size was based on estimates of numbers needed to compile growth curves for preterm children in the Netherlands. This led to a planned inclusion of 500 early preterms and 1000 moderate preterms, which enabled us to detect a difference in growth restraint (ie, below the 10th percentile of full-term children of 10% [ie, 20% instead of 10%] between full-terms and preterms per week of GA, separately for boys and girls, with power 80% at $P = .05$). We used a sample of 1690 preterm children with a GA of 25 to 36 weeks and 634 full-term children.

We excluded children with major congenital malformations and syndromes. Children with neurologic abnormalities were included but there were few. We concluded that this sample was fairly representative of the normal population, based on national birth records.[3] We refer to our previous studies for details on the characteristics and sampling of this cohort.[6,14]

Lollipop was approved by our local institutional review board, and written informed consent was obtained from all parents or caregivers.

We collected data on growth for ages 0 to 4.5 years from hospital records and from records kept by the PCHCs visited by the children. Hospitals included tertiary NICUs as well as regional hospitals. We analyzed 38 553 standardized growth measurements. The number of measurements averaged over all children was 9.9. For early preterms, this was 11.5; for moderate preterms, 9.8; and for full-term children, 7.3. Height and weight were measured using standardized measuring devices at each location. Up to the age of 15 months, the child was measured lying supine. From 15 months onward, the child was measured standing. Weight was measured unclothed. In order to detect any registration and data-entry errors, we checked all data, for each child separately, for extreme values in the growth curves. In case of multiple sources for one measurement, in particular occurring neonatally, we cross-checked all sources.

Factors known to potentially influence prenatal and/or postnatal growth were obtained from the medical records. Nonresponding mothers were more often of non-Dutch origin and had a slightly lower socioeconomic status, measured by level of education, than respondents. Apart from this, we found no significant differences by response status.

GA was expressed as completed weeks of gestation. In >95% of the cases, we calculated GA by using the last menstrual date, confirmed by early ultrasound measurements. Otherwise, clinical estimates based on last menstrual date were checked against clinical estimates after birth. Children whose GA we could not define beyond reasonable doubt were excluded from the analyses.

Analyses

We first described the sociodemographic and perinatal characteristics of the sample. Next, we assessed median growth and the variability in growth of preterm children for height and weight for the first 4.5 years of life and for HC for the first 1.5 years of life, per week of GA and by sex. For all outcomes, measurements for the additional half year that we collected were only used to assess median growth and its variability adequately at the highest age intervals. We constructed separate growth models for height, weight, and HC based on the data of all preterms, by sex. We did not exclude multiples from our analyses, nor did we adjust the models for multiple births.

We modeled weight with the LMS model, for ages 0 to 4 years. In this model, 3 parameters vary with age: the median (P50, M-curve), the coefficient of variation (CV, S-curve), and the λ parameter from the Box-Cox transformation, which models skewness in the data (L-curve). First, a model was fitted to the data of each week separately to obtain a general comprehension of the age-dependent references. After initial model exploration in Generalized Additive Models for Location, Scale and Shape (GAMLSS, http://gamlss.org)[15,16] we found that the age transformation log(age + 0.2) yielded a minimum deviance in both boys and girls, if combined with the penalized smoother (ps).[17] We selected penalized splines with *df* being: $df(\mu) = 4$, $df(\sigma) = 1$, and $df(\nu) = 1$ on the basis of the worm plot.[18]

Next, we modeled height for the ages 0 to 4 years. Given calendar age and GA, we assumed that height would follow a normal distribution. After initial model exploration in GAMLSS,[17,18] we found that the age transformation log(age + 0.2) yielded a minimum deviance in both boys and girls, in combination with the penalized smoother,[19] and analyzing height in the original scale. We chose penalized splines with $df(\mu) = 4$ and $df(\sigma) = 1$ on the basis of the worm plot[18] and Q-statistics.[19]

We modeled HC for ages 0 to 1.5 years assuming that it also followed a normal distribution depending on age and

Table. Characteristics of the sample used for the development of growth charts*

	Early preterms	Moderate preterms	Term-born children	Total
N	612 (26.2%)	1123 (48.0%)	605 (25.8%)	2340 (100%)
Male sex	314 (51.3%)	637 (56.7%)	300 (49.6%)	1251 (53.5%)
GA (wk)				
25-27	99 (16.2%)			99 (4.2%)
28-29	186 (30.4%)			186 (8.0%)
30-31	327 (53.5%)			327 (14.0%)
32-33		360 (32.1%)		360 (15.4%)
34		308 (27.4%)		308 (13.2%)
35		455 (40.5%)		455 (19.4%)
38			101 (16.7%)	101 (4.3%)
39			152 (25.1%)	152 (6.5%)
40			216 (35.7%)	216 (9.2%)
41			136 (22.5%)	136 (5.8%)
Maternal height				
<−2 SDs	31 (5.5%)	75 (7.3%)	35 (6.3%)	141 (6.0%)
−2 SDs to −1 SD	128 (22.8%)	199 (19.2%)	91 (16.4%)	418 (17.9%)
−1 SD to +1 SD	346 (61.7%)	652 (63.1%)	361 (64.9%)	1359 (58.1%)
1 SD to 2 SDs	52 (9.3%)	92 (8.9%)	64 (11.5%)	208 (8.9%)
>2 SDs	4 (0.7%)	16 (1.5%)	5 (0.9%)	25 (1.1%)
Ethnicity				
Indigenous Dutch	539 (94.2%)	1033 (92.0%)	575 (94.8%)	2186 (93.4%)
Former Dutch colony	5 (0.9%)	13 (1.2%)	1 (0.2%)	19 (0.8%)
Labor immigrant	8 (1.4%)	17 (1.5%)	9 (1.6%)	34 (1.5%)
Other non-Dutch	20 (3.5%)	60 (5.3%)	20 (3.5%)	100 (4.3%)
Birth weight				
Mean (SD)	1297 (362)	2241 (467)	3549 (503)	2332 (933)
SGA (<P2)				
Yes	32 (5.2%)	30 (2.7%)	12 (2%)	74 (3.2%)

SGA, small for gestational age.
*In 8.1% of all cases, maternal height was unknown. In 2.8% of all cases, ethnicity was unknown. SGA was based on birth weight and compared to the Kloosterman curves[17,18] and defined as a birth weight of >2 SDs below the mean birth weight for that GA.

GA. The further procedure was similar to that for height. The resulting formulas for weight, height, and HC are in the **Appendix** (available at www.jpeds.com). The analyses assume that the sample is representative at each time point. Because the average participation rate was very high, the potential for any systematic bias was limited. Moreover, as far as we are aware, the reasons for missed visits were unrelated to the outcomes.

Finally, we integrated the data on median values, variation, and, in the case of weight, also skewness, into growth curves by means of an age grid for GAs 25 to 36 weeks, by sex. These formed the basis of the 12 growth charts that we constructed for boys and for girls.

Results

The **Table** contains the sociodemographic and perinatal characteristics of the sample and shows that our cohort consisted of >90% Caucasian mothers. The sample contained many multiples (30%), mostly twins (96%), and some triplets and quadruplets (4%).

Subsequently, we applied the growth models to weight, height, and HC for each GA from 25 to 36 and from 38 to 42 weeks, by sex. Regarding weight, the initial model per gestational week fitted the data poorly. This was due to a diminishing difference in weight gain between preterm and full-term children, which apparently could not be modeled by an additive combination of age and GA. Therefore, we added an interaction term between age and GA to the initial model. This allowed both the M- and S-curves to vary smoothly over the GAs. We present the results in **Figure 1**. In the entire (calendar) age range studied (ie, 0-4 years), median weights were lower for the former preterms across all GAs. Weight gain depended on GA because it declined with decreasing GA compared with full-terms. This pattern was the same for boys and girls. Variability, expressed as CV, however, was greater in boys than in girls, especially at the lower GAs.

Regarding height, the initial model per gestational week could be integrated into one common model, but in general there were fewer cases below the P50 than expected, especially for the boys. Allowance for skewness varying by age, however, did not yield a better fit. As can be seen in **Figure 2**, the median heights of preterms were lower for all GAs for the entire age range studied (ie, 0-4 years [calendar ages of >4 years are not shown]). Height depended on GA; it decreased with decreasing GA compared with full-terms. Growth patterns of boys and girls did not differ although variability, expressed as SD, was greater in boys than in girls, especially at lower GAs.

Regarding HC, the initial model per gestational week fitted poorly. Therefore, as in the case of weight, we added an interaction term to the model between age and GA. We present the results in **Figure 3**. The median growth in HC was lower in preterms during the first months of life. After this initial difference, however, growth in HC was comparable to full-terms. The figures per week of GA suggest that the

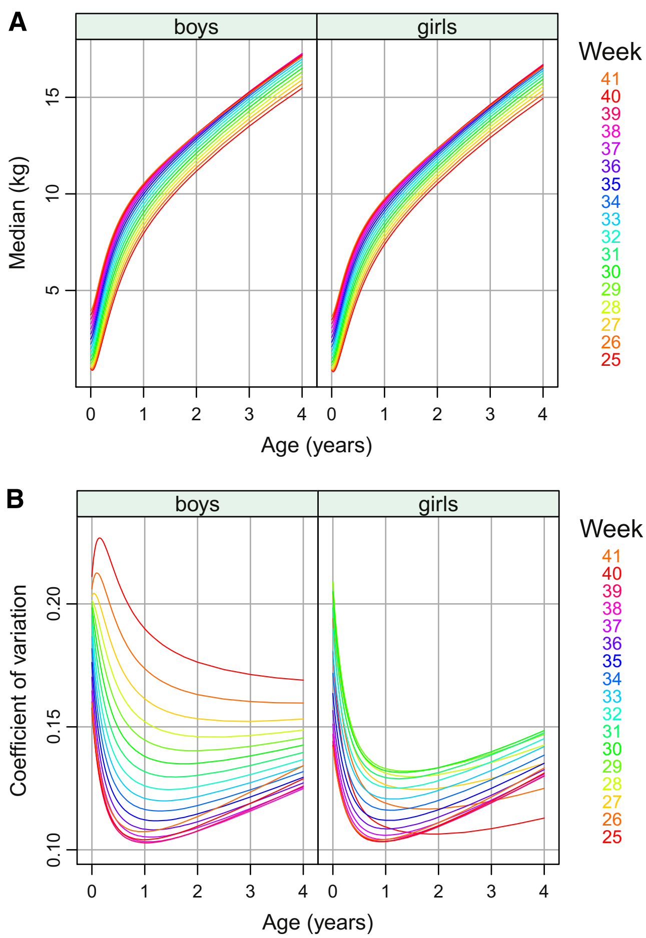

Figure 1. **A,** Growth in weight by GA and sex, ages 0 to 4 years: fitted median curves (p50). **B,** CV curves for weight. (Reprinted with permission from University Medical Center Groningen and TNO Quality of Life.)

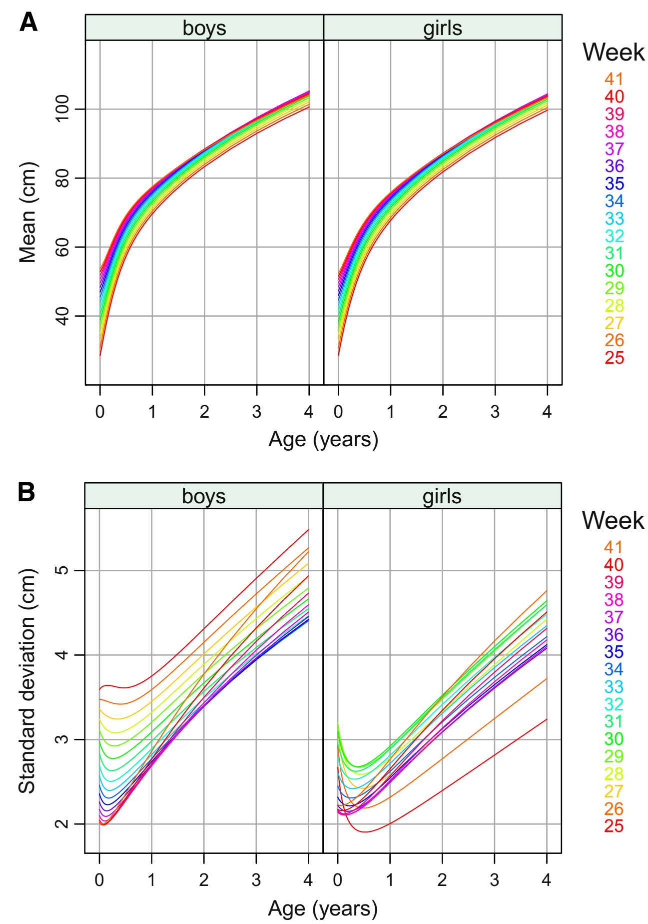

Figure 2. **A,** Growth in length/height by GA and sex, ages 0 to 4 years: fitted median (p50). **B,** Fitted SD curves for length/height. (Reprinted with permission from University Medical Center Groningen and TNO Quality of Life.)

growth of HC in utero is reduced after week 34 of gestation. This was the same for both sexes. Variability, expressed as SD, was again greater in boys than in girls, especially at the lower GAs.

Finally, we integrated the L-, M-, and S-curves into growth curves for preterms, by GA week and by sex for ages 0 to 15 months. The full range of these 24 growth curves can be accessed at: http://www.tno.nl/content.cfm?context=thema&content=prop_case&laag1=891&laag2=902&laag3=69&item_id=1738&Taal=2. At this site, similar curves are also available for full-term children. The data underlying these curves, as well as curves for children 0 to 4 years of age, are available from the authors.

Discussion

This study demonstrated that median growth of early and moderately preterm children differed from that of full-term children. Being born before 37 weeks' gestation substantially lowered the height, weight, and HC attained by a child at age 4. The lower the GA, the lower was the median value (P50). The medians of the distributions increased continuously with increasing GAs from 25 to 36 weeks. On the one hand, we found that the absolute differences in centimeters or kilograms were approximately constant up to the age of 4 years, implying that the relative differences decreased. On the other hand, the differences in HC (measured in centimeters) diminished with age and were small from the calendar age of 6 months onward. For all 3 measures of growth, variability was greater in boys than in girls, particularly for the lower GAs. This study provides the most precise growth curves that are available for preterms.

Increases in weight and height for the ages 0 to 4 years were similar for children of different GAs. Thus, on the absolute scale there was no catch-up growth. Of course, when expressed as a percentage of the height or weight attained, the difference between the GAs groups diminished over time. It is shown consistently that early preterms have a higher prevalence of growth restraint.[4,5] Recently, this was also reported for moderate preterms.[6]

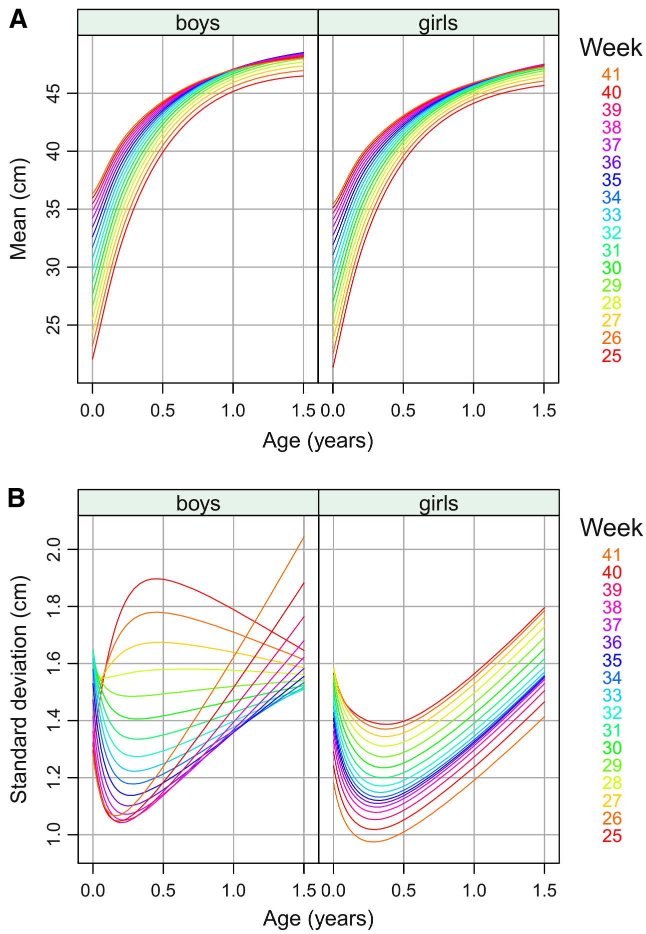

Figure 3. **A,** Growth in HC by GA and sex, ages 0 to 1.5 years: fitted median curves (p50). **B,** Fitted SD curves for HC. (Reprinted with permission from University Medical Center Groningen and TNO Quality of Life.)

We found that the HC of preterm children, at the end of the first year, was comparable with that of full-term children. Growth in HC tapers off toward the end of pregnancy and is followed by accelerated growth for the first 6 months after birth, during which time preterms grow more rapidly than full-terms. Other recent studies reported similar findings.[20,21] Perhaps HC growth in late pregnancy is prevented by the mother because uneventful birth depends on the HC of the fetus not being too large. Presumably, this restrictive mechanism is lacking in preterms causing HC growth not to be reduced.

We found greater variability in growth by GA among boys compared with girls. The greatest sex differences concerned the lower GAs (ie, ≤30 weeks). Possibly, this finding was a reflection of the fact that preterm boys are more susceptible than girls to those complications of preterm birth that influence growth. Other studies show a higher prevalence of predictors of abnormal growth in early preterm boys.[22,23] This explanation requires additional study.

It is well known that maternal height is associated with the child's (target) height and that short mothers (maternal height <−1 SD) are more likely to have short offspring in a general population.[24] The effects of short maternal height are partly mediated through small for gestational age birth.[25] This also holds true for preterm-born children. Recently, growth in early and moderately preterm-born infants was found to be largely affected by maternal height.[6] In itself, however, to our knowledge, short maternal height is not associated with preterm birth, so we did not adjust for maternal height.

A poor maternal nutritional status is associated with a lower birth weight of the offspring,[26] which might theoretically explain some of the lower weight and height of preterms. However, maternal nutritional status is generally good in the Netherlands, also in case of low socioeconomic status in the Netherlands because of the well-developed social welfare system. It is therefore unlikely that this had a large influence on birth weights or longitudinal growth in our cohort.

The major strengths of our study were the use of longitudinal data from a large, representative community-based sample including the entire range of preterm GAs, which provides more valid estimates of longitudinal growth of preterms than both did the Niklasson and World Health Organization charts. The Niklasson charts have been constructed from birth weights and postnatal growth after term. The World Health Organization charts have been mainly based on cross-sectional data regarding only healthy full-term children of breastfeeding, nonsmoking mothers living in optimal conditions for growth. The latter does not apply to most preterm-born infants. For every week of GA, from 25 to 36 weeks and for boys and girls separately, we constructed easy-to-use growth charts by integrating all the GAs in one model. This stabilized the estimates per GA and yielded easy-to-read, smoothed growth charts. An additional strength of our approach was that postnatal growth was not derived from growth in utero as it was in the approach of Guo et al.[9-11] Our findings show that the assumption that growth in utero is similar to growth ex utero does not hold.

We also recognize some limitations. Our cohort consisted of >90% Caucasian mothers. However, growth charts for newborns based on data from Caucasian children can also be used for populations of other ethnic and socioeconomic backgrounds.[27,28] Additional research is needed to support this generaliziblilty.

We did not exclude multiples from our analyses, nor did we adjust the models for multiple birth, but growth patterns may vary between multiples and singletons, in particular in the first 2 years of life.[29] In the long term, the influence of multiple birth on growth outcome is less clear than during infancy or slightly beyond and is not associated with long-term growth restriction.[6,30] Additional research on growth patterns of preterm multiples compared with singletons might clarify this issue further.

This study has several implications. It is important to recognize that preterms will not follow growth patterns of full-term–born children, even when corrected for GA. Normal growth charts are thus not useful for monitoring growth in the relatively large group of preterms. Moreover, the weight, height, and HC attained differed substantially by GA but also within a GA group. This implies the need to monitor growth closely for each preterm child. Our charts portray the normal variation between children depending on their GAs. Abnormal growth in preterms can thus be identified more precisely in Caucasian populations in industrialized countries and probably also in African American populations.[27,28] This may lead to a better targeted treatment regimen of interventions. It may also offer opportunities to optimize feeding strategies for preterm infants. ■

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Appendix

All functions for growth were programmed in R (www.r-project.org). The R code for fitting the common models was:

Weight

```
library(gamlss)
data <- boys
data2 <- data.frame(data,
  t.age = log(data$age+0.2),
  WE = data$GA-40,
  int = (data$GA-40)*(log(data$age+0.2)))
fit.wgt <- gamlss(
  wgt ~ ps(t.age,df=4)+ps(WE,df=1)+ps(int,df=1),
  sigma.formula = ~ ps(t.age,df=1)+ps(WE,df=1)
  +ps(int,df=1),
  nu.formula = ~ ps(t.age,df=1),
  data = data2, family = BCCG)
```

Height

```
fit.hgt <- gamlss(
  hgt ~ ps(t.age,df=4)+ps(WE,df=1)+ps(int,df=1),
  sigma.formula = ~ ps(t.age,df=1)+ps(WE,df=1)
  +ps(int,df=1),
  data = data2, family = NO)
```

HC

```
fit.hc <- gamlss(
  hc ~ ps(t.age,df=4)+ps(WE,df=1)+ps(int,df=2),
  sigma.formula = ~ ps(t.age,df=2)+ps(WE,df=1)
  +ps(int,df=1),
  data = data2, family = NO)
```

The *df* values were identical for boys and girls.