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Summary

Background Charts of size at birth are used to assess the postnatal growth of preterm babies on the assumption that extrauterine growth should mimic that in the uterus.

Methods The INTERGROWTH-21st Project assessed fetal, newborn, and postnatal growth in eight geographically defined populations, in which maternal health care and nutritional needs were met. From these populations, the Fetal Growth Longitudinal Study selected low-risk women starting antenatal care before 14 weeks' gestation and monitored fetal growth by ultrasonography. All preterm births from this cohort were eligible for the Preterm Postnatal Follow-up Study, which included standardised anthropometric measurements, feeding practices based on breastfeeding, and data on morbidity, treatments, and development. To construct the preterm postnatal growth standards, we selected all live singletons born between 26 and before 37 weeks' gestation without congenital malformations, fetal growth restriction, or severe postnatal morbidity. We did analyses with second-degree fractional polynomial regression models in a multilevel framework accounting for repeated measures. Fetal and neonatal data were pooled from study sites and stratified by postmenstrual age. For neonates, boys and girls were assessed separately.

Findings From 4607 women enrolled in the study, there were 224 preterm singleton births, of which 201 (90%) were enrolled in the Preterm Postnatal Follow-up Study. Variance component analysis showed that only 0·2% and 4·0% of the total variability in postnatal length and head circumference, respectively, could be attributed to between-site differences, justifying pooling the data from all study sites. Preterm growth patterns differed from those for babies in the INTERGROWTH-21st Newborn Size Standards. They overlapped with the WHO Child Growth Standards for term babies by 64 weeks' postmenstrual age.

Interpretation Our data have yielded standards for postnatal growth in preterm infants. These standards should be used for the assessment of preterm infants until 64 weeks' postmenstrual age, after which the WHO Child Growth Standards are appropriate. Size-at-birth charts should not be used to measure postnatal growth of preterm infants.

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Introduction

Preterm birth is the leading cause of neonatal mortality worldwide.[1–3] Surviving infants are at increased risk of hypertension,[4] metabolic syndrome,[5] and impaired neurodevelopment.[6] Monitoring of postnatal growth in preterm infants is based on estimates of fetal weight from ultrasonography scans, charts of size at birth for gestational age, or values for preterm or low-birthweight babies established from longitudinal studies of the general preterm population. Many charts from longitudinal data, however, are based on studies with conceptual and methodological limitations.[7]

Early postnatal growth in all neonates should be as physiological as possible for optimum survival and long-term outcomes.[8,9] Identification of growth patterns within the normal range requires comparison with prescriptive standards based on growth of babies classified as healthy. Additionally, standards can be used to monitor and assess the effectiveness of interventions and avoid ill-effects, such as overnutrition.[10] Preterm standards should complement those for babies born at term to low-risk mothers,[10,11] as recommended by WHO,[12] and should be conceptually equivalent to those used to construct the WHO Child Growth Standards.[13] In the Preterm Postnatal Follow-up Study (PPFS) of the INTERGROWTH-21st Project,[14] we assessed fetal and postnatal growth patterns to produce prescriptive standards for preterm babies. The project protocol is available online and in print.[14]

Methods

Study design and participants

INTERGROWTH-21st was a multicentre population-based study done between 2009 and 2014, in eight locations worldwide: Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle, WA, USA; Shunyi County, Beijing, China; central Nagpur, India; and Parklands suburb, Nairobi, Kenya.[14] Participants eligible for the Fetal Growth

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For the **protocol** see http://www.intergrowth21.org.uk

Research in context

Evidence before this study
We did a systematic review of longitudinal studies, with two or more measurements of a participant over time, in which the primary objective was to create postnatal growth charts for preterm infants. We searched MEDLINE, Embase, CINAHL, LILACS, and Google Scholar for papers published from Jan 1, 1945, to April 15, 2014, with the search terms "preterm infant", "premature infant", "infant, premature", "infant, extremely premature", "infant, low birth weight", "infant, very low birth weight", "infant, newborn", "growth charts", "growth curves", "anthropometric charts", "intrauterine growth charts", "neonatal growth charts", "weight growth", "growth velocity", "postnatal growth", "catch-up growth", and "postnatal growth failure". To identify additional publications, we searched the reference lists of the retrieved articles. No language restrictions were imposed. We excluded comparisons between different populations, reanalyses of previously published charts, or cross-sectional data. The overall quality of methods in the 61 studies selected was fair to low on the basis of the a priori quantified criteria. The most common shortcomings seen in the selected studies were related to anthropometric assessments, estimation of gestational age, duration of follow-up, reporting of postnatal care and morbidity, assessment of outliers and covariates, and the presentation of charts.

Added value of this study
To overcome the poor quality of previous studies in creating preterm postnatal growth standards, we aimed to derive measurements from a cohort of healthy preterm neonates. Our data build on previous work and represent standards for monitoring postnatal growth in preterm babies, especially after 32 weeks' postmenstrual age. They complement the international standards for crown–rump length in the first trimester of pregnancy, fetal growth, newborn size, and postnatal growth for term infants. These standards should be used instead of charts of size at birth to evaluate preterm infants until 64 weeks' postmenstrual age, after which use of the WHO Child Growth Standards is appropriate.

Implications of all the available evidence
When integrated, the INTERGROWTH-21st Newborn Size Standards, the Preterm Postnatal Growth Standards, and the WHO Child Growth Standards will allow appropriate comparisons to be made throughout infancy and across populations.

Longitudinal Study (FGLS) component of this project[15] were women of any ethnic origin who had started antenatal care before 14 weeks' gestation, based on reliable menstrual dates and a confirmatory ultrasound dating scan.[16] Most of their health and nutritional needs were met and adequate antenatal care was provided.[14] Women were not exposed to major environmental hazards during pregnancy.[17]

All singleton preterm babies born to FGLS participants (at 26 to less than 37 weeks' gestation) were eligible for enrolment in PPFS (appendix).[10] We considered on a case-by-case basis whether to include preterm neonates with birthweight or length for gestational age less than the third centile of the INTERGROWTH-21st Project Newborn Size Standards[18] or evidence of fetal growth restriction. The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee, the research ethics committees of the participating institutions, and the relevant health authorities.

See Online for appendix

Measurements
Weight, length, and head circumference were measured within 12 h of birth and thereafter every 2 weeks in the first 2 months and every 4 weeks until postnatal age 8 months (with leeway of 10% of age in days younger or older); for the latest babies to be born (ie, at 36 to less than 37 week's gestation) measurements were made for at least 5 months after the term due date. All babies were followed up for a minimum of 64 postmenstrual weeks.[14,19] Information was also obtained about the babies' health, morbidity, feeding practices, and food intake at each visit, and data were recorded on specially designed forms.

Trained anthropometrists took all measurements[20] using the same methods and equipment as used to obtain the WHO Child Growth Standards:[21,22] electronic scales (Seca, Hamburg, Germany) for weight, Harpenden infantometers (Chasmors, London, UK) for length, which were calibrated twice weekly, and metallic tape measures (Chasmors) for head circumference.[22] The anthropometrists were regularly assessed to ensure that they were adhering to the standard approach. The intra-observer and inter-observer margins of error of measurement were 0·3 and 0·5 cm, respectively, for length and 0·3 and 0·4 cm, respectively, for head circumference.[20] Two anthropometrists took each measurement independently. If the difference between the two measurements exceeded the maximum allowable difference (weight 50 g, length 7 mm, and head circumference 5 mm), both observers had to retake measurements a second and, if necessary, a third time until acceptable agreement was reached.

Parents were asked to report at the 1 year and 2 year follow-up visits the postnatal age at which WHO milestones for gross motor development (sitting without support, standing without assistance, and walking alone) were achieved. Values were compared with those for term infants.[23]

Feeding practices
Promotion of clinical care and feeding practices was standardised across study sites and were based on the findings of a systematic review.[24–27] Recommended feeding practices for preterm neonates were breastfeeding or bottle feeding of expressed maternal

milk; most sites also had human donor milk available. The recommended starting volume was 80 mL/kg on day 1, with daily increases of 10–20 mL/kg daily to 160–180 mL/kg by the end of the week 1. Feeding was allowed via nasogastric tube if required.[28] For babies born at less than 32 weeks' gestation, we allowed trophic feeding with small amounts of human milk (10–24 mL/kg daily) introduced on day 1.[29] The recommended duration of exclusive breastfeeding was 6 months, supplemented with 1 mg vitamin K given intramuscularly at birth[26,30] and with 400 IU vitamin D per day started in the first days of life[26,31] and 2–3 mg/kg iron per day from 2 to 8 weeks after birth. Human milk fortifiers containing 0·8–1·1 g proteins, 1·1–3·6 g carbohydrates, and minerals (eg, calcium 51–117 mg and phosphorus 34–67 mg) per serving could be added to expressed human milk until a baby's weight reached 1800–2000 g.[26]

Statistical analysis

The statistical methods were based on those used to construct the INTERGROWTH-21st Fetal Growth Standards.[15,32,33] We calculated intrauterine growth centiles for fetuses born preterm.[15] For initial assessment, measurements of postnatal weight, length, and head circumference were considered in five gestational age strata: 27–32 weeks, 33 weeks, 34 weeks, 35 weeks, and 36 weeks.

We applied variance component analysis to calculate the percentage of variance between and within sites from repeated measures of length and head circumference (fat-free-mass measurements). An exploratory crude analysis stratified by gestational age at birth, for boys and girls combined, was first done by fitting different models to each stratum of gestational age at birth. Next, multilevel, linear regression analysis was applied to the whole study population, with adjustment for postmenstrual age, which was treated as a fixed effect; sites and individuals were treated as random effects.[34,35] Weight and length, but not head circumference, exhibited a non-normal distribution and, therefore, we log-transformed the data (natural log). Assessment of outliers and the distribution of residuals showed no evidence of non-normality after log-transformation and, therefore, other methods that allow for skewness,[36–38] platykurtosis, and leptokurtosis[39] were not needed.

The best-fitting powers for median postnatal growth were provided by second-degree fractional polynomials and further modelled in a multilevel framework to account for repeated measures in the longitudinal design.[40,41] To obtain an equation for the SD, we used fractional polynomials to model the variance components resulting from the multilevel model to account for correlations between and within individuals. The data structure had two levels (ie, measurements within and between individuals) and, therefore, we fitted a random-effects model with a two-level hierarchical structure to the longitudinal postnatal data as a function of postmenstrual age, with the "runmlwin" package in Stata.[42] We included sex as a term in the model to account for differences between boys and girls. Gestational age at birth was tested in exploratory fractional polynomial models but was not significant and was not included in the final model. Goodness of fit assessments incorporated visual inspection of overall model fit by a quantile-to-quantile plot of the residuals, plots of residuals versus fitted values, and the distribution of fitted *Z* scores across gestational ages. All analyses were done with Stata, version 11.2.

Data were managed in a specially designed online system, in which data were entered locally.[43]

For **MedicSciNet INTERGROWTH-21st** see http://www.medscinet.com

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

4607 pregnant women were enrolled into FGLS,[15] of whom 224 had singleton preterm babies (appendix). 21 neonates were excluded after birth because of death (n=6), HIV/AIDS (n=1), treatment for sepsis after a positive blood culture (n=6), severe congenital malformations (n=7), or delivery at 23 weeks' gestation (n=1). Additionally, six neonates had birthweight for gestational age less than the third centile, of whom two were excluded because of patterns strongly suggestive of fetal growth restriction on antenatal ultrasonography. The remaining 201 neonates (99 boys and 102 girls) constituted the PPFS cohort: 36 (18%) from Brazil; 18 (9%) from China; 31 (15%) from India; 24 (12%) from Italy; 30 (15%) from Kenya; 30 (15%) from Oman; 22 (11%) from the UK; and ten (5%) from the USA.

159 (79%) babies had measurements taken at seven or more postnatal follow-up visits. 1759 sets of measures were obtained, of which 1446 (82%) were within the postnatal age window stipulated in the study protocol. The mean gestational age at birth of the preterm infants was 35·5 (SD 1·7) weeks, as compared with 39·6 (1·2) weeks for the remaining term neonates (n=4116; appendix). The distribution of preterm gestational ages at birth was 28 (14%) at 33 weeks or less, 68 (34%) at 34–35 weeks, and 105 (52%) at 36 weeks to less than 37 weeks; 12 neonates were born very preterm (27–32 weeks). Mean weights, lengths, and head circumferences for preterm and term neonates, respectively, were 2452 g (SD 519) and 3268 g (443), 45·6 cm (2·7) and 49·4 cm (1·9), and 31·7 cm (1·8) and 33·9 cm (1·3). The intrauterine growth and neonatal size characteristics of preterm babies were compatible with the INTERGROWTH-21st Fetal Growth[15] and Newborn Size Standards[18] up to 37 weeks' gestation (appendix). 82 (41%) of the preterm neonates were admitted to neonatal intensive care for at least 1 day. At

hospital discharge, 145 (72%) of preterm neonates were being exclusively breastfed (appendix).

Enteral feeding was started within 72 h of birth in 189 (94%) neonates, and 191 (95%) had reached full enteral feeding within 7 postnatal days. The prevalence of any breastfeeding at hospital discharge was 89% (Brazil 100%, China 28%, India 84%, Italy 96%, Kenya 100%, Oman 100%, UK 86%, and USA 100%), and was 88% at 3 months and 74% at 6 months. The prevalence of exclusive breastfeeding was 72% at hospital discharge, 55% at 3 months (58% in babies born at 34 to less than 37 weeks' gestation and 44% in babies born at 33 weeks' gestation or less), 38% at 5 months, and 13% at 6 months. The median length of hospital stay after birth was 4·0 days (IQR 2·0–8·0). The median postnatal age at weaning was 6·0 months (IQR 5·1–6·8); at 8 months 141 (70%) of babies were still being breastfed partly or exclusively.

The most prevalent neonatal complications were hyperbilirubinaemia, transient tachypnoea, and respiratory distress syndrome (appendix). During the postnatal period up to 6 months of life, the most frequently reported or diagnosed disorders were acute respiratory infections, diarrhoea, skin disorders, and febrile episodes (appendix).

The mean parent-reported postnatal ages at which the WHO milestones for gross motor development were achieved in preterm babies were 6·9 months (SD 1·3) for sitting without support, 9·8 months (1·3) for standing without assistance, and 13·1 months (1·5) for walking alone, compared with 6·0 (1·1), 7·6 (1·4), and 12·1 (1·8) for the WHO term babies.[23]

The proportion of variance between study sites was 0·2% and 4·0%, and between individuals within sites

	Measurements of length (n=1645)		Measurements of head circumference (n=1657)	
	Estimate (SE)	Proportion (%)	Estimate (SE)	Proportion (%)
Variance between study sites	0·02 (0·1)	0·2%	0·10 (0·1)	4·0%
Variance between individuals within study sites	3·95 (0·5)	57·1%	0·97 (0·1)	38·8%
Residual variance	2·96 (0·1)	42·7%	1·44 (0·1)	57·2%

Estimates are adjusted for age as a fixed effect; study site and individual are treated as random effects.

***Table*: Variance component analysis for repeated measures of length and head circumference**

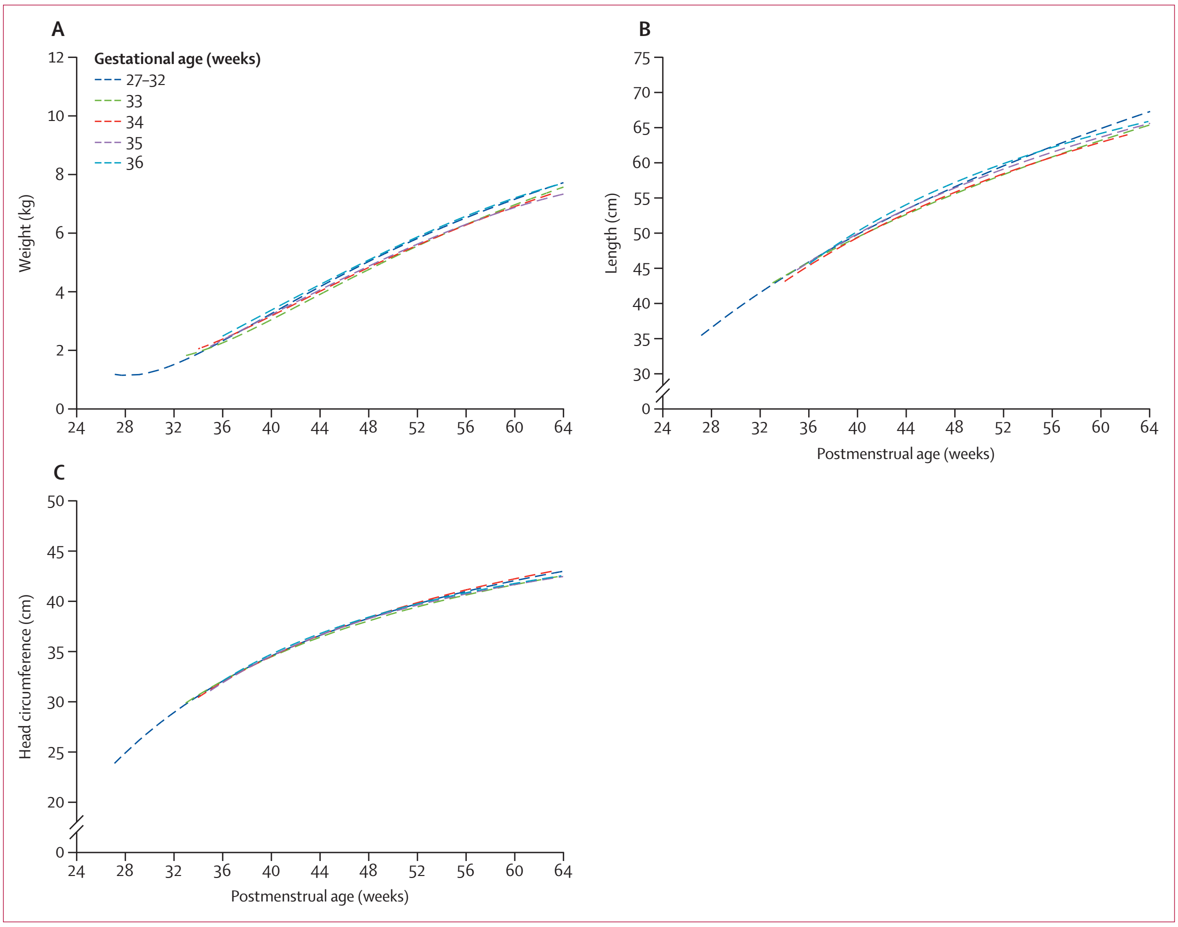

***Figure 1*: 50th centiles for postnatal weight, length, and head circumference over time in preterm babies, by gestational age at birth**

was 57% and 39% for length and head circumference, respectively (table). In short, our population had adequate intrauterine growth on ultrasonography, largely followed recommended feeding practices,[27] experienced only minor to moderate postnatal morbidity, and reached motor developmental milestones not greatly different from those in the WHO Child Growth Standards.[23]

The superimposed fitted 50th centiles for weight, length, and head circumference for the five strata of gestational age at birth were parallel and very close together (figure 1). The very preterm subgroup showed growth flattening in the first few weeks after birth, but weight gain was linear for babies born after 32 weeks' gestation. At 40 weeks' postmenstrual age, the maximum absolute difference in the 50th centiles between all preterm gestational ages at birth, combined and separately, was 240 g for weight, 0·55 cm for length, and 0·13 cm for head circumference. These values are equivalent to SD 0·45 for weight, 0·26 for

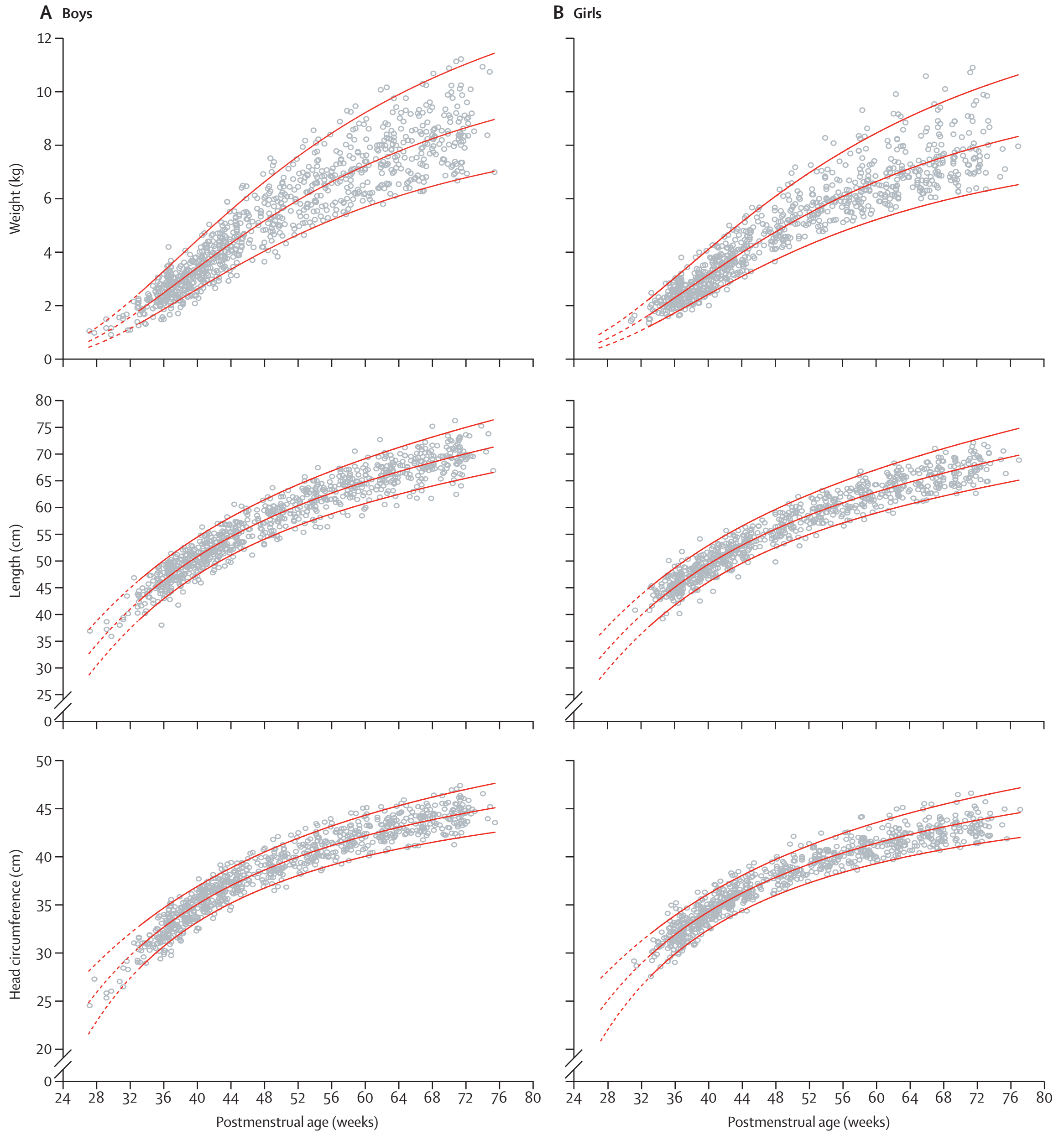

***Figure 2*: Third, 50th, and 97th centiles for postnatal weight, length, and head circumference over time in preterm babies**
Data were calculated with fractional polynomial powers in a multilevel framework to account for repeated measures. Adjustment for gestational age at birth (27–32 weeks' gestation *vs* 33–36 weeks' gestation) and interaction between sex and age did not modify the overall fit. Dashed lines represent periods with a small sample size for boys and extrapolated values for girls. Individual observations are shown with open circles.

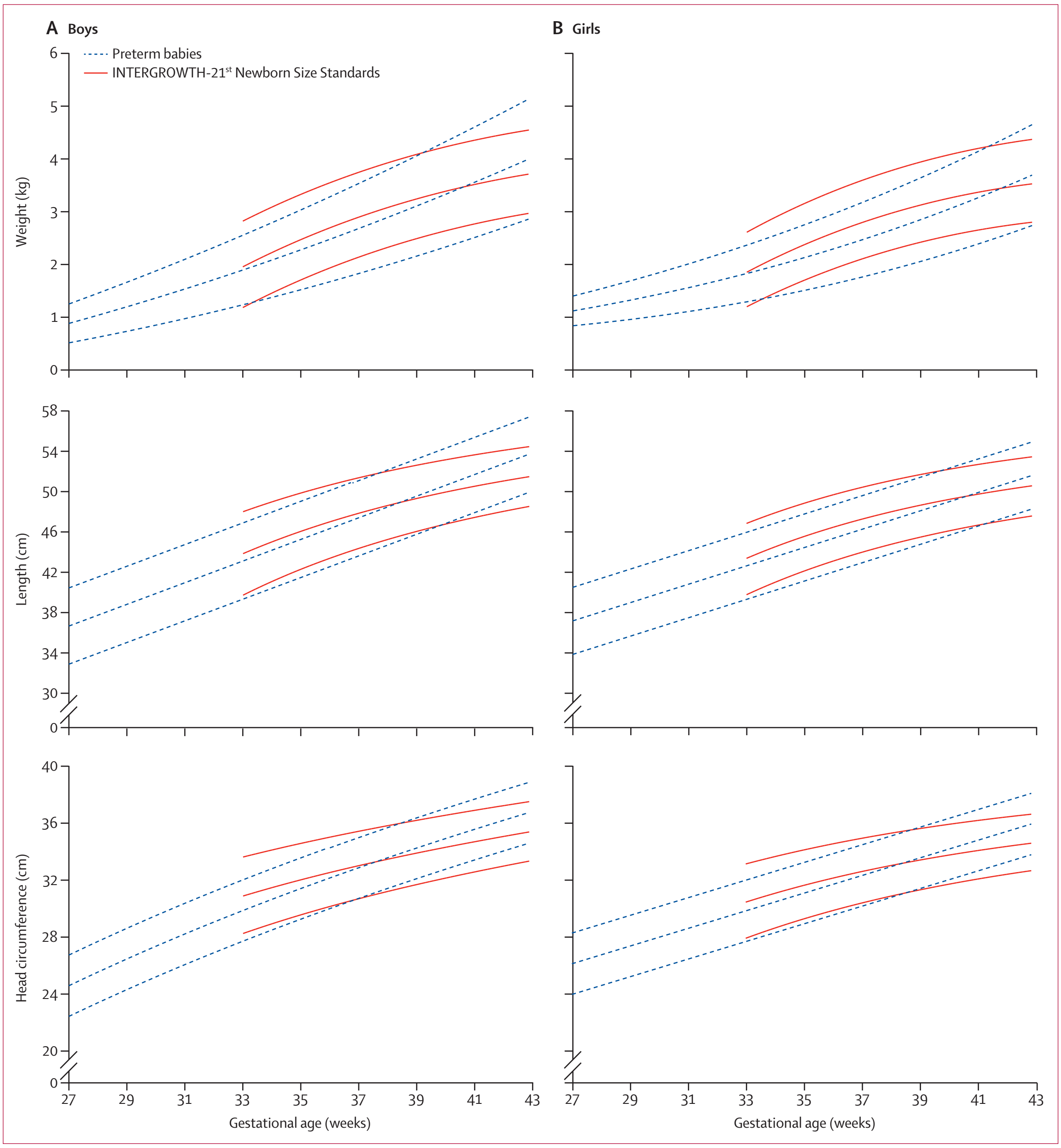

Figure 3: **Third, 50th, and 97th centiles for postnatal weight, length, and head circumference over time in preterm babies compared with INTERGROWTH-21st Newborn Size Standards[18]**

length, and 0·11 for head circumference of the combined data. Thus, the separately fitted curves differ minimally from the curve fitted for all preterm babies.

Figure 2 shows the fitted centile curves for weight, length, and head circumference in the total population for age and sex. The addition of gestational age at birth (27–32 weeks' gestation *vs* 33–36 weeks' gestation) and accounting for the interaction between sex and age in the regression models did not modify the overall fit.

Comparison of the centiles up to 42 weeks and 6 days' postmenstrual age for the preterm cohort with the corresponding gestational age, sex-specific centiles from the INTERGROWTH-21st Newborn Size Standards[18] showed that the patterns for weight, length, and head circumference differed: the pattern of postnatal growth for the preterm neonates presented in this paper (longitudinal data) is an upward concave curve to 42 weeks' gestation; conversely, anthropometry measurements at birth (cross-sectional data) from the Newborn Size Standards show a convex curve pattern with flattening towards 40 weeks' gestation (figure 3).

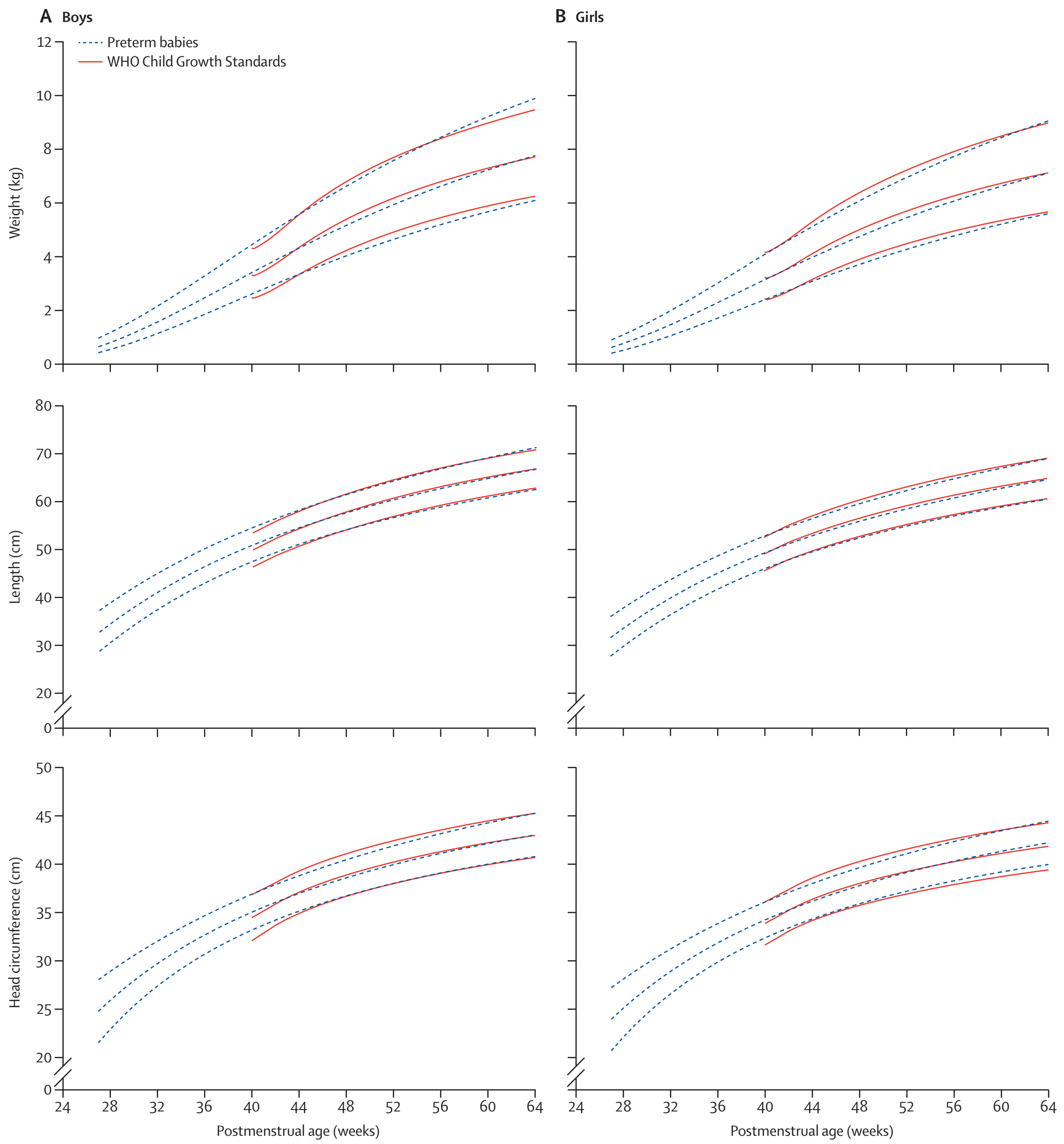

Figure 4: **Third, 50th, and 97th centiles for postnatal weight, length, and head circumference over time in preterm babies compared with the WHO Child Growth Standards[13]**

The length trajectories of the preterm infants were very similar to those of the WHO Child Growth Standards for term neonates[13] throughout the postnatal period, but weight and head circumference differed consistently from the WHO standards for term neonates until 64 weeks' postmenstrual age, particularly for the 50th and third centiles (figure 4).

Figure 5 shows the third, tenth, 50th, 90th, and 97th centiles for weight, length, and head circumference, which represent the preterm postnatal growth standards. Smoothed centiles according to age and sex and equations for the calculation of median and SD values are shown in the appendix.

Discussion

We have produced standards for postnatal growth in preterm infants with data derived from a cohort of accurately dated, uncomplicated pregnancies with adequately grown fetuses. The evidence from the detailed evaluation of growth, feeding practices, and morbidity presented here further support the supposition that the cohort was as healthy as possible.

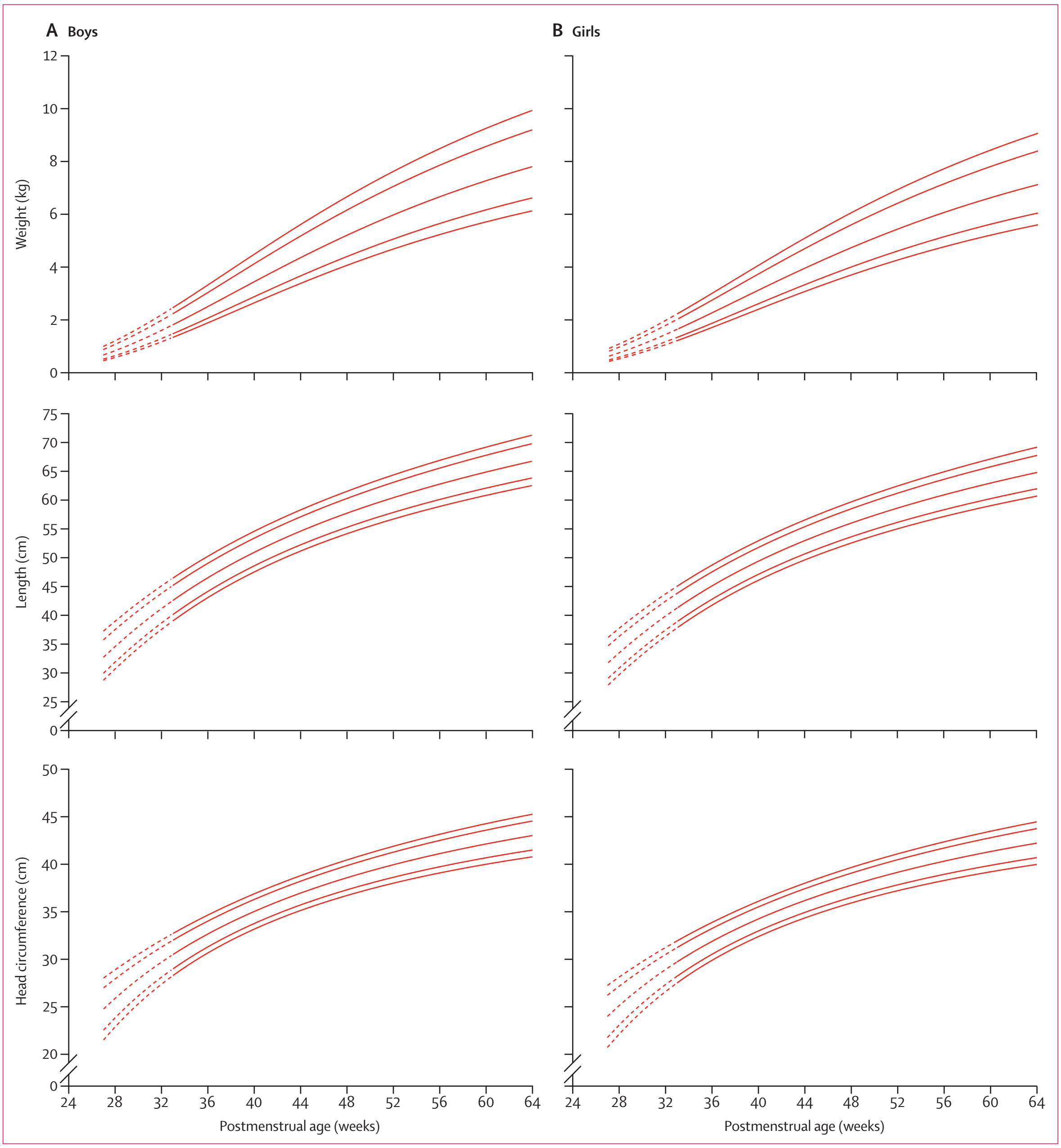

***Figure 5*: Third, tenth, 50th, 90th, and 97th centiles for weight, length, and head circumference over time in preterm babies**
Data were calculated with fractional polynomial powers in a multilevel framework to account for repeated measures. Adjustment for gestational age at birth (27–32 weeks' gestation *vs* 33–36 weeks' gestation) and interaction between sex and age did not modify the overall fit. Dashed lines represent periods with a small sample size for boys and extrapolated values for girls.

Only 0·2–4·0% of total variability in skeletal growth in the preterm babies we studied was related to differences between study sites (ie, values were very similar to those previously reported for fetal growth,[35] postnatal length in term infants,[13] and child height[44]). Conversely, variance between individuals within sites was 57% for length and 39% for head circumference. Moreover, the 50th centile curves by gestational age at birth followed almost identical, nearly linear trajectories that were consistent with those in previous reports, albeit from studies involving very preterm infants.[45–47] These findings support the pooling of data from different study sites and from different gestational age at birth strata.

We believe our standards are unique for the following reasons: we followed WHO recommendations;[12] data were collected specifically for the study; assessment of intrauterine growth showed no evidence of fetal growth restriction; we standardised all methods, equipment, training, and quality control processes across study sites; feeding practices were standardised and monitored and exclusive breastfeeding was promoted; and the analytical approach was consistent with those used in the WHO[19] and INTERGROWTH-21st studies.[33]

The need to focus on healthy pregnancies to construct the standards was the most important constraint of the study. More than 80% of the preterm neonates were born at 34 weeks' gestation or later. Only 28 preterm neonates born at 33 weeks' gestation or earlier contributed data to the standard and, therefore, it is robust for neonates with gestational age at birth of 33–36 completed weeks. Despite this distribution, we believe our study design and repeated measurements analysis compensate for the small subgroup with low gestational ages.

The construction of growth standards rather than references for neonates born before 30 weeks' gestation remains problematic because of their poor clinical status, ethical issues, and the long-term economic and health implications. We suggest that this could be viewed as a "therapeutic" dilemma that needs to be tested by comparing different feeding regimens in large, multicentre, randomised, controlled trials, with growth and development as outcomes.

We collected data at only three timepoints in the first month of life, which is a critical time period for very preterm neonates. Reassuringly, however, the pattern observed for weight gain in the very preterm infants in the first 3 weeks after birth was similar to that previously reported.[45,46]

Our study limitations should be considered in the context of the 61 postnatal growth charts for preterm infants identified in our systematic review and assessed by a priori methodological criteria (see Research in context panel).[7] These studies had substantial shortcomings in the quality of anthropometric assessment (the main outcome variable), gestational age estimation (if any), length of follow-up, and reporting of postnatal care, feeding regimens, and morbidity. Additional issues were the handling of outliers and covariates and the presentation of the charts. None of these 61 charts met the definition of a growth standard.[7]

We compared our postnatal standards with the INTERGROWTH-21st Newborn Size Standards, which were derived from cross-sectional data at birth,[18] up to postmenstrual age 42 weeks and 6 days. This comparison is most relevant for neonatologists because neonatal size charts are used to monitor postnatal growth in preterm babies and are based on the unproven assumption that extrauterine growth should mimic the intrauterine growth of fetuses matched for gestational age. The pattern of longitudinal postnatal growth in the healthy preterm babies we studied differed notably from that of their intrauterine counterparts: the convex curve with late flattening of "growth" described in cross-sectional birth charts is in contrast to the upward curve of postnatal growth in preterm infants (figure 3). Therefore, we strongly discourage the use of size-at-birth charts to monitor postnatal growth in preterm neonates because they are based on different populations, biological processes, and nutritional environments. Importantly, expecting preterm infants to grow in the same way as fetuses could result in overfeeding, to prevent or treat extrauterine growth restriction, which could result in harmful consequences for nutrition and health.[45]

The 50th centiles of our data and those for the WHO Child Growth Standards merged for all measures by 64 weeks' postmenstrual age, which shows that preterm infants without severe perinatal or postnatal complications, living in adequate conditions, and who are predominantly breastfed can progressively recuperate in early postnatal life. However, even "healthy" preterm infants have an increased morbidity risk[48] and we found that they achieved WHO gross motor developmental milestones around 1 month later than is expected for healthy term infants.[23] We are completing 2-year follow-up analyses to explore these effects further.

Finally, we believe our prescriptive growth standards are generalisable to other populations because increasing evidence shows that human growth across different ethnic and geographical groups is similar if individuals are healthy, well nourished, and free from environmental and socioeconomic constraints on growth. Additionally, the WHO Child Growth Standards, which were derived from a similarly designed study of postnatal growth, have been implemented in 125 countries.[49]

Our data build on previous work[45–47] and represent standards for monitoring postnatal growth in preterm babies, especially after 32 weeks' postmenstrual age. They complement the international standards for crown-rump length in the first trimester of pregnancy,[16] fetal growth,[15] newborn size,[18] and child growth for term infants.[13] Thus, growth and development can be monitored from the first trimester of pregnancy until age 5 years, irrespective of location, ethnic origin, or timing of birth.

Contributors

JV and SHK conceptualised and designed the INTERGROWTH-21st Project. JV, DGA, JAN, and SHK prepared the original protocol, with input from ZAB, LCI, FCB, and ATP. JV, FG, ZAB, LCI, AL, and ATP supervised and coordinated the project overall. JV, FG, EOO, DGA, and ATP were responsible for data management and analysis. EB, FCB, MGG, MP, RP, RO, and YAJ collaborated in the overall project and implemented it in their respective countries. JV, FG, CV, and SHK wrote the report with input from all coauthors. All authors read the report and made suggestions on its content.

Declaration of interests

We declare no competing interests.

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