International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project

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Summary

Background **In 2006, WHO published international growth standards for children younger than 5 years, which are now accepted worldwide. In the INTERGROWTH-21st Project, our aim was to complement them by developing international standards for fetuses, newborn infants, and the postnatal growth period of preterm infants.**

Methods **INTERGROWTH-21st is a population-based project that assessed fetal growth and newborn size in eight geographically defined urban populations. These groups were selected because most of the health and nutrition needs of mothers were met, adequate antenatal care was provided, and there were no major environmental constraints on growth. As part of the Newborn Cross-Sectional Study (NCSS), a component of INTERGROWTH-21st Project, we measured weight, length, and head circumference in all newborn infants, in addition to collecting data prospectively for pregnancy and the perinatal period. To construct the newborn standards, we selected all pregnancies in women meeting (in addition to the underlying population characteristics) strict individual eligibility criteria for a population at low risk of impaired fetal growth (labelled the NCSS prescriptive subpopulation). Women had a reliable ultrasound estimate of gestational age using crown–rump length before 14 weeks of gestation or biparietal diameter if antenatal care started between 14 weeks and 24 weeks or less of gestation. Newborn anthropometric measures were obtained within 12 h of birth by identically trained anthropometric teams using the same equipment at all sites. Fractional polynomials assuming a skewed *t* distribution were used to estimate the fitted centiles.**

Findings **We identified 20 486 (35%) eligible women from the 59 137 pregnant women enrolled in NCSS between May 14, 2009, and Aug 2, 2013. We calculated sex-specific observed and smoothed centiles for weight, length, and head circumference for gestational age at birth. The observed and smoothed centiles were almost identical. We present the 3rd, 10th, 50th, 90th, and 97th centile curves according to gestational age and sex.**

Interpretation **We have developed, for routine clinical practice, international anthropometric standards to assess newborn size that are intended to complement the WHO Child Growth Standards and allow comparisons across multiethnic populations.**

Funding **Bill & Melinda Gates Foundation.**

Lancet 2014; 384: 857–68

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Introduction

In 1994, the main WHO expert committee on the use and interpretation of anthropometry recommended the use of international standards to assess anthropometric measures.[1,2] To implement these recommendations for infants and children, WHO initiated the Multicentre Growth Reference Study (MGRS).[3] In 2006, this study generated WHO Child Growth Standards for children younger than 5 years, which are now accepted worldwide.[4,5] Two characteristics made the WHO MGRS unique and unprecedented: the study included populations from Brazil, Ghana, India, Norway, Oman, and the USA, and it used a prescriptive approach to select the study populations (inclusion of only breast-fed infants from mothers who did not smoke and who had minimum environmental constraints on growth).[6]

Aiming to complement the WHO MGRS, in 2008 the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) launched a multicountry project to develop similar prescriptive standards for fetuses, newborn infants, and the postnatal growth of preterm infants. The INTERGROWTH-21st Project was done in eight countries and completed in 2014.[7] One of its three main studies (the Newborn Cross-Sectional Study) aimed to produce newborn standards for birthweight, length, and head circumference at birth. The approach for the primary analysis[8] was based on that used in the WHO MGRS[3] to compare the similarities in skeletal size and growth of fetuses and newborn infants. The results of the two studies concur and strongly support pooling of the eight INTERGROWTH-21st populations to construct new international newborn standards.

The large number of size charts for use at birth available (104 published since 1990) and their substantial methodological heterogeneity and limitations (unpublished data) complicate the clinical assessment of a newborn infant's

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nutritional status and make comparisons difficult across populations. Available estimates for the prevalence and mortality of small-for-gestational-age babies show that these assessments are a major priority for public health.[9–11] The absence of an international standard has been a major limitation for such estimates because the many references to choose from were derived from individual countries or regions at particular timepoints. Therefore, development of an international standard for newborn infants is important for clinical practice and essential to estimate accurately the prevalence of small-for-gestational-age babies worldwide. In this Article, we present such a set of standards.

Methods

Study design and participants

INTERGROWTH-21st is a multicentre, multiethnic, population-based project done between April 27, 2009, and March 2, 2014, in eight study sites: Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle WA, USA; Shunyi County in Beijing, China; the central area of Nagpur, India; and the Parklands suburb of Nairobi, Kenya.[7] The primary aim of the project was to study growth, health, nutrition, and neurodevelopment from 14 weeks of gestation to age 2 years using the same conceptual framework as the WHO MGRS[6] to produce prescriptive growth standards and a new phenotypic classification for intrauterine growth restriction and preterm birth syndromes.[12]

The methods have been described in detail elsewhere.[7] Populations were first selected by geographical location and then by individual characteristics. At the population level, we chose an urban area (eg, a complete city or county, or part of a city with clear political or geographical limits) where most deliveries occurred in health-care facilities serving pregnant women. The areas had to be located at an altitude of 1600 m or lower; women receiving antenatal care had to plan to deliver in these institutions or in a similar hospital located in the same geographical area; and there had to be an absence or low levels of major, known, non-microbiological contamination such as pollution, domestic smoke due to tobacco or cooking, radiation, or any other toxic substances, assessed during the study period for each site with a data collection form developed specifically for the project.[13] In the eight areas, we selected all institutions providing pregnancy and intrapartum care in which more than 80% of deliveries in the area occurred. We included all newborn infants delivered in these institutions over 12 months, or until the target sample of 7000 babies per site was attained, using the same standardised data collection forms, electronic data management system, manuals of operation, and instruments.

To construct the newborn standards, we divided all pregnancies in NCSS into two groups on the basis of individual characteristics. The first, named the NCSS prescriptive subpopulation, consisted of all pregnancies and newborn infants of women who met the strict individual eligibility criteria for those at low risk of fetal growth impairment. These demographic, clinical, social, and educational criteria were identical to those used in the INTERGROWTH-21st Fetal Growth Longitudinal Study to develop the new prescriptive fetal growth standards.[7,8] We do not consider the second group (composed of all newborn infants from higher-risk pregnancies) further in this Article. The individual exclusion criteria are presented elsewhere,[7] but comprise maternal age younger than 18 years or older than 35 years, maternal height shorter than 153 cm, body-mass index (BMI) 30 kg/m² or higher or lower than 18·5 kg/m², current smoker, medical history, birth of any previous baby weighing less than 2·5 kg or more than 4·5 kg, past two pregnancies ending in miscarriage, any previous stillbirth or neonatal death, or congenital malformation.

To be included in the NCSS prescriptive subpopulation, in addition to meeting individual clinical and demographic criteria, women needed a reliable ultrasound estimate of gestational age from a measurement of crown–rump length before 14 weeks of gestation or biparietal diameter when antenatal care started between 14 and 24 weeks of gestation. All participating hospitals agreed to a policy of routinely estimating gestational age by ultrasound after a strict, standardised protocol. When ultrasound estimation was made after 24 weeks of gestation, which occurred in only 8·2% of women, it was only accepted as reliable if any difference between this estimated gestational age and the one based on the last menstrual period was 7 days or less.[14] We also recommended a policy of a more liberal use of delayed cord clamping,[15,16] which was implemented in the facilities where most births occurred. However, uptake was lower in hospitals with many private obstetricians, and some clinicians expressed concerns about the increased risk of neonatal jaundice and delayed neonatal care. No information was available at the individual patient level.

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee "C" (reference 08/H0606/139), the research ethics committees of the individual participating institutions, and the corresponding regional or national health authorities where the project was done. We obtained institutional consent to use routinely collected data and women gave oral consent.

Procedures

NCSS anthropometric teams, who were specially recruited, trained, and standardised for the study, exclusively obtained the anthropometric measures of the newborn infants. The teams took measurements within 12 h of birth using identical equipment that we provided to all sites—an electronic scale (Seca, Hangzhou, China) for birthweight, a specially designed Harpenden infantometer (Chasmors, London, UK) for recumbent length, and a metallic non-extendable tape (Chasmors) for head circumference.[17] The equipment, which was

calibrated twice a week, was selected for accuracy, precision, and robustness, as shown in previous studies.[18]

Measurement procedures were standardised on the basis of WHO recommendations to ensure maximum validity.[18] During the standardisation sessions, the intraobserver and interobserver error of measurement values for recumbent length ranged from 0·3 to 0·5 cm, and those for head circumference ranged from 0·3 to 0·4 cm. Each measurement was collected independently by two study anthropometrists.[19] If the difference between the two measurements exceeded the maximum allowable difference (birthweight 5 g, length 7 mm, and head circumference 5 mm), then both observers independently retook that measurement a second time and, if necessary, a third time.

The training, standardisation, monitoring processes, and quality control methods used across all sites are described in detail elsewhere.[17,19] Neonatal clinical practices (including those for care in neonatal intensive care units and for feeding) were standardised across sites to follow a basic package of internationally accepted evidence-based practices following an agreed protocol adopted by the project's neonatal study group and promoted across all participating hospitals.[20]

The data processing and management systems are described in detail elsewhere.[21] All documentation used in the INTERGROWTH-21st Project was tested locally and introduced into the specially developed online electronic data entry, cleaning, and management system hosted by MedSciNet. Data were entered locally directly onto the web-based system, and we used the average values of the repeated anthropometric measures. The percentage of times that measurements were taken only once was 2·4% for birthweight, 0·1% for length, and 1·0% for head circumference. In this small number of cases we used that measure in the analysis. During data cleaning, we excluded 75 measures (17 for birthweight, 26 for length, and 32 for head circumference), because they were either implausible within each study site's distribution or they were not within five SDs of the mean of the overall gestational-age-specific values. We excluded 15 newborn infants whose gestational age was older than 44 weeks of gestation.

Statistical analysis

To select the statistical methods to construct our standards, we used the same strategy as the WHO MGRS,[22] complemented by published work[23,24] and our systematic review of neonatal charts. We explored the following four methods: first, a mean and SD method using fractional polynomials;[25] second, a lambda (λ), mu (μ), and sigma (σ; LMS) method,[26–28] which assumes a power transformation at each gestational age to remove skewness, making the data approximately normally distributed; third, an LMST[29] (ie, lambda, mu, sigma, assuming Box-Cox *t* distribution) method, which assumes a shifted and scaled (truncated) *t* distribution to take account of skewness and leptokurtosis; and fourth, a LMSP[30] (lambda, mu, sigma, assuming Box-Cox power exponential distribution) method, which takes account of skewness, platykurtosis, and leptokurtosis. The LMST and LMSP methods are extensions of the LMS method that model skewness and kurtosis for situations in which the Box-Cox transformation cannot transform data close to normality.

The mean and SD method using fractional polynomials is based on the assumption of a normal distribution. The generalised additive models for location, scale, and shape framework (GAMLSS)[31,32] provides the option of fitting various distributions other than the normal (skewed and kurtotic distributions) and modelling other parameters of a distribution that determine scale and shape using fractional polynomials. Furthermore, we assessed three smoothing techniques: fractional polynomials,[25] cubic splines,[33] and penalised splines.[34] Our aim was to produce centiles that change smoothly with gestational age and that maximise simplicity without compromising model fit. To select the best model to construct the standards, we first identified the best model within a class of models (ie, two, three, and four parameter models) and, then chose the best model across different classes of models (ie, fractional polynomials, LMS, LMST, and LMSP methods). We used the Akaike information criterion and Bayesian information criterion to compare models within and across different classes of models.[35] We calculated the best model across different classes in an add-up stepwise form, starting from the simplest class of models.

For the **protocol** see http://www.medscinet.net/Intergrowth/patientinfodocs/Neonatal%20Manual%20Final.pdf

We selected the skew *t* distribution (type 3)[36] with four parameters (μ, σ, υ, and τ) as the most appropriate distribution to construct the curves for birthweight, length, and head circumference. We used fractional polynomials to fit models to the three anthropometric measures using two powers for the mean and one for the SD while keeping the skewness and kurtosis values constant. In all cases, we applied the fractional polynomial smoothing technique. None of the LMS, LMST, and LMSP methods gave a noticeable improvement compared with our chosen approach. We fitted all models separately for boys and girls. We required at least 50 observations for each gestational age to construct the standards. This criterion resulted in 33 weeks as the lower limit. Hence, we excluded 112 babies.

For the **MedSciNet's website** see http://medscinet.com/

Goodness-of-fit was evaluated to inform the decision about whether or not to select a more complex model. This evaluation incorporated both visual inspection of overall model fit using quantile-quantile plots of the residuals; detrended quantile-quantile plots of the residuals (worm plot)[37] and the *Q* statistic for a particular gestational age range[38] to identify regions (intervals) of the explanatory variable within which the model did not adequately fit the data; plots of residual versus fitted values; and the distribution of fitted *Z* scores across gestational ages.

All models and goodness-of-fit assessments were fitted with R statistical software[39] using the GAMLSS framework.[31,32] All graphics were produced using Stata

software (version 11.2). Tables containing means and SDs, centile values, and *Z* scores for boys and girls, expressed in completed weeks of gestation (as recommended by WHO International Statistical Classification of Diseases and Related Health Problems 10 [ICD-10]), and printable charts will be available free by December, 2014, on the INTERGROWTH-21st Project website. A method to calculate the individual centiles and *Z* scores by gestational age (in exact weeks and days) for boys and girls will be made available free on the same website.

For the **INTERGROWTH website** see http://www.intergrowth21.org

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data and all authors made the decision to submit the paper for publication.

Results

Between May 14, 2009, and Aug 2, 2013, we enrolled 59 137 pregnant women at the eight sites, of whom 6056 did not have a reliable estimate of gestational age and 910 had multiple pregnancies. Of the remaining 52 171 women, 20 486 (35% of the total NCSS population) met the individual clinical and demographic eligibility criteria for the standards presented here, had a reliable ultrasound estimate of gestational age, and delivered one live baby without a congenital malformation. These 20 486 newborn infants are the NCSS prescriptive subpopulation. The most common reasons for ineligibility (although some women might have more than one reason) were maternal age younger than 18 years or older than 35 years (7929 women; 25%), maternal height shorter than 153 cm (5932; 19%), BMI 30 kg/m² or higher (6579; 21%) or lower than 18·5 kg/m² (2923; 9%), current smoker (2478; 8%), medical history (8406; 26%), birth of any previous baby weighing less than 2·5 kg or more than 4·5 kg (2310; 7%), past two pregnancies ending in miscarriage (1785; 6%), any previous stillbirth or neonatal death (1077; 3%), or congenital malformation (287; 1%).

The contribution of each site to the subpopulation used in this analysis ranged from 5% (1027 women) for the USA to 18% (3702) from Kenya (table 1); the three high-income countries represented 31% of the sample (14% from the UK, 12% from Italy, and 5% from the USA). China contributed 17% of the population, with 12% from India, and 14% from Oman (table 1). Differences in each country's contribution to this NCSS prescriptive subpopulation reflect the different risk profiles of the populations—ie, inner-city Seattle and Pelotas had fewer eligible women (16% and 24%, respectively) than had Shunyi County, Beijing (48%), the Parklands suburb of Nairobi (48%), Oxford (36%), or Muscat (37%). 32% of women from central Nagpur and 29% of women from Turin were eligible.

A detailed description of each of these study populations has been presented elsewhere.[8] At baseline, the groups at the eight sites were, as expected, similar because the same inclusion criteria were used. However, we note some differences in maternal size: mothers from India were the shortest and those from the UK and the USA were the tallest; UK mothers were the heaviest and Indian mothers the lightest. However, maternal BMI values were similar across all sites. The mean maternal age was 28·0 (SD 4·0) years; most women were married or in cohabitation; educational achievement was high at all sites. Two-thirds of women were nulliparous (table 1).

Table 1 also shows pregnancy and perinatal events by site and for the total population. As expected, there was variability across the sites, but all indicators for mortality and morbidity were consistent with the populations' status as healthy and well nourished—eg, pre-eclampsia rate was 1·2% (ranging from 3·5% in the UK to 0·2% in India). Rates for spontaneous initiation of labour and for caesarean section differed substantially because of well recognised variations in clinical practice in these countries: Brazil had the highest caesarean section rate (65%), and Oman (14%) and the UK (18%) had the lowest rate. The overall preterm birth (<37 weeks of gestation) rate was 5·5% (ranging from 10·0% in India to 3·4% in the UK). The preterm birth rate after spontaneous initiation of labour was 3·1% overall (ranging from 5·0% in Brazil to 1·9% in the UK). For term babies, the overall mean birthweight was 3·3 (SD 0·5) kg, length 49·3 (1·8) cm, and head circumference 33·9 (1·3) cm.

51·2% of newborn babies were boys (ranging from 49·7% in Italy to 53·2% in the USA). Neonatal mortality up to hospital discharge was very low overall and per site, and 88% (ranging from 73% in Italy to 99% in India) of newborn infants were discharged from hospital being exclusively breastfed. These patterns all provide confirmatory evidence of the adequate health and nutritional status of the study population, as required for the construction of standards for neonatal measures of growth.

We assessed similarities between smoothed centiles curves (3rd, 50th, and 97th centiles) estimated using fractional polynomials and the observed centiles by superimposing them by gestational age. Figure 1 shows the individual values, observed, and smoothed centiles for birthweight, length, and head circumference for gestational age, showing almost identical values with very few exceptions at the lower end of the gestational age distribution in which only a small number of individual measures could be made—eg, at the 3rd centile for length at 34–35 weeks of gestation.

Overall, the average differences in absolute values between smoothed and observed centiles were small—45·2 g in boys and 39·8 g in girls for birthweight (figure 1A), 0·22 cm in boys and 0·18 cm in girls for length (figure 1B), and 0·13 cm in boys and 0·12 cm in girls for head circumference (figure 1C). Considering the direction of the variation, the average differences between

the smoothed and observed centiles, independent of sex, were negligible—0·71 g for birthweight; 0·02 cm for length, and 0·001 cm for head circumference.

Figure 2 shows the 3rd, 10th, 50th, 90th, and 97th smoothed centile curves for birthweight, length, and head circumference according to gestational age and sex, which represent the international standards for newborn infants. For length and head circumference, the pattern of growth increased steadily from 33 weeks of gestation onwards. The curves for birthweight show a faster overall increase as gestational age increases. Table 2, table 3, and table 4 present the values for these centiles according to gestational age and sex. Overall, boys were heavier, longer, and had larger head circumferences than girls.

	Brazil (n=1595)	China (n=3551)	India (n=2493)	Italy (n=2358)	Kenya (n=3702)	Oman (n=2821)	UK (n=2939)	USA (n=1027)	Total (n=20 486)
Maternal age (years)	26·4 (4·8)	26·3 (3·0)	27·5 (3·3)	29·9 (4·0)	28·8 (3·5)	26·9 (4·0)	29·1 (4·3)	29·5 (3·9)	28·0 (4·0)
Maternal height (cm)	162·5 (5·4)	161·7 (4·5)	157·6 (3·3)	163·3 (5·6)	162·3 (5·5)	158·8 (4·1)	165·3 (6·1)	164·8 (6·2)	161·8 (5·6)
Maternal weight (kg)	63·2 (8·4)	58·8 (7·6)	57·0 (7·7)	60·4 (7·9)	63·6 (8·5)	60·7 (8·5)	64·4 (8·8)	63·7 (9·0)	61·3 (8·6)
Maternal body-mass index (kg/m²)	23·9 (2·8)	22·5 (2·7)	22·9 (2·9)	22·6 (2·6)	24·1 (2·9)	24·1 (3·1)	23·5 (2·8)	23·4 (2·8)	23·4 (2·9)
Gestational age at first visit (weeks)	14·0 (5·8)	16·2 (5·4)	14·3 (7·5)	13·1 (3·6)	17·1 (7·9)	15·2 (5·7)	13·2 (3·1)	12·0 (4·0)	14·8 (6·0)
Years of formal education	11·3 (3·6)	13·9 (1·9)	16·2 (1·3)	13·7 (3·8)	14·9 (2·3)	13·2 (2·8)	16·0 (3·0)	16·5 (3·2)	14·2 (3·0)
Haemoglobin concentration before 15 weeks' gestation (g/L)	123 (9)	133 (10)	112 (11)	129 (10)	125 (14)	117 (11)	125 (9)	126 (9)	123 (12)
Married or cohabiting (%)	1468 (92·0%)	3548 (99·9%)	2485 (99·7%)	2327 (98·7%)	3525 (95·2%)	2821 (100%)	2762 (94·0%)	941 (91·6%)	19 877 (97·0%)
Nulliparous (%)	998 (62·6%)	3320 (93·5%)	1719 (69·0%)	1472 (62·4%)	1877 (50·7%)	1228 (43·5%)	1753 (59·6%)	629 (61·2%)	12 996 (63·4%)
Pre-eclampsia (%)	23 (1·4%)	49 (1·4%)	6 (0·2%)	13 (0·6%)	40 (1·1%)	8 (0·3%)	102 (3·5%)	15 (1·5%)	256 (1·2%)
Pyelonephritis (%)	25 (1·6%)	0	0	4 (0·2%)	16 (0·4%)	3 (0·1%)	2 (0·1%)	4 (0·4%)	54 (0·3%)
Maternal sexually transmitted infection (%)	20 (1·3%)	0	0	8 (0·3%)	2 (0·1%)	0	2 (0·1%)	36 (3·5%)	68 (0·3%)
Spontaneous initiation of labour (%)	850 (53·3%)	1390 (39·1%)	1528 (61·3%)	1985 (84·2%)	2482 (67·0%)	2494 (88·4%)	2025 (68·9%)	716 (69·7%)	13 470 (65·8%)
PPROM (<37 weeks; %)	62 (3·9%)	65 (1·8%)	48 (1·9%)	24 (1·0%)	47 (1·3%)	35 (1·2%)	37 (1·3%)	20 (1·9%)	338 (1·6%)
Caesarean section (%)	1040 (65·2%)	2077 (58·5%)	1516 (60·8%)	488 (20·7%)	1187 (32·1%)	395 (14·0%)	513 (17·5%)	236 (23·0%)	7452 (36·4%)
NICU admission longer than 1 day (%)	143 (9·0%)	438 (12·3%)	93 (3·7%)	56 (2·4%)	143 (3·9%)	152 (5·4%)	108 (3·7%)	51 (5·0%)	1184 (5·8%)
Preterm birth (<37 weeks; %)	143 (9·0%)	212 (6·0%)	250 (10·0%)	83 (3·5%)	154 (4·2%)	145 (5·1%)	100 (3·4%)	49 (4·8%)	1136 (5·5%)
Preterm birth after spontaneous onset of labour (%)	79 (5·0%)	87 (2·5%)	111 (4·5%)	55 (2·3%)	91 (2·5%)	113 (4·0%)	57 (1·9%)	41 (4·0%)	634 (3·1%)
Term* low birthweight (<2500 g; %)	31 (1·9%)	22 (0·6%)	222 (8·9%)	50 (2·1%)	134 (3·6%)	126 (4·5%)	49 (1·7%)	17 (1·7%)	651 (3·2%)
All low birthweight (<2500 g; %)	92 (5·8%)	75 (2·1%)	338 (13·6%)	91 (3·9%)	206 (5·6%)	183 (6·5%)	100 (3·4%)	44 (4·3%)	1129 (5·5%)
Neonatal mortality (%)	4 (0·3%)	0	4 (0·2%)	0	9 (0·2%)	4 (0·1%)	0	1 (0·1%)	22 (0·1%)
Boys (%)	823 (51·6%)	1861 (52·4%)	1287 (51·6%)	1173 (49·7%)	1850 (50·0%)	1471 (52·2%)	1471 (50·1%)	546 (53·2%)	10 482 (51·2%)
Exclusive breastfeeding at hospital discharge (%)	1499 (94·0%)	2870 (80·8%)	2455 (98·5%)	1720 (72·9%)	3616 (97·7%)	2736 (97·0%)	2281 (77·6%)	815 (79·4%)	17 992 (87·8%)
Mother admitted to intensive care unit (%)	3 (0·2%)	2 (0·1%)	1	7 (0·3%)	5 (0·1%)	18 (0·6%)	1	1 (0·1%)	38 (0·2%)
Term* birthweight (kg)	3·3 (0·4)	3·4 (0·4)	2·9 (0·4)	3·3 (0·4)	3·3 (0·4)	3·1 (0·4)	3·5 (0·5)	3·4 (0·5)	3·3 (0·5)
Term* birthlength (cm)	49·0 (1·7)	49·7 (1·6)	48·6 (1·8)	49·4 (1·7)	49·1 (1·8)	49·0 (1·8)	49·9 (1·9)	49·9 (2·2)	49·3 (1·8)
Term* birth head circumference (cm)	34·2 (1·2)	33·6 (1·2)	33·1 (1·1)	34·0 (1·2)	34·2 (1·2)	33·6 (1·1)	34·5 (1·3)	34·5 (1·4)	33·9 (1·3)

Only includes pregnancies leading to one livebirth birth and no congenital malformations. All values are means (SD) for continuous variables and absolute numbers (percentages) for categorical variables. PPROM=preterm pre-labour rupture of membranes. NICU=neonatal intensive care unit. *Term indicates all babies born at 37 weeks' gestation or later.

***Table 1*: Maternal baseline characteristics, perinatal events, and newborn baby measures**

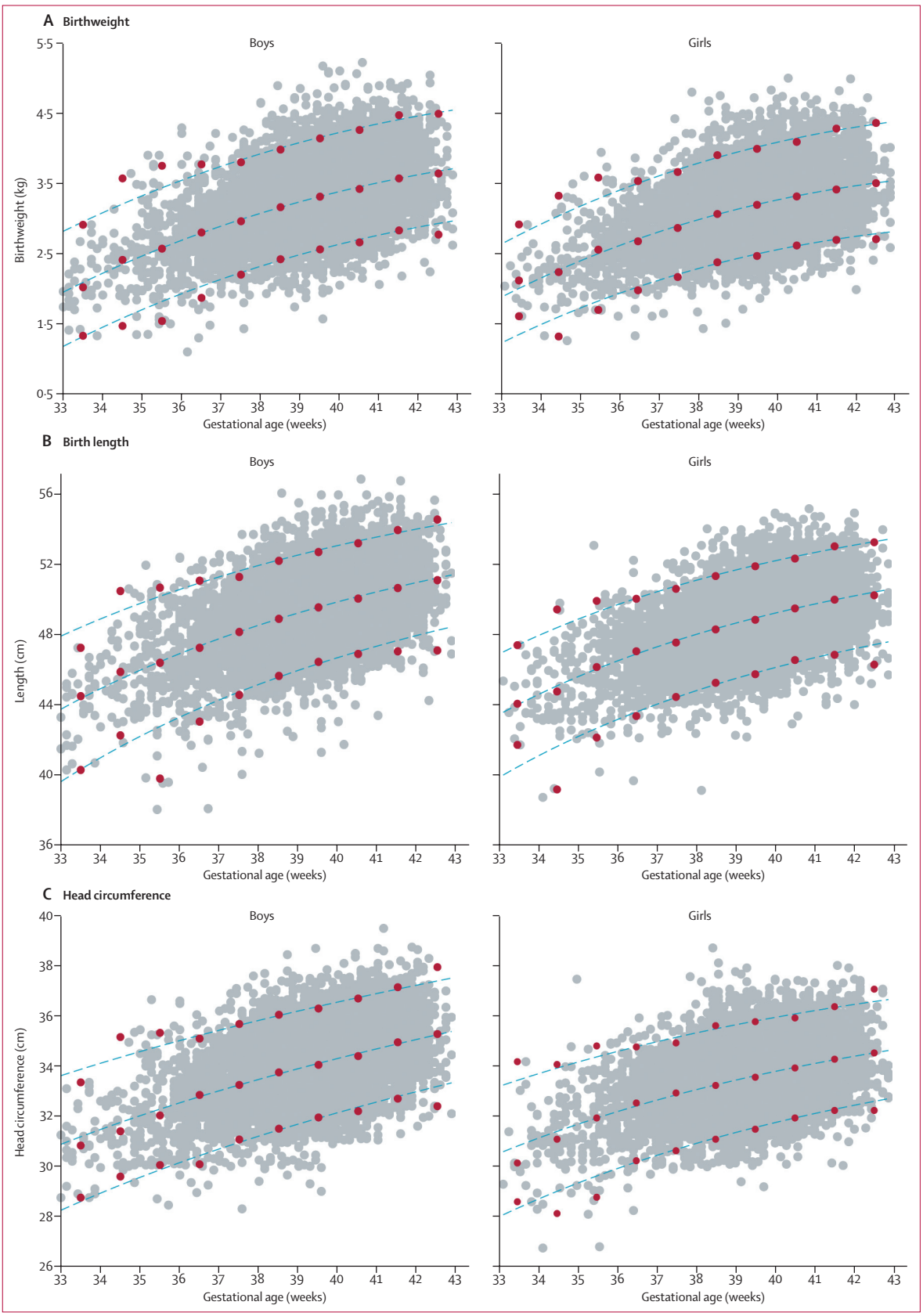

***Figure 1*: Fitted 3rd, 50th, and 97th smoothed centile curves (blue lines) for (A) birthweight, (B) birth length, and (C) head circumference according to gestational age**
Shows empirical values for each week of gestation (red circles) and the actual observations (grey circles).

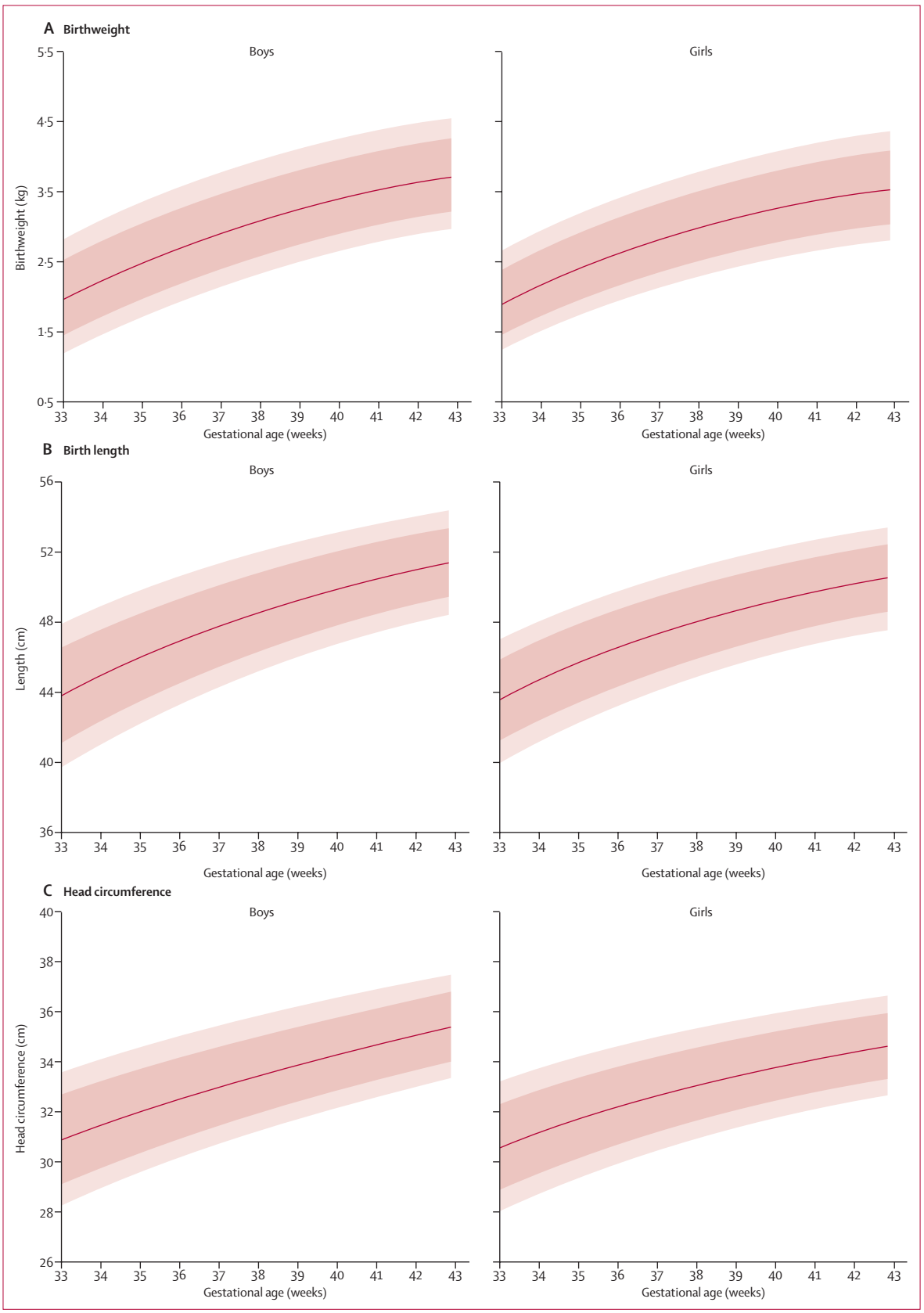

Figure 2: The 3rd, 10th, 50th, 90th, and 97th smoothed centile curves for (A) birthweight, (B) birth length, and (C) head circumference according to gestational age

	Boys						Girls					
	Number of observations	Centiles for birthweight (kg)					Number of observations	Centiles for birthweight (kg)				
		3rd	10th	50th	90th	97th		3rd	10th	50th	90th	97th
33 weeks	34	1·18	1·43	1·95	2·52	2·82	17	1·20	1·41	1·86	2·35	2·61
34 weeks	48	1·45	1·71	2·22	2·79	3·08	65	1·47	1·68	2·13	2·64	2·90
35 weeks	128	1·70	1·95	2·47	3·03	3·32	114	1·71	1·92	2·38	2·89	3·16
36 weeks	323	1·93	2·18	2·69	3·25	3·54	293	1·92	2·14	2·60	3·12	3·39
37 weeks	857	2·13	2·38	2·89	3·45	3·74	803	2·11	2·33	2·80	3·32	3·60
38 weeks	2045	2·32	2·57	3·07	3·63	3·92	1802	2·28	2·50	2·97	3·51	3·78
39 weeks	3009	2·49	2·73	3·24	3·79	4·08	2869	2·42	2·65	3·13	3·66	3·94
40 weeks	2568	2·63	2·88	3·38	3·94	4·22	2523	2·55	2·78	3·26	3·80	4·08
41 weeks	1179	2·76	3·01	3·51	4·06	4·35	1195	2·65	2·89	3·37	3·92	4·20
42 weeks	206	2·88	3·12	3·62	4·17	4·46	224	2·74	2·98	3·46	4·01	4·30
Total	10 397	..	..	..	..	..	9905	..	..	..	..	..

Table 2: Smoothed centiles for birthweight of boys and girls according to gestational age

	Boys						Girls					
	Number of observations	Centiles for length (cm)					Number of observations	Centiles for length (cm)				
		3rd	10th	50th	90th	97th		3rd	10th	50th	90th	97th
33 weeks	33	39·69	41·09	43·81	46·55	47·97	17	39·79	41·01	43·39	45·70	46·85
34 weeks	48	41·05	42·38	44·98	47·59	48·94	65	41·04	42·22	44·55	46·79	47·92
35 weeks	128	42·26	43·54	46·03	48·53	49·82	111	42·14	43·30	45·57	47·76	48·86
36 weeks	320	43·36	44·58	46·97	49·38	50·62	292	43·13	44·26	46·48	48·62	49·69
37 weeks	849	44·34	45·52	47·82	50·14	51·34	799	44·01	45·11	47·29	49·39	50·44
38 weeks	2031	45·22	46·37	48·59	50·83	51·99	1786	44·79	45·88	48·01	50·07	51·10
39 weeks	2983	46·02	47·13	49·29	51·46	52·59	2846	45·49	46·56	48·65	50·68	51·69
40 weeks	2531	46·75	47·83	49·92	52·03	53·13	2486	46·12	47·17	49·23	51·23	52·22
41 weeks	1146	47·41	48·46	50·50	52·56	53·62	1180	46·68	47·72	49·75	51·72	52·70
42 weeks	202	48·01	49·04	51·03	53·03	54·07	218	47·19	48·21	50·22	52·15	53·12
Total	10 271	..	..	..	..	..	9800	..	..	..	..	..

Table 3: Smoothed centiles for birth length of boys and girls according to gestational age

	Boys						Girls					
	Number of observations	Centiles for head circumference (cm)					Number of observations	Centiles for head circumference (cm)				
		3rd	10th	50th	90th	97th		3rd	10th	50th	90th	97th
33 weeks	33	28·25	29·11	30·88	32·71	33·62	17	27·92	28·76	30·46	32·24	33·14
34 weeks	48	28·93	29·76	31·47	33·23	34·11	65	28·64	29·44	31·08	32·78	33·65
35 weeks	127	29·56	30·37	32·02	33·73	34·58	111	29·28	30·06	31·64	33·28	34·12
36 weeks	322	30·15	30·93	32·53	34·19	35·02	293	29·87	30·62	32·14	33·74	34·55
37 weeks	848	30·69	31·46	33·02	34·63	35·43	798	30·40	31·13	32·61	34·15	34·94
38 weeks	2032	31·21	31·95	33·47	35·04	35·83	1783	30·88	31·59	33·03	34·53	35·30
39 weeks	2985	31·69	32·42	33·90	35·44	36·20	2849	31·32	32·01	33·41	34·88	35·62
40 weeks	2532	32·15	32·86	34·31	35·81	36·56	2486	31·72	32·39	33·76	35·19	35·92
41 weeks	1147	32·58	33·28	34·70	36·17	36·91	1180	32·08	32·74	34·08	35·48	36·19
42 weeks	204	32·99	33·68	35·07	36·52	37·24	218	32·41	33·06	34·37	35·74	36·44
Total	10 278	..	..	..	..	..	9800	..	..	..	..	..

Table 4: Smoothed centiles for head circumference of boys and girls according to gestational age

Because some variability existed in the number of women that each study site contributed to the total population, we did predetermined sensitivity analyses to assess the effects of excluding country-specific data on our overall standards. These separate exclusions had a negligible effect.

Discussion

The INTERGROWTH-21st Project aimed to produce, for the first time (panel), international standards for newborn size for each gestational age based on data from its NCSS subpopulation, which conformed at population and individual levels to the prescriptive approach used in the WHO MGRS.[3] These new standards are considered to be a conceptual and practical link to WHO Child Growth Standards, which have been adopted by more than 125 countries worldwide.[40,41] They will bridge gaps in clinical and population assessments[42] for fetuses, neonatal babies, and infants through provision of similar instruments to monitor child growth seamlessly from early pregnancy to age 5 years and to screen for stunting and wasting. Later in 2014, we will provide, on *The Lancet*'s website and through the INTERGROWTH-21st Project website and the Global Health Network, software for clinical and epidemiological use free of charge, including an app to calculate *Z* scores and centiles.

We believe these standards are unique because, in the study protocol, we deliberately addressed most of the important limitations that were previously identified.[43,44] First, the standards are prescriptive—ie, they describe optimum size in newborn infants without congenital abnormalities—whereas reference charts describe only newborn infant size at a given place and time, which might be several decades in the past. Thus, the standards were constructed with use of data collected specifically for that purpose from populations selected on the basis of their socioeconomic, health, and nutritional status, creating a low-risk environment for fetal growth impairment. Second, the standards are population-based, multiethnic, multicountry, and sex-specific, and they arise from a prospective study. We have shown (using several analytical strategies) that the eight populations were consistently similar and could be pooled to create the standards.[8] Third, several processes were applied across all eight study sites—eg, uniform research methods and one protocol for gestational age estimation by ultrasound for all participants, plus standardised identical equipment, training, a centralised electronic data management system, and close monitoring of staff, which, to our knowledge, have never before been attempted in perinatal research. Fourth, the analytical approach followed that of the WHO MGRS in terms of how to present the observed and smoothed data and explore the best fitting model with an a-priori strategy.[22] The data are reported according to completed weeks of gestation (WHO ICD-10) as smoothed centiles, which were shown to be consistent with the raw data, increasing confidence in the curves that we produced. Fifth, we present centiles for birthweight, length, and head circumference by sex and gestational age based on a prescriptive approach that are integrated with the corresponding fetal growth standards.

This prescriptive approach required us to select populations at low risk of fetal growth impairment and, within these populations, select healthy well-nourished women who were receiving adequate antenatal care and whose pregnancies were not complicated by any major clinical problems. The samples represented 34·6% of the total NCSS population, indicating that we did not select a group with low external validity to the populations in which the standards will be used. Nevertheless, the study population did have a very low rate (5·5%) of preterm birth (births before 37 weeks of gestation), mostly consisting of late preterm births—ie, after 34 weeks of gestation and before 37 weeks of gestation and a very low rate of low birthweight in term babies (3·2%). The preterm birth rate in our study is similar to that recently reported for European countries,[45] providing further evidence that our study population was genuinely low-risk. The caesarean section rate noted in these populations is higher than would be expected for their level of risk, but it is consistent with worldwide trends.[46]

The women whose babies contributed to the construction of the standards reported here were selected on the basis that they were living in environments in which exposure to risk factors known to affect fetal growth was as low as

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Panel: Research in context

Systematic review

We did a systematic review of all charts and references published since 1990 that aimed to evaluate anthropometric measures of newborn infants. We searched PubMed, Medline, Embase, CINAHL, LILACS, and Google Scholar using MeSH terms related to infants at birth ("neonate" OR "newborn" OR "fetal growth" OR "intrauterine growth"), anthropometric variables ("weight" OR "length" OR "head circumference" OR "BMI" OR "ponderal index"), distribution of the variable ("percentiles" OR "centiles" OR "curves" OR "charts"), and "gestational age", while omitting "velocity" to exclude longitudinal fetal growth studies. We examined the references of retrieved full-text articles for additional articles. We included studies published between Jan 1, 1990 and Dec 31, 2012 (updated up to April, 2014) with the main aim of creating neonatal anthropometric charts. No language restriction was applied. We identified 104 relevant studies of varying quality and size (data not shown). The substantial methodological heterogeneity and the large number of charts available complicate the clinical assessment of a newborn infant's nutritional status and make comparisons difficult across populations. Therefore, international standards for newborn size were needed.

Interpretation

We present international, sex-specific standards for weight, length, and head circumference for gestational age at birth that complement the available WHO Child Growth Standards and allow comparisons across populations. The international standard for length at birth for gestational age, in particular, when incorporated into routine neonatal care, will provide a method for the early diagnosis of stunting, which can be then be monitored during infancy and childhood using the corresponding WHO Child Growth Standards.

possible and that they themselves were healthy, non-obese, and without any factors or disorders that would affect fetal growth. Hence, the standards characterise optimum fetal growth—ie, they describe how fetuses everywhere should grow when there are minimum constraints. The standards are universal and independent of time: they are not intended to be representative of a given population or region at a given time, as opposed to a reference, and they can be used to assess the size of newborn infants, irrespective of ethnicity, locality, socioeconomic status, or health-care provision. The standards complement the WHO Child Growth Standards, which were also derived from six populations of babies born to healthy, non-smoking women with low rates of obesity.[3]

A shortcoming of studying such a low-risk group is that there were relatively few early preterm births despite the large sample size; hence, we had to limit the range of the standards by setting the lower limit of the curves to those born at 33 weeks of gestation. It might not be feasible to construct standards for very preterm newborn infants (<33 weeks of gestation) using such a strictly defined subpopulation of preterm babies who are at higher risk of intrauterine growth restriction and other major pregnancy and neonatal complications. We have discussed this issue previously[47] in the context of how to select a preterm population for the construction of postnatal growth standards—ie, which baby could be considered a healthy preterm? We have recommended criteria to select uncomplicated preterm births—ie, those without severe neonatal disorders (other than those expected physiologically because of their degree of immaturity)—to construct a reference chart for healthy very preterm newborn infants.

With regard to implementation of the new standards, two limitations have to be considered that apply to any evaluation of size: the cross-sectional nature of the study population and the use of statistics-based cutoff points to define small-for-gestational-age babies rather than impaired fetal growth. These limitations are more apparent when using birthweight alone or when assessing preterm birth, for which present reference charts are reported to have poorer sensitivity for the detection of small-for-gestational age babies than for the assessment of term babies.[48] There is no ideal solution—because we are constructing size (rather than growth) standards, each child was only measured at birth. For babies at gestational ages less than 33 weeks, a complementary clinical approach would be to estimate fetal weight at each gestational age by ultrasound examination of well dated healthy pregnant women whose fetuses remained in utero until term. This strategy would allow construction of estimated fetal weight charts for healthy preterm infants and allow comparisons between the estimated fetal weight by ultrasound and the actual newborn weight measured for healthy preterm births.[49] Such analyses are being done with the dataset and will be the subject of a future report. We have provided several centiles and will provide corresponding equations and *Z* scores to calculate others as needed. The decision about which cutoff point to use depends on several issues related to the clinical resources available for local care or referral of at-risk newborn babies, and to risk factors associated with the population where the standards are used. These statistic-based cutoffs, ideally, should be replaced by perinatal, risk-based, cutoff points so as to design an evidence-based triage for neonatal care.

Comparisons with local reference charts currently in use are very difficult because not only are there a large number of them (we identified 104 in our systematic review) but they have methodological limitations, including poor standardisation of equipment and measurement methods used in the primary outcome variables, the unreliability of gestational age estimates, and unselected populations studied. In addition, our international standards are not intended for comparison with these references, but to complement the WHO Child Growth Standards,[3] which start at birth but only include term newborn infants—ie, they are not gestational age specific at birth. Adoption of the international standards presented here is likely to affect global estimates of the number of babies who are small for gestational age, but assessment of the direction and size of these changes is beyond the scope of this Article.

A key conceptual and practical issue was to show that the populations in INTERGROWTH-21st Project and WHO Child Growth Standards[3,4] were comparable. This comparability was to be expected because we selected the groups using the same population and individual criteria and we used the same methods and equipment for all measurements and analyses. Therefore, it is important to emphasise that, when the two studies overlap (ie, term newborn infants), the means and SDs for the main anthropometric measures are almost identical—the mean birthweight of babies older than 37 weeks of gestation in our study population was 3·3 (0·5) kg and it was 3·3 (0·5) kg in the WHO MGRS.[50] The data for the mean length in our population was 49·3 cm (1·8 cm) and 49·5 cm (1·9 cm) in WHO's population.[50] For head circumference, the mean and SD in our study was 33·9 (1·3) cm versus 34·2 (1·3) cm in the MGRS.[50]

Finally, the international standard for length at birth for gestational age incorporates, for the first time into routine neonatal care, a method for the early diagnosis of stunting that can be then monitored during infancy and childhood using the corresponding WHO Child Growth Standards. This strategy is in the context of the global efforts to reduce stunting during the first 1000 days, a recognised important period for growth and development.[51,52] This procedure will need some adaptation to the routine care of newborn infants, but our extensive experience of measuring newborn length supports its feasibility. Several global initiatives now focus on improving nutrition for mothers and infants in the first 1000 days of life (from conception to 2 years of age). Therefore, robust international methods are needed to monitor growth and,

in particular, screen for stunting as early as possible. The present newborn international standards, together with the fetal growth standards that are also being published,[53,54] provide gestational-age specific standards at birth that can be used before the WHO standards become relevant. This strategy allows the size and growth of fetuses and babies to be monitored worldwide, in individuals and populations, across the first 1000 days of life using essentially the same instruments.

Contributors

JV and SHK conceptualised and designed the INTERGROWTH-21st Project. JV, SHK, DGA, and AJN prepared the original protocol, with later input from ATP, LCI, FCB, and ZAB. JV, ATP, LCI, AL, and ZAB supervised and coordinated the project's overall undertaking. EOO, DGA, FCB, and CGV did data management and analysis in collaboration with JV. RP, FCB, MC, YAJ, EB, MGG, MP, and IOF collaborated in the overall project and implemented it in their respective countries. CC and LCI led the quality control of the anthropometric component of the project. JV and SK wrote the report with input from all coauthors. All coauthors read the report and made suggestions on its content.

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Declaration of interests

We declare no competing interests.

Acknowledgments

The study was supported by a grant (49038) from the Bill & Melinda Gates Foundation to the University of Oxford. We thank the Health Authorities in Pelotas, Brazil; Beijing, China; Nagpur, India; Turin, Italy; Nairobi, Kenya; Muscat, Oman; Oxford, UK; and Seattle, WA, USA, who helped with the project by allowing participation of these study sites as collaborating centres. We thank Philips Healthcare for providing the ultrasound equipment and technical assistance throughout the project and MedSciNet UK for setting up the INTERGROWTH-21st website and for the development, maintenance, and support of the online data management system. We also thank the parents and infants who participated in the studies and the more than 200 members of the research teams who made the implementation of this project possible. The participating hospitals included: Brazil, Pelotas (Hospital Miguel Piltcher, Hospital São Francisco de Paula, Santa Casa de Misericórdia de Pelotas, and Hospital Escola da Universidade Federal de Pelotas); China, Beijing (Beijing Obstetrics and Gynecology Hospital, Shunyi Maternal and Child Health Centre, and Shunyi General Hospital); India, Nagpur (Ketkar Hospital, Avanti Institute of Cardiology, Avantika Hospital, Gurukrupa Maternity Hospital, Mulik Hospital and Research Centre, Nandlok Hospital, Om Women's Hospital, Renuka Hospital and Maternity Home, Saboo Hospital, Brajmonhan Taori Memorial Hospital, and Somani Nursing Home); Kenya, Nairobi (Aga Khan University Hospital, MP Shah Hospital, and Avenue Hospital); Italy, Turin (Ospedale Infantile Regina Margherita Sant' Anna and Azienda Ospedaliera Ordine Mauriziano); Oman, Muscat (Khoula Hospital, Royal Hospital, Wattayah Obstetrics and Gynaecology Poly Clinic, Wattayah Health Centre, Ruwi Health Centre, Al-Ghoubra Health Centre, and Al-Khuwair Health Centre); UK, Oxford (John Radcliffe Hospital) and USA, Seattle (University of Washington Hospital, Swedish Hospital, and Providence Everett Hospital). Full acknowledgment of all those who contributed to the development of INTERGROWTH-21st Project are online and in the appendix.

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

See **Online** for appendix

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New growth charts for newborn babies

In 2006, the WHO-initiated Multicentre Growth Reference Study published new infant and child growth standards to allow evaluation of growth from birth to age 5 years, with use of the same conceptual methods across populations worldwide.[1] This was a major practical improvement for the universal screening of growth changes in the most crucial period of life. An important finding was that birthweight and growth velocity were similar between different countries, provided that an optimum and healthy population is carefully selected.[1]

In *The Lancet*, José Villar and colleagues[2] report cross-sectional growth charts from newborn babies born between 33 and 42 weeks of gestation from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project. The investigators compiled carefully selected data from more than 20 000 deliveries from urban areas of eight countries: Brazil, China, India, Italy, Kenya, Oman, the UK, and the USA to establish universal multiethnic growth charts. However, does one newborn growth chart fit all?

This is a meticulous and well carried out study that includes healthy populations from each site. Instead of extracting data from available charts, trained teams measured infants within 12 h of birth. Most data were based on duplicate measurements. There was

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close agreement in the measured variables between the eight sites. At 40 completed weeks of gestation, the 50th (3rd–97th) percentile measurements for boys were birthweight 3·38 kg (2.63–4.22), length 49·92 cm (46·75–53·13), and head circumference 34·31 cm (32·15–36·56). For girls, the corresponding values were 3·26 kg (2·55–4·08), 49·23 cm (46·12–52·22), and 33·76 cm (31·72–35·92).

Birthweight is determined by several factors, including parity, maternal birthweight, age, body-mass index (BMI), diet during pregnancy, and exposure to infections such as malaria.[3,4] Maternal weight gain in pregnancy is significantly associated with birthweight for girl babies only, and paternal birthweight is significantly associated with birthweight for boy babies only.[3] These findings show the complexity of defining an optimum birthweight, and INTERGROWTH-21st did not account for all these factors. In addition, the study included babies from mothers with a wide range of maternal BMIs (18·5–30·0 kg/m²), even though there might be measurable differences in the birthweights of babies born to women with BMIs towards either end of the range.[3]

Mean birthweights in Scandinavian countries are 0·3 kg higher than in the WHO charts, and it has been argued that the WHO standards underestimate weight, height, and head circumference for newborn babies from this region.[5] However, a recent Danish reference study showed birthweights for boys at term that were equivalent to the WHO study.[6] The extra 0·3 kg in mean birthweight might therefore result from the obesity epidemic among pregnant women. The norm in Scandinavia should therefore perhaps be closer to the WHO standards.[6] However, higher birthweights in affluent areas might partly reflect healthier maternal diets, including a rich intake of fish oil.[4] More attention to the diet of the enrolled pregnant women could have increased the universality of Villar and colleagues' charts.

The teams measured birthweight within 12 h of delivery. However, birthweight decreases linearly during the first 2 days, with a mean decrease in bodyweight of about 10–20 g per kg for a full-term baby after 12 h.[7,8] The investigators do not discuss the implications of this naturally occurring phenomenon for measurement and interpretation of these birthweights against the proposed reference standard. In addition, there is a worldwide trend to delay cord clamping, which WHO endorses.[9] Investigators have reported mean increases in birthweight of 53 g[10] and 101 g[11] in term infants after delayed cord clamping, and this is a large increase from an epidemiological point of view. The difference in registered weight of a baby for whom cord clamping is delayed and weight taken immediately, versus the birthweight of a baby for whom the cord is clamped immediately and birthweight registered 12 h post-delivery, could be as high as 50 g per kg in the same baby. This is a substantial difference, especially given that Villar and colleagues' study protocol called for no more than 5 g difference between the two measurements.

Villar and colleagues' newborn growth charts[2] are essential to guide clinical practice and could become a basic way to promote global child health. Despite careful standardisation in the study protocol, variations might exist in birthweights because of timing of cord clamping and when birthweight was recorded after delivery. Still, the charts show that previously recorded geographical differences in fetal growth are caused mainly by different environments.

These growth charts[2] could become a valuable method to identify non-optimum conditions for the newborn infant. Surveillance of a child's somatic growth against a reference standard can assess child health and development. Deviation from the standard should be identified quickly to detect stunting, which might also be related to adult disease.[12] The new international standards are also more appropriate than local charts for early detection of overweight at birth, and hence might contribute to earlier prevention of obesity worldwide. Villar and colleagues' growth charts allow international comparisons of newborn size from 33–42 weeks of gestation and should be endorsed by the international community.

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I declare no competing interests.

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