

## A New Population-based Reference for Gestational Age-specific Size-at-birth of Singapore Infants

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### Abstract

**Introduction:** There is currently a lack of representative data for local gestational age-specific size-at-birth percentile charts. Existing charts also suffer from limitations relating to the measurement of gestational age (GA) and an outdated population. We aim to construct reference values and charts for size-at-birth from 35 to 41 weeks, based on the healthy local population. **Materials and Methods:** Prospective observational birth cohort study which recruited pregnant mothers from the 2 major public hospitals with obstetric service in Singapore, at <14 weeks gestation and data was collected for birth weight, length and head circumference of infants born from November 2009 to May 2011. Percentile curves were created separately for male and female infants using the lambda-mu-sigma (LMS) method. The new percentile curves were then compared with other internationally published growth charts. **Results:** Smoothened curves for birth weight, length and head circumference centiles were created from 863 infants (460 males, 403 females). Male infants consistently exceeded female infants in all 3 variables at each GA. For a male and female Singapore infant at 38 weeks gestation, the 10-50-90<sup>th</sup> centile values for weight would be 2663-3096-3597 vs. 2571-2966-3417 grams, for length 46.4-48.6-51.1 vs. 45.6-48.0-50.4 cm, and for head circumference 32.0-33.5-35.2 vs. 31.4-32.9-34.6 cm. There was no statistically significant difference between ethnic groups. On comparing our birth weight curves with data from Finland across all gestations, birth weights in our term infants (GA ≥37 weeks) were found to be lower across the 10-50-90<sup>th</sup> percentiles. **Conclusion:** The new centile charts in this study may be used as reference charts for size-at-birth for a subgroup of near-term and term infants. The use of foreign charts may lead to misclassification of small for gestational age (SGA) or large for gestational age (LGA) infants.

Ann Acad Med Singapore 2014;43:439-47

**Key words:** Birth head circumference, Birth length, Birth weight

### Introduction

Size-at-birth (birth weight, length and head circumference) is a simple clinical measure that is of importance to both neonatologists and obstetricians. It is commonly used in clinical practice to assess neonatal health. Birth weight and length have been demonstrated to be strong determinants of perinatal morbidity and survival;<sup>1</sup> they are important clinical indicators that are widely used for evaluation of prenatal growth and for identifying infants who are at higher risk of mortality.<sup>2,3</sup> Head circumference is often used by clinicians to identify infants with malformations in the central nervous

system and it carries prognostic implications.<sup>4</sup> Size-at-birth charts provide a basis for the assessment of growth and monitoring.

There are readily available size-at-birth for gestational age (GA) reference charts for newborns of several populations, such as Canada,<sup>5</sup> Sweden,<sup>6</sup> United States<sup>7,8</sup> and United Kingdom.<sup>9</sup> Despite evidence<sup>10-12</sup> to assume postnatal growth trajectories are similar across countries and ethnicity, there is insufficient data on whether size-at-birth for GA is comparable across countries and ethnicity.

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In addition, some of these suffer from limitations related to the measurement of GA. Some of the charts measured GA to the nearest week,<sup>13</sup> rather than truncating it to completed weeks, as recommended by World Health Organization (WHO) guidelines.<sup>14</sup> Even for charts that were measured in completed weeks, they are limited by using GA based on date of onset of last menstrual period<sup>15</sup> which has been shown to underestimate those born preterm and overestimate those with post-term GA when compared with early ultrasound measurements.<sup>16</sup>

In this study, we have constructed GA-specific size-at-birth percentile charts, based on the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort study, which overcame some of the deficits discussed. GUSTO is a birth cohort study designed to capture both prenatal and infant growth predictors in a longitudinal fashion in Singapore. The aim of this paper is to present reference values and charts for size-at-birth from 35 to 41 weeks, based on the healthy GUSTO birth cohort members.

## Methodology

### *Study Population*

GUSTO is set up to examine developmental origins of health and diseases. Pregnant women aged 18 years and above in their first trimester were recruited from the 2 major public hospitals with obstetric service in Singapore, the KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). Women approached were Singapore citizens or permanent residents who were of Chinese, Malay or Indian ethnicity with homogeneous parental ethnic background, had intention of delivering in NUH or KKH and residing in Singapore for the next 5 years. During recruitment, the eligibility criteria were designed to allow examination of differences between ethnically homogeneous groups, hence recruitment was completed with oversampling of Malays and Indians. Those who were on chemotherapy, psychotropic drugs or Type I diabetes mellitus were excluded from the study. Questionnaires were administered to capture demographics, socioeconomic status, lifestyle, maternal well-being, obstetrics and medical history, and use of medicines and supplements. This study was approved by both the National Healthcare Group Domain Specific Review Board and the SingHealth Centralised Institutional Review Board.

### *Assessment of GA*

The method of determining GA was by ultrasonography. In all women, GA was first assessed in the first ultrasound dating scan when they were recruited during the first trimester. They returned to the hospital again at 19 to 21, 26 to 28 and 32 to 34 weeks gestation to have follow-up ultrasound

scans for assessment of fetal growth and size. Scans were conducted in a standard manner at both hospitals by trained ultrasonographers. GA was reported in completed weeks.

### *Anthropometry Measurements*

Birth weight, length and head circumference were measured by trained hospital staff. During the first few hours after delivery, infant birth weight was recorded to the nearest gram using a calibrated scale (SECA 334 Weighing Scale, SECA Corp) for weighing the infant. Standard test weights of 1, 2, 5, 10 and 20 kg were used to calibrate the weighing scale. The variation for the SECA 334 weighing scale is between 5 to 10 g. Recumbent birth length was measured from the top of the head to the soles of the feet using an infant mat (SECA 210 Mobile Measuring Mat, SECA Corp) to the nearest 0.1 cm with the aid of 2 research staff. One person supports the infant's head and ensures that the head is positioned in the Frankfort horizontal plane. A second person aligns the legs by placing one hand gently but with mild pressure over the knees. Head circumference was also measured with the aid of 2 research staff. The infant is held by a health professional while the examiner uses a tape measure to measure the child's head. Maximum head circumference was measured across the frontal bones of the skull and over the occipital prominence at the back of the head, using a non-stretchable measuring band (SECA 212 Measuring Tape, Seca Corp).

### *Analysis Population*

In order to give size-at-birth reference values based on a "healthy" population, we excluded deliveries with (a) stillbirths, (b) twins, (c) complications during pregnancy with potential effects on foetal growth (gestational diabetes mellitus, anaemia, pre-eclampsia), and (d) newborns with significant neonatal malformations. There were also a limited number of observations in the lower GA (less than 35 weeks); these data were also excluded from the analysis. Outlying data points more than 3 times the interquartile range were identified using Box-and-Whisker plots, by GA and gender for each variable. These data points were then cross-referenced against hardcopy data; incorrect entries were then rectified into the database to ensure that high quality data was used for analysis.

### *Statistical Analysis and Chart Development*

The LMS method<sup>17</sup> using maximum penalised likelihood was utilised to create anthropometric centiles for birth weight, length and head circumference. This method estimates anthropometric measurement centiles in terms of 3 age-sex specific cubic spline curves: L curve (measure of skewness based on the Box-Cox transformation), M curve

(median) and the S curve (coefficient of variation). The transformation creates a standardised variable:

$$z(t) = \frac{[y(t)/M(t)]^{L(t)} - 1}{L(t)S(t)}$$

where  $t$  represents GA and  $y$  represents anthropometric measurement. Knowing the values of the 3 parameters  $L(t)$ ,  $M(t)$  and  $S(t)$ , the  $100\alpha$  percentile is given by:

$$P_{100\alpha}(t) = M(t) [1 + L(t)S(t)Z_{\alpha}]^{1/L(t)}$$

where  $Z_{\alpha}$  is the standard normal deviate that gives  $100\alpha\%$  cumulative probability.

GA and sex-specific size-at-birth centile charts for 3<sup>rd</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup> and 97<sup>th</sup> percentiles were generated using LMS Chartmaker software (Medical Research Council, UK). The modelling process began with an initial set of “equivalent degrees of freedom” (EDFs) for the parameters  $L$ ,  $M$  and  $S$  respectively and the transformation that gave the lowest deviance was preferred. The EDFs were then changed, first for  $M$ , then  $S$  and  $L$ , using the Generalised Akaike Information Criterion with a penalty constant of 3 [GAIC(3)] as a guide. Graphical examinations are then used to finetune and confirm the choice of parameters to be used.

Quantile regression models for size-at-birth variables for 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles were performed to assess their association with GA and ethnicity. The interaction effect between GA and ethnicity were also explored in above models which were stratified by gender.

## Results

A total of 3335 women were screened for eligibility, out of which 1880 women were eligible, and 1163 pregnant women (62% of eligible women screened) were recruited. Anthropometric measurements were completed on the infants of the remaining 1163 mothers. A total of 300 infants were excluded from analysis as a result of being born with significant neonatal malformations, or born to mothers with pregnancy complications (gestational diabetes, anaemia, pre-eclampsia). Infants whose mothers had no oral glucose tolerance test (OGTT) data were also excluded in this study. After exclusion, 863 infants were included in the analysis. Table 1 summarises the characteristics of the mothers and study infants.

Table 2 shows the frequency distribution ( $n$ ) of GA and the observed 3<sup>rd</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup>, 97<sup>th</sup> percentile of size-at-birth variables for male and female infants. At each GA, male infants consistently exceeded female infants in all 3 variables. The EDFs for the fitted LMS spline curves for both male and female infants were, respectively: 2, 3 and 1 for weight and head circumference; and 2, 2 and 1

Table 1. Characteristics of Mothers and the Study Infants

| Measures                             | n   | Mean (SD) or % |
|--------------------------------------|-----|----------------|
| Maternal age (yr)                    | 863 | 30.4 ± 5.1     |
| Marital status (%)                   | 845 |                |
| Married                              |     | 96.1           |
| Single                               |     | 3.9            |
| Highest education attained (%)       | 852 |                |
| Below ‘A’ levels/diploma             |     | 41.8           |
| ‘A’ levels/diploma or higher         |     | 58.2           |
| Type of housing (%)                  | 852 |                |
| Government                           |     | 86.2           |
| Private                              |     | 13.8           |
| Household income (%)                 | 806 |                |
| Below \$6000                         |     | 71.0           |
| Above \$6000                         |     | 29.0           |
| Ethnicity (%)                        | 863 |                |
| Chinese                              |     | 58.7           |
| Malay                                |     | 26.3           |
| Indian                               |     | 14.9           |
| Infant gender (%)                    | 863 |                |
| Male                                 |     | 53.3           |
| Female                               |     | 46.7           |
| Gestational age at delivery (weeks)  | 863 | 38.4 ± 1.2     |
| Infant birth weight (g)              | 863 | 3109 ± 411     |
| Infant birth length (cm)             | 863 | 48.7 ± 2.1     |
| Infant birth head circumference (cm) | 863 | 33.4 ± 1.8     |

for length. Increasing any of the LMS parameters by one EDF for birth weight, birth length and head circumference only increased the GAIC(3) score by 2.3, 2.5 and 2.9 units respectively. Table 3 lists the LMS values for each measurement by GA and gender. Figures 1 to 3 show the gestational age-specific smoothed percentile curves for birth weight, length and head circumference respectively, for each gender. The curves are smoothed and evenly spaced with no biologically implausible bumps preterm or flattening out post-term.

Quantile regression models for 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles of the size-at-birth variables showed no statistically significant evidence for association between the size-at-birth variables and ethnicity for both genders in models with quadratic terms for GA and ethnic-GA interaction terms (each  $P > 0.05$ ). In more parsimonious models that excluded the statistical non-significant quadratic and interaction terms, out of 18 regression analyses (2 gender \* 3 anthropometric variables \* 3 percentiles), there was only 1 statistically significant ethnic difference: median head circumference was 0.5 cm shorter in Indian boys than Chinese boys ( $P < 0.05$ ).

Table 2. Observed Percentile Values of Birth Weight (Gram), Birth Length (cm) and Birth Head Circumference (cm) of Male and Female Infants By Gestational Age (Week)

| GA                       | Males        |                 |                  |                  |                  |                  |                  |                  |     |                 | Females          |                  |                  |                  |                  |                  |  |  |  |  |
|--------------------------|--------------|-----------------|------------------|------------------|------------------|------------------|------------------|------------------|-----|-----------------|------------------|------------------|------------------|------------------|------------------|------------------|--|--|--|--|
|                          | Birth Weight |                 |                  |                  |                  |                  |                  |                  |     |                 | Birth Length     |                  |                  |                  |                  |                  |  |  |  |  |
|                          | n            | 3 <sup>rd</sup> | 10 <sup>th</sup> | 25 <sup>th</sup> | 50 <sup>th</sup> | 75 <sup>th</sup> | 90 <sup>th</sup> | 97 <sup>th</sup> | n   | 3 <sup>rd</sup> | 10 <sup>th</sup> | 25 <sup>th</sup> | 50 <sup>th</sup> | 75 <sup>th</sup> | 90 <sup>th</sup> | 97 <sup>th</sup> |  |  |  |  |
| 35                       | 6            | 2108            | 2234             | 2379             | 2566             | 2789             | 3027             | 3310             | 10  | 1907            | 2074             | 2241             | 2424             | 2604             | 2765             | 2921             |  |  |  |  |
| 36                       | 24           | 2248            | 2390             | 2552             | 2756             | 2990             | 3233             | 3509             | 18  | 2084            | 2252             | 2425             | 2620             | 2817             | 299              | 3177             |  |  |  |  |
| 37                       | 80           | 2376            | 2537             | 2716             | 2937             | 3182             | 3428             | 3697             | 51  | 2250            | 2418             | 2595             | 2800             | 3014             | 3215             | 3420             |  |  |  |  |
| 38                       | 142          | 2481            | 2663             | 2860             | 3096             | 3350             | 3597             | 3858             | 118 | 2404            | 2571             | 2751             | 2966             | 3196             | 3417             | 3650             |  |  |  |  |
| 39                       | 127          | 2576            | 2780             | 2996             | 3248             | 3511             | 3757             | 4010             | 127 | 2554            | 2719             | 2902             | 3125             | 3371             | 3615             | 3879             |  |  |  |  |
| 40                       | 75           | 2657            | 2888             | 3124             | 3391             | 3661             | 3907             | 4152             | 73  | 2708            | 2873             | 3058             | 3289             | 3552             | 3821             | 4123             |  |  |  |  |
| 41                       | 6            | 2731            | 2992             | 3250             | 3532             | 3810             | 4055             | 4294             | 6   | 2854            | 3018             | 3205             | 3444             | 3724             | 4020             | 4365             |  |  |  |  |
| Birth Length             |              |                 |                  |                  |                  |                  |                  |                  |     |                 |                  |                  |                  |                  |                  |                  |  |  |  |  |
| 35                       | 6            | 43.7            | 44.5             | 45.4             | 46.5             | 47.7             | 49               | 50.5             | 10  | 42.0            | 43.2             | 44.3             | 45.5             | 46.7             | 47.7             | 48.7             |  |  |  |  |
| 36                       | 24           | 44.3            | 45.1             | 46.1             | 47.2             | 48.5             | 49.7             | 51.1             | 18  | 42.9            | 44.0             | 45.1             | 46.3             | 47.5             | 48.6             | 49.7             |  |  |  |  |
| 37                       | 80           | 44.8            | 45.8             | 46.7             | 47.9             | 49.2             | 50.4             | 51.7             | 51  | 43.7            | 44.8             | 45.9             | 47.2             | 48.4             | 49.5             | 50.6             |  |  |  |  |
| 38                       | 142          | 45.4            | 46.4             | 47.4             | 48.6             | 49.9             | 51.1             | 52.3             | 118 | 44.5            | 45.6             | 46.7             | 48.0             | 49.2             | 50.4             | 51.5             |  |  |  |  |
| 39                       | 127          | 46.0            | 47.0             | 48.1             | 49.4             | 50.6             | 51.8             | 53.0             | 127 | 45.2            | 46.4             | 47.5             | 48.8             | 50.1             | 51.2             | 52.4             |  |  |  |  |
| 40                       | 75           | 46.5            | 47.6             | 48.8             | 50.1             | 51.3             | 52.5             | 53.6             | 73  | 46.0            | 47.1             | 48.3             | 49.6             | 50.9             | 52.1             | 53.3             |  |  |  |  |
| 41                       | 6            | 47.0            | 48.3             | 49.5             | 50.8             | 52.1             | 53.2             | 54.3             | 6   | 46.8            | 47.9             | 49.1             | 50.4             | 51.8             | 53.0             | 54.2             |  |  |  |  |
| Birth Head Circumference |              |                 |                  |                  |                  |                  |                  |                  |     |                 |                  |                  |                  |                  |                  |                  |  |  |  |  |
| 35                       | 6            | 30.2            | 30.9             | 31.5             | 32.3             | 33.1             | 33.9             | 34.7             | 10  | 30.0            | 30.6             | 31.2             | 32.0             | 32.8             | 33.7             | 34.6             |  |  |  |  |
| 36                       | 24           | 30.7            | 31.3             | 32.0             | 32.7             | 33.6             | 34.4             | 35.2             | 18  | 30.3            | 30.9             | 31.5             | 32.3             | 33.2             | 34.0             | 34.9             |  |  |  |  |
| 37                       | 80           | 31.1            | 31.7             | 32.4             | 33.2             | 34.0             | 34.8             | 35.7             | 51  | 30.5            | 31.2             | 31.8             | 32.6             | 33.5             | 34.3             | 35.2             |  |  |  |  |
| 38                       | 142          | 31.4            | 32.0             | 32.7             | 33.5             | 34.3             | 35.2             | 36.0             | 118 | 30.7            | 31.4             | 32.1             | 32.9             | 33.8             | 34.6             | 35.5             |  |  |  |  |
| 39                       | 127          | 31.7            | 32.3             | 33.0             | 33.8             | 34.7             | 35.5             | 36.4             | 127 | 31.0            | 31.7             | 32.4             | 33.2             | 34.1             | 34.9             | 35.8             |  |  |  |  |
| 40                       | 75           | 32.0            | 32.6             | 33.3             | 34.1             | 35.0             | 35.8             | 36.7             | 73  | 31.4            | 32.1             | 32.8             | 33.7             | 34.5             | 35.4             | 36.2             |  |  |  |  |
| 41                       | 6            | 32.2            | 32.8             | 33.5             | 34.3             | 35.2             | 36.1             | 37.0             | 6   | 31.8            | 32.5             | 33.3             | 34.1             | 35.0             | 35.8             | 36.6             |  |  |  |  |

GA: Gestational age

Table 3. LMS Coefficients By Gestational Age (Week) and Gender For the Anthropometric Measurements At Birth

| GA | Birth Weight |      |      |         |      |      | Birth Length |      |      |         |      |      | Birth Head Circumference |      |      |         |      |      |
|----|--------------|------|------|---------|------|------|--------------|------|------|---------|------|------|--------------------------|------|------|---------|------|------|
|    | Males        |      |      | Females |      |      | Males        |      |      | Females |      |      | Males                    |      |      | Females |      |      |
|    | L            | M    | S    | L       | M    | S    | L            | M    | S    | L       | M    | S    | L                        | M    | S    | L       | M    | S    |
| 35 | -1.15        | 2566 | 0.12 | 1.19    | 2424 | 0.11 | -4.12        | 46.5 | 0.04 | 2.07    | 45.5 | 0.04 | -1.52                    | 32.3 | 0.04 | -2.68   | 32.0 | 0.04 |
| 36 | -0.76        | 2756 | 0.12 | 0.81    | 2620 | 0.11 | -3.07        | 47.2 | 0.04 | 1.68    | 46.3 | 0.04 | -1.59                    | 32.7 | 0.04 | -2.23   | 32.3 | 0.04 |
| 37 | -0.38        | 2937 | 0.12 | 0.43    | 2800 | 0.11 | -2.01        | 47.9 | 0.04 | 1.35    | 47.2 | 0.04 | -1.67                    | 33.2 | 0.04 | -1.78   | 32.6 | 0.04 |
| 38 | 0.02         | 3096 | 0.12 | 0.05    | 2966 | 0.11 | -0.96        | 48.6 | 0.04 | 1.11    | 48.0 | 0.04 | -1.75                    | 33.5 | 0.04 | -1.31   | 32.9 | 0.04 |
| 39 | 0.43         | 3248 | 0.12 | -0.33   | 3125 | 0.11 | 0.09         | 49.4 | 0.04 | 0.96    | 48.8 | 0.04 | -1.83                    | 33.8 | 0.04 | -0.83   | 33.2 | 0.04 |
| 40 | 0.83         | 3391 | 0.12 | -0.71   | 3289 | 0.11 | 1.14         | 50.1 | 0.04 | 0.83    | 49.6 | 0.04 | -1.91                    | 34.1 | 0.04 | -0.33   | 33.7 | 0.04 |
| 41 | 1.23         | 3532 | 0.12 | -1.09   | 3444 | 0.11 | 2.19         | 50.8 | 0.04 | 0.71    | 50.4 | 0.04 | -1.99                    | 34.3 | 0.04 | 0.17    | 34.1 | 0.04 |

GA: Gestational age

Table 4. Comparison of the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> Percentiles of Gestational Age (Week) Specific Birth Weights (Gram) of Singapore Male and Female Infants With From Those of Finland

| GA | Male             |                  |                  |         |      |         | Female           |                  |                  |         |      |         |
|----|------------------|------------------|------------------|---------|------|---------|------------------|------------------|------------------|---------|------|---------|
|    | GUSTO            |                  |                  | Finland |      |         | GUSTO            |                  |                  | Finland |      |         |
|    | 10 <sup>th</sup> | 50 <sup>th</sup> | 90 <sup>th</sup> | -1.28SD | Mean | +1.28SD | 10 <sup>th</sup> | 50 <sup>th</sup> | 90 <sup>th</sup> | -1.28SD | Mean | +1.28SD |
| 35 | 2234             | 2566             | 3027             | 2175    | 2731 | 3287    | 2074             | 2424             | 2765             | 2079    | 2642 | 3205    |
| 36 | 2390             | 2756             | 3233             | 2418    | 2991 | 3564    | 2252             | 2620             | 2997             | 2323    | 2899 | 3475    |
| 37 | 2537             | 2937             | 3428             | 2663    | 3239 | 3815    | 2418             | 2800             | 3215             | 2561    | 3132 | 3703    |
| 38 | 2663             | 3096             | 3597             | 2892    | 3456 | 4020    | 2571             | 2966             | 3417             | 2774    | 3326 | 3878    |
| 39 | 2780             | 3248             | 3757             | 3075    | 3625 | 4175    | 2719             | 3125             | 3615             | 2948    | 3483 | 4018    |
| 40 | 2888             | 3391             | 3907             | 3216    | 3766 | 4316    | 2873             | 3289             | 3821             | 3094    | 3624 | 4154    |
| 41 | 2992             | 3532             | 4055             | 3325    | 3883 | 4441    | 3018             | 3444             | 4020             | 3200    | 3735 | 4270    |

GA: Gestational age; GUSTO: Growing Up in Singapore Towards Healthy Outcomes

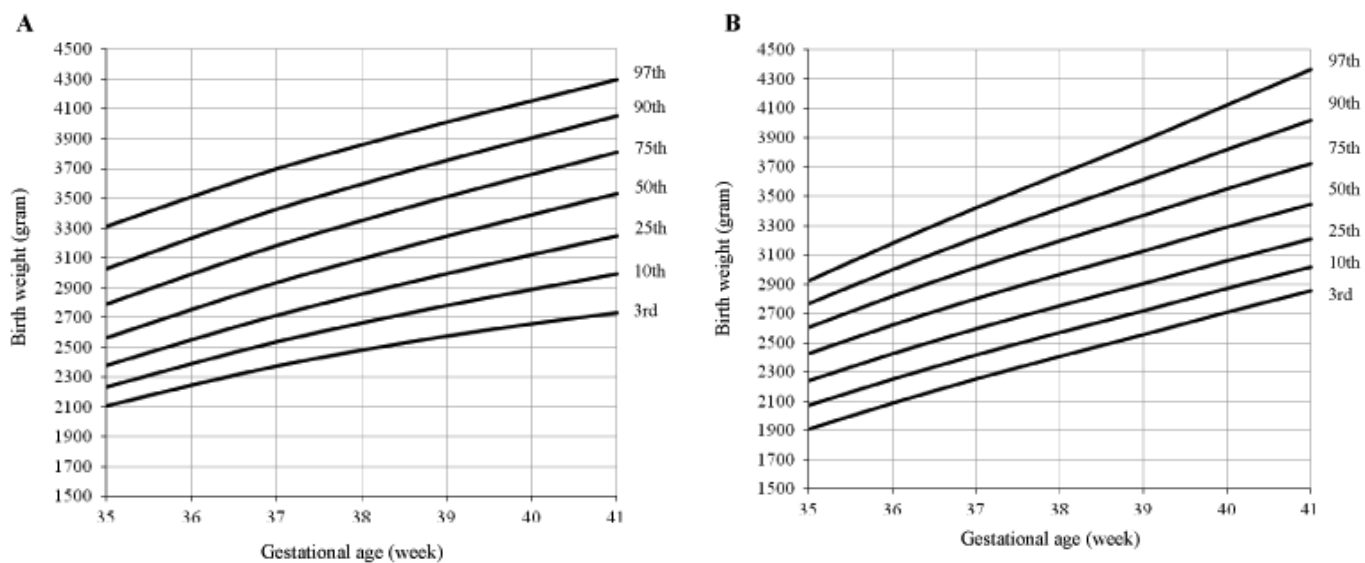


Fig. 1. Smoothed percentiles for birth weight. (A) Male infants, (B) female infants.

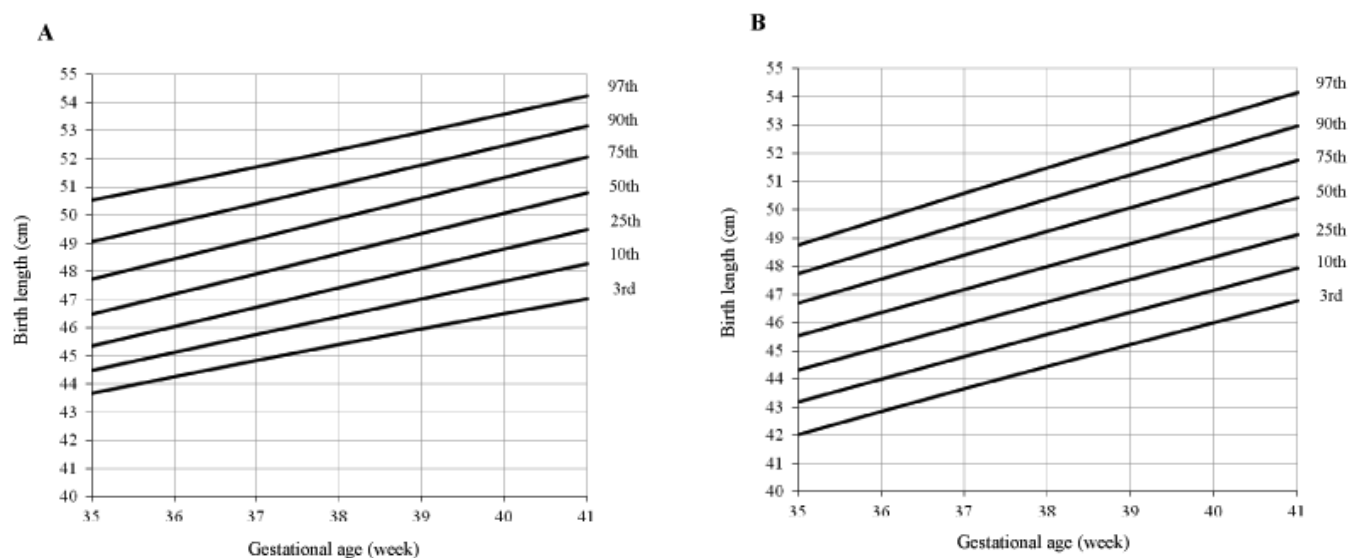


Fig. 2. Smoothed percentiles for birth length. (A) Male infants, (B) female infants.

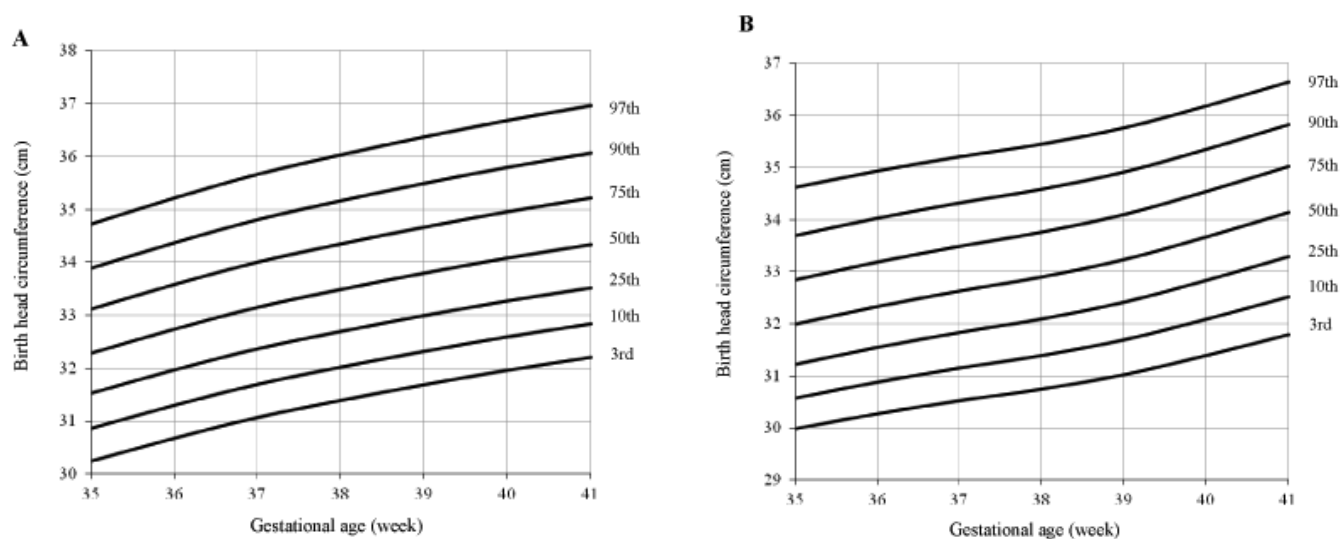


Fig. 3. Smoothed percentiles for birth head circumference. (A) Male infants, (B) female infants.

We also compared the birth weights of male and infants in our cohort with population-based references for singleton infants from Finland (Table 4).<sup>18</sup> When compared with infants from the Finland cohort, GUSTO male term and preterm infants had birth weights between 28 to 423 g lower at the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles (corresponding to -1.28SD, mean and +1.28SD for the Finland cohort) respectively. GUSTO female preterm and term infants had birth weights between 5 to 488 g lower at the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles when compared with the Finland cohort.

## Discussion

We report the percentiles and smoothened curves of size-at-birth variables in a cohort of Singapore neonates born at 35 to 41 completed weeks of gestation. Our study utilised more precise dating and measurement techniques which differed from population-based references. Also, the present sample is selected from GUSTO to form a “healthy” cohort for the purpose of providing growth standards. These charts assume optimal growth and can be used to identify near-term or term newborns at risk of adverse health outcomes associated with abnormal intrauterine growth. There has been much controversy on the inclusion of only “healthy newborns” in deriving growth charts. Ideally, a study population which includes both low- and high-risk pregnancies, and both normal and abnormal perinatal outcomes would be more suitable as a reference chart. Standard charts on the other hand are based on low-risk pregnancies with a normal outcome, and the growth curves would reflect optimal, healthy, linear growth of newborns who fully expressed their growth potential. When “population reference” and “standard” charts are applied to an individual foetus or infant, interpretation of the findings would differ. Using a population reference would yield a relative foetal size in relation to the total population; a standard will assess a foetal size in comparison to normally grown foetuses. Thus, a standard may have more clinical utility than a population reference.

The availability of local gestational age-specific size-at-birth percentile charts is essential for obstetricians and neonatologists in their perinatal practice. Earlier charts generated by Cheng et al<sup>13</sup> for the Singapore population are now several decades old; this would not be reflective of infants that were born in more recent years, where there has been a rapid improvement in the quality of living and health indices. The GUSTO charts takes into account an improved standard of living, of which more than half of mothers in the cohort are better educated (completed at least GCE ‘A’ Levels or polytechnic education) and resided in better accommodation (at least 4- to 5-room Housing and Development Board (HDB) flats). The average maternal age of the GUSTO participants was 30.4 years, slightly

older than that reported in birth weight charts by Tan et al<sup>15</sup> at 29.2 years; this appears to be reflective of the trend of delayed childbearing amongst women in Singapore.<sup>19</sup> Our charts also pooled Chinese, Malay and Indian infants together into one chart. Earlier studies on birth weights in the Singapore population had identified that Indians have the highest proportion of low birth weight,<sup>20,21</sup> and also tend to weigh lesser than their Chinese and Malay counterparts.<sup>22</sup> Similarly, Indians in our study sample exhibited smaller birth weights compared to Chinese and Malays; however these differences were not statistically significant. Additionally, there was no statistical evidence to suggest that size-for-GA pattern was different between ethnic groups at the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles. In a recent discussion about the cross-ethnic applicability of the WHO Multicentre Growth Reference Study (MGRS) child growth standards, it was suggested that a difference in median of less than +/- 0.4 SD is a clinically non-significant difference.<sup>23</sup> In the present study, there was a lack of clinical significance between the 3 ethnic groups. Comparing the statistically significant difference in median head circumference between Indian and Chinese boys and the statistically non-significant differences in medians of birth weight and length against the SD reflected by the M and S curves of the LMS models, there was no clinically significant difference across ethnic groups. These observations substantiate our pooling of the 3 ethnic groups together into one overall chart, rather than stratifying into ethnic-specific charts. These factors differentiate the GUSTO charts from other local published charts, hence providing a new reference for size-at-birth of Singapore newborns.

Despite evidence to assume postnatal growth trajectories are similar across countries and ethnicity,<sup>10-12</sup> there is much less data on whether size-at-birth is comparable across countries and ethnicity. We compared the birth weights of our infants with published gender-specific references for birth weight-for-GA from the Finland cohort; both the GUSTO as well the Finland study reported GA based on ultrasound assessment, and only “healthy newborn” infants were included. The time period of the Finland study was from 1996 to 2008, relatively closer with that of GUSTO and hence allowing for comparison of the growth curves between these 2 studies. GUSTO term infants were observed to be lighter across the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles when compared with the Finland cohort. This implies that the use of non-local charts could lead to misclassification of small for gestational age (SGA) or large for gestational age (LGA) infants. Using the Finland charts with our data led to overestimation of SGA infants and underestimation of LGA infants; the consequence of which some infants appropriate for gestational age (AGA) would be wrongly identified as SGA and LGA infants would be overlooked as

AGA. This supports the suggestion that population-specific growth charts should be used for classification of infants into SGA, AGA or LGA; additionally, it seems that compared with Caucasian infants, Asian infants are smaller at birth.

The use of ultrasound for more precise dating of GA, performed at the first trimester period presents as a strength of this study. Ultrasound dating measurements are usually used to confirm last menstrual period dates or if menstrual history is unreliable.<sup>24</sup> Unlike other studies<sup>13,15</sup> where GA was based on date of onset of last menstrual period, which can underestimate the number born preterm, and overestimate post-term GA, ultrasound dating helps to avoid erroneous estimation of GA.<sup>16</sup> Some studies have used anthropometric data documented in birth records.<sup>25</sup> While this retrospective technique allows for inclusion of a large sample number of infants, it often necessitates statistical exclusion of extreme outliers arising from errors in documentation.<sup>25-27</sup> Thus, the prospective nature of the GUSTO cohort adds strength to the study; it allows for accurate measurement of the anthropometric variables, hence exclusion of extreme outliers in data was not required.

Similar to most population-based references, our growth charts have one important limitation, which is the cross-sectional nature of the data. The data analysed in this study are based on size-at-birth anthropometrics of different newborns at different GA, which is not reflective of the intrauterine growth of the foetus. Hence, these charts would not be suitable for evaluation of foetal growth velocity. A longitudinal analysis of individual foetuses would be required for a more detailed study on intrauterine growth velocity. Another limitation of the present study is that the sample size of GUSTO was not estimated for the purpose of constructing size at birth reference charts. However, the use of modern analytic methods like LMS makes good use of data in that each data point contributes toward the estimation of the centiles of not only the GA interval it belongs to but also the adjacent GA. Hence the relatively small sample size was partially compensated by the relatively efficient statistical methods. Future studies with even larger sample size and for a wider range of gestational weeks will be useful. Additionally, the GUSTO sample in this study does not represent the local newborn population; practical logistic issues hindered obtaining samples from other maternity units, which could have further strengthened the applicability of the findings. The GUSTO data however, was collected from 2 of Singapore's major maternity units (NUH and KKH) which strengthened the applicability of the findings as compared to single centre studies.

Our study also lacks sufficient sample size at preterm (less than 37 weeks), as well as at post-term GA (41 weeks). Our cohort is also limited by the small sample size for the Indian population, which necessitates the need for further

research especially regarding the size-for-GA pattern for the Indian population. Whilst growth curves at the lower GA (24 to 34 weeks) would add significant clinical value, our charts would still be useful for clinicians and researchers; it represents a new reference for birth weight, length and head circumference based on a recent population of near-term and term infants, which would be crucial to evaluate birth size correctly. Population-based birth size references representing optimal foetal growth and based on the current population are sparse especially for Singapore, where existing charts are based on populations that are decades old. As changing social trends may influence birth size, birth size references based on a more recent population would be useful for correct evaluation of newborns SGA, AGA or LGA. Correct identification of SGA infants is important since these infants are at an increased risk of perinatal morbidity and mortality and long-term adverse consequences such as neurodevelopmental problems, adult-onset cardiovascular disease, and metabolic alterations. For researchers, our charts would allow for proper categorisation of groups of infants to study aetiologic determinants of birth size as well as short- or long-term prognosis.

## Conclusion

Our study findings provide a new reference for size-at-birth of Singapore newborns at 35 to 41 weeks of GA. For clinicians, it allows for a more suitable classification of infants as SGA, AGA or LGA. Given the importance of the relationship between size-at-birth and future health risks, these charts would be useful for the care of newborns.

## Acknowledgements

*The authors would like to acknowledge the following fellow investigators of the GUSTO study group: Dennis Bier, Arijit Biswas, Cai Shirong, Helen Chan, Jerry Chan, Yiong Huak Chan, Cornelia Chee, Audrey Chia, Chiang Wen Chin, Chng Chai Kiat, Mary Chong, Chong Shang Chee, Chua Mei Chien, Wayne Cutfield, Mary Daniel, Ding Chun Ming, Anne Ferguson-Smith, Eric Andrew Finkelstein, Marielle Fortier, Doris Fok, Anne Goh, Daniel Goh, Joshua J Gooley, Han Wee Meng, Mark Hanson, Mikael Hartman, Michael Heymann, Stephen Hsu Chin-Ying, Hazel Inskip, Jeevesh Kapur, Joanna Holbrook, Keith M Godfrey, Lee Bee Wah, BFP Leutscher-Broekman, Lim Sok Bee, Loh Seong Feei, Low Yen Ling, Iliana Magiati, Susan Morton, Krishnamoorthy N, Cheryl Ngo, Pang Wei Wei, Prathiba Agarwal, Qiu Anqi, Quah Boon Long, Victor S Rajadurai, Jen Richmond, Anne Rifkin-Graboi, Allan Sheppard, Lynette Pei-Chi Shek, Borys Shuter, Leher Singh, So Wing Chee, Walter Stunkel, Su Lin Lin, Tan Kok Hian, Tan Soek Hui, Teoh Oon Hoe, Terry Yoke Yin Tong, Hugo Van Bever, Rob Van Dam, Sudhakar Venkatesh, Helena Marieke Verkooijen, Inez By Wong, PC Wong, George SH Yeo. Keith M Godfrey is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre. This study is under Translational Clinical Research (TCR) Flagship Programme on Developmental Pathways to Metabolic Disease, NMRC/TCR/004-NUS/2008, funded by the National Research Foundation (NRF) and administered by the National Medical Research Council (NMRC), Singapore.*

**Clinical Trial Registration**

This study is registered under the Clinical Trials identifier NCT01174875; <http://www.clinicaltrials.gov/ct2/show/NCT01174875?term=GUSTO&rank=2>.

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