OBSTETRICS

# INTERGROWTH-21st vs customized birthweight standards for identification of perinatal mortality and morbidity

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**BACKGROUND:** The recently published INTERGROWTH-21st Project international population standard for newborn size is intended for global use, but its ability to identify small infants at risk of adverse outcomes in a general obstetric population has not been reported.

**OBJECTIVE:** The objective of the study was to compare adverse neonatal outcomes among small-for-gestational-age (SGA) infants between the INTERGROWTH-21st standard and a customized birthweight standard (accounting for maternal characteristics of height, weight, parity, and ethnicity). We hypothesized that in a multiethnic general obstetric population in Auckland, New Zealand, a customized birthweight standard would better identify SGA infants at-risk of neonatal morbidity/mortality and stillbirth than the INTERGROWTH-21st standard.

**STUDY DESIGN:** Using prospectively gathered maternity data from a general obstetric population in Auckland, New Zealand, from 2006 to 2013 (n = 53,484 births at ≥ 33 weeks), infants were classified as SGA (birthweight < 10th centile) by INTERGROWTH-21st and customized standards. Infants were further categorized as SGA by both criteria, INTERGROWTH-21st only, customized only, or not SGA (met neither criteria). Composite adverse neonatal outcome was defined as neonatal death, neonatal intensive care admission > 48 hours, or ventilation > 4 hours or 5-minute Apgar score < 7. Relative risks for primary outcomes were estimated using modified Poisson regression, with the non-SGA group as the referent.

**RESULTS:** Incidence of SGA was 4.5% by INTERGROWTH-21st and 11.6% by customized standard. Compared with those not SGA, infants identified as small for gestational age by both criteria had the highest risk of adverse neonatal outcome (relative risk [RR], 4.1, 95% confidence interval [CI], 3.7−4.6) and stillbirth (RR, 8.3, 95% CI, 5.1−13.4). Infants SGA by customized standard only (n = 4015) had an increased risk of adverse neonatal outcome (RR, 2.0, 95% CI, 1.8−2.2) and stillbirth (RR, 3.0, 95% CI, 1.7−5.3). Few infants were identified as SGA by INTERGROWTH-21st only (n = 172), and risks of adverse neonatal outcome and stillbirth were not increased. Findings were unchanged when analyses were limited to term infants (n = 50,739). The INTERGROWTH-21st standard identified more Indian (12.8%) and Asian (5.8%) but fewer European (3.0%) and Pacific (2.9%) infants as SGA ($P < .01$). Customized criteria identified more than 3 times as many SGA infants among Maori (14.5%), Pacific (13.5%), and European (11.2%) infants and twice as many among Asian (10.3%) infants (P<0.01) compared with INTERGROWTH-21st criteria. The majority of SGA infants by INTERGROWTH-21st only were born to Indian and Asian mothers (95.4%).

**CONCLUSIONS:** In our general obstetric population, birthweight customization identified more SGA infants at risk of perinatal mortality and morbidity compared with the INTERGROWTH-21st standard. The INTERGROWTH-21st standard failed to detect many at-risk SGA infants, particularly among ethnic groups with larger maternal size while disproportionately identifying higher rates of SGA among those with smaller maternal size. Local validation is needed prior to implementation of the INTERGROWTH-21st standard to avoid misclassification of infant birth size.

**Key words:** customized birthweight, INTERGROWTH-21st Project, perinatal morbidity, perinatal mortality, small for gestational age

Recent publication of the multinational INTERGROWTH-21st Project standards for newborn anthropometry has provided a new benchmark for international comparisons across multiethnic populations.[1] Importantly, in women at low risk of fetal growth impairment, optimum infant size at birth was described as almost identical among the 8 included countries. This international standard is intended for use in clinical practice both within populations and for comparisons between nationalities. The ability of the INTERGROWTH-21st standard to identify infants at risk of adverse outcomes has not yet been reported.

Population birthweight standards have traditionally been used to identify infants who are small for gestational age (SGA) that may have experienced intrauterine growth restriction. Such infants are at increased risk of neonatal death and morbidity; however, use of population birthweight standards may underestimate risk for some infants and overestimate risk for others. For example, preterm birth is inherently pathological and population standards consistently underestimate optimal birthweight in preterm infants compared with ultrasound estimates of fetal weight at preterm gestations in infants subsequently born at term.[2,3] Conversely, in ethnic groups with smaller-than-average maternal size, some SGA infants are constitutionally small and not growth restricted and vice versa.[4,5]

Customized birthweight standards differ from population standards in that they use ultrasound-based measures of fetal size and account for maternal characteristics that influence birthweight, including maternal height, weight, parity, and ethnicity.[6] Infants who are SGA by customized criteria generally show increased rates of perinatal morbidity and mortality compared with population birthweight reference data.[7-9]

New Zealand has a multiethnic birthing population with more than a third of women of Maori or Pacific

**Cite this article as:** Anderson NH, Sadler LC, McKinlay CJD, et al. INTERGROWTH-21st vs customized birthweight standards for identification of perinatal mortality and morbidity. Am J Obstet Gynecol 2016;214:509.e1-7.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.10.931

Island ethnicity,[10] groups that were not included in the INTERGROWTH-21st standard. Our aims were to compare the following: (1) the INTERGROWTH-21st population birthweight standard to a customized birthweight standard in a general obstetric population from Auckland, New Zealand,[5] for the detection of SGA infants at increased risk of neonatal mortality and morbidity, and (2) rates of stillbirth among infants classified as SGA between the respective standards.

Based on previous work,[7] we hypothesized the following: (1) infants classified as SGA by customized criteria alone compared with INTERGROWTH-21st criteria alone would have a higher risk of neonatal mortality and morbidity, and stillbirth; (2) infants classified as SGA by INTERGROWTH-21st criteria alone would have similar neonatal outcomes to infants not SGA by either standard; (3) obstetric risk factors for SGA would be more common in mothers whose infants were classified as SGA by customized criteria alone compared with INTERGROWTH-21st criteria alone; and (4) compared with those of European ethnicity, the incidence of SGA by the INTERGROWTH-21st criteria would be lower in those of Pacific Island ethnicity and higher in those of Indian and Asian ethnicities.

## Materials and Methods

This was an analysis of prospectively gathered maternity data from National Women's Health (NWH), Auckland City Hospital, Auckland, New Zealand, from January 2006 to December 2013. NWH is a tertiary referral hospital with a diverse ethnic population and approximately 7500 births annually. The NWH database records maternity data for all births occurring $\geq$ 20 weeks' gestation, including demographics, antenatal complications, delivery details, and neonatal outcomes. Data are routinely checked for completeness, outliers, and inconsistency. Ethical approval was obtained from the Research Board of the Auckland District Health Board (study number 4632).

To accord with data available from the INTERGROWTH-21st project[1] singleton infants born at NWH from 33 to 42 weeks' gestation without major malformations were included in this analysis. Infants were excluded if mothers were unbooked, transferred to NWH during pregnancy or labor, or if data for maternal customization were missing.

Gestation-specific customized birthweight centiles were calculated as previously described[6] using locally derived coefficients,[5] adjusting for maternal height and weight at booking, parity, ethnicity, and infant sex. Birthweights were compared with both the customized and INTERGROWTH-21st birthweight centiles,[1] with SGA defined as $<$ 10th centile. Infants were categorized as follows: SGA by both criteria (SGA-both), SGA by INTERGROWTH-21st criteria alone (SGA-IG only), SGA by customized criteria only (SGA-cust only), or not SGA by either criterion (non-SGA).

Gestational age was calculated from the first day of the last menstrual period (LMP) if certain, adjusted if fetal ultrasound measurements differed from LMP gestational age according to the Australasian Society for Ultrasound in Medicine guidelines or by dating ultrasound if the LMP was uncertain.[11,12] The majority of women at NWH undertake a first-trimester ultrasound. From 2009, gestational age for stillborn infants was defined as the estimated gestation at time of death, determined by maternal report of when fetal movements ceased. We used the median latency between estimated gestation at death and birth of these stillbirths (2 days) to estimate gestation at death for stillbirths from 2006–2008.

Maternal height (centimeters) and weight (kilograms) were measured at the first antenatal visit. Parity was defined as the number of liveborn infants of any birthweight or gestation or stillborn infants from 20 weeks' gestation or where the infant weighed 400 g or more if gestation was unknown.[10] Self-reported maternal ethnicity was grouped and prioritized in order of Maori, Pacific Peoples, Asian, Indian, Other and European.[13] Asian ethnicity included women from China, South-East Asia, Japan and Korea. Indian ethnicity included women from India and those of Fijian-Indian origin.

Risk factors for SGA were smoking during pregnancy and pregnancy-induced hypertension (PIH), defined as gestational hypertension or preeclampsia/eclampsia.[14] Preterm birth was defined as delivery at less than 37 weeks' gestation.

Groups were compared for the primary outcomes of the following: (1) composite adverse neonatal outcome, defined as neonatal death (death occurring within the first 28 days of life of a liveborn infant) or neonatal morbidity, defined as admission to neonatal intensive care unit (NICU) for $>$ 48 hours, positive pressure respiratory support $>$ 4 hours or 5-minute Apgar score $<$ 7; and (2) stillbirth. These neonatal morbidity measures have been shown to be important predictors of adverse neonatal outcome.[15-19]

### Statistics

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc, Cary, NC). SGA and ethnic groups were compared using generalised linear models with adjustment for multiple comparisons. Risk ratios for primary outcomes were estimated by Poisson regression with robust error estimates. Primary outcomes are presented as risk ratios with 95% confidence intervals using the non-SGA group as the referent. An adjusted two-sided value of $P < .05$ was considered statistically significant. Stillborn infants were excluded from analyses for neonatal outcomes. A sensitivity analysis of primary outcomes confined to term infants was performed, using the same methodology as above.

Sensitivity, specificity, and predictive values were calculated for composite adverse neonatal outcome for both birthweight standards.

## Results

A total of 56,638 singleton non-anomalous infants were born at 33–42 weeks' gestation from January 2006 to December 2013. Customized birthweight centiles were calculated for 53,484 infants because 3152 women had missing data for customized centiles (maternal height or weight, n = 3150, and birthweight, n = 2). Nearly half of mothers were of European ethnicity, followed by Asian

(20.3%), Pacific (13.5%), Indian (7.4%), Maori (6.8%), and other ethnicity (3.5%) (Table 1). Mean (SD) maternal body mass index (BMI) at booking was 25.3 (6.1) kg/m$^2$ and gestational age at delivery was 39.4 (1.5) weeks (Table 1). Preterm birth occurred in 5.1% of our cohort (Table 1).

The incidence of SGA was 4.5% and 11.6% by INTERGROWTH-21st and customized criteria, respectively. Of infants identified as SGA by INTERGROWTH-21st criteria, 89% were also identified as SGA by customized criteria. The customized standard, however, identified an additional 7.5% of infants as SGA (Table 1).

The incidence of neonatal death or morbidity was 17.2% in infants identified as SGA by INTERGROWTH-21st and 12.1% in those identified as SGA by customized criteria. The risk of this composite adverse neonatal outcome was highest in the SGA-both group (RR, 4.1, 95% CI, 3.7−4.6). Composite

**TABLE 1**
**Cohort characteristics**

| SGA classification | Total (n = 53,484) | Non-SGA (n = 47,090) (88.0%) | SGA-IG only (n = 172) (0.4%) | SGA-cust only (n = 4015) (7.5%) | SGA-both (n = 2207) (4.1%) | *P* value |
|---|---|---|---|---|---|---|
| Maternal characteristics | | | | | | |
| Age, y | 31.4 (5.6) | 31.4 (5.6)[a] | 28.7 (4.5)[b] | 31.4 (5.8)[a] | 31.0 (5.8)[c] | < .05 |
| Nulliparous | 25,857 (48.4%) | 22,552 (48.0%)[a] | 154 (89.5%)[b] | 1698 (42.5%)[c] | 1399 (64.1%)[d] | < .05 |
| Ethnicity | | [a] | [b] | [a] | [b] | |
| Maori | 3659 (6.8%) | 3128 (6.6%) | 0 (0.0%) | 372 (9.3%) | 159 (7.2%) | < .05 |
| Pacific | 7248 (13.5%) | 6272 (13.3%) | 1 (0.6%) | 768 (19.1%) | 207 (9.4%) | |
| Asian | 10,829 (20.3%) | 9658 (20.5%) | 55 (32.0%) | 546 (13.6%) | 570 (25.8%) | |
| Indian | 3936 (7.4%) | 3331 (7.1%) | 109 (63.4%) | 100 (2.5%) | 396 (17.9%) | |
| Other | 1867 (3.5%) | 1649 (3.5%) | 7 (4.0%) | 121 (3.0%) | 90 (4.1%) | |
| European | 25,945 (48.5%) | 23,052 (49.0%) | 0 (0.0%) | 2108 (52.5%) | 785 (35.6%) | |
| Height | 165 (6.8) | 165 (6.8)[a] | 154 (5.2)[b] | 166 (6.3)[c] | 162 (6.7)[d] | < .05 |
| Weight | 69.3 (17.9) | 69.1 (17.7)[a] | 48.7 (5.9)[b] | 75.6 (19.8)[c] | 63.7 (15.3)[d] | < .05 |
| BMI, kg/m$^2$ | 25.3 (6.1) | 25.3 (6.0)[a] | 20.3 (2.6)[b] | 27.2 (7.0)[c] | 24.2 (5.4)[d] | < .05 |
| SGA risk factors | | | | | | |
| Smoking | 4100 (7.7%) | 3253 (6.9%)[a] | 1 (0.6%)[a] | 581 (14.5%)[b] | 265 (12.0%)[c] | < .05 |
| PIH | 3234 (6.1%) | 2548 (5.4%)[a] | 8 (4.7%)[a,b] | 386 (9.6%)[b] | 292 (13.2%)[c] | < .05 |
| Infant characteristics | | | | | | |
| Gestation, wks | 39.4 (1.5) | 39.5 (1.4)[a] | 39.3 (1.2)[a,b] | 39.3 (1.7)[b] | 38.8 (1.8)[c] | < .05 |
| Preterm birth | 2745 (5.1%) | 2131 (4.5%)[a] | 6 (3.5%)[a,b] | 331 (8.2%)[b] | 277 (12.5%)[c] | < .05 |
| Birthweight, g | 3433 (515) | 3526 (457)[a] | 2667 (195)[b] | 2893 (317)[c] | 2469 (349)[d] | < .05 |
| Birthweight term infants, g[e] | 3475 (478) | 3560 (428)[a] | 2684 (175)[b] | 2957 (233)[c] | 2562 (238)[d] | < .05 |
| Neonatal death[f] | 12 0.2/1000 | 9[a] 0.2/1000 | 0 0.0/1000 | 0 0.0/1000 | 3[b] 1.4/1000 | < .05 |
| NICU admission > 48 h[f] | 2032 (3.8%) | 1390 (3.0%)[a] | 6 (3.5%)[a,b] | 283 (7.1%)[b] | 353 (16.2%)[c] | < .05 |
| Ventilation > 4 h[f] | 1207 (2.3%) | 975 (2.1%)[a] | 3 (1.7%)[a,b] | 136 (3.4%)[b] | 93 (4.3%)[b] | < .05 |
| Apgar score < 7 at 5 min[f] | 651 (1.2%) | 457 (1.0%)[a] | 1 (0.6%)[a,b] | 60 (1.5%)[b] | 36 (1.7%)[b] | < .05 |
| Composite neonatal outcome[f] | 2695 (5.0%) | 1974 (4.2%)[a] | 6 (3.5%)[a,b] | 338 (8.4%)[b] | 379 (17.4%)[c] | < .05 |
| Stillbirth | 97 1.8/1000 | 59[a] 1.3/1000 | 0 0.0/1000 | 15[b] 3.7/1000 | 23[b] 10.4/1000 | < .05 |

*BMI*, body mass index; *cust*, customized; *IG*, INTERGROWTH-21st; *NICU*, neonatal intensive care unit; *PIH*, pregnancy-induced hypertension, *SGA*, small for gestational age.

[a-d] Indicate different groups ($P < .05$ with adjustment for multiple comparisons); [e] Infants > 37 weeks' gestation: n = 50,739 (non-SGA, n = 44,959; SGA-IG only, n = 166; SGA-cust only, n = 3684; SGA-both, n = 1930); [f] Denominators for neonatal outcomes exclude stillbirths: n = 53,387.

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adverse neonatal outcome was also twice as common in SGA-cust only infants (RR, 2.0, 95% CI, 1.8−2.2), but risks were not increased in infants identified as SGA-IG only (RR, 0.8, 95% CI, 0.4−1.8) (Figure). Similarly, the risk of stillbirth was highest in the SGA-both group (RR, 8.3, 95% CI, 5.1−13.4) and was also increased 3-fold in SGA-cust only infants (RR, 3.0, 95% CI, 1.7−5.3). There were no stillbirths among infants who were identified as SGA-IG only (Figure).

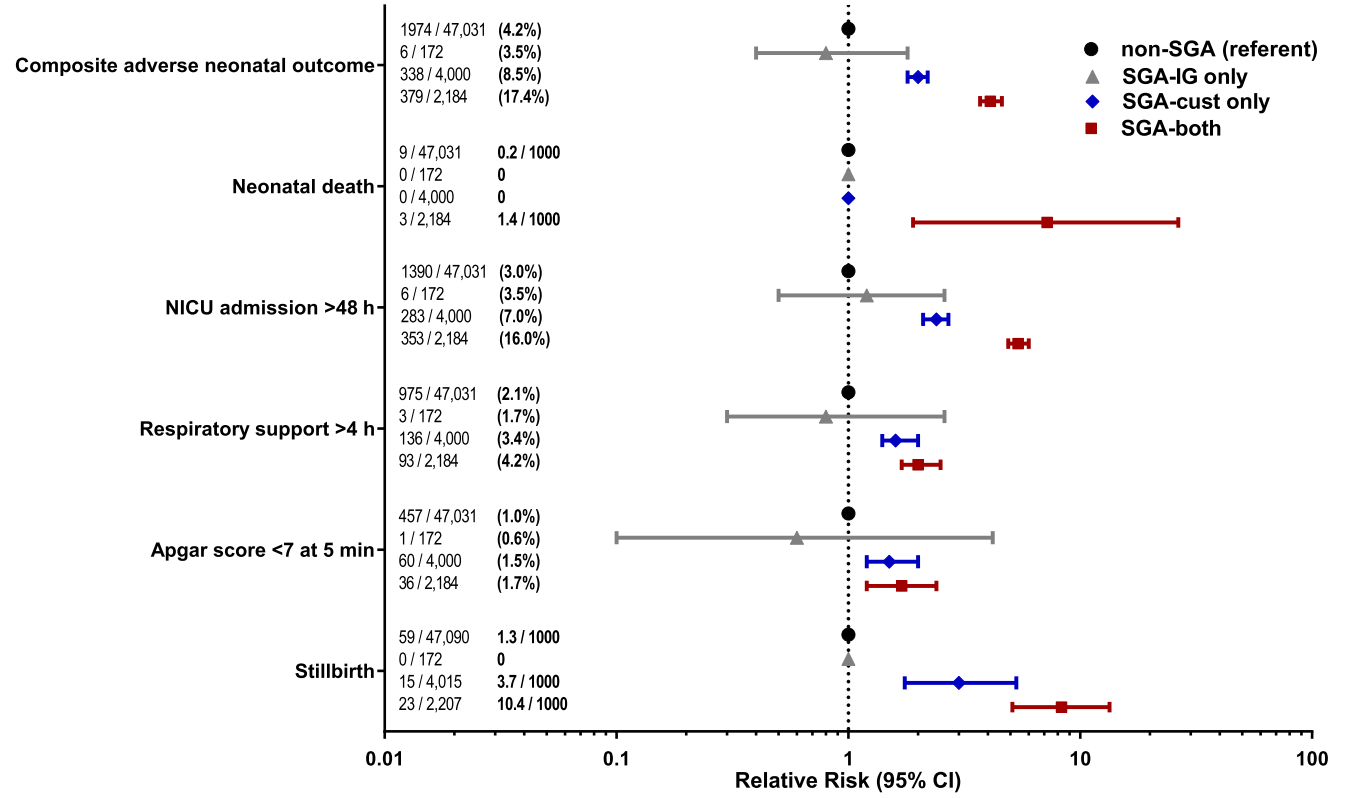
In a sensitivity analysis that excluded infants born at less than 37 weeks' gestation, results were very similar (n = 50,739); the risk of adverse neonatal outcome was increased in the SGA-both (RR, 3.3, 95% CI, 2.8−3.8) and SGA-cust only (RR, 1.5, 95% CI, 1.3−1.8) groups but not in those classified as SGA-IG only (RR, 1.1, 95% CI, 0.5−2.6). In term-born infants, the risk of stillbirth was highest in the SGA-both group (RR, 6.0, 95% CI, 3.1−11.5) and was also increased in the SGA-cust only infants (RR, 2.6, 95% CI, 1.2−5.2).

The sensitivity and specificity of INTERGROWTH-21st criteria for composite adverse neonatal outcome among SGA infants were 14.3% (95% CI, 13.0−15.7%) and 96.1% (95% CI, 95.9−96.3%), respectively, with positive and negative predictive values of 16.3% (95% CI, 14.9−17.9%) and 95.5% (95% CI, 95.3−95.7%), respectively. For customized criteria, sensitivity and specificity were 26.6% (95% CI, 24.9−28.3%) and 89.2% (95% CI, 88.9−89.5%), respectively, with positive and negative predictive values of 11.6% (95% CI, 10.8%−12.4%) and 95.8% (95% CI, 95.6−96.0%).

Compared with the non-SGA group, obstetric risk factors for SGA (smoking and PIH) were approximately twice as common in SGA-cust only and SGA-both groups ($P < .05$) but were not more common in the SGA-IG only group (Table 1). Preterm birth was also more common in the SGA-cust only and SGA-both groups ($P < .05$) but not in the SGA-IG only group (Table 1).

INTERGROWTH-21st birthweight Z-scores ranged from a mean (SD) of −0.2 (1.0) in infants born to Indian women to 0.8 (1.1) in those born to Pacific women (Table 2). Compared with European, infants of Indian mothers were more than 4 times as likely to be classified as

**FIGURE**
**Perinatal death and morbidity by small-for-gestational-age classification**




Relative risks and 95% confidence intervals for perinatal death and morbidity by SGA classification with non-SGA as referent. Composite adverse neonatal outcome was defined as one or more of the following: neonatal death, NICU admission > 48 hours, positive pressure respiratory support > 4 hours, or Apgar score < 7 at 5 minutes.

*cust*, customized; *IG*, INTERGROWTH-21st; *NICU*, neonatal intensive care unit; *SGA*, small for gestational age.

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**TABLE 2**
**Maternal and infant characteristics by ethnicity**

| Ethnicity | Maori (n = 3649) (6.8%) | Pacific (n = 7248) (13.5%) | Asian (n = 10,829) (20.3%) | Indian (n = 3936) (7.4%) | Other (n = 1867) (3.5%) | European (n = 25,945) (48.5%) | *P* value |
|---|---|---|---|---|---|---|---|
| Maternal characteristics | | | | | | | |
| Height, cm | 166 (6.2)[a] | 166 (6.1)[a] | 161 (5.7)[b] | 159 (6.2)[c] | 159 (6.2)[d] | 167 (6.4)[e] | <0.05 |
| Weight, kg | 78 (19.9)[a] | 91 (21.9)[b] | 58 (9.8)[c] | 63 (12.1)[d] | 66 (13.3)[e] | 68 (13.6)[f] | <0.05 |
| BMI, kg/m$^2$ | 28.7 (6.9)[a] | 32.7 (7.4)[b] | 22.2 (3.6)[c] | 24.6 (4.6)[d] | 25.1 (4.8)[e] | 24.3 (4.7)[f] | <0.05 |
| Infant characteristics | | | | | | | |
| Birthweight, g | 3444 (536)[a] | 3585 (548)[b] | 3300 (465)[c] | 3130 (474)[d] | 3385 (495)[e] | 3491 (501)[f] | <0.05 |
| Birthweight term infants, g[g] | 3497 (485)[a] | 3633 (501)[b] | 3335 (435)[c] | 3181 (432)[d] | 3423 (461)[e] | 3535 (461)[f] | <0.05 |
| Intergrowth 21st Z-score | 0.5 (1.0)[a] | 0.8 (1.1)[b] | 0.1 (0.9)[c] | −0.2 (1.0)[d] | 0.3 (1.0)[e] | 0.6 (1.0)[f] | <0.05 |
| SGA status | | | | | | | |
| SGA-IG | 159 (4.4%)[a] | 208 (2.9%)[b] | 625 (5.8%)[c] | 505 (12.8%)[d] | 97 (5.2%)[a,c] | 785 (3.0%)[b] | <0.05 |
| SGA-cust | 531 (14.5%)[a] | 975 (13.5%)[a,b] | 1116 (10.3%)[c] | 496 (12.6%)[a,b,d] | 211 (11.5%)[b,c,d] | 2893 (11.2%)[c,d] | <0.05 |

Data are presented as mean (SD) or n (percentage) as appropriate.

*BMI*, body mass index; *cust*, customized; *IG*, INTERGROWTH-21st; *SGA*, small for gestational age.

[a-f] Indicate different groups ($P < .05$ with adjustment for multiple comparisons); [g] Infants > 37 weeks' gestation (n = 50,739: Maori, n = 3432; Pacific, n = 6860; Asian, n = 10,348; Indian, n = 3674; Other, n = 1779; European, n = 24,646).

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SGA by INTERGROWTH-21st criteria, and for Asian infants, twice as likely ($P < .05$, Table 2). However, the rate of SGA by INTERGROWTH-21st criteria for Maori, Pacific, and European infants was less than a third that of customized criteria, and for Asian and infants in the category of other, this ratio was approximately half.

Between ethnicities, maternal anthropometric characteristics and mean infant birthweights varied significantly ($P < .05$). There was an 8 cm difference in mean maternal height between Indian and European women, a 33-kg difference in mean early pregnancy weight between Asian and Pacific women, and a 450-g difference in birthweight between Indian and Pacific infants (Table 2). Birthweight remained significantly different between ethnic groups when adjusted for gestational age at delivery ( $P < 0.05$).

Mothers of infants who were classified as SGA-IG only were almost all of Indian (63.4%) or Asian (32.0%) ethnicity. These women, compared with those whose infants were SGA-cust only, were shorter (mean difference 11.8 cm) and lighter (mean difference 26.9 kg). SGA-IG only mothers were also younger and more likely to be nulliparous (89.5%) than any other group (Table 1).

Smoking rates varied significantly by ethnicity (Maori, 35.2%; Pacific, 17.4%; European, 4.8%; Asian, 1.9%; Indian, 1.2%; and Other, 3.5%, $P < .05$). When adjusted for ethnicity, smoking remained significantly elevated among the SGA-cust only and SGA-both groups compared with the non-SGA group ($P < .05$). SGA-IG only mothers had very low rates of smoking (Table 1).

## Comment

Application of the INTERGROWTH-21st birthweight standard to a multiethnic New Zealand general obstetric population identified fewer infants as SGA than a customized standard (4.5% vs 11.6%). Furthermore, although infants who were identified as SGA by both standards had the highest risk of composite adverse neonatal outcome and stillbirth, risks were also increased in infants who were identified as being SGA by customized criteria alone (SGA-cust only). These infants were more likely to be exposed to traditional risk factors for SGA such as maternal smoking and PIH. The small proportion of infants who were identified as SGA by INTERGROWTH-21st criteria alone (SGA-IG only) did not have increased exposure to these risk factors and did not have increased risk of adverse outcome.

Consistent with our hypothesis, substantial differences in rates of SGA-IG occurred between ethnicities, with infants of Indian and Asian women (ie, women of smaller stature) being overrepresented among SGA-IG infants. Infants of Pacific mothers, however, had similar rates of SGA-IG to European infants.

The INTERGROWTH-21st project produced international standards for newborn size to provide a "conceptual and practical link to World Health Organization Child Growth Standards" to "monitor child growth seamlessly from early pregnancy to age 5 years."[1,20,21] These standards are designed to be an estimate of physiological or normal growth under ideal conditions because

participant mothers were specifically selected based on their low-risk status. These women were younger (18−35 years), well nourished with no medical conditions, nonsmokers with extremes of maternal size excluded (height less than 153 cm, BMI $< 18.5$ or $> 30$ kg/m$^2$).

This standard is intended to be multiethnic and multicountry[1] with sex-specific birthweight charts developed for international use and readily available for download.[22] However, when applied to our multiethnic general obstetric population, New Zealand infants have on average higher INTERGROWTH-21st Z-scores, meaning substantially fewer SGA infants are identified. In our population suboptimal infant growth is underestimated by INTERGROWTH-21st criteria.

One fifth of our population is of Maori or Pacific descent (ethnicities not included in the INTERGROWTH-21st standard), who are on average taller and heavier than Asian and Indian women. We also have a high proportion of overweight and obese women.

Differences in SGA-IG rates between ethnicities can be related to differences in maternal size. Increasing maternal height and weight are correlated with increasing infant birthweight, even for women of normal BMI.[23,24] Within the INTERGROWTH-21st study, this association was evident, with the smallest babies born to the shortest and lightest women (Indian term birthweight 2.9 kg) and the largest babies born to the tallest and heaviest women (UK term birthweight, 3.5 kg).[1]

Given that these differences in birthweight were reported in the original study, it is not surprising that our population, which includes a significant number of women whose anthropometric measurements lie at the extremes of the populations included in the INTERGROWTH-21st sample, will show the limitations of the standard. In our population the low overall rate of SGA-IG results from higher-than-average birthweight compared with INTERGROWTH-21st, which may be explained by New Zealand mothers being on average taller (3 cm) and heavier (8 kg) than the INTERGROWTH-21st participants. Because maternal size is well established to have an influence on birthweight, customized birthweight standards that account for these characteristics may better identify infants with intrauterine growth restriction who are at increased risk of neonatal complications as well as having a higher association with SGA-related stillbirth.

The customized birthweight standard identified more preterm infants as SGA compared with INTERGROWTH-21st because of the use of an ultrasound-defined fetal growth standard. This effect could have potentially accounted for the higher rates of mortality and morbidity among SGA-cust only infants; however, exclusion of preterm infants did not change our findings. At preterm gestations, the INTERGROWTH-21st standard may not reflect optimal fetal growth because preterm birth is inherently pathological and is commonly associated with fetal growth restriction.[2,3] This is compounded in the INTERGROWTH-21st analysis by the much higher preterm birth rate reported among Indian women (10.0% compared with 3.4% of UK women)[1] (ie, infants from the smallest stature mothers contributed disproportionately to the generation of the preterm INTERGROWTH-21st birthweight reference).

The majority of infants classified as SGA by INTERGROWTH-21st criteria were also identified as SGA by customized criteria (89%), whereas customization identified an additional group of 4015 at-risk SGA infants (7.5%). These infants not only have a 2-fold increased risk of composite adverse neonatal outcome but also have a 3-fold increased chance of being stillborn. Use of the INTERGROWTH-21st standard in our population would miss 13% of all infants with composite adverse neonatal outcome. In contrast, the INTERGROWTH-21st standard did not identify any additional at-risk infants.

The INTERGROWTH-21st standard provides important normative data on infant size at birth, enabling comparisons between populations. However, in ethnicities with larger-than-average maternal size, INTERGROWTH-21st underestimates SGA-related composite adverse neonatal morbidity risk while overestimating this risk in ethnic groups with smaller stature.

Implementation of the INTERGROWTH-21st birthweight standard without prior local validation has the potential to classify infants who are normally grown as SGA or inappropriately normalize pathologically small infant size at birth. We recommend, as suggested by the INTERGROWTH-21st authors, that international standards still need to be tailored to local populations and that statistic-based cutoffs (such as $<$ 10th or $>$ 90th centile) should ideally be replaced by perinatal risk-based cutoffs to provide an evidence-based triage for neonatal care.[1] The development of charts for size at birth that have been published on the INTERGROWTH-21st web site[22] for free download allows for easy access to this international birthweight chart, but there remains the risk that widespread use may occur without local evaluation.

## Strengths and limitations

Our general obstetric cohort of more than 53,000 infants born at 33 weeks' gestation onward has data that were prospectively collected throughout pregnancy through to postnatal care and routinely checked for accuracy. We were able to include an analysis of neonatal morbidity, which is infrequently included in other cohort studies. Some infants inevitably experience more than one morbidity outcome (eg, respiratory support for $>$ 4 hours and admitted to the NICU for $>$ 48 hours), meaning our composite adverse neonatal outcome gives a better overall assessment of risk for an individual infant.

A limitation of our study is that only a limited range of infant morbidity measures were able to be reported, but these are objective measures that have been shown to identify infants at high risk of major morbidity.[15-19] Longer-term infant and child outcomes were also not available; however, low Apgar score and admission to neonatal intensive care have been associated with poorer

neurodevelopment,[15-17] particularly in term infants.

Because customization identified a larger number of infants as SGA compared with INTERGROWTH-21st, customization had a higher sensitivity for composite adverse neonatal outcome (26.6% SGA-cust, 14.6% SGA-IG), with a concurrent loss of specificity (89.2% SGA-cust, 96.1% SGA-IG). Positive and negative predictive values for both standards were, however, poor because the majority of adverse neonatal outcomes occur among non-SGA infants.

## Conclusion

In our multiethnic, general obstetric population, a customized birthweight standard identified more SGA infants at increased risk of composite adverse neonatal outcome than the INTERGROWTH-21st birthweight standard. The INTERGROWTH-21st standard failed to detect many at-risk SGA infants, particularly among ethnic groups with larger maternal size while disproportionately identifying higher rates of SGA among those with smaller maternal size. Implementation of this birthweight standard in international populations should occur only after a local evaluation of the impact it would have on the detection of at-risk SGA infants. Future research should include additional short- and long-term data on infant outcomes among SGA infants (by customized and INTERGROWTH-21st criteria) (eg, neonatal hypoglycemia, later neurodevelopment and growth). ■

## References


1. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. Lancet 2014;384:857-68.
2. Groom KM, Poppe KK, North R, et al. Small-for-gestational-age infants classified by customized or population birthweight centiles: Impact of gestational age at delivery. Am J Obstet Gynecol 2007;197:e1-5.
3. Gardosi J. Prematurity and fetal growth restriction. Early Hum Dev 2005;81:43-9.
4. Moser K, Stanfield KM, Leon DA. Birthweight and gestational age by ethnic group, England and Wales 2005: introducing new data on births. Health Stat Q 2008:Autumn: 22-31, 34-55.
5. Anderson N, Sadler L, Stewart A, McCowan L. Maternal and pathological pregnancy characteristics in customised birthweight centiles and identification of at-risk small-for-gestational-age infants: a retrospective cohort study. BJOG 2012;119:848-56.
6. Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound Obstet Gynecol 1995;6:168-74.
7. McCowan LME, Harding JE, Stewart AW. Customised birthweight centiles predict SGA pregnancies with perinatal morbidity. BJOG 2005;112:1026-33.
8. Figueras F, Figueras J, Meler E, et al. Customized birthweight standards accurately predict perinatal morbidity. Arch Dis Child Fetal Neonatal Ed 2007;92:F277-80.
9. Gardosi J, Francis A. Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. Am J Obstet Gynecol 2009;201:e1-8.
10. Perinatal and Maternal Mortality Review Committee. Seventh annual report of the Perinatal and Maternal Mortality Review Committee: reporting mortality, 2011. Wellington, New Zealand: Health Quality and Safety Commission; 2013.
11. Australasian Society for Ultrasound in Medicine. Guidelines for the mid trimester obstetric scan (D2). Australasian Society for Ultrasound in Medicine. 2007. Available at: http://www.asum.com.au/site/policies.php. Accessed Sept. 6, 2015.
12. Australasian Society for Ultrasound in Medicine. Statement on normal ultrasonic fetal measurements (D7). Australasian Society for Ultrasound in Medicine. 2007. Available at: http://www.asum.com.au/site/policies.php. Accessed Sept. 6, 2015.
13. Ministry of Health. Ethnicity data protocols for the health and disability sector. 2004. Available at: http://www.nzhis.govt.nz/documentation/ethnicity/index.html. Accessed Sept. 6, 2015.
14. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20: ix-xiv.
15. Iliodromiti S, Mackay DF, Smith GC, Pell JP, Nelson SM. Apgar score and the risk of cause-specific infant mortality: a population-based cohort study. Lancet 2014;384: 1749-55.
16. Moster D, Lie RT, Irgens LM, Bjerkedal T, Markestad T. The association of Apgar score with subsequent death and cerebral palsy: a population-based study in term infants. J Pediatr 2001;138:798-803.
17. Darlow BA, Horwood LJ, Wynn-Williams MB, Mogridge N, Austin NC. Admissions of all gestations to a regional neonatal unit versus controls: 2-year outcome. J Paediatr Child Health 2009;45: 187-93.
18. Morosini A, Davies MW. Predicting the need for ventilation in term and near-term neonates. J Paediatr Child Health 2004;40: 438-43.
19. Schiariti V, Klassen AF, Hoube JS, Synnes A, Lisonkova S, Lee SK. Perinatal characteristics and parents' perspective of health status of NICU graduates born at term. J Perinatol 2008;28:368-76.
20. de Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO multicentre growth reference study: planning, study design, and methodology. Food Nutr Bull 2004;25(Suppl 1):S15-26.
21. World Health Organization Multicentre Growth Reference Study Group. WHO child growth standards based on length/height, weight and age. Acta Paediatr Suppl 2006;450: 76-85.
22. The International Fetal and Newborn Growth Consortium for the 21st Century. INTERGROWTH-21st newborn size at birth chart. Available at: https://intergrowth21.tghn.org/articles/intergrowth-21st-newborn-size-birth-chart/. Accessed July 14, 2015.
23. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65: 663-737.
24. Gardosi J, Clausson B, Francis A. The value of customized centiles in assessing perinatal mortality risk associated with parity and maternal size. BJOG 2009;116: 1356-63.


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Received Sept. 1, 2015; revised Oct. 25, 2015; accepted Oct. 29, 2015.

The authors report no conflict of interest.

A preliminary summary of some of these findings were presented at the RCOG World Congress 2015, Brisbane, Australia, April 12-15, 2015.



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