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ARTICLE

Neonatal morbidity and small and large size for gestation: a comparison of birthweight centiles

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Abstract

Objective To compare rates of small- and large-for-gestational age (SGA and LGA) neonates using four different weight centiles, and to relate these classifications to neonatal morbidity.

Study design Neonates born at 33–40 weeks' gestation in a multiethnic population were classified as SGA or LGA by population reference (Fenton), population standard (INTERGROWTH), fetal growth curves (WHO), and customized (GROW) centiles. Likelihood of composite morbidity was determined compared with a common appropriate-for-gestational age referent group.

Result Among 45,505 neonates, SGA and LGA rates varied up to threefold by different centiles. Those most likely to develop neonatal morbidity were SGA or LGA on both the population reference and an alternative centile. Customized centiles identified over twice as many at-risk SGA neonates.

Conclusions Customized centiles were most useful in identifying neonates at increased risk of morbidity, and those that were small on both customized and population reference centiles were at the highest risk.

Introduction

Neonates are frequently classified as small (SGA) or large-for-gestational age (LGA), typically defined as <10th or >90th sex-specific weight centile at birth, respectively, to identify those at increased risk of early morbidity and to plan transitional care. SGA and LGA neonates have an increased risk of low Apgar score, respiratory distress, hypoglycemia, infection, feeding difficulty, and neonatal death [1–3]. These risks are increased if neonates are also born preterm, especially those that are SGA. Thus, some centers have specialized care pathways for these neonates, including prolonged inpatient observation, glucose monitoring, newborn early warning scores, intensified breastfeeding support, and weight monitoring [4]. In addition to short-term risks [5], neonates born SGA or LGA have an increased risk of adverse health outcomes in later life, including hypertension, obesity, type 2 diabetes mellitus, and vascular disease [6], and may be considered for early cardiometabolic screening [7, 8]. Thus, it is important that neonates are optimally classified, not only to minimize adverse outcomes but also to prevent unnecessary intervention.

Although there is clinical utility in identifying small and large neonates, there is a lack of consensus about which birthweight centiles are most appropriate [9]. There are four main types: population birthweight references, population birthweight standards, fetal growth curves, and customized centiles. Each differ in how they account for normal *in utero* constraint of fetal growth to detect either pathological undergrowth, also termed fetal growth restriction (FGR), or

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overgrowth, sometimes referred to as macrosomia. Population reference centiles aggregate cross-sectional sex- and gestation-specific birthweights across whole populations [10], whereas population standards characterize sex- and gestation-specific cross-sectional birthweights in low-risk pregnancies without any major environmental threats to normal fetal growth [11]. Fetal growth curves represent sex- and gestation-specific estimations of fetal weight derived from serial ultrasound measures of fetuses born at term [12]. Customized centiles incorporate fetal growth curves but also maternal factors that affect normal constraint of fetal growth, including weight, height, ethnicity, and parity [13].

Classification of neonates by birthweight centiles is complicated by the fact that many FGR neonates are SGA, but FGR can also occur within the normal birthweight range, and some SGA neonates are not pathologically small but simply constrained in their growth [14]. Similarly, most macrosomic neonates are LGA, but not all LGA neonates are pathologically large [3]. An ideal weight centile chart would distinguish both small and large neonates at an increased risk of short and long-term morbidity from those without increased risk.

It has been argued that international population standards obviate the need to account for population or ethnic differences in fetal growth [15] but we have previously shown in a multiethnic obstetric population that using a population standard failed to identify many smaller neonates at an increased risk of neonatal morbidity compared with customized centiles, especially in ethnic groups with larger than average maternal size [16]. However, customization has been criticized because of the potential difficulty in describing ethnicity and the possibility of normalizing larger fetal size [17]. More recently, the World Health Organisation (WHO) released sex-specific fetal growth curves, providing yet another option for assessment of birthweight [12].

There is additional complexity in that growth-restricted neonates are more likely to be born preterm, whereas smaller fetuses that are simply constrained are more likely to remain *in utero* until term [18]. Further, larger neonates are often born late preterm or early term, especially when associated with maternal diabetes [19]. There is also increasing recognition that early term birth is itself a risk factor for long-term adverse respiratory, cardiometabolic, neurodevelopmental, cognitive, and social outcomes [20, 21], although it remains unclear the extent to which this is due to preterm birth per se or confounding by the social determinants of health.

The aims of this study were to: (1) compare rates of SGA and LGA at birth using four different types of weight centiles, namely, a population birthweight reference (Fenton) [10], population birthweight standard (INTERGROWTH) [22], fetal growth curves (WHO) [12], and customized centiles (GROW) [13]; (2) assess the influence of gestation length and ethnicity on SGA and LGA classification; and (3) determine the likelihood of composite neonatal morbidity in SGA and LGA neonates using different weight centiles at different gestations.

Subjects and methods

Study population

This study was undertaken using a dataset of babies born at National Women's Health (NWH), Auckland City Hospital, Auckland, New Zealand that we have previously used to assess the role of customization in detection of small babies at risk of neonatal morbidity [16]. It comprises prospectively collected maternity data from January 2006 to December 2013. NWH is a tertiary referral hospital with an annual birth rate of ~7500 from a multiethnic population. The NWH databases collect maternity and neonatal data for all births occurring ≥20 weeks' gestation, including demographics, antenatal complications, delivery details, and neonatal outcomes. Data are routinely checked for completeness, outliers, and or other inconsistencies. Approval to use these data was obtained from the Research Review Committee of the Auckland District Health Board, and data were provided in an anonymized form.

Gestational age was calculated from 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 at the time or by dating ultrasound if the LMP was uncertain [23, 24]. A first trimester ultrasound is undertaken by the majority of women birthing at NWH.

Maternal height and weight were measured or self-recalled at the first antenatal visit. Parity was defined as the number of pregnancies of ≥20 completed weeks' gestation or of at least 400 g if gestation was unknown [25]. Self-reported maternal ethnicity was grouped and prioritized in order of Māori, Pacific Peoples, Indian, Asian, Other, and European [26]. Asian ethnicity included women from China, South-East Asia, Japan, and Korea. Indian ethnicity included women from India and those of Fijian-Indian origin.

Statistical analysis

Analysis was performed using Base SAS® 9.4 Software (SAS Institute Inc., Cary, NC, USA) and included singleton neonates born at NWH from 33 to <41 weeks' gestation. These gestation limits were required because there were insufficient data at higher or lower gestations for some weight centiles. Neonates were excluded if they were

stillborn, had major malformations, or missing data for birthweight or gestational age at delivery. Neonates were also excluded if their mothers were unbooked, transferred to NWH during pregnancy or labor, or had missing data required for customization.

Neonates were classified as SGA or LGA by birthweight using the population birthweight reference (Fenton 2013) [10] and three alternative centiles: a population birthweight standard (INTERGROWTH) [27], fetal growth curves (WHO 2016) [12], and customized centiles (GROW) [28]. The Fenton centiles are currently the most widely used birthweight reference in New Zealand. The Fenton, INTERGROWTH, and WHO weight centiles are specific for gestation length and sex. Customized birthweights were determined using the GROW calculator (GROW, version 6.7.8.3; Perinatal Institute; Birmingham, UK), which includes locally derived coefficients [29], adjusting for maternal height and weight at booking (or earliest estimate in pregnancy), parity, ethnicity, and infant sex. For each weight centile, SGA was defined as <10th percentile and LGA as >90th percentile. Neonates were also categorized as moderate to late preterm (≥33 to <37 weeks), early term (≥37 and <39 weeks), and term (≥39–41 weeks' gestation) [30].

The primary outcome for this study was composite neonatal morbidity, defined as any of as follows: neonatal unit (NNU) admission >48 h for acute complications (not solely for prematurity without other ICD-10 diagnosis code), respiratory support >4 h, Apgar score <7 at 5 min, or neonatal death. Secondary outcomes included the components of this composite outcome.

Maternal and neonatal characteristics, and primary and secondary outcomes were compared among gestation groups using analysis of variance for continuous data, and chi-square test for frequency data. The rates of SGA and LGA using each of the four types of weight centiles were compared for the entire population, each gestation category, and for each maternal ethnicity. Differences in the rates of SGA and LGA between the centiles were analyzed using a generalized linear mixed model, with subject as a random effect. The risk of composite neonatal morbidity associated with classification of SGA or LGA was calculated for each centile using a generalized linear model, in comparison with a common referent group, defined as those neonates whose birthweight was classified between the 10th and 90th percentiles on all weight centiles. Neonates were classified according to whether they were SGA or LGA by only the population reference, by both the population reference and an alternative centile, or only the alternative centile. Exposure effect is presented as odds ratio with a 95% confidence interval. A P value <0.05 was considered statistically significant.

To assess the overall performance of each weight centile for identifying infants at risk of neonatal morbidity, sensitivity, specificity, and positive and negative predictive values were calculated for SGA or LGA status combined, i.e., non-appropriate-for-gestational age (non-AGA) status, as well as positive likelihood ratios with 95% confidence intervals.

Results

Between January 2006 and December 2013, a total of 48,756 singleton nonanomalous neonates were born at 33 to <41 weeks' gestation. Of these, 3,251 neonates were excluded from this analysis due to stillbirth (97) or incomplete data (3154), including maternal height and weight, and birthweight.

Of the remaining 45,505 neonates included in this analysis, 6.0% (2711) were born moderate to late preterm, 33.0% (15,005) early term, and 61.0% (27,789) at term. Of the mothers in this cohort, the mean (SD) age was 31.6 (5.6) years and height was 164.4 (6.8) cm; 46.3% (21048) were nulliparous, 18.4% (8379) had a BMI >30 kg/m^2, 7.7% (3,487) were smoking either during pregnancy or at delivery, and 8.7% (3,973) had hypertension during pregnancy. Nearly half of the mothers were of European ethnicity (47.8%, 21,731), followed by Asian (21.0%, 9,547), Pacific (13.3%, 6,071), Indian (7.7%, 3,517), Māori (6.8%, 3,096), and other ethnicities (3.4%, 1,543) (Table 1). The mean (SD) gestational age at birth was 39.1 (1.3) weeks and birthweight was 3379 (508) g. Only 4.2% (1,905) of neonates were admitted to the NNU for >48 h and 4.3% (1,978) had composite neonatal morbidity, including <0.1% (11) neonatal deaths, 3.0% (1,372) admitted to the NNU at >48 h for acute complications, 2.3% (1,067) requiring respiratory support for >4 h, and 1.0% (458) had an Apgar score <7 at 5 min after birth (Table 1).

Mothers of neonates born moderate to late preterm compared with those born early term and at term were shorter and more likely to be nulliparous, obese, smokers, have hypertension in pregnancy, and be of Māori, Pacific, or Indian ethnicity ($P < 0.0001$, Table 1). The mothers of neonates born early term compared with those born at term were older and less likely to be nulliparous, and more likely to be obese, have hypertension in pregnancy, and be of Asian or Indian ethnicity ($P < 0.0001$, Table 1).

Moderate to late preterm neonates ($N = 2,711$), compared with early term and term neonates, had the highest rates of admission to the NNU > 48 h after birth (41.0%, 1,112), including those with acute complications (25.7%, 697), with respiratory support for >4 h (16.8%, 455), and Apgar score <7 at 5 min after birth (2.6%, 71), each contributing to a

Table 1 Cohort characteristics.

	Total	Moderate to late preterm	Early term	Term	*P*
	N = 45,505	*N* = 2,711	*N* = 15,005	N = 27,789	
Maternal characteristics					
Age (years)	31.6 (5.6)	31.8 (5.9)	32.2 (5.7)	31.2 (5.6)	<0.0001
Height (cm)	164.4 (6.8)	163.7 (6.9)	164.0 (6.9)	164.8 (6.7)	<0.0001
Nulliparous	46.3% (21,048)	49.4% (1,338)	41.8% (6,268)	48.4% (13,442)	<0.0001
BMI > 30 kg/m^2	18.4% (8,379)	23.2% (630)	20.3% (3,050)	16.9% (4,699)	<0.0001
Smoking	7.7% (3,487)	9.7% (263)	7.8% (1,163)	7.4% (2,061)	0.0001
Hypertension in pregnancy	8.7% (3,973)	19.9% (539)	11.4% (1,718)	6.2% (1,716)	<0.0001
Ethnicity					<0.0001
Māori	6.8% (3,096)	8.2% (223)	6.8% (1,020)	6.7% (1,853)	
Pacific	13.3% (6,071)	14.1% (381)	12.9% (1,933)	13.5% (3,757)	
Asian	21.0% (9,547)	17.5% (474)	21.9% (3,290)	20.8% (5,783)	
Indian	7.7% (3,517)	9.6% (260)	9.0% (1,345)	6.9% (1,912)	
Other	3.4% (1,543)	3.2% (87)	3.2% (479)	3.5% (977)	
European	47.8% (21,731)	47.4% (1,286)	46.2% (6,938)	48.6% (13,507)	
Neonatal characteristics					
Gestation (weeks)	39.1 (1.3)	35.7 (1)	38.2 (0.5)	39.9 (0.6)	<0.0001
Birthweight (g)	3379 (508)	2633 (537)	3235 (458)	3529 (439)	<0.0001
Neonatal death	<0.1% (11)	0.1% (3)	<0.1% (5)	<0.1% (3)	0.004
All NNU admissions >48 h	4.2% (1,905)	41.0% (1,112)	2.9% (436)	1.3% (357)	<0.0001
NNU admissions >48 h with acute complications[a]	3.0% (1,372)	25.7% (697)	2.6% (385)	1.0% (290)	<0.0001
Respiratory support >4 h	2.3% (1,067)	16.8% (455)	2.0% (296)	1.1% (316)	<0.0001
Apgar score <7 at 5 min	1.0% (458)	2.6% (71)	1.1% (170)	0.8% (217)	<0.0001
Composite neonatal morbidity[b]	4.3% (1,978)	29.3% (793)	4.0% (601)	2.1% (584)	<0.0001

Data are mean (standard deviation) or percent (number). Includes singleton live births from ≥33 to <41 weeks' gestation. Moderate to late preterm, ≥33 to <37 weeks'; early term, ≥37 and <39 weeks'; and term, ≥39 to <41 weeks' gestation.

BMI body mass index, *NNU* neonatal unit.

[a]Excludes NNU admission solely for prematurity or known congenital anomalies.

[b]Composite neonatal morbidity defined as one or more of: NNU admission >48 h for acute complications (not solely for prematurity or known congenital anomaly), respiratory support >4 h, Apgar score <7 at 5 min, or neonatal death. *P* value is for comparison of gestation groups.

higher proportion of neonates with composite neonatal morbidity (29.3%, 793) ($P < 0.0001$, Table 1).

SGA rates and neonatal morbidity

For the entire cohort, the SGA rate was the lowest using the population reference (3.8%) but was up to threefold higher using centiles that accounted for normal fetal growth (fetal growth curves 9.7%, customized 11.5%); the SGA rate was intermediate using the population standard (4.8%) ($P < 0.0001$, Table 2). This pattern was seen in all gestational age groups, although at term, SGA rates were similar using the population reference and population standard (Table 2).

Using the population reference, population standard, and fetal growth curves, SGA rates were lowest in Pacific neonates (2.5–6.5%) but were up to fourfold higher in Indian neonates (10.6–23.3%) (Table 2). Using customized centiles, which account for ethnicity, SGA rates were more similar across different ethnic groups (10.1–14.7%) (Table 2).

In moderate to late preterm neonates, the population standard, fetal growth curves, and customized centiles identified all neonates who were SGA by the population reference (5.7%), i.e., no moderate to late preterm neonates were identified as SGA by only the population reference (Table 3). Neonates identified as SGA using both the population reference and one of the alternative centiles

Table 2 SGA rates at birth using different weight centiles in neonates of different gestational age and ethnicity.

	N	Weight centiles				*P*
		Population reference (Fenton) [10]	Population standard (INTERGROWTH) [27]	Fetal growth curves (WHO) [12]	Customized (GROW) [13]	
Entire cohort	45,505	3.8% (1,746)	4.8% (2,183)	9.7% (4,433)	11.5% (5,241)	<0.0001
Gestation						
Moderate to late preterm	2,711	5.7% (155)	11.1% (302)	16.5% (447)	21.8% (590)	<0.0001
Early term	15,005	3.8% (570)	5.8% (877)	9.8% (1,469)	12.7% (1,909)	<0.0001
Term	27,789	3.7% (1,021)	3.6% (1,004)	9.1% (2,517)	9.9% (2,742)	<0.0001
Maternal ethnicity						
Māori	3,096	4.0% (124)	4.8% (148)	9.3% (289)	14.7% (456)	<0.0001
Pacific	6,071	2.5% (151)	3.0% (184)	6.5% (394)	13.1% (794)	<0.0001
Asian	9,547	4.8% (459)	6.1% (580)	12.9% (1,229)	10.1% (965)	<0.0001
Indian	3,517	10.6% (374)	13.3% (468)	23.3% (820)	12.8% (450)	<0.0001
Other	1,543	4.3% (66)	5.6% (86)	11.9% (184)	11.0% (169)	<0.0001
European	21,731	2.6% (572)	3.3% (717)	7.0% (1,517)	11.1% (2,407)	<0.0001

Data are percent (number) detected as SGA. Includes singleton live births from ≥33 to < 41 weeks' gestation. Gestation groups defined as: moderate to late preterm, ≥33 to <37 weeks'; early term, ≥37 and <39 weeks'; and term, ≥39 to <41 weeks' gestation. Maternal ethnicity prioritized in order: Māori, Pacific, Indian, Asian, Other, and European. *P* value is for comparison of weight centiles.

SGA small-for-gestational age (<10th centile).

(5.7%) had the highest risk of neonatal morbidity (OR 11.9, 95% CI 8.1–17.8). Those identified as SGA using only one of the alternative centiles but not using the population reference (population standard, 5.4%; fetal growth curves, 10.8%; customized centiles, 16.0%) also had approximately a threefold increased likelihood of neonatal morbidity (Table 3).

In early term neonates, the fetal growth curves but not the population standard (<0.1%) or customized centiles (0.2%) identified all neonates who were SGA by the population reference, i.e., no early term neonates were identified as SGA by only the population reference (Table 3). However, the risk of neonatal morbidity was not increased for these neonates. Neonates identified as SGA using both the population reference and one of the alternative centiles (3.6–3.8%) had approximately a sixfold increased likelihood of neonatal morbidity (Table 3). Those identified as SGA using only one of the alternative centiles but not by the population reference (population standard, 2.1%; fetal growth curve, 6.0%; customized centile, 9.1%) also had a nearly twofold increased likelihood of neonatal morbidity (Table 3).

In term neonates, the fetal growth curve identified all neonates who were SGA by the population reference (3.7%), but a small proportion of these neonates were not identified as SGA using the population standard (0.6%) or customized centile (0.4%). However, the risk of neonatal morbidity was not increased for the latter (Table 3). Neonates identified as SGA using both the population reference and one of the alternative centiles (3.1–3.7%) had a threefold increased likelihood of neonatal morbidity; this was the highest using the customized centiles (OR 3.8, 95% CI 2.8–5.1) (Table 3). Neonates identified as SGA by only the fetal growth curves (5.4%) or customized centiles (6.6%) but not by the population reference, had a small increased likelihood of neonatal morbidity (Table 3). Few term neonates were SGA using only the population standard (0.5%).

LGA rates and neonatal morbidity

In the entire cohort, the LGA rate was the highest using the population standard (20.0%), intermediate using the fetal growth curves (16.3%), and the lowest using the population reference (11.7%) and customized centiles (9.3%) (Table 4). In moderate to late preterm neonates, LGA rates were the highest using the fetal growth curve (21.6%) but in term neonates, rates were the highest using the population standard (21.3%) (Table 4).

Using the population reference, population standard, and fetal growth curve, LGA rates were the lowest in Indian neonates (3.6–6.5%) but were more than fivefold higher in Pacific neonates (20.0–31.8%). Using the customized centiles, which account for ethnicity, LGA rates were similar across different ethnic groups (8.4–10.8%) (Table 4).

In moderate to late preterm neonates, LGA using any centile, or combination thereof, was not associated with

Table 3 Risk of composite neonatal morbidity in neonates defined as SGA by the population reference and alternative weight centiles.

Gestation	Alternative weight centile	SGA by only the population reference (Fenton) [10] and not alternative weight centile		SGA by both the population reference and alternative weight centile		SGA by only an alternative weight centile and not the population reference (Fenton)	
		SGA % (*n*)	OR (95% CI)	SGA % (*n*)	OR (95% CI)	SGA % (*n*)	OR (95% CI)
Moderate to late preterm *N* = 2,711	Population standard (INTERGROWTH) [27]	0 (0)[a]	–	5.7 (155)	11.9 (8.1–17.8)	5.4 (147)	4.7 (3.3–6.6)
	Fetal growth curves (WHO) [12]	0 (0)[a]	–	5.7 (155)	11.9 (8.1–17.8)	10.8 (292)	3.4 (2.6–4.4)
	Customized (GROW) [13]	0 (0)[a]	–	5.7 (155)	11.9 (8.1–17.8)	16.0 (435)	2.7 (2.1–3.3)
Early term *N* = 15,005	Population standard (INTERGROWTH) [27]	0 (5)[a]	–	3.8 (565)	5.7 (4.4–7.4)	2.1 (312)	1.9 (1.2–3.2)
	Fetal growth curves (WHO) [12]	0 (0)[a]	–	3.8 (570)	5.7 (4.4–7.3)	6.0 (899)	1.9 (1.4–2.6)
	Customized (GROW) [13]	0.2 (23)	–	3.6 (547)	6.0 (4.6–7.7)	9.1 (1,362)	1.6 (1.2–2.1)
Term *N* = 27,789	Population standard (INTERGROWTH) [27]	0.6 (157)	1.1 (0.3–3.4)	3.1 (864)	3.8 (2.8–5.1)	0.5 (140)	0.8 (0.2–3.2)
	Fetal growth curves (WHO) [12]	0 (0)[a]	–	3.7 (1,021)	3.4 (2.5–4.5)	5.4 (1,496)	1.7 (1.2–2.3)
	Customized (GROW) [13]	0.4 (110)	1.5 (0.5–4.9)	3.3 (911)	3.6 (2.7–4.8)	6.6 (1,831)	1.7 (1.3–2.3)

Data are percent (number) of small-for-gestational age neonates per gestation group, and odds ratio (95% confidence interval) of morbidity relative to referent. Referent is appropriate-for-gestational age by all weight centiles (moderate to late preterm, $n = 1{,}482$; early term, $n = 9{,}470$; term, $n = 18{,}249$). Table includes singleton live births from ≥33 to <41 weeks' gestation. Gestation groups defined as: moderate to late preterm, ≥ 33 to < 37 weeks'; early term, ≥ 37 and <39 weeks'; and term, ≥39 to <41 weeks' gestation. Composite neonatal morbidity defined as one or more of: neonatal unit admission >48 h for acute complications (not solely for prematurity or known congenital anomaly), respiratory support >4 h, Apgar score <7 at 5 min, or neonatal death.

OR odds ratio, *CI* confidence interval, *SGA* small-for-gestational age (<10th centile).

[a]No neonates were SGA by only the population reference (Fenton) and not an alternative reference, i.e., the alternative references detected all neonates that were SGA by the population reference.

increased likelihood of neonatal morbidity (Table 5). At early term and term gestations, only neonates who were identified as LGA using both the population reference and one of the alternative references (early term 9.4–15.9%; term 5.4–9.0%) had a small increased likelihood of neonatal morbidity (OR from 1.5 to 1.7) (Table 5). In term neonates, the population standard alone classified many neonates as LGA (12.3%) who did not have increased likelihood of neonatal morbidity (Table 5).

Overall performance of weight centiles

In the overall study population, non-AGA status by the population reference had the highest specificity for composite neonatal morbidity, while non-AGA status by the customized centiles had highest sensitivity (Table 6). In post hoc analysis, performance was improved by combining the population reference and customized centiles, such that non-AGA status was defined as either SGA by the customized centiles or LGA by both the customized centiles and population reference. This resulted in the highest positive likelihood ratio (2.2, 95% CI 2.1, 2.3) and positive predictive value (9.1%), while maintaining a high negative predictive value (96.7%) and minimizing the overall non-AGA rate (18.5%) (Table 6).

Discussion

In our multiethnic obstetric population, we found that among singletons born between 33 and <41 weeks' gestation, rates of SGA and LGA varied two- to three-fold when assessed using the four different weight centiles. For moderate to late preterm and Pacific neonates, there was even greater variation in SGA rates with a four- to five-fold difference among centiles. Compared with the population reference (Fenton), weight centiles based on fetal growth (WHO and GROW) identified approximately twice as many neonates as SGA, and these neonates had increased likelihood of neonatal morbidity. Across all gestations, neonates identified as small relative to both population cross-sectional birthweights (Fenton) and fetal growth (WHO and GROW), which accounted for ~3–6% of all neonates, had the greatest likelihood of neonatal morbidity, especially those born moderate to late preterm, in whom odds were increased almost 12-fold. For LGA neonates, the risk of neonatal morbidity was increased only in those born at early term and term, and only in neonates who were large relative to both population cross-sectional birthweights and centiles based on optimal pregnancy conditions (INTERGROWTH) or fetal growth (WHO and GROW). Defining SGA by customized centiles and LGA by customized centiles and population reference was associated with higher positive

Table 4 LGA rates at birth using different weight centiles in neonates of different gestational age and ethnicity.

	N	Weight centiles				*P*
		Population reference (Fenton) [10]	Population standard (INTERGROWTH) [27]	Fetal growth curves (WHO) [12]	Customized (GROW) [13]	
Entire cohort	45,505	11.7% (5,320)	20.0% (9,115)	16.3% (7,396)	9.3% (4,219)	<0.0001
Gestation						
Moderate to late preterm	2,711	15.9% (430)	12.5% (340)	21.6% (586)	11.0% (299)	<0.0001
Early term	15,005	15.9% (2,389)	19.0% (2,848)	20.9% (3,135)	11.0% (1,657)	<0.0001
Term	27,789	9.0% (2,501)	21.3% (5,927)	13.2% (3,675)	8.1% (2,263)	<0.0001
Maternal ethnicity						
Māori	3,096	13.0% (403)	21.3% (660)	18.0% (556)	9.2% (285)	<0.0001
Pacific	6,071	20.0% (1,216)	31.8% (1,933)	26.5% (1,608)	9.7% (591)	<0.0001
Asian	9,547	5.9% (568)	11.0% (1,046)	8.8% (839)	8.4% (799)	<0.0001
Indian	3,517	3.6% (126)	6.5% (230)	5.2% (183)	9.8% (344)	<0.0001
Other	1,543	9.1% (140)	14.8% (229)	12.8% (197)	10.8% (167)	<0.0001
European	21,731	13.2% (2,867)	23.1% (5,017)	18.5% (4,013)	9.4% (2,033)	<0.0001

Data are percent (number) detected as SGA. Includes singleton live births from ≥33 to <41 weeks' gestation. Gestation groups defined as: moderate to late preterm, ≥33 to <37 weeks'; early term, ≥37 and <39 weeks'; and term, ≥39 to <41 weeks' gestation. Weight centiles: population reference, Fenton; population standard, INTERGROWTH; fetal growth curve, WHO; customized, GROW. Maternal ethnicity prioritized in order: Māori, Pacific, Indian, Asian, Other, and European. *P* value is for comparison of weight centiles.

LGA large-for-gestational age (>90th centile).

likelihood ratio for composite neonatal morbidity than any individual centile. Overall, our study shows that there are substantial differences among the various weight centiles for the detection of small or large neonates at the risk of neonatal morbidity, and that the combined use of population cross-sectional birthweights and customized centiles may provide a more comprehensive assessment of *in utero* growth.

Defining normal fetal growth is complex both in concept and practice, as growth *in utero* is primarily determined by nutritional supply rather than genetic potential but is also normally constrained by the maternal environment [31]. Fetal growth hormones, such as insulin and the insulin-like growth factors, primarily serve to match fetal growth to substrate supply [32]. FGR occurs when there are pathological conditions that limit nutrient supply or, more rarely, when there is a defect of the fetal endocrine mechanisms that support normal substrate-driven growth. In developed countries, the most common cause of FGR is placental insufficiency due to impaired placentation [33, 34]. Risk factors for placental insufficiency include maternal smoking, previous FGR, and adverse maternal cardiovascular or metabolic conditions, such as hypertension, dyslipidemia, and insulin resistance [35–38]. Identification of FGR is important because of its association with preterm birth, perinatal death, and neonatal morbidity, as well as an increased risk of later cardiometabolic disease [39].

In contrast, constraint refers to the normal limits placed on fetal growth by the capacity of the uteroplacental unit to supply the fetus with nutrients. This phenomenon has been demonstrated in various cross-breeding and embryo transfer experiments in which smaller breeds have higher birthweight when carried by mothers of larger breeds, and vice versa [40–42]. From an evolutionary perspective, it is important that birth size is appropriate for maternal physical characteristics to allow a successful, unaided, and delivery [43]. However, as fetal growth capacity normally exceeds nutrient supply, fetal growth is constrained by physiological factors related to uteroplacental capacity, such as maternal stature, weight, parity, and age [43].

Due to this high in utero growth potential, fetal size increases when there is less constraint [44, 45] but fetal growth can also be excessive, surpassing what is typically expected for maternal characteristics when there is a pathological increase of nutrient availability, such as in diabetes [46]. Sometimes called overgrowth or macrosomia, these neonates are not only LGA but also have excess skin adiposity and increased fat mass for length [47]. Being born LGA is also more common in maternal obesity and this may represent reduced constraint or overgrowth secondary to impaired glucose tolerance and dyslipidemia, or both [48].

Our study shows that in a multiethnic population, cross-sectional population birthweight centiles (Fenton) fail to detect many smaller neonates at the risk of neonatal

Table 5 Risk of composite neonatal morbidity in neonates defined as LGA by the population reference and alternative weight centiles.

Gestation	Alternative weight centile	LGA by only the population reference (Fenton) [10] and not alternative weight centile		LGA by both the population reference and alternative weight centile		LGA by only an alternative weight centile and not the population reference (Fenton)	
		LGA % (*n*)	OR (95% CI)	LGA % (*n*)	OR (95% CI)	LGA % (*n*)	OR (95% CI)
Moderate to late preterm *N* = 2,711	Population standard (INTERGROWTH) [27]	3.7 (99)	1.1 (0.7–1.8)	12.2 (331)	1.1 (0.8–1.4)	0.3 (9)	0.4 (0.1–3.5)
	Fetal growth curves (WHO) [12]	0 (0)	–	15.9 (430)	1.1 (0.8–1.4)	5.8 (156)	1.1 (0.8–1.7)
	Customized (GROW) [13]	5.7 (154)	0.7 (0.5–1.1)	10.2 (276)	1.3 (1.0–1.7)	0.8 (23)	1.0 (0.4–2.6)
Early term *N* = 15,005	Population standard (INTERGROWTH) [27]	0.3 (40)	0.8 (0.1–5.9)	15.7 (2,349)	1.5 (1.2–1.9)	3.3 (499)	1.5 (1.0–2.4)
	Fetal growth curves (WHO) [12]	0 (0)	–	15.9 (2,389)	1.5 (1.2–1.9)	5.0 (746)	1.4 (1.0–2.1)
	Customized(GROW) [13]	6.5 (982)	1.2 (0.8–1.7)	9.4 (1,407)	1.7 (1.3–2.2)	1.7 (250)	0.8 (0.3–1.8)
Term *N* = 27,789	Population standard (INTERGROWTH) [27]	0 (0)	–	9.0 (2,501)	1.6 (1.3–2.1)	12.3 (3,426)	0.8 (0.6–1.1)
	Fetal growth curves (WHO) [12]	0 (0)	–	9.0 (2,501)	1.6 (1.3–2.1)	4.2 (1,174)	0.9 (0.6–1.4)
	Customized (GROW) [13]	3.6 (1,005)	1.5 (1.0–2.2)	5.4 (1,496)	1.7 (1.2–2.3)	2.8 (767)	1.0 (0.6–1.7)

Data are percent (number) of large-for-gestational age neonates per gestation group, and odds ratio (95% confidence interval) of morbidity relative to referent (Referent is appropriate-for-gestational age by all weight centiles (moderate to late preterm, $n = 1482$; early term, $n = 9470$; term, $n = 18,249$)). Includes singleton live births from ≥33 to <41 weeks' gestation. Composite neonatal morbidity defined as one or more of: neonatal unit admission >48 h for acute complications (not solely for prematurity or known congenital anomaly), respiratory support >4 h, Apgar score <7 at 5 min, or neonatal death. Gestation groups defined as: moderate to late preterm, ≥33 to <37 weeks'; early term, ≥37 and <39 weeks'; and term, ≥39 to <41 weeks' gestation. Weight centiles: population reference, Fenton; population standard, INTERGROWTH; fetal growth curve, WHO; customized, GROW.

OR odds ratio, *CI* confidence interval, *LGA* large-for-gestational age (>90th centile).

Table 6 Diagnostic test properties of non-AGA status for composite neonatal morbidity ($N = 45,505$).

	Total non-AGA population % (*n*)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio (95% CI)	Positive predictive value (%)	Negative predictive value (%)
SGA or LGA by population reference (Fenton)	15.5 (7,066)	27.6	85.0	1.9 (1.8, 2.0)	7.7	96.3
SGA or LGA by population standard (INTERGROWTH)	24.8 (11,298)	35.2	75.7	1.5 (1.4, 1.5)	6.2	96.3
SGA or LGA by fetal growth curves (WHO)	26.0 (11,829)	44.2	74.8	1.8 (1.7, 1.9)	7.4	96.7
SGA or LGA by customized centiles (GROW)	20.8 (9,468)	39.8	80.1	2.0 (1.9, 2.1)	8.3	96.7
SGA by customized centile (GROW) or LGA by customized centiles (GROW) and population reference (Fenton)	18.5 (8,420)	38.6	82.4	2.2 (2.1, 2.3)	9.1	96.7

Composite neonatal morbidity defined as one or more of: neonatal unit admission >48 h for acute complications (not solely for prematurity or known congenital anomaly), respiratory support >4 h, Apgar score <7 at 5 min, or neonatal death.

CI confidence interval, *LGA* large-for-gestational age (>90th centile), *SGA* small-for-gestational age (<10th centile), *AGA* appropriate-for-gestational age.

morbidity, who are likely growth-restricted. There are two main reasons for this: (1) population references do not account for normal variation in maternal constraint; and (2) population birthweights are progressively negatively skewed with increasing prematurity due to the fact that placental insufficiency often results in indicated or spontaneous preterm birth [49]. Population standards (INTERGROWTH) account for constraint to a limited degree by excluding women at the risk of excessive constraint, such as short stature, and the women included in standard populations may be at the lower risk of placental insufficiency [22]. Thus, it has been argued that standards permit detection of fetal under- and over-growth irrespective of "ancestry, nationality and skin color" [50]. However, there is no adjustment for individual variation in constraint, which can be considerable in a multiethnic population [16]. Fetal growth curves (WHO) account for the influence of prematurity by referencing birthweight to fetal growth in ongoing pregnancies. Customized centiles (GROW) have the advantage of accounting for both individual variation in constraint and the effect of preterm birth on the birthweight distribution. Thus, in our study SGA rates were the highest with the GROW centiles, but overall the two centiles based on fetal growth (GROW and WHO) identified more neonates as SGA, with an increased likelihood of neonatal morbidity, than cross-sectional centiles (Fenton and INTERGROWTH).

This suggests that if a single birthweight centile is used to identify neonates at an increased risk of morbidity, especially SGA, those based on fetal growth may be preferable. Importantly, the centiles based on fetal growth identified virtually all neonates that were SGA by the population reference, but also identified additional small neonates with increased likelihood of morbidity. Although still within the normal population birthweight range, their smaller size relative to their in utero peers suggests the presence of a pathological restriction of growth, rather than simply physiological constraint. Combined use of a population reference and another weight centile referenced to fetal growth may be useful in identifying small at-risk neonates (SGA by GROW or WHO centiles) and those at the highest risk of neonatal morbidity (SGA by both population reference and GROW or WHO centiles).

There has been concern that birthweight customization could incorrectly "normalize" larger fetal size. Indeed, we found that in Māori, Pacific, and European neonates the LGA rate was up to two- to three-fold lower using customized centiles than using any other centiles. However, the increased likelihood of neonatal morbidity associated with LGA status was small, and this was significant only in near-term and term infants who were LGA on both the population reference (Fenton) and an alternative centile. Again, this indicates that these neonates were large relative not only to the general newborn population, but also their expected degree of constraint.

Across all centiles, AGA status had high negative predictive value for neonatal morbidity. However, positive predictive value was low, indicating that birthweight centiles may need to be combined with other tools, such as early warning scores, to readily infants at increased risk of early morbidity [51]. Nevertheless, the positive likelihood ratio was modestly increased by combining the population reference and customized centiles, such that SGA was defined by the customized centiles and LGA by both the customized centiles and population reference.

In all ethnic groups, apart from Indian, using the population standard (INTERGROWTH) identified more neonates as being LGA than using any other centile. This is most likely due to more constraint in the standard population than in our general multiethnic obstetric population. For example, women in the INTERGROWTH population were more likely to be nulliparous (64% vs 44%) and were shorter on average than women in our population [16, 27]. Thus, use of the INTERGROWTH standard in our population classifies many neonates as LGA who appear to be an appropriate size for maternal constraint and do not have increased neonatal morbidity. In moderate to late preterm and early term groups, fetal growth curves (WHO) also identified many neonates as being LGA (21–22%), which may reflect the increased risk of preterm birth among fetuses with true overgrowth, who would be excluded from such cohorts.

Our study has several limitations. First, we did not have any data on neonatal hypoglycemia, which may be particularly relevant for interpretation of the morbidity associated with the different classifications of size at birth. Further research on which SGA and LGA neonates are at greatest risk of neonatal hypoglycemia is needed. Nevertheless, neonates with severe hypoglycemia would usually be admitted to NNU for >48 h and so would have been included in the composite outcome. Second, we did not have any measures of neonatal body composition which would have aided in the interpretation of SGA and LGA classifications. Third, we did not have data on long-term outcomes, and it cannot be assumed that associations between the different SGA or LGA classifications and neonatal morbidity apply to long-term health risks.

Conclusion

In our multiethnic general obstetric population, there was significant variation in the rates of SGA and LGA at birth using the different weight centiles, reflecting the different approaches used to account for normal constraint on fetal growth and the effect of preterm birth on birthweight

distributions. Across all gestations, neonates at the greatest risk of neonatal morbidity were those classified as SGA using both the Fenton population reference and one of the alternative centiles. Compared with the Fenton population reference, the customized centiles identified more than twice as many at-risk SGA neonates. Larger early term and term neonates were at increased likelihood of neonatal morbidity only if classified as LGA using both the Fenton population reference and one of the alternative centiles. Overall, our data suggest that the combined use of the Fenton population reference and customized GROW centiles may provide optimal assessment of birthweight for the detection of infants at the risk of neonatal morbidity.

Author contributions RDC and CJDM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: RDC and CJDM. Acquisition, analysis, or interpretation of data: all authors. Drafting of the paper: RDC and CJDM. Critical revision of the paper for important intellectual content: all authors. Statistical analysis: RDC and CJDM. Administrative, technical, or material support: JEH and CJDM. Supervision: JEH and CJDM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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