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Customized large-for-gestational-age birthweight at term and the association with adverse perinatal outcomes

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Abstract

Objective—Using a cohort of 110,447 singleton, term pregnancies, we aimed to validate the previously proposed customized standard of LGA birthweight, derive an additional customized LGA model excluding maternal weight, and evaluate the association between differing definitions of customized LGA and perinatal morbidities.

Study Design—Three customized LGA classifications, in addition to population-based 90th percentile (LGA_{Pop}), were made according to the principals described by Gardosi: 1) customized LGA using Gardosi's previously published coefficients (LGA_{Gard}), 2) customized LGA using coefficients derived by a similar method but from our larger cohort, and 3) derived without customization for maternal weight. Associations between the LGA classifications and various perinatal morbidity outcomes were evaluated.

Results—Coefficients derived here for physiologic and pathologic effects on birthweight were similar to those previously reported (LGA_{Gard}). Customized LGA (any method) generally identified more births to younger, non-white, nulliparous mothers with female neonates of lower birthweight compared to LGA_{Pop}. Rates of maternal and neonatal morbidity were greatest in births classified by both LGA_{Pop} and customized LGA (any method). However, the model which excluded customization for maternal weight, revealed a greater proportion of women previously unidentified by LGA_{Pop} who were more frequently black (40 vs. 25%) and obese (30 vs. 5.1 %), along with greater rates of shoulder dystocia, neonatal intensive care unit admission and neonatal respiratory complications, than with LGA_{Gard}.

Conclusion—The utility of customized methods of defining LGA was not decisively superior compared to LGA_{Pop}, but custom LGA may be improved by modification of the parameters included in customization.

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Keywords

large for gestational age; macrosomia; customized birthweight; neonatal morbidity; neonatal mortality; delivery complications

INTRODUCTION

High birthweight may occur due to multiple physiologic (e.g. genetics) or pathologic (e.g. excess adipose deposition) factors.¹ Excessively high birthweight is associated with increased neonatal intensive care unit (NICU) admission rate, hypoglycemia, shoulder dystocia, delivery injury, postpartum maternal hemorrhage and cesarean delivery,^{2,3} as well as long term child health risks related to obesity, cardiovascular and metabolic disease.^{4,5} Despite this knowledge of heightened risks for potentially serious maternal and/or neonatal complications with overly large birth size, defining overgrowth in clinical practice and epidemiologic research remains challenging. Clinical definitions to describe fetal overgrowth and high birthweight include large-for-gestational-age (LGA), using a cut-off such as the 90th percentile of birthweight in a reference population,⁶ or macrosomia defined as birth weight > 4000 or 4500 grams.^{7,8} Using the 90th percentile, by definition, results in approximately 10% of births being classified as LGA, but the proportion of neonates with overgrowth varies depending on the prevalence of pathologies such as maternal obesity and diabetes in the population. Furthermore, such cut-offs will not identify neonates with a “normal” population-based birthweight percentile (e.g. 60th), but having a fetal growth trajectory greater than their genetic potential due, for example, to excess fetal nutrient supply.

Customized birthweight percentiles have been proposed to help differentiate babies born large, but healthy from those with intrauterine overgrowth by accounting for inherent differences in birthweight attributable to presumed non-pathologic factors including maternal race, stature, parity and neonatal sex, according to gestational age.^{6,9–13} Prior studies have typically examined customization for small-for-gestational-age (SGA) citing improvement in prediction of perinatal morbidity and mortality,^{14,15} but the few studies investigating customized LGA have reported either maternal delivery outcomes only¹⁶ or limited neonatal health data in smaller cohorts.^{17,18} Understanding the relationship between customized LGA and neonatal health outcomes is important for clinical practice, however. For example, changing the definition of LGA will affect which babies are screened for hypoglycemia as prescribed by current guidelines.¹⁹ Furthermore, debate continues regarding which factors contribute to physiologic vs. pathologic variation in birthweight and whether a more complicated approach to identifying excessively large birthweight adds value to clinical care and research.^{20–24} Given the prevalence of maternal obesity and its perinatal comorbidities^{25,26} and the known relationship between increased maternal weight and LGA,²⁷ customization for maternal weight, as has been done previously,¹¹ may be inappropriate for assessment of LGA. Therefore, the aims of the present study, using a large U.S. birth cohort, were to 1) validate the previously proposed¹¹ customized standard of LGA, 2) derive an additional customized LGA model excluding maternal weight to determine its effect on predicting perinatal health outcomes, and 3) evaluate the role of these methods of customized LGA in predicting maternal and neonatal health outcomes compared to the conventional population-based 90th percentile birthweight cut-off.

MATERIALS and METHODS

Subjects

The Consortium on Safe Labor (CSL) was a retrospective cohort study conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.²⁸ The population included deliveries ≥ 23 weeks gestation at 12 clinical study centers (including 19 hospitals) across the U.S. from 2002 to 2008 (n=228,562 births). All study procedures were reviewed and approved by each participating sites' Institutional Review Board. For the present analysis, pregnancies with multiple gestation (n=5,050), preterm birth (< 37 weeks; n=29,612) and/or fetal anomalies (n=17,127) were excluded to be consistent with previous studies.¹¹ In women contributing more than one delivery during the study period (n=19,867), only the first pregnancy recorded in the study database was included, leaving 168,945 eligible pregnancies. Pregnancies with data missing for modeled variables included in the customized LGA equations (maternal race/ethnicity [n=7,545], height/weight [n=53,980], infant sex [n=162], birthweight [n=1,503]), as well implausible birthweight (<615 g; n=7), were also excluded, resulting in a final sample size of 110,447 births.

Maternal and neonatal morbidity and mortality outcomes

Data on delivery and neonatal outcomes were ascertained from electronic medical records supplemented with discharge *International Classification of Diseases*, ninth revision codes (ICD9). Previous work comparing detailed chart review to ICD9 data demonstrated good agreement; these data collection and quality control methods for the CSL have been described in full detail elsewhere.²⁸ If a particular outcome was recorded as present in either chart or ICD9 data, the outcome was considered to be present. For outcomes ascertained through ICD9 only (neonatal hypoglycemia, neonatal jaundice), the code utilized is given. The following LGA-related delivery outcomes were assessed: 3rd and 4th degree perineal lacerations, cervical laceration, shoulder dystocia, cesarean delivery and postpartum maternal hemorrhage. The following neonatal outcomes were also assessed: neonatal hypoglycemia (ICD9 775.6, Neonatal hypoglycemia), respiratory complications (respiratory distress syndrome, meconium aspiration, transient tachypnea of the newborn and/or resuscitation greater than giving oxygen only), neonatal jaundice (ICD9 774.6, Unspecified fetal and neonatal jaundice), 5-minute Apgar score < 4, admission to NICU and perinatal mortality (antepartum, intrapartum or other unspecified stillbirth and/or neonatal death).

Definitions of LGA and analysis

Each neonate was classified as LGA according to each of four LGA definitions. Babies were first classified as LGA if birthweight was greater than a previously published population-based 90th percentile according to week of gestational age (LGA_{pop}).⁶ Three customized LGA classifications were then made according to the principles of Gardosi.¹¹ The first was determined using Gardosi's previously published customized standard for the U.S. population derived from a cohort of 30,837 singleton term births from the National Institutes of Health First- and Second-Trimester Evaluation of Risk Research Consortium (LGA_{Gard}),¹¹ and two other customized LGA classifications were derived from the present CSL study population. Specifically, two predictive models of birthweight were generated using multiple linear regression analysis with backward elimination.^{11,16} Regression models included significant predictors of birthweight considered to be either physiologic (gestational age, neonatal sex, maternal height, race, parity and, for the first model only, maternal prepregnancy weight) or pathologic (smoking, prepregnancy underweight [body mass index (BMI) <18.5 mg/kg²], obesity [BMI ≥ 30], chronic or gestational diabetes, gestational hypertensive disease and, for the second model only, maternal history of other chronic diseases). The inclusion of maternal history of chronic diseases in the final model

was determined using stepwise linear regression; maternal history of heart, renal, gastrointestinal and thyroid diseases were dropped from the models due to lack of significance ($P > 0.05$), whereas maternal depression, asthma and anemia were included ($P < 0.05$). A customized calculation of optimal term birthweight for each woman was then calculated using the coefficients for the physiologic predictors of birthweight only, separately for each of the three custom LGA classifications: 1) using the coefficients previously published by Gardosi¹¹ (as indicated above: LGA_{Gard}), 2) using the coefficients derived from the first predictive model of birthweight in our CSL population based on an analogous model to that reported by Gardosi¹¹ ($LGA_{CSLGard}$), and 3) using the coefficients derived from the second predictive model of birthweight in our CSL population with the addition of maternal health history data and the exclusion of maternal weight (as a continuous physiologic variable) from the model ($LGA_{CSLcust}$). From the calculated optimal birthweight, a customized cut-off for LGA was calculated for each woman using the coefficient of variation (CV) of actual measured birthweight for the entire study population ($CV = 13.3\%$) and a multiplier of 1.28, the z-score used to extrapolate to the 90th percentile from the mean:

$$\text{Custom 90}^{th} \text{ percentile LGA cut-off} = \text{calculated optimal weight} + (\text{calculated optimal weight} \times 0.133 \times 1.28) \quad \text{Eq 1}$$

Customized LGA classification was made if the actual birthweight was greater than the calculated cut-off. This procedure was done separately for each model of customized LGA. As a sensitivity analysis, the procedures were repeated in a sub-sample of pregnancies with no pathology (i.e. no presence of any of the pathologic variables) and the resulting beta-coefficients were nearly identical (data not shown).

Odds ratios and associated c-statistics for the association between each of the LGA classifications and maternal and neonatal outcomes were calculated using logistic regression analysis. The c-statistic is a measure of the area under the receiver operator characteristic curve and in the present analysis was used to compare the overall performance of different definitions of LGA in association with maternal and neonatal morbidities. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were also calculated. Occurrence of all morbidity outcomes was also determined in sub-groups of births excluded from, shared with or additionally captured by LGA_{Gard} and $LGA_{CSLcust}$ compared to LGA_{Pop} . These subgroups were compared using contrast statements within either logistic or linear models (for categorical or continuous variables, respectively) to evaluate the changes in subject characteristics (Table 3) and morbidity prevalence (Table 6) that occurred with the adoption of the different custom methods of LGA in lieu of a population-based cut-off. All analyses were conducted using SAS 9.3 (Cary, NC).

RESULTS

Women included in the analysis ($n=110,447$) were 18% obese, 43% nulliparous, 55% non-Hispanic white, 19% non-Hispanic black and 20% Hispanic (Table 1). The average birthweight was (mean $\pm$ standard deviation [SD]) 3371 ± 447 g and gestational age was 39.2 ± 1.1 weeks. The method with the highest rate of LGA classification was LGA_{Pop} ($n=9,423$; 8.5% of total sample), followed by $LGA_{CSLcust}$ ($n=8,859$; 8.0%), $LGA_{CSLGard}$ ($n=7,783$; 7.0%) and LGA_{Gard} ($n=6,207$; 5.6%). Actual mean ($\pm$ SD) birthweight within each of the four LGA groups was 4218 ± 248 g in LGA_{Pop} , 4147 ± 325 g in $LGA_{CSLcust}$, 4166 ± 334 g in $LGA_{CSLGard}$ and 4150 ± 376 g in LGA_{Gard} .

Comparison of coefficients across models

Predicted term optimal birthweight for a standard mother (non-Hispanic white, 163 cm height, 64 kg weight, nulliparous, 280 d gestation)¹¹ and coefficients for gestational age, neonatal sex, parity and pathologic conditions (diabetes, hypertensive diseases) were similar in the two predictive models of birthweight generated in the CSL population (Table 2), as those reported for LGA_{Gard}, thus validating Gardosi's previously published¹¹ coefficients. However, both LGA_{CSLGard} and LGA_{CSLcust} yielded a positive coefficient for the effect of Hispanic ethnicity on birthweight, whereas LGA_{Gard} had a negative coefficient of nearly twice the magnitude. Also, in the LGA_{CSLcust} model, which excluded customization for maternal weight, the coefficients for maternal height and the (pathological) effect of obesity and underweight on birthweight were markedly greater in magnitude than models which customized for weight.

Deliveries with reclassified LGA status

While there was overlap between LGA_{Pop} and customized LGA, LGA_{Gard} excluded 4,796 (51% of LGA_{Pop}) from LGA classification, while adding 1,580 (1.4% of total population) new cases of LGA (Figure 1A). Likewise, LGA_{CSLcust} excluded fewer at 2,680 (28%) of LGA_{Pop}, while adding 2,116 (1.9% of total population) LGA cases (Figure 1B).

Customized LGA classification (any method) generally identified more births to younger, non-white, nulliparous mothers with female neonates of lower birthweight compared to LGA_{Pop}. However, LGA_{CSLcust} revealed a greater proportion of previously unidentified women who were more frequently black (40 vs. 25%), obese (30 vs. 5.1 %) and with preexisting (3.5 vs. 1.8%) or gestational (10.0 vs. 7.1%) diabetes compared to LGA_{Gard} (Table 3).

Maternal and neonatal morbidity by differing LGA definitions overall

Overall, there were 37,843 (34.3%) deliveries complicated by one or more maternal delivery complications (severe perineal or cervical laceration, shoulder dystocia, cesarean delivery or postpartum hemorrhage), 24,364 (22.1%) deliveries with one or more neonatal complications (hypoglycemia, respiratory problems, jaundice, low Apgar, NICU admission or perinatal mortality), resulting in a total of 51,105 (46.3%) deliveries having at least one complication. In comparison to LGA_{Pop}, customized LGA (any method) identified births with generally higher rates (PPV) and odds of severe perineal and cervical lacerations, cesarean delivery and shoulder dystocia, yet the sensitivity and c-statistic for these outcomes was overall similar across LGA methods and was generally lowest in LGA_{Gard} (Table 4). Differences in the rates and odds of neonatal morbidities were more attenuated, compared to maternal morbidities, among custom LGA definitions versus LGA_{Pop}, with similar or greater PPV using custom methods, but often lower sensitivity than LGA_{Pop} (Table 5). However, all of the customized definitions of LGA detected a slightly higher rate of perinatal mortality compared to LGA_{Pop}, as seen by increased PPV with odds ratio point estimates about 30% greater in LGA_{Gard} and LGA_{CSLcust} than LGA_{Pop}. Yet, the odds of mortality among LGA by any definition was statistically nonsignificant (95% confidence intervals all including 1.0).

Maternal and neonatal morbidity in births with reclassified LGA status

Rates of all morbidities (Table 6) were greatest in those identified as LGA regardless of classification model (sharing both LGA_{Pop} and customized classification), except for postpartum hemorrhage and neonatal jaundice which appeared at similar rates regardless of LGA method. LGA_{Gard} classification that did not overlap with LGA_{Pop} (n=1,580 newly revealed LGA, LGA_{Gard-only}) was associated with a greater rate of perineal and cervical

lacerations ($P < 0.001$) and cesarean delivery ($P < 0.001$), but lower rate of NICU admission ($P < 0.001$) compared to those excluded from LGA classification by LGA_{Gard} ($LGA_{Pop-only}$ group; Table 6). By contrast, and reflective of their differing subject characteristics (Table 3), the additional cases classified as LGA in $LGA_{CSLcust-only}$ ($n = 2,116$ newly revealed LGA) but not as LGA_{Pop} had a greater rate of perineal lacerations ($P < 0.001$), shoulder dystocia ($P < 0.001$), cesarean delivery ($P < 0.001$), neonatal respiratory complications ($P = 0.003$) and NICU admission ($P < 0.001$) than those excluded by the $LGA_{CSLcust}$ classification ($LGA_{Pop-only}$ group). Also, $LGA_{CSLcust}$ identified two additional cases of perinatal mortality, excluding no cases of mortality with reclassification, whereas LGA_{Gard} included one additional case of perinatal mortality while excluding another, compared to LGA_{Pop} . Of the $LGA_{CSLcust-only}$ group having shoulder dystocia and not identified as LGA by LGA_{Gard} ($n = 61$), 51 (84%) were overweight-obese (maternal prepregnancy BMI > 25 kg/m²).

COMMENT

This evaluation of customized LGA identified similar coefficients for most physiologic and pathologic characteristics associated with birthweight as previously reported in a U.S. population.¹¹ However, while customized LGA captured a different subset of mothers/births than population-based LGA, there was not consistent evidence of an improvement in the detection of maternal and/or neonatal complications. Furthermore, a separate model, where maternal weight was excluded from customization, detected a greater proportion of overweight/obese women as well as a greater rate of shoulder dystocia, NICU admission and neonatal respiratory problems that were not identified by LGA_{Pop} . Collectively, these data indicate that clinical utilization of customized LGA birthweight standards may be premature, but there may be room for further improvement in the development of a customized definition of LGA birthweight.

Our findings of generally greater positive prediction and odds for certain delivery complications using customized LGA (by any of the methods) compared to the 90th population percentile-based LGA are comparable to other studies in the U.S.¹⁶ and other regions.^{18,29} However, these smaller (from 2,668 to 32,271 subjects) previous investigations did not report specific neonatal health outcomes and were conducted in cohorts of limited race/ethnic diversity that were not representative of the U.S. population. Furthermore, in the present study, we also evaluated the diagnostic sensitivity for complications using LGA_{Gard} , and found a frequently lower sensitivity than achieved with LGA_{Pop} indicating that the application of current customized LGA standards does not achieve greater diagnostic capability for LGA-related morbidity outcomes. Alternatively, the customization models derived in the current cohort demonstrated frequently greater sensitivity for both delivery and neonatal health outcomes, with the greatest sensitivity often exhibited in $LGA_{CSLcust}$ (which excluded customization for maternal weight). Overall, however, the utility of customized methods of determining LGA for prediction of various perinatal morbidity outcomes, as evaluated by the combination of sensitivity, specificity, c-statistic and positive and negative predictive values, was not decisively superior compared to LGA_{Pop} .

Importantly, the rate of perinatal mortality was not significantly greater in any LGA group compared to the rate of mortality in the overall population, although LGA_{Gard} and $LGA_{CSLcust}$ demonstrated the numerically highest rate (PPV) of mortality (0.19% for each) compared to LGA_{Pop} (0.15%) or the population overall (0.13%). Importantly, $LGA_{CSLcust}$ also exhibited the greatest sensitivity for mortality, which may be a relevant consideration in the clinical context of identifying all births with heightened risk of perinatal death associated with LGA. In contrast, studies of customized birthweight percentiles used to detect SGA report markedly increased associations with perinatal mortality than population-based

SGA.^{9,15} However, overall rates of mortality in these previous studies of SGA were more than double the rates detected in the present study for LGA babies. Thus, examination of custom LGA in a larger dataset is warranted given the rarity of perinatal mortality at term in this cohort. It is also possible that the characteristics which inform customized SGA differ from those best suited for customized LGA, as the etiology and subsequent risk of the two conditions differ.

Given the critical risks to both mother and baby with shoulder dystocia, it is also noteworthy that LGA_{CSLcust} revealed previously non-LGA births which had a significantly greater rate of shoulder dystocia, NICU admission and respiratory complications than those with LGA_{Pop} alone. In contrast, LGA_{Gard} had a generally lower overall association (lower sensitivity, odds ratio estimate, c-statistic) with shoulder dystocia than either LGA_{Pop} or LGA_{CSLcust}. Furthermore, 84% of the additional shoulder dystocia cases revealed by LGA_{CSLcust}, but not LGA_{Gard}, were in overweight and obese mothers, indicating that removal of maternal prepregnancy weight as a customization characteristic for LGA may be important to adequately capture this important at-risk group. Also, with obesity and diabetes being increasingly frequent conditions in the U.S. obstetric population,^{25,30} higher rates of these conditions in the additional births revealed as LGA using LGA_{CSLcust} may be particularly impactful in studies evaluating LGA as an outcome of pregnancy. Of note are studies assessing gestational diabetes diagnosis,³¹ pharmaceutical or lifestyle interventions in diabetic or obese pregnancies,³² gestational weight gain,³³ and studies of subsequent offspring health and disease outcomes,³⁴ some of which have already begun to be explored using customized LGA, in lieu of population-based standards, outside the U.S.^{33,35}

Strengths of this study include a sample size three times greater than the largest comparable study, with race/ethnic diversity similar to that of the U.S. population. A potential weakness of current customization method is the assumption that the effect of each of the customization characteristics is proportional across gestational ages (i.e. the assumption of constant variance), extrapolated from 40 weeks (280 d). Our study included only term births (> 37 weeks), limiting the potential impact of this issue. Investigation of methods allowing the proportions of the effect of pathologic and non-pathologic modifiers of birthweight to vary to improve customization is an interesting future study. It is also important to note that greater detection of delivery complications using customized LGA is clinically useful only if LGA is detected *prior to* delivery, which requires customization of fetal growth prediction using ultrasound measures as has been shown to be useful for SGA.^{9,10,15} Furthermore, LGA customization by either method did little to improve the detection rate of hypoglycemia in this study. This may be a result of established screening guidelines for hypoglycemia in LGA babies that likely increased detection of biochemical hypoglycemia in LGA_{Pop} babies but not those with newly revealed LGA by customization.¹⁹ Furthermore, hypoglycemia was ascertained using ICD9 data alone, as was neonatal jaundice, which may have limited the quality of data for these outcomes. Finally, our non-significant findings of the association of LGA and rate of perinatal mortality should be interpreted with caution given that this was a rare event at term.

These data, from the largest and most comprehensive study of customized LGA to date, demonstrate similar coefficients for most characteristics associated with birthweight as previously published.¹¹ However, our study does not provide substantive support for its clinical use to improve the prediction of perinatal morbidity risk, but does provide initial evidence supporting potential modification of the current customized standard, specifically the removal of maternal weight from the customization scheme for LGA. Similarly, it will be important to consider the relationship between methods of customized LGA and outcomes beyond the perinatal period, such as child health outcomes of maternal diabetes, to adequately assess the utility of customized determination of LGA. Lastly, given the potential

for improving perinatal care through improved detection of pregnancies at risk for complications (e.g. shoulder dystocia, perineal lacerations, hypoglycemia) to permit preemptive care, as well as the future health of both mother and baby, different analytical methods for customizing LGA fetal weight and birthweight should be evaluated which may meaningfully improve the detection of morbidity and mortality.

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Abbreviations

BMI	body mass index
CSL	Consortium on Safe Labor
ICD9	<i>International Classification of Diseases</i> , ninth revision
LGA	large-for-gestational-age
NICU	neonatal intensive care unit
SGA	small-for-gestational-age

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Figure 1. LGA reclassification and overlap

Illustration of overlap in groups classified as LGA by the population-based criteria (LGA_{pop-only}) versus customized LGA definitions either including (LGA_{Gard}) or excluding (LGA_{CSLcust}) customization for maternal weight.

Table 1

Overall population (n=110,447) characteristics

Characteristic	n (%) or mean $\pm$ SD
Maternal age (y) ^a	27.6 $\pm$ 6.1
Maternal height (cm)	163.5 $\pm$ 7.3
Maternal weight (kg)	67.7 $\pm$ 17.3
BMI (kg/m ²)	
< 18.5	5,933 (5.4)
18.5 to < 25	59,919 (54.3)
25 to < 30	24,686 (22.4)
30	19,909 (18.0)
Parity	
0	47,722 (43.2)
1	31,819 (28.8)
2	17,593 (15.9)
3	7,968 (7.2)
4+	5,345 (4.8)
Race/ethnic group	
Non-Hispanic white	60239 (54.5)
Non-Hispanic black	21457 (19.4)
Hispanic	21982 (19.9)
Asian/Pacific Islander	4160 (3.8)
Other or multiracial	2609 (2.4)
Smoking	7193 (6.5)
Maternal diabetes	
Preexisting	1279 (1.2)
Gestational	5067 (4.6)
Maternal hypertensive disease	
Chronic hypertension	1824 (1.7)
Gestational hypertension	3058 (2.8)
Mild preeclampsia	2875 (2.6)
Severe preeclampsia	678 (0.6)
Superimposed preeclampsia	546 (0.5)
Eclampsia	67(0.1)
Unspecified hypertension	391 (0.4)
Antepartum bleeding or abruption	2616 (2.4)
Gestational age at delivery (wk)	39.2 $\pm$ 1.1
Infant birthweight (g)	3370.7 $\pm$ 447.1

^a Maternal age missing for 54 women.

Table 2

Comparison of coefficients among different models of birthweight

<i>Physiologic variables</i>	$LG A_{Gard}^d$	$LG A_{CSL\,Gard}$	SE	P	$LG A_{CSL\,cust}$	SE	P
Intercept	3453.4	3481.4	2.7	<0.001	3452.8	2.6	<0.001
Gestational age (from 280 d)							
Linear term	22.86	17.4	0.26	<0.001	17.6	0.27	<0.001
Quadratic term	-0.311	-0.35	0.02	<0.001	-0.35	0.02	<0.001
Cubic term	-0.007	-0.004	0.001	<0.001	0.00	0.001	<0.001
Sex							
Male	66.0	65.8	1.2	<0.001	65.6	1.2	<0.001
Female	-66.0	-65.8	1.2	<0.001	-65.6	1.2	<0.001
Maternal height (from 163 cm)							
Linear term	6.398	7.33	24.1	<0.001	11.7	21.3	<0.001
Quadratic term		5.40	141.2	0.0001	3.59	141.6	0.01
Cubic term	-0.003	-2.72	579.3	<0.001	-3.72	580.9	<0.001
Maternal prepregnancy weight (from 64 kg)							
Linear term	7.578	6.20	0.17	<0.001			
Quadratic term	-0.087	-0.10	0.01	<0.001			
Cubic term	0.0005	0.001	0.0001	<0.001			
Race							
Non-Hispanic black	-161.0	-164.2	3.2	<0.001	-155.9	3.2	<0.001
Hispanic	-38.6	14.8	3.3	<0.001	20.9	3.3	<0.001
Asian/Pacific Islander		-27.8	6.4	<0.001	-44.6	6.4	<0.001
Other or multiracial	-140.8	-45.7	7.9	<0.001	-42.0	7.9	<0.001
Parity							
1	96.2	79.5	2.9	<0.001	87.0	2.9	<0.001
2	121.9	91.2	3.6	<0.001	102.3	3.6	<0.001
3	125.9	110.1	4.9	<0.001	122.9	4.9	<0.001

	LGA _{Gard} ^a	LGA _{CSL_{Gard}}	SE	P	LGA _{CSL_{cust}}	SE	P
4+	122.7	124.4	5.8	<0.001	138.1	5.8	<0.001
Pathologic variables							
Smoking ^b		-148.9	4.8	<0.001	-145.5	4.9	<0.001
Underweight (BMI <18.5 kg/m ²)	-20.4	-32.3	6.2	<0.001	-149.9	5.3	<0.001
Obese (BMI ≥30 kg/m ²)	-63.4	-22.4	5.5	<0.001	95.3	3.2	<0.001
Maternal diabetes							
Preexisting	241.7	200.0	11.1	<0.001	216.5	11.2	<0.001
Gestational		114.3	5.7	<0.001	129.8	5.7	<0.001
Maternal hypertensive disease							
Chronic hypertension					-14.4	9.5	0.13
Gestational hypertension	-26.8	-25.4	7.3	0.001	-13.8	7.3	0.06
Mild preeclampsia		-36.1	7.5	<0.001	-29.4	7.5	<0.001
Severe preeclampsia	-60.7	-156.3	15.2	<0.001	-155.2	15.2	<0.001
Superimposed preeclampsia		-67.9	16.9	<0.001	-55.2	17.0	0.001
Eclampsia		-136.6	47.9	0.004	-143.9	48.2	0.003
Unspecified hypertension		-20.3	19.9	0.31	-5.0	20.1	0.80
Antepartum bleeding or abruption	-41.2	-62.4	7.8	<0.001	-60.5	7.8	<0.001
History of preterm birth ^c		-67.9	5.4	<0.001	-67.8	5.5	<0.001
Maternal health history ^d							
Depression					-23.1	6.1	<0.001
Asthma					-24.0	4.7	<0.001
Anemia					46.4	4.1	<0.001

BMI, body mass index; SE, standard error.

Analysis centered on 280 days gestation for a white mother of height 163 cm, weight 64 kg, parity 0.

^a Coefficients reported from similar analysis of previous cohort of 30,837 births by Gardosi.¹¹

^b Smoking was reported by Gardosi¹¹ in number/day (coefficients: 1-9 n/d, -99.2; 10-19, -174.9; 20, -246.3).

^c Maternal birth history was reported separately for history of miscarriage (coefficient: 12.9) a single preterm birth (-55.1) or 2 preterm births (-77.6) by Gardosi.¹¹

Maternal history of heart, renal, gastrointestinal and thyroid diseases were also evaluated, but were dropped from the models due to lack of significance ($P>0.05$).

Table 3

Subject characteristics of groups excluded from customized LGA (LGA_{Pop-only}), classified as LGA by both population and customized definitions (dark shaded columns) and additionally revealed (those not included as LGA_{Pop}) using customized LGA (LGA_{Gard-only}, LGA_{CSLcust-only}).

	LGA _{Pop} vs. LGA _{Gard}				LGA _{Pop} vs. LGA _{CSLcust}			
	LGA _{Pop-only} n=4,796	LGA _{Pop+Gard} n=4,627	LGA _{Gard-only} n=1,580	LGA _{Pop-only} n=2,680	LGA _{Pop+CSLcust} n=6,743	LGA _{CSLcust-only} n=2,116		
Maternal age (y)	29.2 ± 5.7	29.0 ± 6.0	26.7 ± 6.5*	29.6 ± 5.6	28.9 ± 6.0	27.1 ± 6.4*		
BMI (kg/m ²)								
< 18.5	1.2	2.9	11.1*	2.8	1.8	2.3*		
18.5 to < 30	66.6	75.4	83.8*	77.1	68.5	67.7*		
30	32.3	21.7	5.1*	20.2	29.8	30.0*		
Parity								
0	28.7	40.3	63.2*	25.8	37.8	56.6*		
1	32.5	30.3	22.2*	34.0	30.4	25.2*		
2	20.8	16.0	9.1*	19.9	17.9	11.3*		
3	10.6	7.8	3.3*	12.2	8.1	4.4*		
4+	7.4	5.6	2.2*	8.1	5.9	2.6*		
Race/ethnic group								
White	70.2	50.0	26.0*	74.5	54.6	32.5*		
Black	10.3	16.5	24.9*	4.4	16.9	40.3*		
Hispanic	17.4	25.8	27.9*	18.3	22.8	19.0*		
Asian/Pac Islander	0.7	4.3	14.6*	1.1	3.0	5.1*		
Other or Multiracial	1.4	3.4	6.7*	1.7	2.6	3.2*		
Smoking (any)	4.7	4.0	1.9*	4.3	4.4	3.1		
Maternal diabetes								
Preexisting	1.6	4.2	1.8*	0.8	3.7	3.5*		
Gestational	5.9	10.6	7.1*	3.9	9.9	10.0*		
Maternal hypertensive disease								

	LGA _{Pop} vs. LGA _{Gard}			LGA _{Pop} vs. LGA _{CSLeust}		
	LGA _{Pop-only} n=4,796	LGA _{Pop+Gard} n=4,627	LGA _{Gard-only} n=1,580	LGA _{Pop-only} n=2,680	LGA _{Pop+CSLeust} n=6,743	LGA _{CSLeust-only} n=2,116
Chronic hypertension	1.9	2.3	1.7	1.1	2.5	3.0*
Gestational hypertension	3.1	3.0	2.6	2.2	3.4	3.0*
Mild preeclampsia	2.3	3.3	3.3*	1.7	3.2	4.3*
Severe preeclampsia	0.3	0.6	1.0*	0.2	0.5	1.1*
Superimposed preeclampsia	0.4	0.6	0.4	0.1	0.7	1.1*
Eclampsia	0.1	0.1	0.1	0	0.04	0.1
Unspecified hypertension	0.5	0.5	0.4	0.5	0.5	0.5
Antepartum bleeding or abruption	1.5	2.0	2.0	1.4	1.9	2.5*
Gestational age at delivery (wk)	39.8 ± 1.0	39.1 ± 1.1	38.3 ± 1.0*	39.9 ± 1.0	39.3 ± 1.1	38.6 ± 1.1*
Infant birthweight (g)	4138 ± 150	4300 ± 298	3711 ± 188*	4101 ± 116	4264 ± 271	3775 ± 166*
Infant sex (% M)	73	56	31*	83	57	27*

Data are proportion (%) or mean ± SD. Categories correspond to those illustrated in Figure 1.

* Custom-only group (LGA_{Gard-only} or LGA_{CSLeust-only}) significantly different than in LGA_{Pop-only} (P<0.05).

Table 4

Positive and negative predictive values (PPV, NPV), sensitivity, specificity, odds and c-statistic of maternal/delivery complications according to different LGA categories.

Classification	n	PPV ^b	NPV	Sensitivity	Specificity	Odds ratio (95% CI)	c-statistic (95% CI)
3 rd , 4 th degree perineal lacerations ^a							
Overall population	81,693	3.38					
LGA _{Pop}	5,813	6.45	93.6	13.6	93.1	2.13 (1.90, 2.38)	0.53 (0.53, 0.54)
LGA _{Gard}	3,474	8.46	91.5	10.7	96.0	2.84 (2.50, 3.22)	0.53 (0.53, 0.54)
LGA _{CSL_{Gard}}	4,443	7.92	92.1	12.8	94.8	2.67 (2.38, 3.00)	0.54 (0.53, 0.54)
LGA _{CSL_{Leust}}	4,947	7.44	92.6	13.3	94.2	2.50 (2.23, 2.80)	0.54 (0.53, 0.54)
Cervical laceration ^a							
Overall population	81,693	0.50					
LGA _{Pop}	5,813	0.48	99.5	6.88	92.9	0.97 (0.66, 1.42)	0.50 (0.49, 0.51)
LGA _{Gard}	3,474	0.81	99.2	6.88	95.8	1.67 (1.14, 2.45)	0.51 (0.50, 0.53)
LGA _{CSL_{Gard}}	4,443	0.74	99.3	8.11	94.6	1.54 (1.08, 2.20)	0.51 (0.50, 0.53)
LGA _{CSL_{Leust}}	4,947	0.63	99.4	7.62	94.0	1.28 (0.89, 1.85)	0.51 (0.49, 0.52)
Shoulder dystocia ^a							
Overall population	81,693	1.87					
LGA _{Pop}	5,813	9.44	90.56	35.9	93.4	7.98 (7.16, 8.89)	0.65 (0.63, 0.66)
LGA _{Gard}	3,474	9.99	90.01	22.7	96.1	7.24 (6.39, 8.20)	0.59 (0.58, 0.60)
LGA _{CSL_{Gard}}	4,443	10.13	89.87	29.5	95.0	7.96 (7.10, 8.93)	0.62 (0.61, 0.63)
LGA _{CSL_{Leust}}	4,497	10.71	89.29	34.7	94.5	9.11 (8.16, 10.16)	0.65 (0.63, 0.66)
Cesarean delivery							
Overall population	110,447	26.0					
LGA _{Pop}	9,423	38.3	75.1	12.6	92.9	1.88 (1.80, 1.96)	0.53 (0.53, 0.53)
LGA _{Gard}	6,207	44.0	75.0	9.50	95.8	2.37 (2.25, 2.49)	0.53 (0.52, 0.53)
LGA _{CSL_{Gard}}	7,783	42.9	75.3	11.6	94.6	2.29 (2.18, 2.40)	0.53 (0.53, 0.53)
LGA _{CSL_{Leust}}	8,859	44.2	75.6	13.6	93.9	2.44 (2.34, 2.55)	0.54 (0.54, 0.54)
Postpartum hemorrhage							
Overall population	110,447	5.74					
LGA _{Pop}	9,423	6.56	94.3	9.75	91.5	1.17 (1.07, 1.27)	0.51 (0.50, 0.51)
LGA _{Gard}	6,207	6.48	94.3	6.34	94.4	1.15 (1.03, 1.27)	0.50 (0.50, 0.51)
LGA _{CSL_{Gard}}	7,783	6.51	94.3	8.00	93.0	1.16 (1.05, 1.27)	0.51 (0.50, 0.51)

Classification	n	PPV ^b	NPV	Sensitivity	Specificity	Odds ratio (95% CI)	c-statistic (95% CI)
LGA _{CSL caust}	8,859	6.52	94.3	9.12	92.1	1.16 (1.06, 1.27)	0.51 (0.50, 0.51)

^a Cesarean delivery excluded from analysis.

^b For Overall Population, prevalence of outcome is given.

Positive and negative predictive values (PPV, NPV), sensitivity, specificity, odds and c-statistic of neonatal health complications according to different LGA categories

Table 5

	Classification	N	ppv ^b	NPV	Sensitivity	Specificity	Odds ratio (95% CI)	c-statistic (95% CI)
Hypoglycemia	Overall pop	110,447	0.88					
	LGA _{Pop}	9,423	1.93	99.2	18.8	91.6	2.51 (2.13, 2.95)	0.55 (0.54, 0.56)
	LGA _{Gard}	6,207	2.06	99.2	13.2	94.5	2.59 (2.15, 3.12)	0.54 (0.53, 0.55)
	LGA _{CSL_{Gard}}	7,783	1.88	99.2	15.1	93.0	2.37 (1.98, 2.83)	0.54 (0.53, 0.55)
	LGA _{CSL_{Leust}}	8,859	1.85	99.2	16.9	92.1	2.36 (1.99, 2.78)	0.55 (0.53, 0.56)
Respiratory problems	Overall pop	110,447	5.24					
	LGA _{Pop}	9,423	7.74	95.0	12.6	91.7	1.59 (1.47, 1.73)	0.52 (0.52, 0.53)
	LGA _{Gard}	6,207	8.02	94.9	8.61	94.6	1.63 (1.48, 1.80)	0.52 (0.51, 0.52)
	LGA _{CSL_{Gard}}	7,783	7.98	95.0	10.7	93.2	1.64 (1.50, 1.79)	0.52 (0.52, 0.52)
	LGA _{CSL_{Leust}}	8,859	8.09	95.0	12.4	92.2	1.68 (1.55, 1.82)	0.52 (0.52, 0.53)
Jaundice	Overall pop	110,447	15.20					
	LGA _{Pop}	9,423	17.40	85.0	9.77	91.7	1.19 (1.13, 1.26)	0.51 (0.50, 0.51)
	LGA _{Gard}	6,207	17.45	84.9	6.45	94.5	1.19 (1.11, 1.28)	0.51 (0.50, 0.51)
	LGA _{CSL_{Gard}}	7,783	16.88	84.9	7.83	93.1	1.14 (1.08, 1.22)	0.51 (0.50, 0.51)
	LGA _{CSL_{Leust}}	8,859	17.07	85.0	9.01	92.2	1.16 (1.10, 1.23)	0.51 (0.50, 0.51)
5-min Apgar < 4 ^a	Overall pop	110,429*	0.35					
	LGA _{Pop}	9,422	0.42	99.7	10.4	91.5	1.25 (0.90, 1.74)	0.51 (0.49, 0.52)
	LGA _{Gard}	6,207	0.43	99.7	7.05	94.4	1.28 (0.86, 1.89)	0.51 (0.49, 0.52)
	LGA _{CSL_{Gard}}	7,783	0.40	99.7	8.09	93.0	1.16 (0.80, 1.68)	0.50 (0.49, 0.52)
	LGA _{CSL_{Leust}}	8,857	0.43	99.7	9.92	92.0	1.27 (0.90, 1.77)	0.51 (0.49, 0.52)
NICU admission	Overall pop	110,447	5.65					
	LGA _{Pop}	9,423	8.74	94.6	13.2	91.8	1.69 (1.57, 1.83)	0.53 (0.52, 0.53)
	LGA _{Gard}	6,207	9.71	94.6	9.66	94.6	1.88 (1.72, 2.06)	0.52 (0.52, 0.53)
	LGA _{CSL_{Gard}}	7,783	9.46	94.6	11.8	93.2	1.84 (1.70, 2.00)	0.53 (0.52, 0.53)

Classification	N	PPV ^b	NPV	Sensitivity	Specificity	Odds ratio (95% CI)	c-statistic (95% CI)
LGA _{CSLeust}	8,859	9.62	94.7	13.7	92.3	1.90 (1.76, 2.05)	0.53 (0.53, 0.53)
Perinatal mortality	Overall pop	110,447	0.13				
LGA _{Pop}	9,423	0.15	99.9	9.7	91.5	1.15 (0.66, 1.99)	0.50 (0.48, 0.53)
LGA _{Gard}	6,207	0.19	99.9	8.28	94.4	1.52 (0.84, 2.74)	0.50 (0.49, 0.54)
LGA _{CSLGard}	7,783	0.17	99.9	8.97	93.0	1.30 (0.74, 2.30)	0.50 (0.49, 0.53)
LGA _{CSLeust}	8,859	0.19	99.9	11.7	92.0	1.52 (0.92, 2.52)	0.50 (0.49, 0.54)

^aData of 5-min Apgar score missing for 18 neonates in perinatal death category; all else missing (n=212) assumed <4.

^bFor Overall Population, prevalence of outcome is given.

Table 6

Morbidity/mortality prevalence of groups excluded from customized LGA (LGA_{Pop-only}), classified as LGA by both population and customized definitions (dark shaded columns) and additionally revealed (those not included as LGA_{Pop}) using customized LGA (LGA_{Gard-only}, LGA_{CSLcust-only}).

	LGA _{Pop} vs. LGA _{Gard}			LGA _{Pop} vs. LGA _{CSLcust}		
	LGA _{Pop-only} n=4,796 (n=3,315 ^d)	LGA _{Pop+Gard} n=4,627 (n=2,498 ^d)	LGA _{Gard-only} n=1,580 (n=976 ^d)	LGA _{Pop+CSLcust} n=6,743 (n=3,775 ^d)	LGA _{CSLcust-only} n=2,116 (n=1,172 ^d)	
	%	%	%	%	%	%
Maternal/delivery						
3 rd – 4 th degree perineal lacerations ^a	4.7	8.8 [†]	7.6 [*]	7.5 [†]	7.3 [*]	
Cervical laceration ^a	0.39	0.60	1.33 [*]	0.56		0.85 [*] p=0.10
Shoulder dystocia ^a	7.4	12.2 [†]	4.3	11.6 [†]	7.9 [*]	
Cesarean delivery	30.9	46.0 [†]	38.2 [*]	44.0 [†]	44.6 [*]	
Postpartum hemorrhage	6.3	6.8	5.5	6.7	5.9	
Neonatal						
Hypoglycemia	1.50	2.38 [†]	1.14	2.15 [†]	0.90	
Respiratory problems	6.6	9.0 [†]	5.3	8.5 [†]	6.9 [*]	
Jaundice	17.1	17.8	16.5	17.4	15.9	
5-min Apgar < 4	0.27	0.58	-	0.50 [†]	0.19	
NICU admission	6.7	10.9 [†]	6.3 [*]	10.0 [†]	8.3 [*]	
Perinatal mortality	0.06	0.24 [†]	0.06	0.21	0.14	

Data are proportion (%). Categories correspond to those illustrated in Figure 1.

^aCesarean deliveries excluded from analysis.

^{*} Custom-only group (LGA_{Gard-only} or LGA_{CSLcust-only}) significantly different than in LGA_{Pop-only} (P<0.05).

[†] Proportion in center column (overlapping category) greater than both of the two neighboring columns (LGA_{Pop} and LGA_{Gard-only} / LGA_{CSLcust-only}; P<0.05).