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Customized *vs* population-based growth charts to identify neonates at risk of adverse outcome: systematic review and Bayesian meta-analysis of observational studies

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KEYWORDS: adverse perinatal outcome; customized growth charts; intrauterine growth disturbance; large-for-gestational age; population growth charts; small-for-gestational age

ABSTRACT

Objective *To compare the effectiveness of customized* vs *population-based growth charts for the prediction of adverse pregnancy outcomes.*

Methods *MEDLINE, ClinicalTrials.gov and The Cochrane Library were searched up to 31 May 2016 to identify interventional and observational studies comparing adverse outcomes among large- (LGA) and small- (SGA) for-gestational-age neonates, when classified according to customized* vs *population-based growth charts. Perinatal mortality and admission to the neonatal intensive care unit (NICU) of both SGA and LGA neonates, intrauterine fetal demise (IUFD) and neonatal mortality of SGA neonates, and neonatal shoulder dystocia and hypoglycemia as well as maternal third- and fourth-degree perineal lacerations in LGA pregnancies were evaluated.*

Results *The electronic search identified 237 records that were examined based on title and abstract, of which 27 full-text articles were examined for eligibility. After excluding seven articles, 20 observational studies were included in a Bayesian meta-analysis. Neonates classified as SGA according to customized growth charts had higher risks of IUFD (odds ratio (OR), 7.8 (95% CI, 4.2–12.3)), neonatal death (OR, 3.5 (95% CI, 1.1–8.0)), perinatal death (OR, 5.8 (95% CI, 3.8–7.8)) and NICU admission (OR, 3.6 (95% CI, 2.0–5.5)) than did non-SGA cases. Neonates classified as SGA according to population-based growth charts also had increased risk for adverse outcomes, albeit the point estimates of the pooled ORs were smaller: IUFD (OR, 3.3 (95% CI, 1.9–5.0)), neonatal death (OR, 2.9 (95% CI, 1.2–4.5)), perinatal death (OR, 4.0 (95% CI, 2.8–5.1)) and NICU admission (OR, 2.4 (95% CI, 1.7–3.2)). For LGA* vs *non-LGA, there were no differences in pooled ORs for perinatal death, NICU admission, hypoglycemia and maternal third- and fourth-degree perineal lacerations when classified according to either the customized or the population-based approach. In contrast, both approaches indicated that LGA neonates are at increased risk for shoulder dystocia than are non-LGA ones (OR, 7.4 (95% CI, 4.9–9.8) using customized charts; OR, 8.0 (95% CI, 5.3–10.1) using population-based charts).*

Conclusions *Both customized and population-based growth charts can identify SGA neonates at risk for adverse outcomes. Although the point estimates of the pooled ORs may differ for some outcomes, the overlapping CIs and lack of direct comparisons prevent conclusions from being drawn on the superiority of one method. Future clinical trials should compare directly the two approaches in the management of fetuses of abnormal size. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Deviations in fetal growth, and secondarily birth weight, are associated with adverse pregnancy outcomes, and infants born small-for-gestational age (SGA; birth weight < 10^{th} centile) or large-for-gestational age (LGA; birth weight > 90^{th} centile) may be at increased risk of short- as well as long-term adverse health outcomes[1–6]. Birth weight is determined by a combination of genetic,

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intrauterine and environmental influences; traditionally, evaluation of fetal growth has been addressed by comparing estimated fetal weight with population-based norms that are derived from either heterogeneous or highly selected patient cohorts and do not account for individual variability[6–8]. Population-based norms do not differentiate between abnormal growth and constitutionally large or small, but otherwise healthy, fetuses. Relying on these norms can therefore lead to misclassification of birth weight and over- or underdiagnosis of fetal growth abnormalities[9,10].

In order to circumvent the limitations of population-based standards, a number of customized norms have been developed. Customized norms model optimal fetal growth by accounting for individual variables that are known to affect growth, as they allow measurement of deviations from an ideal fetal growth potential, rather than deviations from an expected norm for a population[10]. One of the more widely used models is that of Gardosi *et al.*[10–12].

As abnormal fetal growth has been associated with adverse neonatal outcomes, early studies showed how customized models can better identify neonates at risk[13–16]; however, more recent reports do not support such conclusions[17–19].

Our goal was to perform a systematic review of the published data regarding customized and population-based growth charts in order to determine which classification has the strongest association with adverse outcomes when birth weight is outside the norm. Therefore, we conducted a Bayesian meta-analysis to compare the risk of intrauterine fetal demise (IUFD), neonatal mortality, perinatal mortality and admission to the neonatal intensive care unit (NICU) among SGA neonates, classified with customized or population-based approaches, when compared with non-SGA neonates. Similarly, we investigated the risk of perinatal mortality, NICU admission, neonatal hypoglycemia, maternal third- and fourth-degree perineal lacerations and neonatal shoulder dystocia among LGA pregnancies classified according to customized *vs* population-based growth charts, when compared with non-LGA pregnancies.

METHODS

Information sources

An electronic search of MEDLINE, ClinicalTrials.gov (www.clinicaltrials.gov) and The Cochrane Collaboration databases was performed from inception to 31 May 2016, using a combination of text words including 'customized fetal growth', 'customized growth chart', 'customized birth weight', 'customized antenatal growth charts', 'pregnancy', 'antenatal', 'growth' and 'customized'.

Eligibility criteria

Studies were included if they compared adverse neonatal or maternal outcomes among SGA or LGA neonates, defined according to both customized and population-based norms.

Study selection

As customized norms have been used to address different adverse perinatal outcomes in the setting of fetal growth disturbance, the initial step consisted of identifying such outcomes in the eligible studies. Two reviewers (G.C. and M.M.C.) evaluated independently the titles and abstracts of all citations produced by the electronic searches. Studies were included in the final analysis if they classified LGA and SGA by population-based and customized approaches, if they compared adverse perinatal outcomes among LGA and SGA neonates and if perinatal outcomes were considered clinically relevant by the reviewers and were reported in more than one study. Studies were excluded if they did not meet all the abovementioned criteria. We chose to study perinatal mortality and NICU admission among SGA and LGA neonates. We investigated IUFD and neonatal mortality among SGA neonates, and shoulder dystocia, maternal third- and fourth-degree perineal lacerations and neonatal hypoglycemia among LGA neonates only. Although clinically relevant, we did not consider the following as potential study outcomes: composite neonatal outcomes, preterm delivery, placental abruption, duration of NICU stay and hypertensive disorders, as they represent heterogeneous groups that were classified differently in the various studies. We did not include Cesarean delivery among our study outcomes, as both macrosomic and growth-restricted fetuses have a higher likelihood of Cesarean delivery, but Cesarean delivery can also be performed electively owing to such diagnoses[5]. Finally, we chose not to consider Apgar scores, umbilical-cord blood pH and neonatal resuscitation as outcomes, as they may depend on multiple factors other than fetal-growth patterns.

Discordance between reviewers was resolved by discussion or, if not possible, by consultation with a third author (G.R.S.). In the case of multiple publications on the same population, the main study was used as reference. If there were data queries, an attempt was made to contact the original study investigator. Data were extracted in a standardized manner by one author (G.C.).

If more than one customized approach was investigated in the same study, the model of Gardosi *et al.*[10–12] was chosen and compared with the population norms. If this model was not utilized, data obtained with the alternative customized growth approach were utilized.

Data reporting and risk of bias in individual studies

As only observational studies addressed our study question, we followed the guidelines for reporting meta-analyses and systematic reviews of observational studies[20]. Two authors (G.C. and M.M.C.) assessed the risk of bias of the included observational studies using the

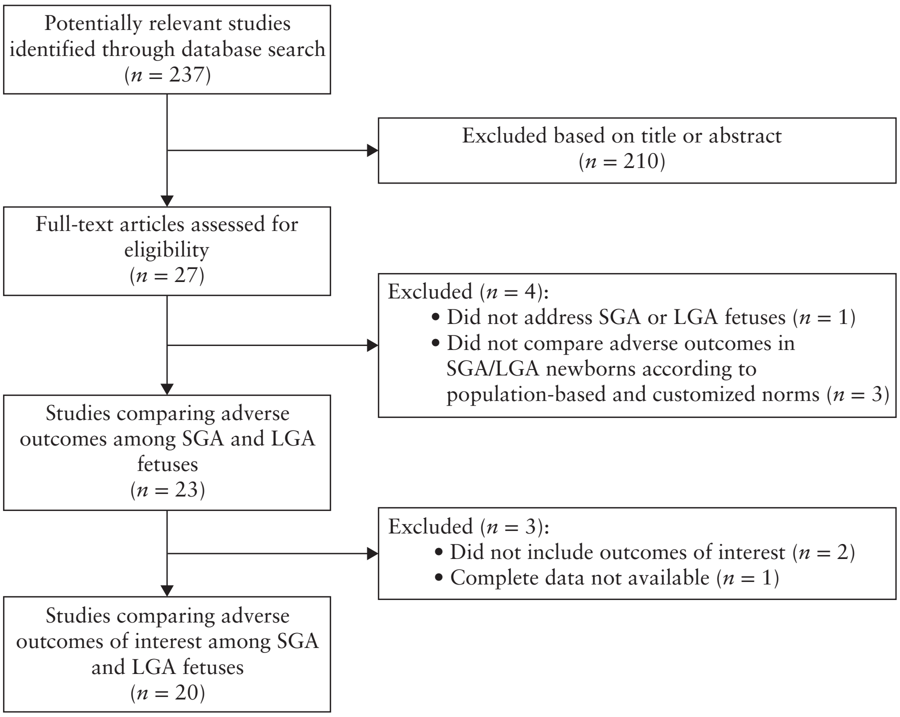


Figure 1 Flowchart of studies included in systematic review and meta-analysis reporting on adverse outcome of small- (SGA) and large- (LGA) for-gestational-age neonates, classified according to customized and population-based growth charts.

Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI)[21]. Disagreements were resolved by consensus.

Statistical analysis

A random-effects Bayesian meta-analysis was performed to compute pooled odds ratios (ORs) of adverse maternal and neonatal outcomes among SGA and LGA pregnancies, classified according to population-based or customized norms, when compared with non-SGA and non-LGA neonates, respectively. Compared with the frequentist approach, a Bayesian meta-analysis has several advantages, which include naturally accounting for the full uncertainty in all parameters, more easily interpretable inferences and inclusion of prior evidence of treatment effects or magnitudes[22,23].

For outcomes for which all studies reported the number of cases and non-cases, Bayesian models assume that the number of adverse outcomes from each study follow a binomial distribution, with the probability of the outcome allowed to vary by study. For outcomes for which some studies reported only ORs and 95% CIs, the Bayesian models assume that log-transformed ORs from each study follow a normal distribution, with the mean representing the average logOR across all studies and variance indicating between-study variability. In all analyses, a neutral prior distribution centered at an OR of 1.0 with a 95% CI of 0.14–7.0 (normal distribution with mean of 0 and SD of 1 on the logOR scale) was used for the overall logOR. The range for this prior distribution excludes extremely large treatment effects that are almost never reported with clinical interventions[24,25]. For the between-study SD, we used a weakly informative half-normal distribution (mean of 0 and SD of 0.65) consistent with reported heterogeneity in meta-analyses[26]. We report Bayesian estimates of study-specific and pooled ORs using the posterior median (given the skewed posterior distribution of the ORs, the median is preferred over the mean) and 95% CIs.

All analyses were implemented via Markov Chain Monte Carlo (MCMC) methods in OpenBUGS (version 3.2.3; www.openbugs.net/w/Downloads). For each model, we used three MCMC chains with 20 000 iterations after an initial burn-in of 10 000 iterations. Convergence was assessed and confirmed through visual inspection of trace plots of all parameters. Publication bias was not formally assessed because each analysis included fewer than 10 studies[27].

RESULTS

A flowchart of the electronic search and selection process is shown in Figure 1. We identified 237 potentially relevant publications and reviewed 27 articles for eligibility. The following adverse fetal and neonatal outcomes were addressed in the studies on SGA: IUFD[15,16,28–32,39], neonatal death[15,16,28,33], death in the NICU[16], perinatal mortality[14–16,28,34,35], composite neonatal outcome[14,17,36–38], NICU admission[14,16,17,30,34,37–42], oligohydramnios[36], hospital stay[14], Apgar score[16,17,33,34,38,41], neonatal resuscitation[14,36,41], oxygen requirement[17,36], umbilical-cord blood pH[16,34], metabolic acidosis[38], neonatal jaundice[40], fetal distress[36] and body fat mass[43,44]. Hypertensive disorders[15,16,33,36,41,45], preterm birth (indicated or spontaneous)[14,15,35,36,39,46], Cesarean[14,16,17,34,36,39,41] or operative[37,41,47] delivery, preterm prelabor rupture of membranes[36] and placental abruption/antepartum hemorrhage[15,17,33,36] represented the maternal adverse outcomes studied among SGA neonates. The following fetal and neonatal outcomes were investigated among LGA neonates: IUFD[49], neonatal death[47], perinatal mortality[34,48], composite neonatal outcome[18,37], NICU admission[34,37,47,48], Apgar score[34,47,48], umbilical-cord blood pH[34], hypoglycemia[18,48], hyperinsulinemia[18], hyperbilirubinemia[18], respiratory problems[48] and neonatal jaundice[48]. Cesarean[34,47–49] and operative[34,37,47] delivery, shoulder dystocia[34,37,47–49], third- and fourth-degree perineal lacerations[48,49], cervical lacerations[48] and postpartum hemorrhage[48] were the adverse maternal outcomes studied among LGA neonates.

A total of 20 studies (including 1 095 589 women) with usable outcome data were eligible for inclusion in our meta-analysis. No randomized controlled trial addressed the research question, therefore, only observational studies were included; their main characteristics are summarized in Table 1. Abnormal growth was classified according to birth weight in all but two studies, which used ultrasound-estimated fetal weights[31,39]. Infants were classified as SGA if birth weight was $< 10^{th}$ centile for gestational age and LGA if birth weight was $> 90^{th}$ centile for gestational age. Kase *et al.*[39] and Smith *et al.*[31] used the same cut-offs to define SGA and LGA, but the calculated growth percentiles were based on ultrasound-estimated fetal weight rather than on birth weight.

Customized centiles were obtained according to the approach described by Gardosi *et al.*[10–12] in all studies except that by Smith *et al.*[31], which referred to the more complex model by Bukowski *et al.*[50]. In addition to maternal height, weight, parity, ethnic origin and gestational age at delivery that are included in the Gardosi method, the approach by Bukowski *et al.*[50] also takes into consideration prior pregnancies, marital status, maternal education and first- and second-trimester screening results. Population-based centiles were derived from sex-adjusted standards specific for the population enrolled in each study. Studies differed in their definitions of the various outcomes: Odibo *et al.*[29] and Moon *et al.*[32] explicitly defined IUFD as *in-utero* demise after 20 weeks' gestation, while Ego *et al.*[16] defined it as loss after 22 weeks. Ego *et al.*[16] defined perinatal death as stillbirth or death prior to NICU admission or during a stay in the NICU. Costantine *et al.*[17] defined NICU admission as a stay of > 48 h, while Odibo *et al.*[30] defined it as a stay of > 7 days.

Figures 2 and 3 show the data summary of each included study and the pooled OR estimates of the meta-analysis for each study outcome. There was evidence of study heterogeneity, with estimated between-study variability ranging from 0.03 to 0.65 for SGA analyses and 0.01 to 0.30 for LGA analyses, which are comparable with values reported in other meta-analyses[26]. However, the 95% CIs for this parameter were wide owing to the small number of studies included in the analyses.

The ORs of specific adverse perinatal outcomes were calculated, comparing SGA with non-SGA neonates and LGA with non-LGA neonates. Using population-based norms, SGA neonates were at higher risk for IUFD (OR, 3.3 (95% CI, 1.9–5.0)), neonatal death (OR, 2.9 (95% CI, 1.2–4.5)), perinatal death (OR, 4.0 (95% CI, 2.8–5.1)) and NICU admission (OR, 2.4 (95% CI, 1.7–3.2)). The corresponding ORs using customized growth charts were 7.8 (95% CI, 4.2–12.3) for IUFD, 3.5 (95% CI, 1.1–8.0) for neonatal death, 5.8 (95% CI, 3.8–7.8) for perinatal death and 3.6 (95% CI, 2.0–5.5) for NICU admission (Figure 2). According to population-based norms, LGA pregnancies had a similar risk of perinatal death (OR, 1.3 (95% CI, 0.5–3.3)), NICU admission (OR, 1.6 (95% CI, 0.8–2.3)), maternal third- and fourth-degree perineal lacerations (OR, 2.1 (95% CI, 0.9–3.4)) and neonatal hypoglycemia (OR, 1.6 (95% CI, 0.5–3.9)) when compared with non-LGA pregnancies. The corresponding ORs using customized growth charts were 1.6 (95% CI, 0.6–3.8) for perinatal death, 1.7 (95% CI, 0.9–2.5) for NICU admission, 2.6 (95% CI, 0.9–4.2) for maternal third- and fourth-degree perineal lacerations and 1.7 (95% CI, 0.5–3.9) for neonatal hypoglycemia. In contrast, LGA neonates were at higher risk for shoulder dystocia according to both population-based (OR, 8.0 (95% CI, 5.3–10.1)) and customized (OR, 7.4 (95% CI, 4.9–9.8)) norms (Figure 3).

Table 2 shows the risk of bias according to the ACROBAT-NRSI[21]. Most included studies had a low overall risk of bias. Only three studies were ranked as having moderate or serious risk of bias[16,33,41], as a large proportion of births were excluded from the analyses, in part owing to missing data.

DISCUSSION

Using either customized or population-based growth charts, SGA neonates appear to be at greater risk for IUFD, neonatal death, perinatal death and NICU admission than do non-SGA neonates. Although the point estimates between customized and population-based charts may differ for some outcomes, the CIs for these indirect comparisons overlap. LGA pregnancies did not appear to be at increased risk for perinatal death, NICU admission, maternal third-/fourth-degree perineal lacerations or neonatal hypoglycemia compared with non-LGA pregnancies, using either customized or population-based growth charts. However, both approaches indicated an increased risk for shoulder dystocia among LGA neonates.

To our knowledge, this is the first meta-analysis evaluating adverse perinatal outcomes among SGA and LGA neonates identified by customized growth charts as compared with population-based norms. Our review has some limitations. As patient-level data were not

Table 1 Characteristics of studies included in systematic review and meta-analysis reporting on adverse outcomes of small- (SGA) or large- (LGA) for-gestational-age neonates classified according to customized and population-based growth charts

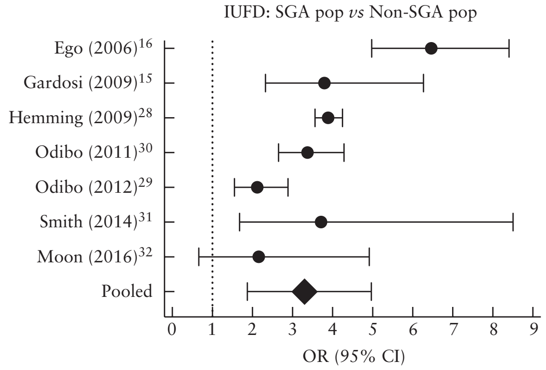
Study	*Country*	*Study design*	*Participants (n)*	*Definition of SGA*/LGA†*	*Exclusion criteria*	*GA at delivery (weeks)*
McCowan (2005)[14]	NZ	Retrospective	12 789	< 10th centile*	Congenital anomalies, multiple pregnancy	NR
Ego (2006)[16]	France	Retrospective	56 599	< 10th centile*	Congenital anomalies, multiple pregnancy	NR
Groom (2007)[35]	NZ	Prospective	17 855	< 10th centile*	Congenital anomalies, chromosomal anomalies, multiple pregnancy, multiparity, transfer to the hospital after delivery, DM, chronic hypertension, renal disorder, autoimmune disorder	> 22
Gardosi (2009)[15]	USA	Prospective	34 712	< 10th centile*	NR	NR
Hemming (2009)[28]	Sweden	Prospective	782 303	< 10th centile*	IUFD > 28 weeks	> 22
Larkin (2011)[49]	USA	Retrospective	23 717	> 90th centile†	IUFD	NR
Odibo (2011)[30]	USA	Retrospective	12 456	< 10th centile*	NR	NR
Cha (2012)[47]	Korea	Retrospective	8279	> 90th centile†	DM, hypertension	37–41
Larkin (2012)[33]	USA	Retrospective	23 541	< 10th centile*	NR	> 24
Odibo (2012)[29]	USA	Retrospective	24 184	< 10th centile*	Multiple pregnancy, congenital anomalies, spontaneous loss or termination < 20 weeks	> 20
Kase (2012)[39]	USA	Retrospective	782	< 10th centile*	Multiple pregnancy, congenital anomalies, chromosomal anomalies, IUFD	> 24
van Eerd (2012)[41]	Australia	Prospective	302	< 10th centile*	Multiple pregnancy, DM, hypertension, thrombophilia, autoimmune disorder, BMI > 40 kg/m^2	> 32
Costantine (2013)[18]	USA	Prospective, secondary analysis of RCT	2083	> 90th centile†	Women without gestational DM, congenital anomalies	NR
Costantine (2013)[17]	USA	Prospective, secondary analysis of RCT	5149	< 10th centile*	Congenital anomalies, multiple pregnancy	NR
Khandaker (2014)[40]	India	Prospective	647	< 10th centile*	Multiple pregnancy, congenital anomalies, booking > 22 weeks, no ultrasound dating	NR
Smith (2014)[31]	USA	Retrospective case–control	246	< 10th centile*	Multiple pregnancy, congenital anomalies, IUFD related to PPROM, maternal trauma or life-threatening maternal illness	> 24
Sjaarda (2014)[48]	USA	Retrospective	81 693	> 90th centile†	Multiple pregnancy, congenital anomalies	> 37
González-González (2015)[34]	Spain	Retrospective	1921	< 10th centile*, > 90th centile†	Women without pregestational or gestational DM, multiple pregnancy, birth weight < 500 g	> 26
Moon (2016)[32]	Korea	Retrospective	2354	< 10th centile*	NR	NR
Sovio (2015)[38]	UK	Prospective	3977	< 10th centile*	Multiple pregnancy, delivery < 28 weeks	> 28

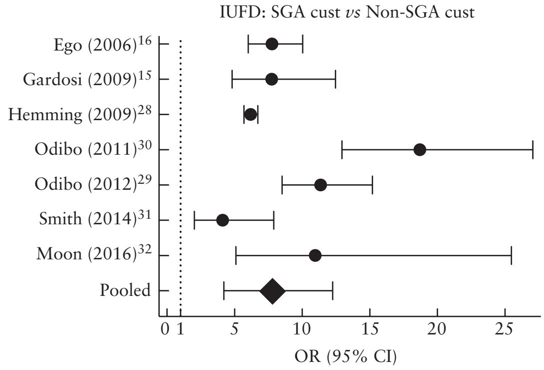
Only first author of each study is given. SGA* and LGA† defined according to specific weight centiles for gestational age. BMI, body mass index; DM, diabetes mellitus; GA, gestational age; IUFD, intrauterine fetal demise; NR, not reported; NZ, New Zealand; PPROM, preterm prelabor rupture of the membranes; RCT, randomized controlled trial.

(a) IUFD

Study	SGA pop		Non-SGA pop	
	IUFD	No IUFD	IUFD	No IUFD
Ego (2006)[16]	121	7740	111	48 627
Gardosi (2009)[15]	17	3252	41	31 402
Hemming (2009)[28]	696	75 889	1658	704 060
Odibo (2011)[30]	144	3281	116	8915
Smith (2014)[31]	6	6	43	191
Moon (2016)[32]	2	133	40	2179

Study	SGA cust		Non-SGA cust	
	IUFD	No IUFD	IUFD	No IUFD
Ego (2006)[16]	132	8209	100	48 158
Gardosi (2009)[15]	29	3983	29	30 671
Hemming (2009)[28]	952	77 337	1402	702 612
Odibo (2011)[30]	227	3027	33	9169
Smith (2014)[31]	16	27	33	170
Moon (2016)[32]	5	21	37	2288

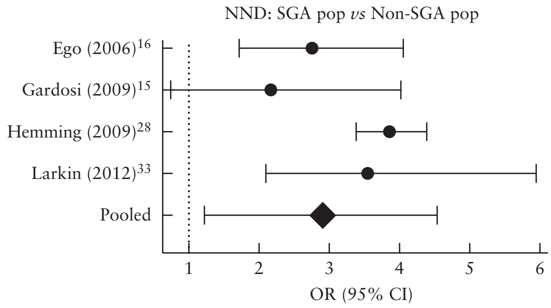


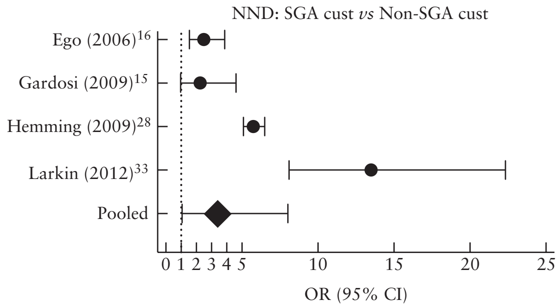


(b) NND

Study	SGA pop		Non-SGA pop	
	NND	No NND	NND	No NND
Ego (2006)[16]	25	7836	53	48 692
Gardosi (2009)[15]	4	3246	22	31 173
Hemming (2009)[28]	325	76 260	762	704 956
Larkin (2012)[33]	14	1607	41	21 879

Study	SGA cust		Non-SGA cust	
	NND	No NND	NND	No NND
Ego (2006)[16]	25	8316	53	48 212
Gardosi (2009)[15]	7	3976	19	30 443
Hemming (2009)[28]	426	77 863	661	703 353
Larkin (2012)[33]	30	1380	25	22 106

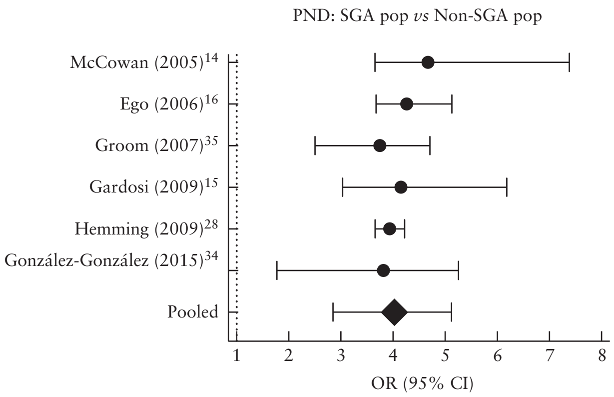




(c) PND

Study	SGA pop		Non-SGA pop	
	PND	No PND	PND	No PND
McCowan (2005)[14]	38	1110	59	11 672
Ego (2006)[16]	192	7669	269	48 476
Groom (2007)[35]	35	2076	78	15 666
Gardosi (2009)[15]	21	3248	37	31 406
Hemming (2009)[28]	1021	75 564	2420	703 298
González-González (2015)[34]	5	224	13	1679

Study	SGA cust		Non-SGA cust	
	PND	No PND	PND	No PND
McCowan (2005)[14]	48	1259	49	11 523
Ego (2006)[16]	207	8134	254	48 011
Groom (2007)[35]	43	1804	70	15 938
Gardosi (2009)[15]	36	3976	22	30 678
Hemming (2009)[28]	1378	76 911	2063	701 951
González-González (2015)[34]	6	167	12	1736



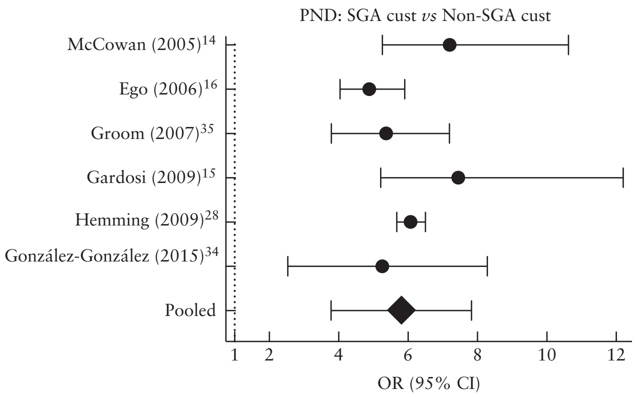


Figure 2 *continued over*

(d) NICU admission

Study	SGA pop		Non-SGA pop	
	NICU	No NICU	NICU	No NICU
McCowan (2005)[14]	296	852	1371	10 360
Ego (2006)[16]	1771	6090	4625	43 794
Odibo (2011)[30]	319	3106	211	8820
Kase (2012)[39]	13	17	110	642
van Eerd (2012)[41]	37	96	24	145
Khandaker (2014)[40]	0	37	11	599
González-González (2015)[34]	11	218	58	1634
Sovio (2015)[38]	47	515	185	3233

Study	SGA cust		Non-SGA cust	
	NICU	No NICU	NICU	No NICU
McCowan (2005)[14]	386	922	1281	10 290
Ego (2006)[16]	1827	6514	4569	43 370
Odibo (2011)[30]	7	30	4	606
Kase (2012)[39]	46	72	77	587
van Eerd (2012)[41]	43	88	18	154
Khandaker (2014)[40]	7	30	4	606
González-González (2015)[34]	15	158	54	1694
Sovio (2015)[38]	36	374	185	3233

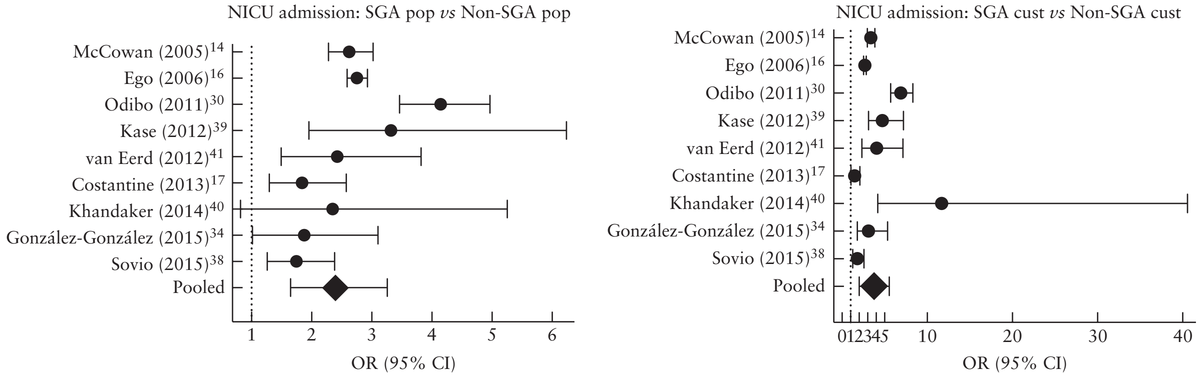


Figure 2 Forest plots of risk of adverse outcome among small-for-gestational-age (SGA) neonates, classified according to customized (cust) *vs* population-based (pop) growth charts: (a) intrauterine fetal demise (IUFD); (b) neonatal death (NND); (c) perinatal death (PND); and (d) admission to neonatal intensive care unit (NICU). Tables present crude numbers. Odibo (2012)[29] and Costantine (2013)[17] did not report these for IUFD and NICU admission, respectively. Only first author of each study is given. OR, odds ratio.

available, it was not possible to determine if the ORs for each outcome were significantly different when fetuses were classified by customized *vs* population-based norms. A customized approach led to higher ORs for the studied outcomes among SGA neonates when compared with population-based standards, suggesting that the criteria of the former classification may better identify patients at risk. However, any conclusion regarding the superiority of this method is hindered by the overlapping CIs.

No differences were detected when comparing LGA with non-LGA pregnancies regarding perinatal death, NICU admission, hypoglycemia and maternal third-/fourth-degree perineal lacerations, regardless of whether LGA was defined using customized or population-based growth charts, although macrosomia was associated with higher perinatal mortality and neonatal morbidity in a previous meta-analysis[51]. This seems to be because of the limited number of studies addressing these outcomes.

Most studies in this analysis used delivery data, while adverse outcomes such as IUFD, neonatal shoulder dystocia and maternal perineal lacerations occur before birth weight is known. However, customized models, like the one of Gardosi *et al.*[10–12], utilize birth-weight data to elaborate a weight-for-gestational-age function to construct individual intrauterine weight curves. Evaluating differences in adverse outcomes when birth weight is outside the norm may provide a rationale for future studies aimed at assessing pregnancy complications when intrauterine fetal growth is followed prospectively according to customized, rather than population-based, standards.

As the model of Gardosi *et al.*[10–12] was the most commonly used one, we mainly compared this approach with population-based norms, notwithstanding that many other analytical methods for customizing fetal weight have been described and have been shown to perform even better[29,48].

Through developmental programing, adult diseases can be linked to birth weight and the latter has been used as a measure of prenatal development[52]. Owing to the potential limitations of population-based norms[9,10], the use of other non-customized growth curves, such as the ones derived from the INTERGROWTH-21st study, has been proposed[53]. This approach advocates the adoption of a universal standard for fetal growth, based on the rationale that optimal maternal conditions, in terms of education, nutrition and relative socioeconomic status, will lead to similar patterns of fetal growth, despite diverse cultural settings. Although the adoption of such a standard might seem to have the potential to make obstetric care more uniform, it does not consider the specific characteristics that make different populations unique[54]. In fact, application of the INTERGROWTH-21st birth-weight standard to an obstetric population in New Zealand classified fewer infants as SGA, identifying fewer stillbirths and fewer cases of composite adverse neonatal outcomes than a customized standard based on the model of Gardosi *et al.*[55].

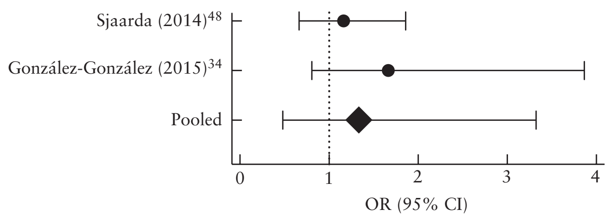
The differences in the relationship between maternal characteristics and fetal growth emphasize that one

(a) PND

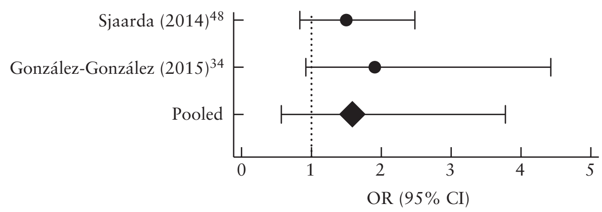
Study	LGA pop		Non-LGA pop	
	PND	No PND	PND	No PND
Sjaarda (2014)[48]	14	9409	130	100 894
González-González (2015)[34]	8	371	10	1532

Study	LGA cust		Non-LGA cust	
	PND	No PND	PND	No PND
Sjaarda (2014)[48]	12	6195	132	104 108
González-González (2015)[34]	7	286	11	1617

PND: LGA pop *vs* Non-LGA pop



PND: LGA cust *vs* Non-LGA cust

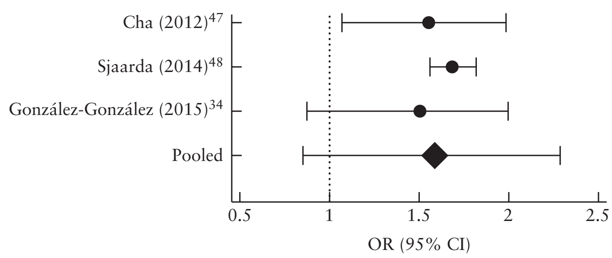


(b) NICU admission

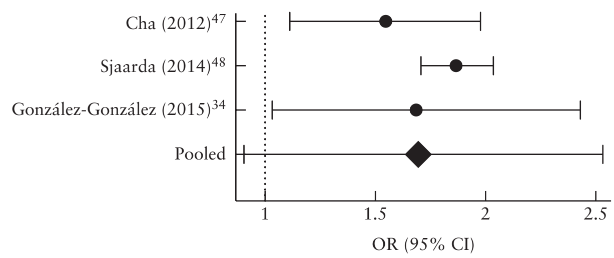
Study	LGA pop		Non-LGA pop	
	NICU	No NICU	NICU	No NICU
Cha (2012)[47]	31	517	301	7430
Sjaarda (2014)[48]	825	8598	5415	95 609
González-González (2015)[34]	17	362	52	1490

Study	LGA cust		Non-LGA cust	
	NICU	No NICU	NICU	No NICU
Cha (2012)[47]	49	847	283	7100
Sjaarda (2014)[48]	603	5604	5637	98 603
González-González (2015)[34]	16	277	53	1575

NICU admission: LGA pop *vs* Non-LGA pop



NICU admission: LGA cust *vs* Non-LGA cust

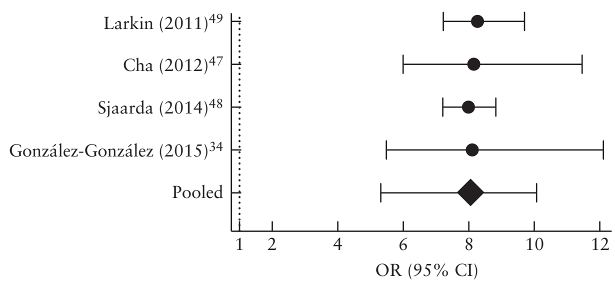


(c) Shoulder dystocia

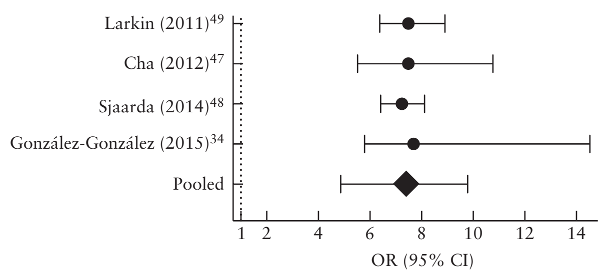
Study	LGA pop		Non-LGA pop	
	Dystocia	No dystocia	Dystocia	No dystocia
Larkin (2011)[49]	228	1691	336	21 462
Cha (2012)[47]	19	231	39	4718
Sjaarda (2014)[48]	549	5264	979	74 901
González-González (2015)[34]	17	362	3	1539

Study	LGA cust		Non-LGA cust	
	Dystocia	No dystocia	Dystocia	No dystocia
Larkin (2011)[49]	150	1042	414	22 111
Cha (2012)[47]	25	376	33	4573
Sjaarda (2014)[48]	345	3129	1183	77 036
González-González (2015)[34]	17	276	3	1625

Shoulder dystocia: LGA pop *vs* Non-LGA pop



Shoulder dystocia: LGA cust *vs* Non-LGA cust

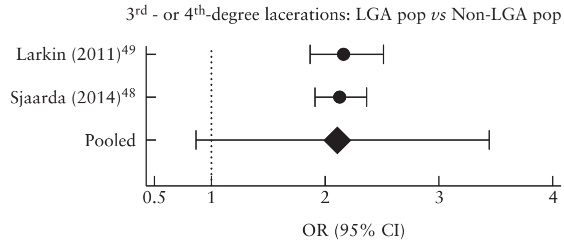


(d) Third- or fourth-degree perineal lacerations

Study	LGA pop		Non-LGA pop	
	Laceration	No laceration	Laceration	No laceration
Larkin (2011)[49]	183	1736	1000	20 798
Sjaarda (2014)[48]	376	5437	2385	73 495

Study	LGA cust		Non-LGA cust	
	Laceration	No laceration	Laceration	No laceration
Larkin (2011)[49]	129	1063	1054	21 471
Sjaarda (2014)[48]	294	3180	2467	75 752

3rd - or 4th-degree lacerations: LGA pop *vs* Non-LGA pop



3rd - or 4th-degree lacerations: LGA cust *vs* Non-LGA cust

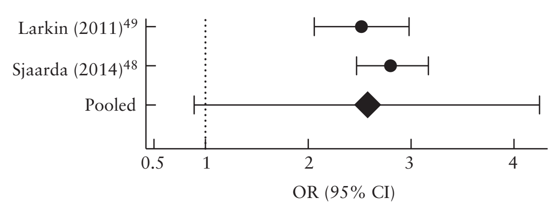


Figure 3 *continued over*

(e) Hypoglycemia

Study	LGA pop		Non-LGA pop	
	Hypoglycemia	No hypoglycemia	Hypoglycemia	No hypoglycemia
Costantine (2013)[18]	29	174	236	1644
Sjaarda (2014)[48]	182	9241	790	100 234

Study	LGA cust		Non-LGA cust	
	Hypoglycemia	No hypoglycemia	Hypoglycemia	No hypoglycemia
Costantine (2013)[18]	44	244	221	1574
Sjaarda (2014)[48]	128	6079	844	103 396

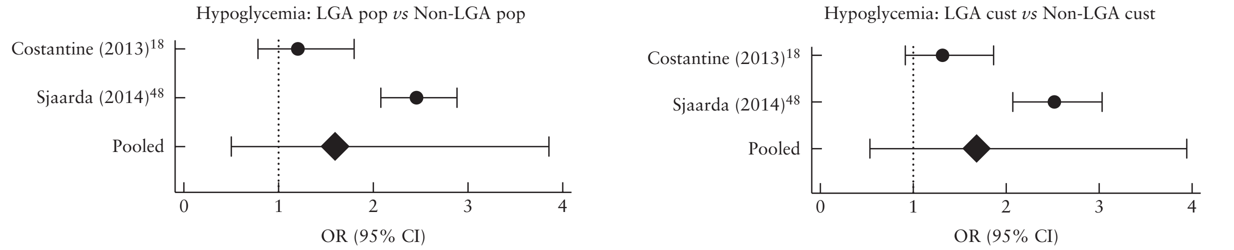


Figure 3 Forest plots of risk of adverse outcome among large-for-gestational-age (LGA) neonates, classified according to customized (cust) *vs* population-based (pop) growth charts: (a) perinatal death (PND); (b) admission to neonatal intensive care unit (NICU); (c) shoulder dystocia; (d) maternal third- or fourth-degree perineal laceration; and (e) hypoglycemia. Tables present crude numbers. Only first author of each study is given. OR, odds ratio.

Table 2 Risk of bias according to ACROBAT-NRSI for studies on small-for-gestational-age (SGA) neonates and those on large-for-gestational-age (LGA) neonates

Study	*Confounding*	*Selection of participants*	*Measurement of intervention*	*Departure from intended intervention*	*Missing data*	*Measurement of outcomes*	*Selection of reported results*	*Overall risk of bias*
SGA								
McCowan (2005)[14]	Low	Low	Low	Low	Low	Low	Low	Low
Ego (2006)[16]	Low	Low	Low	Low	Mod*	Low	Low	Mod
Groom (2007)[35]	Low	Low	Low	Low	Low	Low	Low	Low
Gardosi (2009)[15]	Low	Low	Low	Low	Low	Low	Low	Low
Hemming (2009)[28]	Low	Low	Low	Low	Low	Low	Low	Low
Odibo (2011)[30]	Low	Low	Low	Low	Low	Low	Low	Low
Larkin (2012)[33]	Low	Low	Low	Low	Mod†	Low	Low	Mod
Odibo (2012)[29]	Low	Low	Low	Low	Low	Low	Low	Low
Kase (2012)[39]	Low	Low	Low	Low	Low	Low	Low	Low
van Eerd (2012)[41]	Low	Serious‡	Low	Low	Low	Low	Low	Serious
Costantine (2013)[17]	Low	Low	Low	Low	Low	Low	Low	Low
Khandaker (2014)[40]	Low	Low	Low	Low	Low	Low	Low	Low
Smith (2014)[31]	Low	Low	Low	Low	Low	Low	Low	Low
González-González (2015)[34]	Low	Low	Low	Low	Low	Low	Low	Low
Moon (2016)[32]	Low	Low	Low	Low	Low	No info	Low	No info
Sovio (2015)[38]	Low	Low	Low	Low	Low	Low	Low	Low
LGA								
Larkin (2011)[49]	Low	Low	Low	Low	Low	Low	Low	Low
Cha (2012)[47]	Low	Low	Low	Low	Low	Low	Low	Low
Costantine (2013)[18]	Low	Low	Low	Low	Low	Low	Low	Low
Sjaarda (2014)[48]	Low	Low	Low	Low	Low	Low	Low	Low
González-González (2015)[34]	Low	Low	Low	Low	Low	Low	Low	Low

Only first author of each study is given. *Approximately 25% of births were excluded owing to missing data; rates of intrauterine fetal demise and neonatal death were higher among excluded births than included ones and missing data were not addressed in analysis. †Approximately 26% of births were excluded owing to missing data. ‡Only some appropriate-for-gestational-age neonates in initial cohort were included in analysis. info, information; Mod, moderate.

trajectory of fetal growth does not fit all and that evaluation of growth involves more than just assessment of size. In fact, recent reports have indicated that body composition may be a better measure of nutritional status than birth weight, as it also correlates with postnatal growth and subsequent health[56].

The focus on intrauterine growth in the prevention of stillbirth is justified, as intrauterine growth restriction constitutes the largest single at-risk category among normally formed fetuses experiencing *in-utero* demise. Intrauterine growth restriction is also associated with increased risks of perinatal mortality, morbidity, cerebral palsy and long-term adverse health outcomes[1–3,5,6]. In most pregnancies with fetal growth restriction, the growth restriction is due to late-onset placental insufficiency and the babies are born at term. Antenatal recognition of this condition may lead to appropriate investigations and improved outcomes through antenatal testing and appropriate timing of delivery. In fact, it has been shown that the majority of deaths associated with fetal-growth problems are potentially avoidable through better assessment of risk factors and surveillance of growth during pregnancy[57,58]. Our meta-analysis does not conclude that customized norms can better define a population of pathologically small fetuses that are at higher risk of adverse perinatal outcomes, although a recent prospective observational study suggested such a conclusion. Specifically, Gardosi *et al.*[59] reported that, in England, regions with a high uptake of an accreditation program in customized fetal growth experienced a significant reduction in stillbirths when compared with areas in which uptake was low.

Macrosomia is a common obstetric condition that has been associated with higher perinatal mortality and neonatal morbidity[4,51]. Clinicians are often faced with deciding the appropriate route to deliver macrosomic fetuses in order to achieve the best maternal and neonatal outcome; moreover, these infants require closer postnatal surveillance to prevent complications such as hypoglycemia. Pre-emptive care has the potential for improving perinatal care through antenatal detection of pregnancies with macrosomic fetuses, which are at higher risk for complications. Our meta-analysis indicates that, with the exception of shoulder dystocia, neither customized nor population-based growth charts seem to identify macrosomic fetuses with a statistically significant risk of adverse outcomes. Given this result, it may be that absolute weight is more important in determining outcome in these large fetuses compared with an individualized approach.

Both customized and population-based growth charts can detect intrauterine growth disturbances that are associated with adverse perinatal outcomes, particularly for SGA neonates. Although point estimates of pooled ORs may differ for some of these outcomes, their overlapping CIs do not allow us to draw firm conclusions about the superiority of one method or the other in this indirect comparison. Future prospective randomized controlled trials are needed to determine whether applying this information would actually improve outcomes.

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A slide presentation, prepared by Dr Yael Raz, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Ruben Dario Fernandez.

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Gráficas de crecimiento personalizadas frente a gráficas basadas en la población para la identificación de neonatos con riesgo de un resultado adverso: revisión sistemática y metaanálisis bayesiano de estudios observacionales

RESUMEN

Objetivo Comparar la eficacia de las gráficas de crecimiento personalizadas frente a las gráficas basadas en la población para la predicción de resultados adversos del embarazo.

Métodos Se realizó una búsqueda en MEDLINE, ClinicalTrials.gov y The Cochrane Library hasta el 31 de mayo de 2016, para identificar estudios de intervención y de observación que habían comparado los resultados adversos entre neonatos grandes (GEG) y pequeños (PEG) para la edad gestacional, clasificados así mediante gráficas de crecimiento personalizadas frente a gráficas basadas en la población. Se evaluó: la mortalidad perinatal y la admisión a la unidad de cuidado intensivo neonatal (UCIN) de recién nacidos PEG y GEG; el éxitus intrauterino (IUFD, por sus siglas en inglés) y la mortalidad neonatal de neonatos PEG; la distocia de hombros y la hipoglucemia en los neonatos, así como desgarros perineales maternos de tercer y cuarto grado en embarazos GEG.

Resultados La búsqueda electrónica identificó 237 registros, en los cuáles se examinó el título y el resumen, y entre ellos se examinó la totalidad del texto de 27 artículos para evaluar su elegibilidad. Después de excluir siete artículos, se incluyeron 20 estudios observacionales en un metaanálisis bayesiano. Los neonatos clasificados como PEG de acuerdo con las gráficas de crecimiento personalizadas presentaron mayores riesgos de IUFD (razón de momios (RM) 7,8 (IC 95%, 4,2–12,3)), de muerte neonatal (RM 3,5 (IC 95%, 1,1–8,0), de muerte perinatal (RM 5,8 (IC 95%, 3,8–7,8)) y de admisión en la UCIN (RM 3,6 (IC 95%, 2,0–5,5)), que los casos de neonatos que no eran PEG. Los neonatos clasificados como PEG de acuerdo a las tablas de crecimiento basadas en la población tuvieron un riesgo mayor de resultados adversos, aunque las estimaciones puntuales de las RM combinadas fueron más pequeñas: IUFD (RM 3,3 (95% CI, 1.9–5.0)), muerte neonatal (RM 2,9 (IC 95%, 1,2–4,5)), muerte perinatal (RM 4,0 (IC 95%, 2,8–5,1)), y admisión en la UCIN (RM 2,4 (IC 95%, 1,7–3,2)). La comparación entre GEG frente a no-GEG no mostró diferencias en las RM combinadas para la muerte perinatal, la admisión en la UCIN, la hipoglucemia y los desgarros perineales maternos de tercer y cuarto grado cuando se clasificaron de acuerdo con el enfoque personalizado o con el basado en la población. En contraste, ambos enfoques indicaron que los neonatos GEG tienen un mayor riesgo de distocia de hombros que los no GEG (RM 7,4 (IC 95%, 4,9–9,8) si se usan gráficas personalizadas, y RM 8,0 (IC 95%, 5,3–10,1) si se usan gráficas basadas en la población).

Conclusiones Tanto las gráficas de crecimiento personalizadas como las basadas en la población permiten identificar a los neonatos PEG con riesgo de resultados adversos. Aunque las estimaciones puntuales de las RM combinadas pueden diferir para algunos resultados, los IC solapados y la falta de comparaciones directas impiden alcanzar conclusiones sobre la superioridad de cualquiera de estos métodos. Los ensayos clínicos futuros deberían comparar directamente ambos enfoques para el tratamiento de los fetos de tamaño anómalo.

采用定制的和基于人群的生长曲线识别具有不良结局风险的新生儿：观察性研究的系统评价和贝叶斯 meta 分析

目的：比较定制的和基于人群的生长曲线预测不良妊娠结局的有效性。

方法：检索 MEDLINE、ClinicalTrials.gov 和 The Cochrane Library，时间截止至 2016 年 5 月 31 日，查找根据定制的和基于人群的生长曲线分为大于胎龄儿（large-for-gestational-age，LGA）和小于胎龄儿（small-for-gestational-age，SGA），对二者不良结局进行比较的干预性研究和观察性研究。对 SGA 和 LGA 的围产期死亡率和入住新生儿重症监护室（neonatal intensive care unit，NICU）、SGA 的胎死宫内（intrauterine fetal demise，IUFD）和新生儿死亡率、LGA 的新生儿肩难产和低血糖以及母亲会阴三度和四度裂伤进行评估。

结果：根据题目和摘要，计算机检索到 237 条文献，检查其中 27 篇全文的入选资格。排除 7 篇文献，贝叶斯 meta 分析纳入 20 项观察性研究。根据定制的生长曲线为 SGA 的新生儿与非 SGA 相比，发生 IUFD[比值比（odds ratio，OR），7.8（95% CI，4.2~12.3）]、新生儿死亡[OR，3.5（95% CI，1.1~8.0）]、围产期死亡[OR，5.8（95% CI，3.8~7.8）]和入住 NICU[OR，3.6（95% CI，2.0~5.5）]的风险较高。根据基于人群的生长曲线为 SGA 的新生儿发生不良结局的风险也增加，尽管合并 ORs 的点估计值较小：IUFD[OR，3.3（95% CI，1.9~5.0）]、新生儿死亡[OR，2.9（95% CI，1.2~4.5）]、围产期死亡[OR，4.0（95% CI，2.8~5.1）] 和入住 NICU[OR，2.4（95% CI，1.7~3.2）]。根据定制的或基于人群的生长曲线分类时，LGA 与非 LGA 相比，围产期死亡、入住 NICU、低血糖和母亲会阴三度和四度裂伤的合并 ORs 无差异。相反，两种分类方法均显示，LGA 与非 LGA 相比，发生肩难产的风险增加[采用定制的生长曲线：OR，7.4（95% CI，4.9~9.8）；采用基于人群的生长曲线：OR，8.0（95% CI，5.3~10.1）]。

结论：定制的和基于人群的生长曲线均能识别具有不良结局风险的 SGA。尽管某些结局的合并 ORs 的点估计值不同，但由于 CIs 重叠以及未进行直接比较，不能证实哪种方法更好。未来的临床试验应直接比较两种方法对异常大小胎儿的处理。

