OBSTETRICS

Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles

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OBJECTIVE: The objective of the study was to investigate the association between pregnancy complications and small for gestational age (SGA) birthweight, comparing SGA based on the customized growth potential with SGA based on the birthweight standard of the same population.

STUDY DESIGN: This was a retrospective analysis of a database from a US multicenter study. Pregnancy complications included threatened preterm labor, antepartum hemorrhage, pregnancy-induced hypertension, preeclampsia, stillbirth, and early neonatal death.

RESULTS: Compared with SGA by the birthweight standard, SGA by customized growth potential showed higher risk for each of the 6 adverse indicators. A third of the SGA group was small by customized centiles but not by population-based centiles, yet was strongly associated with each of the pregnancy complications studied. This subgroup of unrecognized SGA babies included 26% preterm deliveries. In contrast, a subgroup that was SGA by the population standard but not by the customized standard (17.2%), was not associated with any of the indicators of adverse outcome.

CONCLUSION: SGA defined by customized growth potential improves the differentiation between physiologically and pathologically small babies.

Key words: birthweight, customized growth charts, fetal growth, growth potential

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Fetal growth restriction is associated with adverse perinatal outcome including stillbirth, perinatal morbidity, and neonatal mortality.[1] The growth status of the fetus is usually implied from its size, and small for gestational age (SGA) measured against a population standard is often taken as a proxy for fetal growth restriction. However, a generic weight standard is imprecise because it includes physiological/constitutional variation as well as pathological weights from pregnancies affected by suboptimal factors such as smoking, diabetes, or premature delivery.

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★ EDITORS' CHOICE ★

For an accurate assessment of an individual baby's fetal weight and birthweight, it is important first to predict a baby's growth potential which should be expected to be reached by the end of an uncomplicated pregnancy. Such an optimal, individually customized standard needs to be accurately dated, individually adjusted for physiological characteristics, exclude pathological factors, and have a fetal (rather than a neonatal) weight trajectory based on normal term pregnancies.[2,3] We have recently been able to apply such principles to a US database to derive coefficients to adjust for normal variation[4] and have incorporated these into an American version of the freely available customized centile calculator software program (GROW, Gestation Related Optimal Weight, www.gestation.net).

At the limits of normal weight distribution, adjustment for physiological variables can result in substantial variation in the proportion of babies considered SGA.[4] Ultimately though, the proof of value of such a standard based on growth potential has to lie in whether it is a better predictor of adverse pregnancy outcome than a conventional, unadjusted standard derived from the same population. Birthweight curves need to be based on ultrasonically dated pregnancies,[5] but American population standards have often been marred by dating error, resulting in wide ranges at preterm gestations and artificial flattening of the birthweight curve at term. Because the current database under investigation was derived from ultrasound dated pregnancies, it also allowed the generation of the relevant population-based standard for making comparisons.

The purpose of this study was therefore to investigate and compare the association between SGA and several indices of pregnancy complications and adverse outcome, using population birthweight limits and customized growth potential limits for SGA based on the same population.

Materials and Methods

Study population

Anonymized data were obtained from a National Institutes of Health-sponsored

TABLE 1
Smoothed centiles for birthweight

Gestational age	Centile		
Weeks	10th	50th	90th
24	440	620	794
25	467	677	866
26	497	761	969
27	560	871	1102
28	653	1006	1263
29	775	1163	1450
30	923	1342	1660
31	1095	1539	1890
32	1288	1751	2137
33	1498	1976	2396
34	1720	2208	2663
35	1949	2445	2932
36	2180	2680	3196
37	2407	2909	3450
38	2622	3124	3684
39	2818	3319	3892
40	2986	3487	4063
41	3117	3619	4186
42	3199	3706	4252

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study conducted at 15 centers across the United States to evaluate pregnancy screening tests in singleton pregnancies. The study was conducted from October 1999 to December 2002, with institutional review board approval and participants' informed consent. All pregnancies were dated by ultrasound, and entry to the study was between gestational age of 10 weeks 3 days through 13 weeks 6 days according to fetal crown-rump measurement. Details of the database have been described elsewhere.[6] By agreement with the original study team, the data obtained for this study were analyzed by us independently.

Of a total of 38,033 cases, 2798 were excluded because of missing or inconsistent values for gestation and/or birthweight, leaving 35,235 cases for further analysis. The characteristics of this population have been previously described.[4]

TABLE 2
Maternal characteristics of babies defined as SGA by population and customized standards

	SGA population standard $n_1 = 3269$		SGA customized standard $n_2 = 4047$	
Variable	OR	95% CI	OR	95% CI
Maternal age (y)				
< 20	1.6	1.3-1.9	1.3	1.1-1.5
20-29[a]	1		1	
30-34	0.8	0.8-0.9	1.0	0.9-1.1
≥ 35	1.0	0.9-1.0	1.2	1.1-1.3
Maternal height (cm)				
< 155	2.2	1.9-2.4	1.1	0.9-1.2
155-159	1.6	1.4-1.8	1.0	0.9-1.2
160-164[a]	1		1	
165-169	1.3	1.2-1.5	1.0	0.9-1.1
≥ 170	0.7	0.6-0.8	0.9	0.9-1.0
Maternal weight (kg)				
< 50	2.8	2.4-3.2	1.2	1.1-1.4
50-59	1.5	1.4-1.6	1.0	0.9-1.1
60-69[a]	1		1	
70-79	0.9	0.8-1.0	1.2	1.1-1.3
80-99	0.8	0.7-1.0	1.4	1.2-1.5
100+	0.7	0.6-0.9	1.4	1.2-1.7
BMI (kg/m^2)				
< 20	1.4	1.3-1.6	1.2	1.1-1.3
20-24.9[a]	1		1	
25-29.9	0.8	0.8-0.9	1.2	1.1-1.3
30-34.9	0.8	0.7-0.9	1.5	1.3-1.7
≥ 35	0.8	0.7-1.0	1.5	1.3-1.7
Parity				
0	1.7	1.5-1.8	1.1	1.1-1.2
1[a]	1		1	
≥ 2	0.8	0.7-0.9	1.0	0.9-1.1
Ethnic origin				
African American	1.5	1.4-1.6	1.1	1.1-1.2
European[a]	1		1	
Hispanic	2.0	1.8-2.3	1.3	1.1-1.5
Other	1.7	1.4-1.9	1.1	0.9-1.2
Smoking				
No[a]	1		1	
Yes	2.1	1.8-2.3	2.2	2.0-2.5

n = 34,712 cases having both centiles calculated.
BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio; *SGA*, small for gestational age.
[a] Reference for ORs.
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A further 523 cases (1.5%) had insufficient detail to calculate customized birthweight centiles, which left a final total of 34,712 cases for this study.

Small for gestational age

Two methods were used to define SGA (less than the 10th birthweight centile):

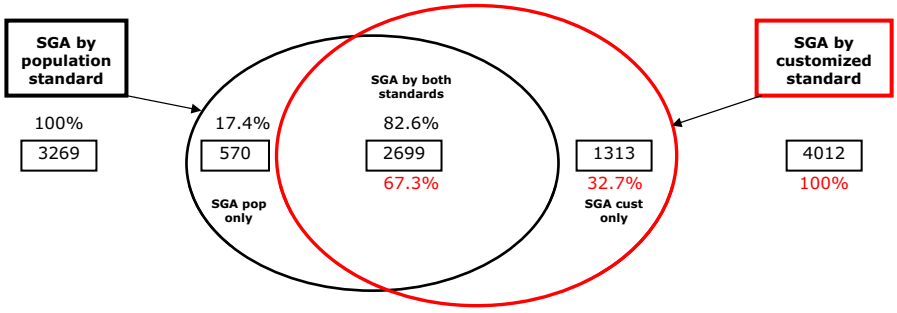
1. Population SGA (SGA_{pop}). A standard was derived from the same data to allow fair comparisons and exclude variation due to different case mix, method of dating, and other factors between different population samples. Kolmogoroff-Smirnov tests at each gestation week showed significant nonnormality of the data. Therefore, an LMS model[7] (described in the following text) was applied, with nontransformed age scale and degrees of freedom for Box-Cox power, median, and coefficient of variation of 5, 13, and 8, respectively. Essentially, this method allows calculation of the optimal power to obtain normality at each gestational age and the trend summarized by a smooth (L) curve. Trends in the mean (M) and coefficient of variation (S) are similarly smoothed. This transformation allowed generation of smoothed gestational age-specific weight curves for 10th, 50th, and 90th centiles from 24 to 42 weeks (Table 1).

   Cases with birthweights below the 10th centile limit were classified as SGA_{pop}. This resulted in 3269 (9.4%) cases, slightly lower than 10% because of the effect of data transformation and smoothing of the population curve.

2. Customized SGA (SGA_{cust}). Customized birthweight centiles were calculated using coefficients derived previously from this population[4] to be able to adjust for maternal height, weight, parity, ethnic origin, and fetal sex. To study the effect of maternal body mass index (BMI), adjustment for maternal weight was made without the BMI limits (20-30 kg/m^2) used in the clinical version of the customized chart software.

   To establish the individual growth potential, first a term optimal weight is calculated together with limits for

FIGURE 1
SGA by population and customized standard



Relative proportions of babies designated as small for gestational age (SGA) by the population standard (n = 3269) and the customized standard (n = 4047). The diagram also shows the subgroups that are SGA by both methods and SGA by population standard or customized standard only, respectively.

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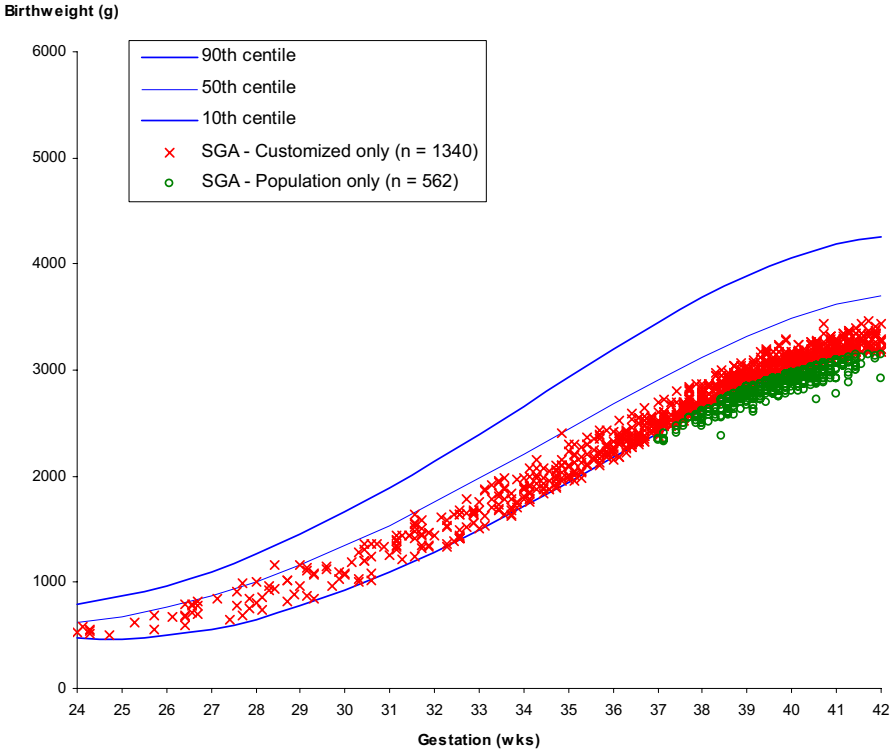
FIGURE 2
Population birthweight curve and SGA categories



Birthweight curve for the study population, representing the population standard, with 90th, 50th, and 10th centile lines. Cases from the 2 subgroups (Figure 1) that are small for gestational age (SGA) only by the population standard and not SGA by the customized standard (n = 562) and those that are SGA only by the customized standard and not by the population standard (n = 1340) are plotted.

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TABLE 3
Comparison between SGA by population standard only and SGA by customized standard only

	SGA population standard only (n = 562)				SGA customized standard only (n = 1340)				
Variable	**Mean**	**SD**	**Median**	**IQR**	**Mean**	**SD**	**Median**	**IQR**	***P* value[a]**
Maternal age (y)	28.1	5.9	28.4	9.8	30.8	5.8	31.1	8.6	< .01
Maternal height (cm)	157.7	5.9	157.5	7.9	167.0	7.2	167.6	10.2	< .01
Maternal weight (kg)	55.0	9.0	53.6	9.5	75.5	17.1	72.7	20.5	< .01
BMI (kg/m^2)	22.1	3.5	21.4	3.3	27.1	6.0	26.2	7.9	< .01
Birthweight (g)	2852.5	149.9	2863.4	170.1	2676.4	625.2	2920.1	643.6	< .01
Gestational age (wk)	39.7	0.9	39.6	1.3	38.0	3.4	39.0	3.6	< .01
Excluding preterm									
Birthweight (g)	2852.5	149.9	2863.4	170.1	2989.4	216.3	3021.5	283.5	< .01
Gestational age (wk)	39.7	0.9	39.6	1.3	39.6	1.3	39.7	0.9	.75

BMI, body mass index; *IQR*, interquartile range; *SGA*, small for gestational age.

[a] Mann-Whitney *U* test.

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TABLE 4
Risk of pregnancy complications in SGA babies defined by population and customized centiles, compared with babies not SGA by either method

				Cases				
Outcome	**Population, n**	**SGA method**	**SGA, n**	**n**	**Rate/1000**	**OR**	**95% CI**	**PAR**
Threatened preterm labor								
n = 1767	34,608	SGA_{pop}	3260	127	39.0	0.73	0.61-0.88	-2.5
		SGA_{cust}	3999	265	66.3	1.38	1.20-1.57	3.9
Antepartum hemorrhage								
n = 544	34,692	SGA_{pop}	3268	61	18.7	1.22	0.93-1.59	2.0
		SGA_{cust}	4010	83	20.7	1.39	1.09-1.75	4.2
Pregnancy induced hypertension								
n = 1574	34,603	SGA_{pop}	3261	219	67.2	1.59	1.37-1.85	5.0
		SGA_{cust}	4000	313	78.3	1.98	1.74-2.25	9.4
Preeclampsia								
n = 810	34,606	SGA_{pop}	3261	137	42.0	2.00	1.66-2.41	8.3
		SGA_{cust}	4001	241	60.2	3.38	2.90-3.95	20.6
Stillbirth								
n = 58	34,712	SGA_{pop}	3269	17	5.2	4.00	2.27-7.06	22.0
		SGA_{cust}	4012	29	7.2	7.70	4.60-12.90	43.5
Neonatal death								
n = 26	34,445	SGA_{pop}	3250	4	1.2	1.75	0.60-5.07	6.6
		SGA_{cust}	3983	7	1.8	2.82	1.19-6.71	17.4

Rates, ORs with CIs, and PAR are shown.
CI, confidence interval; *OR*, odds ratio; *PAR*, population attributable risks; *SGA*, small for gestational age.

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10th and 90th centiles, as previously described.[2,3] Through these points, the proportional growth equation is fitted,[3] based on the original Hadlock fetal weight curve.[8] Thereby, 10th, 50th, and 90th limits are determined for the whole gestational age range.

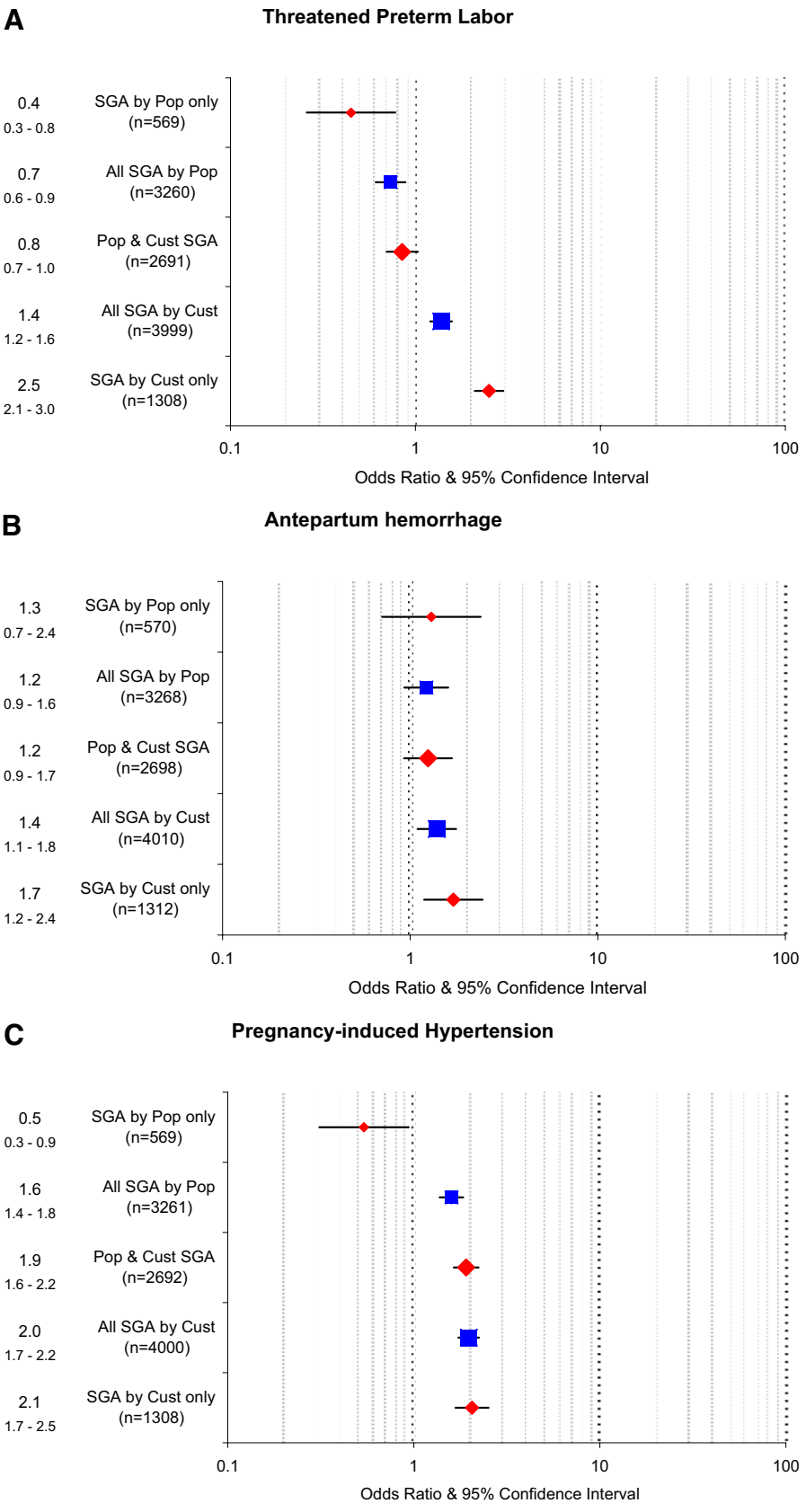
Birthweights below the 10th centile limit were classified as SGA_{cust}. This resulted in 4047 or 11.7% cases, more than 10%, because it included pregnancies with smoking and other pathological factors contributing to fetal growth restriction.

Adverse pregnancy indicators and outcomes

The final cohort contained the following variables representing pregnancy complications or adverse outcomes that were found to be associated with SGA birthweight in the previous multiple regression analysis[4]: threatened preterm labor (n = 1767, a heterogeneous group, which included 878 or 49.7% term deliveries), antepartum hemorrhage (n = 544); pregnancy-induced hypertension (PIH, n = 1574), preeclampsia (PIH with proteinuria: n = 810), stillbirth (n = 58), and neonatal death (n = 26).

For each of these indicators, SGA rates were determined according to population and customized centiles, with odds ratios (ORs), 95% confidence intervals (CIs), and population attributable risks (PARs) to assess the respective strengths of association. Three further subcategories were compared for each of these

FIGURE 3
Perinatal complications and SGA status



Association between small for gestational age (SGA) and **A,** threatened preterm labor, **B,** antepartum hemorrhage, **C,** pregnancy-induced hypertension, **D,** preeclampsia, **E,** stillbirth, and **F,** neonatal death. SGA was defined according to population-based centiles (all SGA by Pop) and SGA by customized centiles (all SGA by Cust), as shown in Table 4 (*blue markers*). In addition, subgroups that are SGA by both methods (Pop and Cust SGA), the population method only (SGA by Pop only), or the customized method only (SGA by Cust only) (*red markers*) are shown. Odds ratios and 95% confidence intervals are listed. *(Continued on the next page)*

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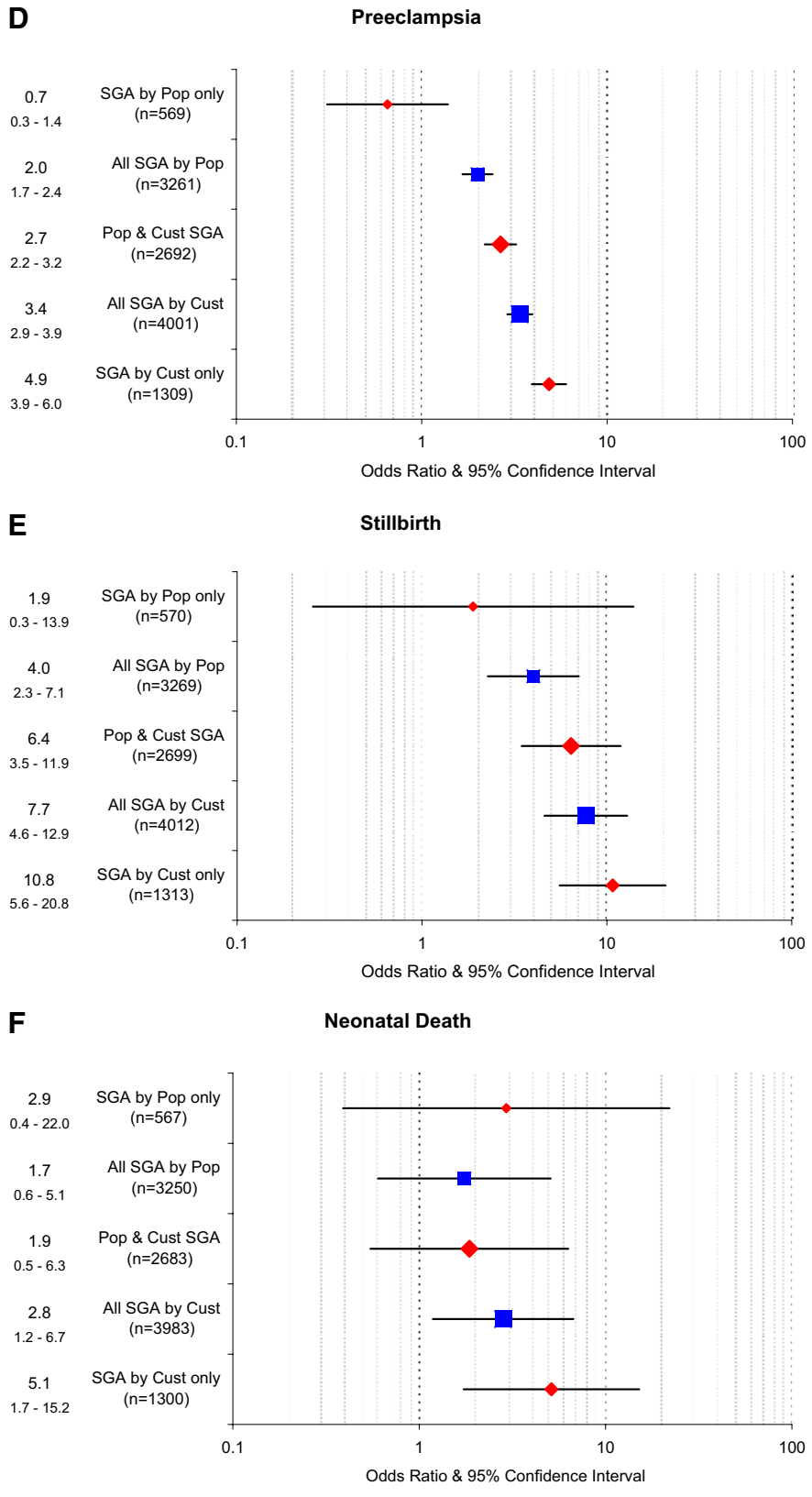
FIGURE 3
Perinatal complications and SGA status *(continued)*



Gardosi. Adverse pregnancy outcome and SGA by birthweight percentiles. Am J Obstet Gynecol 2009.

pregnancy indicators: cases that were SGA by the population standard only, cases that were SGA by the customized standard only, and cases that were SGA by both methods.

RESULTS

Table 2 lists the categories of various maternal physiological characteristics and the respective rates of SGA when population and customized centiles are used. Compared with the reference category, customized SGA rates show less variation across the subgroups, confirming that the customized centiles make the adjustments for physiological differences, as they are intended to do. For example, SGA rates show reduced differences between different ethnic groups when ethnic variation in birthweight is adjusted for using customized centiles. In the case of obesity as defined by high BMI, the high BMI groups had reduced rates of SGA when it was defined by the population standard but elevated risk of SGA as defined by the customized standard.

There was overlap between the babies designated as SGA by the different methods, as illustrated in Figure 1: 17.4 of babies who were SGA by population centiles were not SGA by customized centiles, and 32.7% of babies designated as SGA_{cust} were not recognized as SGA by population centiles.

Figure 2 illustrates where the population-SGA-only and customized-SGA-only cases are plotted on a weight-for-gestational-age chart based on this population (Table 1). The 562 cases considered SGA by the population standard only tended to be clustered just below the 10th centile line at term. In contrast, the 1340 babies who are SGA by the customized method only are distributed mostly just above the 10th centile. Whereas most of these were also at term, these cases spread along the whole range of gestational age, with 346 of 1340 (25.8%) being before 37 weeks' gestation.

The maternal characteristics of these 2 SGA subgroups are listed in Table 3. Compared with the population-SGA-only group, mothers of babies identified as SGA only by the customized standard

were older, taller, and heavier and had a higher BMI. They also tended to be born at earlier gestations, and in fact, there were no preterm babies in the population-SGA-only group, as also demonstrated in Figure 2. However, when preterm deliveries were excluded, birthweights in the customized SGA group were higher than in the population-only group.

In Table 4, numbers, odds ratios, and population attributable risks are listed for each of 6 pregnancy complications or outcomes, comparing cases determined as SGA by population and customized methods. In each category, customized SGA has a stronger association (OR) and "explains" (PAR) more of the instances of that particular adverse indicator than when the population standard is used.

In Figure 3, A-E, these odds ratios and 95% confidence intervals are displayed together with the subgroups arising from the overlap of methods described in Figure 1 (ie, showing pregnancies with babies that are SGA according to both methods and by population or customized method only). The subgroup "SGA by population standard only" had either no or a negative association with the outcome variables. In contrast, the "SGA by customized centiles only" group not only showed significant risks for each of these outcomes, but also this association was at least as strong, and usually stronger, than the group that was SGA by both methods.

COMMENT

Conventionally, local or national population-based reference curves are used to assess the association between birthweight and outcome. In this analysis, we apply newly derived American coefficients for calculating the individually customized growth potential[4] and compare it with the reference norm based on the same population. Our findings suggest that babies identified as SGA with this method have a significantly increased association with adverse pregnancy outcome.

Compared with the population-based standard, the customized standard results in a more even distribution of SGA frequency within subgroups of the population listed in Table 2, because maternal physiological variation is corrected for. Babies who are identified as SGA only by customized centiles are more likely to have larger mothers (Table 3), in whom an average-size baby may not be recognized as small, even though it is smaller than its growth potential.

In addition to adjusting for physiological variation, the customized standard uses a fetal rather than a neonatal weight curve to delineate the true growth potential. This allows better quantification of the association between growth failure and spontaneous preterm delivery.[9] In the current study, this point is illustrated by the fact that 26% of the babies who are additionally recognized as SGA by the customized standard were born at preterm gestations (Figure 2). The identification of a cohort of increased risk SGA babies thus extends across the whole gestational age range. This is an important concept when studying outcomes such as preeclampsia, which is a disease more likely to be associated with SGA at preterm gestations.[10]

The customized standard based on individual growth potential highlights the association between growth failure and pathological pregnancy. For each of the complications or adverse outcomes studied, customized SGA is seen to have an overall stronger association with the conditions studied than population SGA (Figure 3). In fact, pregnancies defined as only population SGA (ie, not SGA by the customized method) are not at increased risk of any of these outcomes. This means that 17.4% of babies conventionally considered SGA are only physiologically or constitutionally small (Figure 1). Conversely, the population standard misses a third of babies (32.7%) that are small by the customized standard; this group of babies has the highest odds ratio for each of the adverse outcomes analyzed (Figure 3).

Our findings are consistent with previous analyses of databases in Holland,[11] Sweden,[12] New Zealand,[13] and France,[14] which showed that SGA defined by a customized standard was better than SGA defined by the respective local birthweight standard in identifying risk, including abnormal Doppler, low Apgar score, cesarean section for fetal distress, admission to neonatal intensive care, preeclampsia, stillbirth, and neonatal death. A recent analysis[15] of the same American database also showed improved recognition of pathology with customized and growth potential norms compared with a traditional population-based birthweight norm.[16]

Our analysis compared customized and population norms from the same population, which allowed us to control for potential confounders such as differing methods used for dating pregnancy. The main message of all these studies is that population based birthweight standards, which are currently in established use to assess birthweight, miss a significant proportion of cases that are pathologically small.

A recent report[17] claimed that most of the difference in observed outcome is due to the use of fetal weight instead of birthweight centiles in the customized model, which identify SGA better at preterm gestations, and that adjustment for maternal and pregnancy characteristics adds little to the strength of association with perinatal mortality. However, the method used[17] was only partially customized and not based on determination of growth potential. Furthermore, clinical usefulness is also related to the number of at-risk cases identified, which was still higher in the customized SGA group. Whereas we found that many missed SGA cases were indeed at preterm gestations, the majority (74%) were at term (Figure 2).

The customized model adjusts for all the physiological variables found to be significantly affecting birthweight in the multivariate analysis.[4] However, whereas such adjustment is demonstrated to improve the prediction of pathological smallness, this should not preclude added vigilance in clinical management of pregnancies that may be at increased risk because of various other factors. For example, primipara tend to have increased rates of complication during pregnancy and labor,[18] and ethnic minorities may have higher rates of social deprivation, which itself is a risk for adverse outcome.[19,20]

High maternal BMI is shown to be associated with an increased incidence of SGA babies but only when SGA is defined by customized centiles (Table 2). This is consistent with the results of the multiple regression analysis in the companion article,[4] which showed that elevated BMI reduced the expected birthweight at term. In contrast, use of the population standard shows no increase of SGA, and even suggests that high BMI *reduces* the risk of having an SGA baby (BMI 30.0-34.9 kg/m^2: OR, 0.8; 95% CI, 0.7-0.9). This effect has been previously reported as a protective factor for SGA[21] but is actually an artifact due to their use of a population standard which includes babies who seem to be of normal size but have failed to reach their own growth potential.

The current database is not large enough to test whether this newly discovered group of "hidden" SGA babies in obese mothers has an increased risk of adverse outcome. However, a recent analysis in a larger Swedish database has shown that these hitherto unrecognized SGA babies had a significantly elevated risk of stillbirth.[22] This has recently also been confirmed when gestation is controlled for by using the same fetal weight standard in both the population SGA and customized SGA groups.[23] Further work is required to study the outcome of these pregnancies, but the preliminary evidence suggests that an elevated incidence of growth failure may be an important contributor to the known association between maternal obesity and increased risk of stillbirth. ■

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