Paediatric and Perinatal Epidemiology
Affiliated to the Society for Pediatric and Perinatal Epidemiologic Research

doi: 10.1111/ppe.12002

Perinatal Outcomes in Large Infants Using Customised Birthweight Centiles and Conventional Measures of High Birthweight

Dharmintra Pasupathy,[a] Lesley M. E. McCowan,[b] Lucilla Poston,[a] Louise C. Kenny,[c] Gus A. Dekker,[d] Robyn A. North[a] on behalf of the SCOPE consortium

[a]*Division of Women's Health, Women's Health Academic Centre, King's Health Partners, King's College London, Guy's and St Thomas' NHS Foundation Trust, London, UK*

[b]*Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*

[c]*Anu Research Centre, Department of Obstetrics and Gynaecology, University College Cork, Republic of Ireland*

[d]*Women's and Children's Division, Lyell McEwin Hospital, The Robinson Institute, University of Adelaide, Adelaide, Australia*

Abstract

Background: Large-for-gestational-age (LGA) or macrosomic infants are associated with adverse maternal and neonatal outcomes. It is unclear if these associations are stronger using customised birthweight centiles. We compared outcomes between term infants defined macrosomic by birthweight >4000 g ($Macro_{4000}$) or LGA by population centiles (LGA_{pop}) with those defined LGA by customised centiles (LGA_{cust}).

Methods: This is a prospective cohort study of 2668 term nulliparous women recruited into the Screening for Pregnancy Endpoints (SCOPE) study centres in Auckland, New Zealand and Adelaide, Australia. Maternal (caesarean delivery, postpartum haemorrhage) and infant (severe neonatal morbidity/mortality and admission to neonatal intensive care) outcomes in $Macro_{4000}$ and LGA groups were compared with appropriate-for-gestational-age infants by customised centiles using logistic regression.

Results: Customised centiles defined fewer infants as LGA (10.3% LGA_{cust}, 14.8% $Macro_{4000}$, 11.2% LGA_{pop}). However customised centiles showed stronger association with adverse outcomes. Pre-labour and intrapartum caesarean section were increased twofold in LGA_{cust} pregnancies, including those that were not $Macro_{4000}$ or LGA_{pop}. Postpartum haemorrhage was increased twofold in mothers of LGA_{cust} infants only when infants were also LGA_{pop}. Severe neonatal morbidity/mortality or admission to neonatal intensive care was increased twofold in LGA_{cust} who were also either $Macro_{4000}$ or LGA_{pop}. Importantly 52.3% of $Macro_{4000}$ and 25.5% of LGA_{pop} infants were AGA_{cust} and not at increased risk of most adverse maternal or neonatal outcomes.

Conclusions: The use of customised centiles are more strongly associated with adverse birth outcomes and its use should be considered in the definition of LGA.

Keywords: *macrosomia*, *large for gestational age*, *caesarean section*, *postpartum haemorrhage*, *severe neonatal morbidity or mortality*.

Pregnancies complicated by macrosomia or large-for-gestational-age (LGA) infants are at increased risk of adverse perinatal outcomes including caesarean section, operative and traumatic vaginal delivery, post-partum haemorrhage (PPH), shoulder dystocia, brachial plexus injury, low Apgar scores, admission to neonatal intensive care, neonatal hyperbilirubinaemia and hypoglycaemia.[1–7] There are no universally agreed criteria for defining macrosomia and LGA. Macrosomia has been defined as birthweight greater than 4000 or 4500 g.[8,9] Traditionally, population birthweight centiles, which correct for infant sex and gestation at delivery, have been used to classify size at birth and LGA has been defined as birthweight greater than the 90th or 95th population centile.[3] These definitions do not adjust for maternal characteristics known to affect fetal growth.

Customised birthweight centiles, which adjust for parity, ethnicity, maternal height and weight in early

Correspondence: Dharmintra Pasupathy, Division of Women's Health, Women's Health Academic Centre, King's Health Partners, King's College London, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK.
E-mail: dharmintra.pasupathy@kcl.ac.uk

pregnancy as well as infant sex and gestational age, have been increasingly used to assess size at birth. A customised centile in the normal range is considered to reflect physiologically appropriate growth for the maternal constitution.[10] When considering infants who are small for gestational age (SGA), several studies have now reported that defining SGA using customised birthweight centiles better identifies those small infants with increased rates of morbidity and mortality.[11,12] Furthermore it has been suggested that these customised SGA infants have failed to reach their optimal growth potential.[11–13] If the same is also true among large infants, those categorised as LGA by customised centiles are more likely to have exceeded their growth potential, require caesarean delivery and experience neonatal morbidity. Conversely some infants defined as 'macrosomic' or 'LGA' by conventional measures in previous studies were likely to have been appropriately grown for maternal constitution and the labour and delivery of these infants may not be associated with increased morbidity.

To further understand the relationship between LGA by customised centiles and pregnancy-related complications, we have investigated the relationship between LGA by customised standards and severe neonatal morbidity in term infants and the risk of caesarean delivery and maternal postpartum haemorrhage in a prospective cohort of primigravidae.

The aim of our study was to compare the risk of adverse maternal and infant outcomes between term infants defined as LGA by customised centiles with infants defined as macrosomic by birthweight greater than 4000 g or LGA by population centiles.

Methods

The participants were 'healthy' primigravidae with singleton pregnancies, and their infants, recruited into the Screening for Pregnancy Endpoints (SCOPE) study between November 2004 and August 2008 in Auckland, New Zealand and Adelaide, Australia. SCOPE is a prospective, multi-centre cohort study, which aims to develop screening tests for the prediction of preeclampsia, preterm birth and SGA.[14,15]

Women were recruited at 14–16 weeks of gestation. Women considered at high risk of preeclampsia, SGA or preterm birth because of underlying medical conditions including pre-gestational diabetes, gynaecological history, three or more previous miscarriages or terminations of pregnancy, known major fetal anomaly or abnormal karyotype or those that received interventions that may modify pregnancy outcome were not eligible.[15] Additional exclusion criteria in the present study were fetal losses or termination of pregnancy before 20 weeks of gestation, infants born before 37 completed weeks of gestation and SGA defined as infants with birthweight less than the 10th customised centile.

The estimated date of delivery was calculated from a certain last menstrual period (LMP) date. The estimated date of delivery was only adjusted if either (i) a scan performed before 16 weeks of gestation found a difference of ≥7 days between the scan gestation and that calculated by the LMP, or (ii) a difference of ≥10 days was found between the 20-week scan gestation and that calculated from the LMP. If the LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery. Participants were interviewed and examined by a research midwife at 15 ± 1 and 20 ± 1 weeks of gestation and underwent an ultrasound scan at 20 ± 1 weeks. Detailed sociodemographic data, medical, family history, dietary and life style in current pregnancy and physical measurements were obtained.[15] Ninety-three per cent of participants were screened for gestational diabetes. Pregnancy, birth and neonatal outcome data were collected usually within 72 h of birth. All data were entered into an internet accessed database (Medscinet[AB], Stockholm, Sweden) and monitored for accuracy and completeness.

Customised birthweight centiles were calculated correcting for gestational age, maternal ethnicity, weight and height in early pregnancy, parity and infant sex.[16] Data on ethnicity in the study was collected consistent with the information on ethnicity required for calculation of customised birthweight centile. In contrast to previous centile calculators, which adjusted birthweight only for maternal body mass index (BMI) within the limits of 20–30, BMI limits were removed from this calculator consistent with recent recommendations by Gardosi.[17] Population birthweight centiles were calculated, correcting for gestational age and fetal sex from the study cohort of low risk primigravidae. LGA by customised or population centiles was defined as birthweight above the 90th centile and appropriate for gestational age (AGA) as birthweight between the 10th and the 90th centile. In the comparison between customised birthweight centiles and absolute birthweight, infants were

classified into one of the following four categories: (i) AGA by customised centiles with birthweight ≤4000 g (AGA_{cust} not $Macro_{4000}$), (ii) AGA by customised centiles with birthweight >4000 g (AGA_{cust} but $Macro_{4000}$), (iii) LGA by customised centiles with birthweight ≤4000 g (LGA_{cust} not $Macro_{4000}$), and (iv) LGA by customised centiles with birthweight >4000 g (LGA_{cust} and $Macro_{4000}$). Similarly in the comparison between customised birthweight centiles and population birthweight centiles, infants were classified into one of the following categories: (i) AGA by both customised and population centiles (AGA_{cust} and AGA_{pop}), (ii) AGA by customised centiles but LGA by population centiles (AGA_{cust} but LGA_{pop}), (iii) LGA by customised centiles but AGA by population centiles (LGA_{cust} but AGA_{pop}), and (iv) LGA by both customised and population centiles (LGA_{cust} and LGA_{pop}).

The primary maternal outcomes were caesarean delivery and major PPH defined as estimated blood loss greater than 1000 ml. Caesarean delivery was further subclassified into two groups; pre-labour caesarean section (defined as caesarean section before the onset of labour) and intrapartum caesarean section (defined as caesarean section during labour). The primary neonatal outcome was a composite of severe neonatal morbidity or mortality defined as one or more of the following: stillbirth, neonatal death or severe neonatal morbidity, which includes one or more of the following: grade II or III hypoxic ischaemic encephalopathy, Apgar score of less than 4 at 5 min, cord arterial pH < 7.0 and or base excess less than −15, neonatal seizures, neonatal ventilation for longer than 24 h or admission to the neonatal unit for longer than 4 days. Secondary neonatal outcome was any admission to the neonatal intensive care unit.

Observed continuous variables were summarised by the median and interquartile range, and comparisons between birthweight groups were made by the Kruskal–Wallis test. Univariable comparisons of dichotomous data were made using the Chi-square test. Data were available for more than 98% of the participants for all variables included in the study.[14] Missing data were imputed for multivariable analyses using expected maximisation,[18] or for variables unrelated to other data points that had <1% missing data, single imputation was performed using the median (continuous variables) or mode (binary/categorical variables). Logistic regression analysis was used to estimate the odds of adverse maternal and neonatal outcome for each birthweight category. The referent category for the comparison between customised birthweight centiles and absolute birthweight was AGA infants by customised centiles with birthweight equal or less than 4000 g and for the comparison between customised and population birthweight centiles the referent category was AGA infants by both population and customised centiles. Multivariable analysis was performed adjusting for known risk factors for each outcome. For all caesarean section and pre-labour caesarean section adjustments were made for maternal age, height, BMI, socio-economic index, ethnicity, smoking, assisted reproduction, gestational hypertension, preeclampsia, gestational diabetes, history of antepartum haemorrhage and maternity care provider. Additional variables in the model for intrapartum caesarean section were induction of labour and gestational age at delivery. Adjustment for risk factors for major postpartum haemorrhage included maternal age, BMI, socio-economic index, ethnicity, preeclampsia, history of antepartum haemorrhage, induction of labour, gestational age and mode of delivery. Because of the low rate of adverse neonatal outcomes in each birthweight category, univariable comparison of events by birthweight category was performed using Fisher's exact test and multivariable analysis was only performed using combined primary and secondary neonatal outcomes. This model was adjusted for maternal age, height, BMI, socio-economic index, ethnicity, smoking, gestational hypertension, preeclampsia, gestational diabetes, history of antepartum haemorrhage, induction of labour, gestational age at delivery and mode of delivery. All women in the study provided written informed consent; ethical approval in New Zealand was gained from the Northern Region Ethics Committee and in Australia approval was granted by Central Northern Adelaide Health Service Ethics of Human Research Committee.

Results

Of the 3426 primigravidae who agreed to participate in the study, 3234 women were recruited and follow-up was complete in 3196 women (99%) (Figure 1). After exclusion of late miscarriages and terminations, preterm births and SGA infants, the final study cohort consisted of 2668 primigravidae with singleton births between 37^{+0} and 43^{+0} completed weeks of gestation.

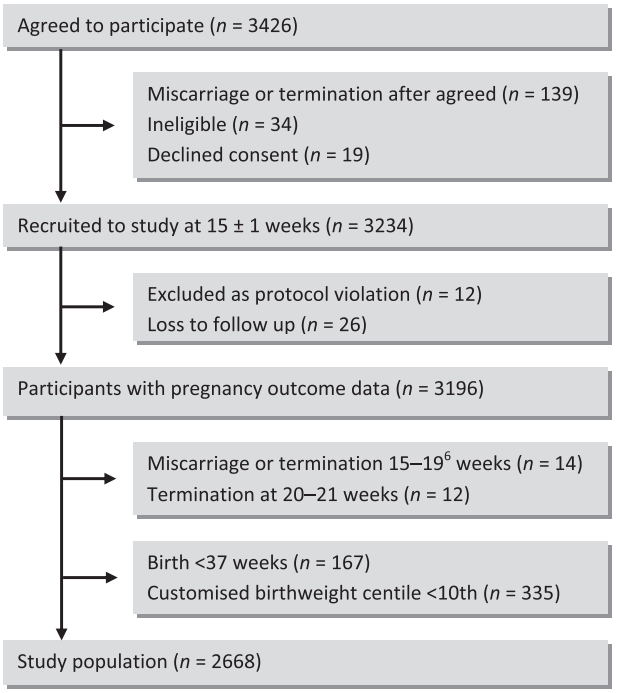

Figure 1. Study profile.

The prevalence of LGA_{cust} was 10.3% (274 of 2668). The mothers of these LGA infants were less likely to be European, to continue smoking in pregnancy and were more likely to develop gestational diabetes and deliver by caesarean compared with appropriately grown infants by customised standards (Table 1). Among LGA_{cust} infants, 187 (68.3%) were $Macro_{4000}$ and 222 (81.0%) were LGA_{pop} (Figure 2). Of the 394 (14.8%) $Macro_{4000}$ infants, 207 (52.5%) were AGA_{cust}. Among the 298 (11.2%) LGA_{pop} infants, 76 (25.5%) were AGA_{cust} and of the 2394 AGA_{cust} infants, 207 (8.7%) were also $Macro_{4000}$ and 76 (3.2%) were LGA_{pop} (Table 1).

The overall rate of caesarean delivery in the study cohort was 30.3% ($n = 809$). Caesarean was performed before the onset of labour in 7.1% and during labour in 23.2% women. In the adjusted comparison between customised centiles and absolute birthweight and with reference to mothers of AGA infants with birthweight equal or less than 4000 g (AGA_{cust} not $Macro_{4000}$), the overall rate of caesarean delivery was 1.6-fold in mothers of AGA_{cust} but $Macro_{4000}$ infants, 2-fold in mothers of LGA_{cust} not $Macro_{4000}$ infants and 3-fold in mothers of LGA_{cust} and $Macro_{4000}$ infants (Table 2a). After exclusion of cases of pre-labour caesarean performed because of suspected fetal distress, the increased rate of pre-labour caesarean persisted in both LGA_{cust} groups (Table 2a). Similar associations were also seen in the comparison between customised and population birthweight centiles (Table 2b). In both comparisons, the risk of pre-labour caesarean was not increased in $Macro_{4000}$ or LGA_{pop} infants who were AGA by customised centiles (Table 2a–b).

Major PPH occurred in 4.8% pregnancies. Women with AGA_{cust} but $Macro_{4000}/LGA_{pop}$ infants were not at increased risk of major PPH (Table 2a–b). After adjustment for confounders including mode of delivery, major PPH was more common in both LGA customised groups independent of absolute birthweight (Table 2a). In contrast, in the comparison between customised and population centiles, major PPH was increased only in LGA_{cust} and LGA_{pop} group (Table 2b), and remained significant after adjusting for confounders ($n = 25$, 11.5%).

Overall, 6.7% of infants delivered at term were admitted to a neonatal unit, 1.6% had severe neonatal morbidity or mortality with 6.8% experiencing either adverse outcome. The risk of severe neonatal morbidity/mortality was increased approximately fourfold in infants classified as LGA_{cust} independent of absolute birthweight or LGA_{pop} classification

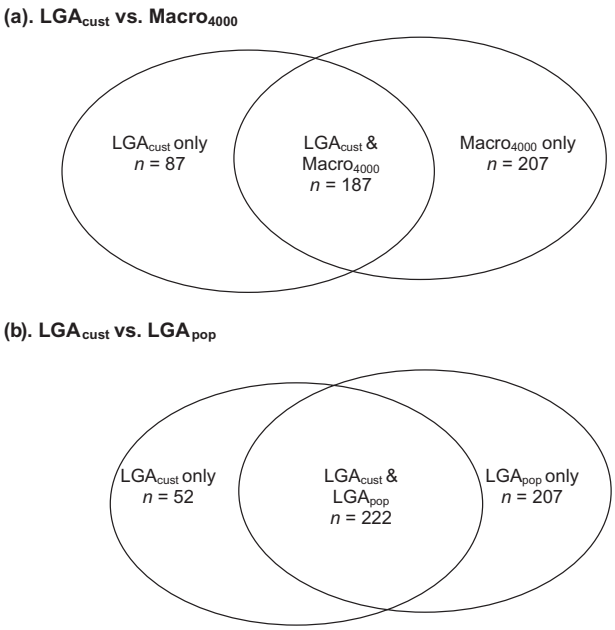

Figure 2. Classification of large for gestational age (LGA) by customised centiles (LGA_{cust}) vs. conventional measures of high birthweight. (a) LGA_{cust} vs. infants with birthweight greater than 4000 g ($Macro_{4000}$). (b) LGA_{cust} vs. LGA by population centile (LGA_{pop}).

Table 1. Maternal characteristics and pregnancy outcomes by appropriate (AGA_{cust}) and large (LGA_{cust}) for gestational age customised status

	AGA_{cust} ($n = 2394$; 89.7%)	LGA_{cust} ($n = 274$; 10.3%)	*P* value[b]
Maternal characteristics[a]			
Age (years)	29 (24–32)	28 (24–32)	0.94
Ethnicity			
European ($n = 2317$)	2091 (87.3)	226 (82.5)	0.02
Asian ($n = 127$)	114 (4.8)	13 (4.7)	0.99
Maori/Pacific Islanders ($n = 96$)	83 (3.5)	13 (4.7)	0.28
Other ($n = 128$)	106 (4.4)	22 (8.0)	0.01
Socio-economic index	45 (26–50)	45 (27–50)	0.88
Maternal weight (kg)	67 (60–77)	67 (60–76)	0.84
Maternal height (cm)	165 (161–169)	165 (160–169)	0.28
BMI	24.4 (21.9–27.8)	24.7 (22.3–28.0)	0.20
Smoking in pregnancy[c]	268 (11.2)	19 (6.9)	0.03
Antepartum haemorrhage	136 (5.7)	16 (5.8)	0.91
End of pregnancy[a]			
Gestational diabetes[d] ($n = 67$)	54 (2.3)	13 (4.7)	0.03
Gestational hypertension ($n = 183$)	165 (7.0)	18 (6.6)	0.84
Preeclampsia ($n = 115$)	99 (4.1)	16 (5.8)	0.18
Induction of labour ($n = 730$)	656 (27.4)	74 (27.0)	0.89
Gestational age at delivery (weeks)	40.0 (39.0–41.0)	39.5 (38.5–41.0)	<0.001
Mode of delivery			
Spontaneous vaginal delivery ($n = 1296$)	1,209 (50.5)	87 (31.8)	<0.001
Assisted vaginal delivery ($n = 563$)	515 (21.5)	48 (17.5)	0.13
Caesarean delivery ($n = 809$)	670 (28.0)	139 (50.7)	<0.001
Infant characteristics[a]			
Birthweight (g)	3480 (3230–3740)	4170 (3910–4435)	<0.001
Birthweight >4 kg ($n = 394$)	207 (8.7)	187 (68.3)	<0.001
Birthweight >90th population centile ($n = 298$)	76 (3.2)	222 (81.0)	<0.001

[a]Results are reported as median Inter Quartile Range (IQR) or number (%) as appropriate.
[b]Univariate comparison using Chi-squared, Fisher's exact or Kruskal–Wallis test as appropriate.
[c]Smoking at both 15- and 20-week visit.
[d]A total of 157 (5.9%) records with unknown status for gestational diabetes. There is no statistical difference in unknown status for gestational diabetes by birthweight categories ($P = 0.3$).
AGA, appropriate for gestational age; BMI, body mass index; LGA, large for gestational age.

(Table 3a–b). The risk of admission to neonatal intensive care was only increased in infants who were both LGA_{cust} and $Macro_{4000}$ or also LGA_{pop}. This was also the only group of infants who were at increased risk of the combined end-point of severe neonatal outcome or NICU admission. Neither of the adverse neonatal outcomes was increased in infants AGA_{cust} regardless of whether they were $Macro_{4000}$ or LGA_{pop} and these associations persisted following multivariable analysis (Table 3a–b).

Comment

In a large prospective cohort of low-risk primigravidae, we found that term infants who were LGA by a customised standard had a fourfold increase in risk of severe neonatal morbidity/mortality compared with appropriately grown infants defined by similar standards. Importantly, this increased risk of neonatal complications was not observed among appropriately grown infants by customised standards with birthweight greater than 4000 g or LGA by population standards. Furthermore the subgroups of LGA infants by customised standards with birthweight greater than 4000 g who were also LGA by population standards were at increased risk of admission to neonatal care. Thus the use of customised centiles defines a subpopulation of at-risk high-birthweight term infants that might otherwise remain unrecognised. Importantly these data have also shown that adverse

Table 2a. Comparison of maternal outcomes between infants classified by customised centiles and absolute birthweight

Maternal outcomes	AGA_{cust} not $Macro_{4000}$[a] (*n* = 2187, 82.0%)	AGA_{cust} but $Macro_{4000}$ (*n* = 207, 7.8%)	LGA_{cust} not $Macro_{4000}$ (*n* = 87, 3.2%)	LGA_{cust} and $Macro_{4000}$ (*n* = 187, 7.0%)	*P* value[b]
Caesarean delivery					
No. (%)					
All	603 (27.6)	67 (32.4)	39 (44.8)	100 (53.5)	<0.001
Pre-labour	144 (6.5)	9 (4.3)	13 (14.9)	24 (12.8)	<0.001
Intrapartum	459 (20.1)	58 (28.0)	26 (29.9)	76 (40.6)	<0.001
Unadjusted OR [95% CI]					
All	Reference	1.3 [0.9–1.7]	2.1 [1.4–3.3]	3.0 [2.2–4.1]	
Pre-labour	Reference	0.6 [0.3–1.3]	2.5 [1.3–4.6]	2.1 [1.3–3.3]	
Intrapartum	Reference	1.4 [1.0–2.0]	1.9 [1.0–3.0]	3.0 [2.2–4.2]	
Adjusted OR [95% CI]					
All	Reference	1.6 [1.1–2.2]	2.1 [1.3–3.3]	3.4 [2.4–4.7]	
Pre-labour	Reference	0.7 [0.3–1.5]	2.7 [1.4–5.3][d]	2.0 [1.2–3.3][d]	
Intrapartum[c]	Reference	1.4 [0.9–2.0]	2.2 [1.3–3.8]	3.4 [2.4–4.9]	
Postpartum haemorrhage					
No. (%)	88 (4.1)	14 (6.9)	8 (9.2)	19 (10.4)	<0.001
Unadjusted OR [95% CI]	Reference	1.7 [1.0–3.1]	2.4 [1.1–5.1]	2.7 [1.6–4.6]	
Adjusted OR [95% CI]	Reference	1.2 [0.7–2.3]	2.7 [1.2–6.2]	2.0 [1.2–3.4]	

[a]Referent category.
[b]Univariable comparison of primary and secondary outcomes by birthweight categories using Chi-squared.
[c]Also adjusted for induction of labour and gestational age.
[d]After exclusion of cases of pre-labour caesarean delivery performed because of suspected fetal distress the increased rate of pre-labour caesarean delivery persisted in LGA_{cust} not $Macro_{4000}$ infants (adjusted OR 3.2 [95% CI 1.6–6.2]) and also in LGA_{cust} and $Macro_{4000}$ (adjusted OR 2.1 [95% CI 1.3–3.5]).
AGA, appropriate for gestational age; CI, confidence interval; LGA, large for gestational age; No., number; OR, odds ratio.

birth outcomes are not increased in those infants who are defined as high birthweight by conventional measures, but appropriately grown by customised standards.

We recommend that the definition of LGA by customised centiles should be considered for adoption in clinical practice; this conclusion is also strengthened by the observation that the mothers of LGA infants by customised standards, regardless of absolute infant birthweight, had a higher rate of both pre-labour and intrapartum caesarean section and twice the rate of major PPH.

Furthermore, although mothers of infants with birthweight greater than 4000 g who were appropriately grown by customised standards had a 1.6-fold increase in the overall rate of caesarean, this was not accompanied by an increase in pre-labour caesarean or postpartum haemorrhage. Given the sample size, it is likely the 40% increase in intrapartum caesarean delivery in this group did not reach statistical significance because of insufficient power. We noted a similar observation in the comparison between customised and population birthweight centiles in relation to maternal morbidity; however, in contrast the twofold increased risk of postpartum haemorrhage was confined only to mothers of infants who were LGA by both customised and population standards.

Obesity is rising among pregnant women in most developed countries, as is the mean birthweight and the incidence of fetal macrosomia and LGA.[19–21] It is therefore important to better understand which pregnancies with 'larger' infants are at greatest risk of important morbidity.[9,22,23] Previous definitions of fetal macrosomia and LGA have not distinguished 'macrosomic' infants who may be appropriately grown for maternal constitution from infants who have exceeded their growth potential.[7,24] Some LGA infants by customised centiles will be classified as appropriately grown based on absolute birthweight or population centiles. Using customised centiles, in our cohort of term infants approximately 4% of infants with birthweight equal or less than 4000 g and 2% of appropriately grown infants by population standards were LGA by customised standards, a group that would not be detected by traditional measures of high birthweight. Conversely, 53% of infants with birthweight

Table 2b. Comparison of maternal outcomes between infants classified by customised and population centiles

Maternal outcomes	AGA_{cust} and AGA_{pop}[a] (n = 2318, 86.9%)	AGA_{cust} but LGA_{pop} (n = 76, 2.9%)	LGA_{cust} but AGA_{pop} (n = 52, 2.0%)	LGA_{cust} and LGA_{pop} (n = 222, 8.3%)	P value[b]
Caesarean delivery					
No. (%)					
All	644 (27.8)	26 (34.2)	25 (48.1)	114 (51.4)	<0.001
Pre-labour	147 (6.3)	6 (7.9)	7 (13.5)	30 (13.5)	<0.001
Intrapartum	497 (21.4)	20 (26.3)	18 (34.6)	84 (37.8)	<0.001
Unadjusted OR [95% CI]					
All	Reference	1.4 [0.8–2.2]	2.4 [1.4–4.2]	2.7 [2.1–3.6]	
Pre-labour	Reference	1.3 [0.5–3.0]	2.3 [1.0–5.2]	2.3 [1.5–3.5]	
Intrapartum	Reference	1.3 [0.8–2.3]	2.2 [1.2–4.1]	2.6 [1.9–3.5]	
Adjusted OR [95% CI]					
All	Reference	1.5 [0.9–2.6]	2.4 [1.3–4.4]	2.9 [2.2–4.0]	
Pre-labour	Reference	1.3 [0.5–3.2]	2.5 [1.0–6.2][d]	2.2 [1.4–3.5][d]	
Intrapartum[c]	Reference	1.6 [0.9–2.9]	2.2 [1.1–4.2]	3.2 [2.3–4.5]	
Postpartum haemorrhage					
No. (%)	98 (4.3)	4 (5.4)	2 (3.9)	25 (11.5)	<0.001
Unadjusted OR [95% CI][e]	Reference	1.3 [0.5–3.6]	0.9 [0.2–3.7]	2.9 [1.8–4.6]	

[a]Referent category.
[b]Univariate comparison of primary and secondary outcomes by birthweight categories using Chi-squared.
[c]Also adjusted for induction of labour and gestational age.
[d]After exclusion of cases of pre-labour caesarean section performed because of suspected fetal distress the increased rate of pre-labour caesarean section persisted in LGA_{cust} but AGA_{pop} infants (OR 2.9 [95% CI 1.2–7.2]) and also in LGA_{cust} and LGA_{popn} infants (OR 2.4 [95% CI 1.5–3.8]).
[e]Multivariable was analysis was not performed because of the small number of events in some categories.
AGA, appropriate for gestational age; CI, confidence interval; LGA, large for gestational age; No., number; OR, odds ratio.

greater than 4000 g and 25% of LGA infants by population standards born at term were appropriately grown by customised centiles. Apart from a slightly higher rate of caesarean section, this group of pregnancies were not at increased risk of other maternal and neonatal complications. Clinical algorithms focused on antenatal detection of LGA infants by ultrasound and induction of labour to reduce morbidity associated with labour have not been found to be cost-effective.[25,26] We propose that implementation and evaluation of customised fetal growth charts in cases of suspected fetal macrosomia may improve the detection of infants who have truly exceeded their growth potential, which could be advantageous for clinical management.[27] The adverse outcomes in LGA infants by customised standards may be a consequence of excessive overall growth relative to maternal constitution or a result of altered body composition, possibly because of an increase in infant adiposity. Specific measures of neonatal adiposity were not available in the Australasian SCOPE cohort reported here, but will be available for future assessment in the recently recruited SCOPE cohort in Ireland.

Our findings are consistent with those from a single study in a North American cohort, which also concluded that a customised standard of LGA identifies a previously unrecognised high risk population of large infants.[28] Larkin and colleagues[28] compared outcomes between macrosomia defined as birthweight greater than 4000 or 4500 g and LGA defined as birthweight greater than the 90th population or customised centile. Neonates identified as LGA by customised standards who were not macrosomic by absolute birthweight or LGA by population standards were at increased risk of shoulder dystocia. Mothers of these infants were at increased risk of third or fourth degree perineal laceration and caesarean delivery for cephalopelvic disproportion. The rate of these adverse outcomes was also increased in infants with birthweight greater than 4000 g and LGA by population standards, with the risk being a similar order of magnitude in these two groups. Other more common complications associated with macrosomia such as caesarean section, postpartum haemorrhage and severe neonatal morbidity were not reported in this retrospective study. In contrast to that study we did

Table 3a. Comparison of neonatal outcomes between infants classified by customised centiles and absolute birthweight

Infant characteristics	Birthweight categories				
	AGA_{cust} not $Macro_{4000}$[a] (n = 2187, 82.0%)	AGA_{cust} but $Macro_{4000}$ (n = 207, 7.8%)	LGA_{cust} not $Macro_{4000}$ (n = 87, 3.2%)	LGA_{cust} and $Macro_{4000}$ (n = 187, 7.0%)	P value[b]
Gestational age (weeks)	40 (39–40)	41 (40–41)	38 (37–39)	40 (39–41)	<0.001
Birthweight (g)	3440 (3200–3660)	4110 (4055–4200)	3810 (3690–3905)	4350 (4160–4520)	
Customised birthweight centile	45 (27–64)	80 (71–85)	94 (92–98)	96 (94–98)	
Neonatal outcomes					
Severe neonatal outcome					
No. (%)	29 (1.3)	1 (0.5)	5 (5.8)	9 (4.8)	<0.001
Unadjusted OR [95% CI]	Reference	0.4 [0.1–2.7]	4.5 [1.7–12.0]	3.8 [1.8–8.0]	
NICU admission					
No. (%)	140 (6.4)	8 (3.9)	9 (10.3)	21 (11.2)	0.01
Unadjusted OR [95% CI]	Reference	0.6 [0.3–1.2]	1.7 [0.8–3.4]	1.8 [1.1–3.0]	
Combined neonatal outcome[c]					
No. (%)	141 (6.5)	8 (3.9)	9 (10.3)	23 (12.3)	0.003
Unadjusted OR [95% CI]	Reference	0.6 [0.3–1.2]	1.7 [0.8–3.4]	2.0 [1.3–3.3]	
Adjusted OR [95% CI]	Reference	0.6 [0.3–1.3]	1.1 [0.5–2.5]	1.9 [1.2–3.2]	

[a]Referent category.
[b]Univariate comparison of primary and secondary outcomes by birthweight categories using Chi-squared or Fisher's exact test as appropriate.
[c]Either severe neonatal outcome or admission to NICU.
AGA, appropriate for gestational age; CI, confidence interval; LGA, large for gestational age; NICU, neonatal intensive care; No., number; OR, odds ratio.

not find an increased risk of maternal or neonatal morbidity in pregnancies of infants with birthweight greater than 4000 g or LGA by population centiles but appropriately grown by customised standards. In addition the authors focused on maternal morbidity (caesarean section and third and fourth degree tears) and detailed neonatal outcomes other than rates of shoulder dystocia were not reported.[28]

The strengths of our study include the large prospective design of the cohort with detailed maternal and neonatal outcome data available for 99% of participants. As the SCOPE study's primary aim is prediction of preeclampsia, SGA and preterm birth, data on perineal trauma and shoulder dystocia and detailed indications for caesarean delivery (other than prelabour caesarean performed for fetal distress) were not collected on all participants. We consider it likely that in mothers of LGA infants by customised standards the higher rate of pre-labour caesarean relates to the obstetric decision to avoid labour following clinical examination or ultrasound assessment of fetal size, but this cannot be corroborated further with available data. It is also probable that the higher rate of intrapartum caesarean is secondary to failure to progress or fetal distress. A weakness of the study is the limited generalisability of our findings to high risk and/or mixed parity populations, as the study was conducted in a population of low-risk primigravidae.

In conclusion, in our study adverse pregnancy outcomes were strongly associated with LGA as determined by customised centiles. Similar analyses in different cohorts are required for confirmation, and to elucidate mechanisms underlying the associated maternal and neonatal morbidities observed. If confirmed, a birthweight greater than the 90th customised centile may be a better indicator of morbidity associated with 'macrosomia' rather than absolute birthweight *per se*.

Acknowledgements

We thank the pregnant women who participated in the SCOPE study, Claire Roberts for her contributions in establishing the SCOPE study in Adelaide, Denise Healy for co-ordinating the Australian SCOPE study, Rennae Taylor for co-ordinating the Auckland SCOPE study, Eliza Chan for data management and extraction and Paul Seed for statistical advice. The SCOPE study

Table 3b. Comparison of neonatal outcomes between infants classified by customised and population centiles

Infant characteristics	Birthweight categories				
	AGA_{cust} and AGA_{pop}[a] (n = 2318, 86.9%)	AGA_{cust} but LGA_{pop} (n = 76, 2.9%)	LGA_{cust} but AGA_{pop} (n = 52, 2.0%)	LGA_{cust} and LGA_{pop} (n = 222, 8.3%)	P value[b]
Gestational age (weeks)	40 (39–41)	40 (39–41)	40 (39–41)	40 (39–41)	<0.001
Birthweight (g)	3465 (3220–3710)	4110 (3945–4215)	3835 (3580–4075)	4250 (4020–4475)	<0.001
Customised birthweight centile	47 (28–66)	85 (82–88)	92 (91–94)	97 (94–99)	
Neonatal outcomes					
Severe neonatal outcome					
No. (%)	29 (1.3)	1 (1.3)	3 (5.8)	11 (5.0)	<0.001
Unadjusted OR [95% CI]	Reference	1.1 [0.1–7.8]	4.8 [1.4–16.4]	4.1 [2.0–8.4]	
NICU admission					
No. (%)	144 (6.2)	4 (5.3)	4 (7.7)	25 (11.7)	0.01
Unadjusted OR [95% CI]	Reference	0.8 [0.3–2.3]	1.3 [0.4–3.5]	2.0 [1.3–3.1]	
Combined neonatal outcome[c]					
No. (%)	145 (6.3)	4 (5.3)	4 (7.7)	28 (12.6)	0.004
Unadjusted OR [95% CI]	Reference	0.8 [0.3–2.3]	1.2 [0.4–3.5]	2.2 [1.4–3.3]	
Adjusted OR [95% CI]	Reference	0.5 [0.2–1.6]	1.0 [0.3–3.1]	1.8 [1.1–2.9]	

[a]Referent category.
[b]Univariate comparison of primary and secondary outcomes by birthweight categories using Chi-squared or Fisher's exact test as appropriate.
[c]Either severe neonatal outcome or admission to NICU.
AGA, appropriate for gestational age; CI, confidence interval; LGA, large for gestational age; NICU, neonatal intensive care; No., number; OR, odds ratio.

was supported by the New Enterprise Research Fund, Foundation for Research Science and Technology; Health Research Council (04/198); Evelyn Bond Fund, Auckland District Health Board Charitable Trust in New Zealand and Premier's Science and Research Fund, the South Australian Government in Australia. D. P. was funded by Tommy's Baby Charity and the National Institute of Health Research, UK.

The study sponsors had no role in study design, data analysis or writing this report. R. A. N. has consultancy relationships with Pronota and with Alere; L. C. K. declares a US patent PCT/EP2010/070446, R. A. N. declares patent PCT number WO/2009/108073 and L. P. declares patent PCT number GB01/04892. The authors report no conflict of interest.

References

1 Boulet SL, Alexander GR, Salihu HM, Pass M. Macrosomic births in the united states: determinants, outcomes, and proposed grades of risk. *American Journal of Obstetrics and Gynecology* 2003; 188:1372–1378.
2 Esakoff TF, Cheng YW, Sparks TN, Caughey AB. The association between birthweight 4000g or greater and perinatal outcomes in patients with and without gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology* 2009; 200:672.e1–672.e4.
3 Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S. Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2003; 111:9–14.
4 Mulik V, Kiran TS, Bethal J, Bhal PS. The outcome of macrosomic fetuses in a low risk primigravid population. *International Journal of Gynecology and Obstetrics* 2003; 80:15–22.
5 Oral E, Cagdas A, Gezer A, Kaleli S, Aydinli K, Ocer F. Perinatal and maternal outcomes of fetal macrosomia. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2001; 99:167–171.
6 Raio L, Ghezzi F, Naro ED, Buttarelli M, Franchi M, Dürig P, *et al*. Perinatal outcome of fetuses with a birth weight greater than 4500 g: an analysis of 3356 cases. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2003; 109:160–165.
7 Boulet SL, Salihu HM, Alexander GR. Mode of delivery and birth outcomes of macrosomic infants. *Journal of Obstetrics and Gynaecology* 2004; 24:622–629.
8 Mocanu EV, Greene RA, Byrne BM, Turner MJ. Obstetric and neonatal outcome of babies weighing more than 4.5 kg: an analysis by parity. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2000; 92:229–233.

9 Heiskanen N, Raatikainen K, Heinonen S. Fetal macrosomia – a continuing obstetric challenge. *Biology of the Neonate* 2006; 90:98–103.
10 Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. *Ultrasound in Obstetrics and Gynecology* 1995; 6:168–174.
11 Clausson B, Gardosi J, Francis A, Cnattingius S. Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. *British Journal of Obstetrics and Gynaecology* 2001; 108:830–834.
12 McCowan LME, Harding JE, Stewart AW. Customised birthweight centiles predict SGA pregnancies with perinatal morbidity. *British Journal of Obstetrics and Gynaecology* 2005; 112:1026–1033.
13 Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. *Lancet* 1992; 339:283–287.
14 McCowan LME, Roberts CT, Dekker GA, Taylor RS, Chan EHY, Kenny LC, *et al*. Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study. *British Journal of Obstetrics and Gynaecology* 2010; 117:1599–1607.
15 North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, *et al*. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *British Medical Journal* 2011; 342:d1875. doi: 10.1136/bmj.d1875
16 McCowan L, Stewart AW, Francis A, Gardosi J. A customised birthweight centile calculator developed for a New Zealand population. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2004; 44:428–431.
17 Gardosi J, Clausson B, Francis A. The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. *British Journal of Obstetrics and Gynaecology* 2009; 116:1356–1363.
18 Molenberghs G, Kenward MG. *Missing Data in Clinical Studies*. Chichester, UK: John Wiley & Sons Ltd, 2007.
19 Ananth CV, Wen SW. Trends in fetal growth among singleton gestations in the United States and Canada, 1985 through 1998. *Seminars in Perinatology* 2002; 26:260–267.
20 LaCoursiere DY, Bloebaum L, Duncan JD, Varner MW. Population-based trends and correlates of maternal overweight and obesity, Utah 1991–2001. *American Journal of Obstetrics and Gynecology* 2005; 192:832–839.
21 Surkan PJ, Hsieh CC, Johansson AL, Dickman PW, Cnattingius S. Reasons for increasing trends in large for gestational age births. *Obstetrics and Gynecology* 2004; 104:720–726.
22 Asplund CA, Seehusen DA, Callahan TL, Olsen C. Percentage change in antenatal body mass index as a predictor of neonatal macrosomia. *Annals of Family Medicine* 2008; 6:550–554.
23 Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. *Diabetes Care* 2009; 32:1639–1643.
24 Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *American Journal of Obstetrics and Gynecology* 2008; 198:517.e1–517.e6.
25 Sanchez-Ramos L, Bernstein S, Kaunitz AM. Expectant management versus labor induction for suspected fetal macrosomia: a systematic review. *Obstetrics and Gynecology* 2002; 100:997–1002.
26 Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. *JAMA* 1996; 276:1480–1486.
27 Boulvain M, Senat M-V, Rozenberg P, Irion O. Induction of labor or expectant management for large-for-dates fetuses; a randomised controlled trial. *American Journal of Obstetrics and Gynecology* 2012; 206:S2.
28 Larkin JC, Speer PD, Simhan HN. A customized standard of large for gestational age to predict intrapartum morbidity. *American Journal of Obstetrics and Gynecology* 2011; 204:499.e1–499.e10.