Birthweight Extremes and Neonatal and Childhood Outcomes after Preterm Premature Rupture of Membranes

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Abstract

Objective   To determine the association between birthweight extremes and risk of adverse neonatal and childhood outcomes following preterm premature rupture of membranes (PPROM).

Study Design   This is a secondary analysis of data from the Beneficial Effects of Antenatal Magnesium Sulfate Trial. Women with nonanomalous singletons and PPROM delivering ≥24.0 weeks were included. Birthweight was classified as small for gestational age (SGA), appropriate for gestational age (AGA), or large for gestational age (LGA). Composite severe neonatal morbidity and childhood outcomes at age 2, were compared between these groups.

Results   One thousand five hundred and ninety-eight infants were included (58 SGA, 1,354 AGA, and 186 LGA). There was an inverse relationship between birthweight and rate of composite major neonatal morbidity (55.2% of SGA, 31.5% of AGA, 18.3% of LGA, $p < 0.001$). Former-SGA children were more likely to be diagnosed with major composite childhood morbidity at age 2 (25.9% of SGA, 8.3% of AGA, 5.9% of LGA, $p < 0.001$). In multivariate models, LGA infants had improved initial neonatal outcomes compared with AGA infants (adjusted odds ratio [aOR], 0.44; 95% confidence interval [CI], 0.28–0.71; $p = 0.001$).

Conclusion   Among infants delivered following PPROM, those who were LGA at delivery had improved composite adverse neonatal outcomes. SGA increases the risk of severe neonatal morbidity, early childhood death, and moderate/severe cerebral palsy at age 2.

Keywords
► small for gestational age
► large for gestational age
► preterm premature rupture of membranes
► neonatal morbidity
► childhood morbidity

Preterm premature rupture of membranes (PPROM) is the leading identifiable cause of preterm birth and affects 3% of all pregnancies.[1] Following PPROM, women are at high risk of additional pregnancy complications including preterm labor, placental abruption, and chorioamnionitis.[2,3] Women with PPROM between 23 and 34 weeks of gestation and without evidence of other immediate complications are typically administered a course of antenatal corticosteroids, intravenous magnesium sulfate for neuroprotection (up to 32 wk), and latency antibiotics, and are hospitalized until delivery.[4–6]

Premature infants, including those born after PPROM, are at risk of both short-term and long-term morbidity and death. Long-term complications of prematurity persist into childhood and beyond, and may include neurodevelopmental

disabilities, failure-to-thrive, vision and hearing impairment, and cerebral palsy (CP).[7,8] Although gestational age at birth is typically regarded as the most important factor influencing the risk of both short- and long-term morbidity, other risk factors are known to affect outcomes, including birthweight, gender, and medication exposure (e.g., antenatal corticosteroids, magnesium sulfate) prior to delivery.[8,9] Birthweight estimates are often used along with gestational age to counsel families regarding infant outcome following preterm delivery and in decisions regarding antenatal testing and intervention, mode of delivery, and postnatal intervention.[10,11] The correlation between ultrasound (US)-based estimates of fetal weight in the setting of PPROM and postnatal birthweight is understudied, and is likely hindered by the high incidence of oligohydramnios and anhydramnios in this population.

The extent to which extremes of birthweight (e.g., being large for gestational age [LGA] or small for gestational age [SGA] compared with birthweight that is appropriate for gestational age [AGA]) affect postnatal outcomes among infants born after PPROM is unknown. We sought to determine the relationship between birthweight extremes (LGA, SGA) and major neonatal and childhood morbidity. We hypothesized that compared with AGA infants delivered after PPROM, LGA infants have lower prevalence of adverse neonatal and childhood outcomes and that SGA infants have higher incidence of adverse neonatal and childhood outcomes.

Materials and Methods

This is a secondary analysis of a multicenter, randomized clinical trial of antenatal magnesium sulfate versus placebo administered to women at imminent risk for early preterm birth (<32 wk) to prevent death and CP in their offspring. The inclusion criteria and randomization protocol for the original trial have been previously reported.[12] Briefly, the original study recruited women from 1997 to 2004 at 20 centers, who were at high risk of preterm delivery between 24 to 31 weeks' gestation for any indication. The majority of enrolled women had pregnancies complicated by PPROM. Per the original protocol, study staff evaluated surviving infants at 6, 12, and 24 months corrected gestational age. Written, informed consent was obtained at the time of the original study from each participant. This secondary analysis used a de-identified dataset, and after review by our Institutional Review Board (IRB) at the University of North Carolina, was considered exempt from IRB oversight.

For the purposes of this secondary analysis, we included women with singleton, nonanomalous gestations with a diagnosis of PPROM who delivered at 24 weeks 0 days through 34 weeks and 6 weeks. Gestational age was determined from standard algorithms using last menstrual period and US criteria.[13] Neonatal birthweight was classified as AGA (10–90 percentile), LGA (≥90 percentile), or SGA (<10 percentile) based upon gender- and gestational age-specific contemporary national norms.[14] The primary neonatal outcome was a composite of severe neonatal morbidity, defined as one or more of the following; neonatal sepsis, grade III or IV intraventricular hemorrhage, periventricular leukomalacia, severe

(stage II or III) necrotizing enterocolitis, bronchopulmonary dysplasia (BPD), and/or death during the initial hospitalization. The primary childhood outcome was a composite of stillbirth or infant death by 1 year of age, or moderate or severe CP, as assessed at the final follow-up visit, prespecified to occur at 2 years of age. Secondary outcomes included individual components of each of the two primary composite outcomes and Bayley Scales of Infant Development II Mental Development Index (MDI) and/or Psychomotor Development Index (PDI) greater than 2 standard deviation (SD) below the mean at age 2. We also compared weight at the time of childhood follow-up assessments to determine whether formerly-SGA infants remained smaller than their formerly-AGA and formerly-LGA counterparts in early childhood.

Bivariate analyses were by chi-square or Fisher's exact for categorical variables, analysis of variance or Kruskal–Wallis equality of proportions rank test when there were greater than two categories. The Wilcoxon-type test for trend as described by Cuzick was utilized to assess trend across ordered groups.[15] Multivariable analysis was performed using stepwise backward elimination logistic regression, and factors with $p < 0.20$ remained in final models. All data were analyzed using STATA version 13.1 (College Station, TX). In the final bivariate and multivariable analyses a p-value of < 0.05 was considered significant.

Results

From the original cohort of 2,241 women, 1,598 women and their infants met inclusion criteria (►**Fig. 1**). Of these, 58 (3.6%) were SGA, 1,354 (84.7%) were AGA, and 186 (11.6%) were LGA. Demographic characteristics are compared by birthweight group in ►**Table 1**. Groups were different with regard to likelihood of diabetes mellitus diagnosis and prepregnancy body mass index (►**Table 1**).

►**Table 2** shows the pregnancy characteristics of our study cohort. Overall, 494 women (30.9%) had a first trimester US (<14 week-gestation), which did not vary by birthweight group (►**Table 2**). Other pregnancy dating criteria, were also similar between groups (►**Table 2**). Women with SGA infants had PPROM, and subsequent delivery at earlier gestational ages than women with AGA and LGA infants; they were also more likely to deliver by cesarean and require a cesarean delivery for fetal intolerance of labor (►**Table 2**).

In bivariate analyses, there was an inverse relationship between neonatal outcomes and birthweight group (►**Table 3**). SGA infants had a higher prevalence of composite major neonatal morbidity compared with AGA and LGA infants (55.2% vs 31.5% vs 18.3%, respectively, $p < 0.001$). This effect was driven by several components of the composite outcome (death prior to initial hospital discharge, BPD, and neonatal sepsis). Former-SGA children were also more likely to be diagnosed with major composite childhood morbidity at age 2 compared with former-AGA and former-LGA children (25.9% vs 8.3% vs 5.9%, respectively, $p < 0.001$), (►**Table 3**). Surviving former-SGA children were also more likely than former-AGA or former-LGA children to have Bayley II MDI scores greater than 2 SD below the mean (24.4% vs 16.9% vs 10.3%, respectively, $p = 0.043$).
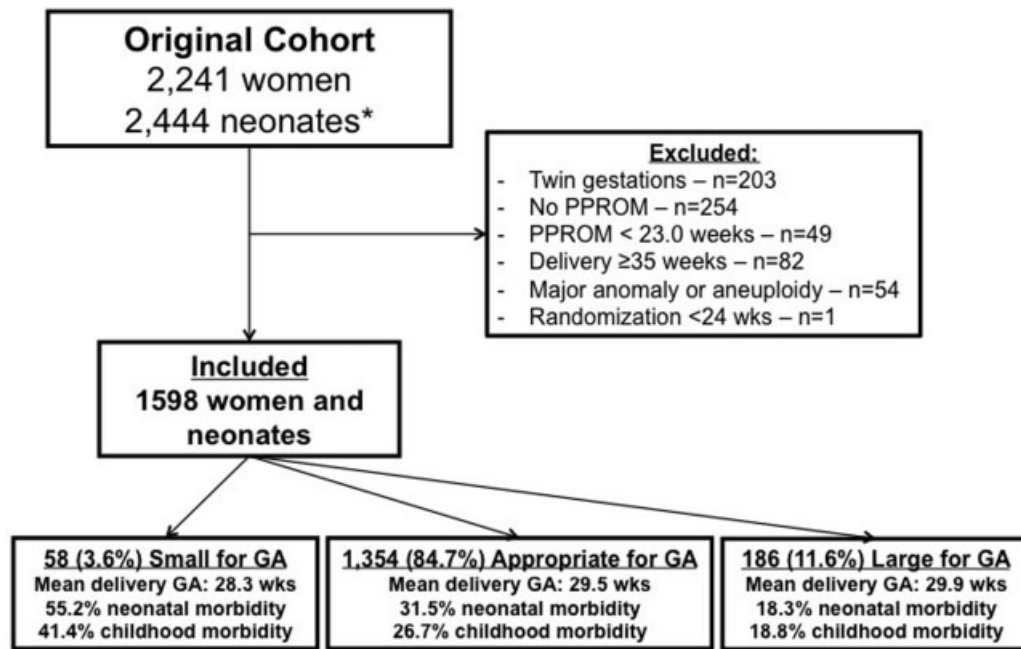
Fig. 1 Study enrollment. GA, gestational age; PPROM, preterm premature rupture of membranes.*There were 203 twin pregnancies.

In multivariable models, several factors remained associated with major neonatal morbidity (►**Table 4**). After controlling for delivery gestational age, compared with AGA infants, LGA infants were less likely (aOR, 0.44; 95% CI, 0.28–0.71; $p = 0.001$), and SGA infants were more likely, (aOR, 2.11; 95% CI, 0.98–4.56; $p = 0.057$) to have a composite adverse outcome. However, former-SGA infants were more likely to develop major childhood morbidity at age 2 (aOR, 2.63; 95% CI, 1.27–5.45; $p = 0.009$), compared with AGA infants, whereas those former-LGA infants had similar risk

Table 1 Demographic characteristics, stratified by birthweight group

Characteristic	Small for gestational age $N = 58$	Appropriate for gestational age $N = 1,354$	Large for gestational age $N = 186$	p-value
Maternal age (y; median, IQR)	25.5 (22–31)	26 (21–30)	27 (22–32)	0.023
Prepregnancy body mass index (kg/m^2; median, IQR)	25.2 (20.6–30.1)	24.4 (21.2–29.8)	26.7 (22.3–30.9)	0.007
Race/ethnicity (n; %)				
African-American	36 (62.1)	612 (45.2)	77 (41.4)	0.302
Caucasian	15 (25.9)	499 (36.8)	74 (39.8)	
Hispanic	6 (10.3)	211 (15.6)	31 (16.7)	
Married (n; %)	26 (44.8)	635 (47.0)	101 (54.3)	0.160
High school education or higher (n; %)	35 (61.4)	865 (63.9)	130 (69.9)	0.248
Alcohol use during pregnancy (n; %)	6 (10.3)	130 (9.6)	18 (9.7)	0.982
Tobacco use during pregnancy (n; %)	15 (25.9)	411 (30.3)	48 (25.8)	0.364
Drug use during pregnancy (n; %)	4 (6.9)	154 (11.4)	18 (9.7)	0.469
Nulliparous (n; %)	25 (43.1)	471 (34.8)	62 (33.3)	0.381
Diabetes (n; %)				
Pregestational	1 (1.7)	19 (1.4)	4 (2.2)	0.550
Gestational	3 (5.2)	39 (2.9)	12 (6.5)	0.030
Any	4 (6.9)	58 (4.3)	16 (8.6)	0.027
Previous preterm birth (n; %)	14 (24.1)	391 (28.9)	48 (25.8)	0.530

Abbreviation: IQR, interquartile range.

Table 2 Current pregnancy and intrapartum characteristics, stratified by birthweight group

Characteristic	Small for gestational age N = 58	Appropriate for gestational age N = 1,354	Large for gestational age N = 186	p-value
Pregnancy dating criteria				
Mean gestational age at first ultrasound (wk; ± SD)	18.8 ± 6.8	18.2 ± 7.2	18.8 ± 8.6	0.537
First ultrasound was prior to 14 wk gestation (n; %)	15 (25.9)	414 (30.6)	65 (35.0)	0.336
Patient had a missing last menstrual period date (n; %)	5 (8.6)	122 (9.0)	20 (10.8)	0.734
Patient reported a "sure" last menstrual period date (n; %)	36 (62.1)	792 (58.5)	107 (57.5)	0.828
Mean gestational age at PPROM (wk; ± SD)	26.9 ± 3.1	28.0 ± 2.5	28.4 ± 2.4	0.005
Randomized to receive magnesium sulfate (n; %)	29 (50)	670 (49.5)	80 (43.0)	0.253
Received antenatal antibiotics (n; %)	58 (100)	1,308 (96.6)	180 (96.8)	0.361
Received antenatal corticosteroids (n; %)	57 (98.3)	1,322 (97.6)	181 (97.3)	0.912
Latency between PPROM and delivery (d; median, IQR)	6.4 (3.8–13.1)	6.9 (3.3–14.1)	6.6 (2.6–15.1)	0.915
Chorioamnionitis (n; %)	8 (13.8)	174 (12.9)	26 (14.0)	0.898
Preeclampsia (n; %)	1 (1.7)	8 (0.6)	1 (0.5)	0.386
Meconium stained amniotic fluid (n; %)	3 (5.2)	31 (2.3)	3 (1.6)	0.261
Cesarean delivery (n; %)	31 (53.5)	510 (37.7)	56 (30.1)	0.005
Cesarean delivery for fetal intolerance of labor (n; %)	14/31 (45.2)	218/510 (42.8)	14/56 (25)	0.034
Cesarean delivery for malpresentation (n; %)	17/31 (54.8)	251/510 (49.2)	31/56 (55.4)	0.589
Mean gestational age at delivery (wk; ± SD)	28.3 ± 3.1	29.5 ± 2.6	29.9 ± 2.4	0.004

Abbreviations: IQR, interquartile range; PPROM, preterm premature rupture of membranes; SD, standard deviation.

compared with former-AGA children (aOR, 0.74; 95% CI, 0.35–1.55; p = 0.425), ►**Table 5**. Male gender was associated with worse outcomes both during the initial neonatal period and at age 2 (►**Tables 4** and **5**).

Finally, we compared the median birthweight in kilograms (kg) and at each childhood follow-up visit, stratified by birthweight group. Children's weights were recorded at the three prespecified follow-up visits and the timing of the follow-up visits did not vary by birthweight group (median of 6, 13 and 25 mo), corrected for prematurity. At each follow-up visit, the former-SGA children remained significantly lighter than their former-AGA counterparts, who in turn were significantly lighter than the former-LGA children (p < 0.001 for all time points studied, ►**Fig. 2**).

Comment

In this large, prospectively collected cohort of women with pregnancies complicated by PPROM, we found that infant birthweight classification is associated with both adverse initial neonatal outcomes and adverse childhood neurodevelopmental outcomes at age 2. These differences appeared most significant for those SGA at delivery, as adverse outcomes persisted to early childhood. The apparent advantage conferred shortly after birth to LGA infants appeared to be short-lived, as neurodevelopmental outcomes were similar between former-LGA and former-AGA children when they were evaluated at age 2.

These findings are consistent with limited previous reports examining the effect of birthweight on preterm morbidity and mortality, particularly among neonates with an antenatal diagnosis of intrauterine fetal growth restriction. Multiple prior studies have demonstrated adverse effects of intrauterine fetal growth restriction (diagnosed antenatally) on initial childhood outcomes as well as neurodevelopmental impairment.[16–18] However, the majority of prior studies have focused specifically on antenatal growth restriction and US parameters, and have used this information for decision making.[19,20] This cohort, where PPROM was the obstetric diagnosis for all women studied, likely represents a different population, given different underlying pathophysiology contributing to premature membrane rupture, and provides valuable information regarding anticipated postnatal outcomes among babies delivered following this complication.

Furthermore, we report information on infants that were LGA at delivery. Although these infants experienced lower morbidity in the neonatal period, this benefit was transient, as they experienced similar neurodevelopmental outcomes at age 2 to former-AGA children. We hypothesize that LGA infants might have improved outcomes due to reduced need for transfusion, and also reduced temperature instability, known risk factors for neonatal morbidity.[21,22] Unfortunately, our study design does not permit us to answer these mechanistic questions directly. For all groups, size at birth was highly correlated with weight across multiple follow-up visits through 2 years of age. The longer term (e.g., adult)

Table 3 Neonatal outcomes, stratified by birthweight group

Characteristic	Small for gestational age N = 58	Appropriate for gestational age N = 1,354	Large for gestational age N = 186	p-value
Male fetus (n; %)	35 (60.3)	726 (53.6)	90 (48.4)	0.222
Median birthweight (kg; IQR)	0.73 (0.57–1.13)	1.35 (0.99–1.67)	1.79 (1.35–2.10)	<0.001
5-min Apgar score < 7 (n; %)	17 (29.3)	252 (18.6)	25 (13.5)	0.023
Birth head circumference < 10% for gestational age (n; %)	31 (56.4)	96 (7.2)	1 (0.6)	<0.001
Birth length < 10% for gestational age (n; %)	27 (47.4)	65 (4.8)	1 (0.6)	<0.001
Composite major neonatal morbidity (n; %)	32 (55.2)	426 (31.5)	34 (18.3)	<0.001
Death prior to initial hospital discharge (n; %)	10 (17.9)	63 (4.7)	4 (2.2)	<0.001
Necrotizing enterocolitis, stage II or III (n; %)	0 (0)	66 (4.9)	4 (2.2)	0.055
Bronchopulmonary dysplasia (n; %)	17 (30.4)	233 (17.3)	15 (8.2)	<0.001
Confirmed neonatal sepsis (n; %)	14 (25.0)	222 (16.5)	15 (8.2)	0.002
Intraventricular hemorrhage, grade III or IV (n; %)	1 (1.9)	21 (1.6)	3 (1.7)	0.981
Periventricular leukomalacia (n; %)	1 (1.9)	21 (1.6)	3 (1.7)	0.981
Composite major childhood morbidity (n; %)	15 (25.9)	112 (8.3)	11 (5.9)	<0.001
Stillbirth or infant death (n; %)	14 (24.6)	92 (7.1)	8 (4.4)	<0.001
Moderate or severe cerebral palsy at age 2[a]	1/43 (1.8)	21/1,201 (1.6)	3/172 (1.7)	0.790
Bayley MDI score > 2 SD below the mean[a]	10/41 (24.4)	185/1,096 (16.9)	16/155 (10.3)	0.043
Bayley PDI score > 2 SD below the mean[a]	4/41 (9.8)	166/1,102 (15.1)	19/157 (12.1)	0.417

Abbreviations: IQR, interquartile range; MDI, mental development index; PDI, psychomotor development index; SD, standard deviation.
[a]Among the 43 small for gestational age, 1,201 appropriate for gestational age, and 172 large for gestational age children surviving to age 2. Not all assessments were completed for each child; numerator for each parameter reflects number of living children with available data.

implications of LGA and SGA birthweight for gestational age growth patterns is unknown.

In this population, traditional risk factors for aberrant fetal growth were uncommon; for example, use of tobacco and illicit drugs was low and did not vary by birthweight group. Pre-eclampsia was also uncommon. Previous studies examining the rate of fetal growth following PPROM or after the onset of spontaneous preterm labor have noted reduced growth velocity, suggesting that slowing of fetal growth may participate in the mechanism of preterm labor.[23,24] Significant placental lesions (e.g., syncytiotrophoblast knot-ting, villous fibrosis, avascular terminal villi, accelerated villous maturation) have been associated with abnormal fetal growth in the setting of preterm delivery, supporting the theory that the development of these complications may be a chronic process.[25,26]

Our finding of a greater proportion (11.6%) of LGA compared with SGA infants (3.6%) is of uncertain significance, and warrants further investigation in other cohorts. The rate of SGA is uncommonly reported following PPROM, but the incidence in our population was similar to that reported in a large cohort (n = 4,102) of women delivering <32 weeks,

Table 4 Multivariate logistic regression model for major neonatal morbidity

Characteristic	OR	95% CI	p-value
Delivery gestational age (per 1 wk interval)	0.50	0.47–0.54	<0.001
Male infant	1.52	1.15–2.00	0.003
Maternal education (per y completed)	1.05	0.99–1.11	0.073
Infant size at delivery			
Small for gestational age	2.11	0.98–4.56	0.057
Appropriate for gestational age	1.00	Ref	Ref
Large for gestational age	0.44	0.28–0.71	0.001

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference group.
Note: Other factors considered in initial model but removed from final models due to p > 0.20 included maternal body mass index, randomization to magnesium sulfate, maternal smoking, and maternal diabetes mellitus.

Table 5 Multivariate logistic regression model for major childhood morbidity at age 2

Characteristic	OR	95% CI	p-value
Male child	1.63	1.08–2.47	0.021
Delivery gestational age (per 1 wk interval)	0.63	0.57–0.69	<0.001
Prepregnancy maternal body mass index (per 1 unit increase)	1.02	0.99–1.05	0.150
Infant size at delivery			
Small for gestational age	2.63	1.27–5.45	0.009
Appropriate for gestational age	1.00	Ref	Ref
Large for gestational age	0.74	0.35–1.55	0.425

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference group.
Note: Other factors considered in initial model but removed from final models due to p > 0.20 included randomization to magnesium sulfate, maternal education level, maternal smoking, and maternal diabetes mellitus.

where 4.7% delivered after PPROM were SGA.[27] A phenotype of rapid fetal growth prior to the occurrence of late preterm birth has been described; we speculate that perhaps this may have contributed to the lower rate of SGA and the higher rate of LGA even though this cohort was primarily earlier preterm.[28] Further mechanistic investigations are needed, and placental pathology information will be crucial to unraveling underlying etiologies of growth disturbances in these fetuses.

Our study has several strengths. This is a large, well-defined cohort of women with PPROM, diagnosed in a standardized fashion. Given that the original study was not focused on fetal growth per se, women were not excluded due to suspected normal or abnormal fetal growth, and we had the distinct advantage of being able to evaluate the impact of SGA and LGA

from within the same cohort. Neonatal and childhood outcomes were also standardized and were rigorously prospectively assessed by trained research staff. We had detailed pregnancy dating information available, reducing the likelihood that infants were misclassified as SGA or LGA due to incorrect pregnancy dating. Furthermore, incorporation of early childhood outcomes at age 2 allowed for more comprehensive assessment regarding the impact of size on outcomes.

Our analysis is not without limitation. As with all secondary analyses, we were limited to the data previously collected as part of the main trial. We did not have information regarding placental pathology, and had minimal details regarding US assessments following PPROM. We also had very limited data regarding estimated fetal weight or amniotic fluid index (AFI) by US following PPROM, and therefore, are unable to examine outcomes based on individual biometric parameters (e.g., abdominal circumference or AFI) or evaluate how various Doppler indices may impact outcomes. The study design did not permit us to examine the mechanism by which SGA contributes to adverse outcomes. Additionally, we were limited by the relatively small number of infants with SGA.

In conclusion, among infants delivered following PPROM, neonatal outcomes were inversely related to size at delivery, with fewer LGA infants experiencing early morbidity compared with AGA and SGA infants. At age 2, former-SGA children had continued adverse effects, with significantly worse neurodevelopmental outcomes compared with former-AGA and former-LGA children. However, the apparent benefit of LGA that was seen during the neonatal period was no longer appreciated in early childhood. These data have implications for counseling patients; future studies should confirm these results and investigate potential mechanisms behind these findings.

Fig. 2 Median weight at birth and at subsequent follow-up visits, stratified by birthweight group. Error bars represent interquartile range. Ages listed for follow-up visits were at corrected gestational ages. Timing of visits did not differ by birthweight group. Follow-up weight examination at visit 1 included 44 formerly-SGA, 1,219 formerly-AGA, and 174 formerly-LGA, at visit 2 included 40 formerly-SGA, 1,130 formerly-AGA, and 167 formerly-LGA, and at visit 3 included 34 formerly-SGA, 847 formerly-AGA, and 120 formerly-LGA children. AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age. *p < 0.001 for each visit.

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