Published in final edited form as:

J Perinatol. 2017 August ; 37(8): 958–962. doi:10.1038/jp.2017.58.

Association between small-for-gestational age and neurocognitive impairment at two years of corrected age among infants born at preterm gestational ages: a cohort study

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Abstract

OBJECTIVE—To investigate the association between small-for-gestational age (SGA) and neurocognitive impairment at 2 years of corrected age among infants born at preterm gestational ages.

STUDY DESIGN—A secondary analysis of a prospectively conducted NICHD/Maternal-Fetal Medicine Units BEAM trial. Non-anomalous pregnancies delivered before 37 weeks of gestation were included in the analysis. Neurocognitive outcomes at 2 years of corrected age were compared between infants who were SGA (< 10% for gestational age) and those appropriately grown (AGA). The primary outcome was a severe or moderate neurocognitive impairment at 2 years of corrected age among survivors, defined as either mental (MDI) or psychomotor (PDI) developmental index score < 70 for severe and < 85 for moderate impairment.

RESULTS—Of 2299 preterm neonates 67 (3%) were SGA. SGA infants were more often twin pregnancies (31% vs 17%, $P = 0.003$) and delivered more often by cesarean section (63% vs 40%, $P < 0.001$) at similar gestational ages (30.0 ± 2.6 vs 29.5 ± 2.8 weeks, $P = 0.11$). At 2 years of corrected age, SGA and AGA survivors had similar rates of neurocognitive impairment (MDI < 70: 18% vs 18%, $P = 1.0$; MDI < 85: 44% vs 46%, $P = 0.96$; PDI < 70: 20% vs 15%, $P = 0.51$; PDI < 85: 40% vs 34%, $P = 0.48$).

CONCLUSION—In this cohort, SGA at preterm gestational ages was associated with similar rates of neurocognitive impairment at two years of corrected age among surviving infants.

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This manuscript was presented in oral format at the 36th Annual Meeting of the Society for Maternal-Fetal Medicine, Atlanta, GA, 1 to 6 February 2016.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INTRODUCTION

With approximately 13 million babies worldwide born each year before 37 weeks gestation,¹ preterm birth continues to be a leading cause of neonatal morbidity and mortality.² Of all preterm neonates, approximately 13 to 20% are small-for-gestational age (SGA), with birth weight less than the 10th percentile.^{3–5} While some SGA neonates result from non-pathologic constitutional growth, others result from intrauterine growth restriction due to placental insufficiency, maternal co-morbidities, or intrinsic fetal etiologies including aneuploidy and structural anomalies.⁶

There is increasing evidence that SGA at term may be associated with adverse neurocognitive outcomes. In two previous studies, infants who were SGA at term were found to be at increased risk for neurocognitive impairment at 8 months (OR = 1.92, 95% CI: 1.64 to 2.25), and 48 months (OR = 1.47, 95% CI: 1.18 to 1.83) when compared with appropriately grown for gestational age (AGA) term infants.⁷ Despite these data, the effect of SGA on neurocognitive outcomes in those born at preterm gestational ages remains unclear. In a study by De Jesus *et al.*,³ SGA infants born before 27 weeks gestation had an increased risk for death or neurocognitive impairment at 18 to 22 months corrected age compared with AGA infants. However, in another cohort of premature infants born before 32 weeks gestation, SGA was not found to be significantly associated with neurocognitive impairment or use of speech and language therapy at 5 years of life.⁴

Given the conflicting data on the effect of SGA on neurocognitive impairment in infants born at preterm gestational ages, and the paucity of data on preterm infants born between 32 and 37 weeks gestation, our objective was to investigate the effects of SGA on neurocognitive impairment at 2 years of corrected age among surviving infants born at all preterm gestational ages.

METHODS

Study population

This study is a secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Maternal-Fetal Medicine Units (MFMU) Network's Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trial. The trial was conducted in 20 participating centers between December 1997 and May 2004. The original trial was a prospective randomized controlled trial assessing the effect of antepartum magnesium sulfate on adverse neonatal outcomes in women at risk for preterm delivery before 32 weeks gestation.⁸ Briefly, women in the original study were eligible for the trial if they were carrying singleton or twin gestations at 24 through 31 weeks gestation and were at increased risk of spontaneous preterm delivery because of advanced preterm labor (cervical dilation of 4 to 8 cm and intact membranes), or if an indicated preterm delivery was anticipated within 2 to 24 h. The duration of gestation was determined using the last menstrual period and the results of the earliest available ultrasound examination.^{8,9} Eligible, consenting women were assigned in double-blinded fashion to receive either intravenous magnesium sulfate or identical appearing placebo. Data extraction was performed by certified study personnel. Infants born in the study were followed for a 2-year time period.⁸

Ethics committees in each of the 20 participating centers approved the study protocol and study subjects gave their written informed consent prior to participating. Because of the deidentified data from the original study, this secondary analysis received a waiver of exemption by Stanford University Institutional Review Board.

Study definitions

SGA was defined in the original data set as a birth weight less than 10th percentile using the Brenner growth curve.¹⁰ The primary outcome for the current analysis was severe or moderate neurocognitive impairment at 2 years of corrected age among survivors, defined as either mental (MDI) or psychomotor (PDI) developmental index score less than 70 for severe, and MDI or PDI less than 85 for moderate impairment, respectively. MDI and PDI scores were obtained using The Bayley Scales of Infant and Toddler Development (BSID-II)¹¹ completed by a certified psychologist or psychometrist performing the exam. The BSID-II is an individually administered tool that evaluates sensory-perception, knowledge, problem solving, early language and memory, and it has been widely used both clinically and in research of preterm infants.^{8,12} Corrected age of the child was used in adjusting the MDI and PDI scores. Fetal or infant death was defined in the original trial as any of the following: stillbirth, death before discharge or death after discharge (between initial discharge and 30 months of corrected age). Neonatal sepsis was defined based on a positive culture of blood, cerebrospinal fluid or urine with suspicious clinical findings of infection, or (in the absence of positive cultures) if there was clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection in a clinically septic infant. Neonatal seizures were recorded if the attending physician or nurse believed that seizures definitely occurred, with or without positive electroencephalogram finding. Bronchopulmonary dysplasia was defined as a need for oxygen therapy (with or without mechanical ventilation/continuous positive airway pressure therapy) and an oxygen requirement ($\text{FiO}_2 > 0.21$) for the first 28 days of life.

Statistical analysis

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in the analysis. Statistical analysis was performed using R application (version 2.15.0, R Development Core Team, 2011, Vienna, Austria). Among twin gestations, each neonate was analyzed separately. Only cases with available data on each variable were analyzed. Neurocognitive outcomes at 2 years of corrected age ($\text{PDI} < 70$; $\text{PDI} < 85$; $\text{MDI} < 70$; $\text{MDI} < 85$) were only analyzed for surviving infants undergoing BSID-II. Univariable analyses were performed using χ^2 test or Fisher's test for categorical variables and Wilcoxon test for continuous variables. Multivariable logistic regression models were constructed to determine the independent association of SGA with neurocognitive impairment while adjusting for potential confounders that were selected based on significance ($P < 0.1$) in the univariable analysis. Results of the model were expressed as odds ratios (OR) and 95% confidence intervals (CI). The level of significance was set at $P < 0.05$.

RESULTS

The original BEAM trial included 2444 fetuses. After excluding cases with missing information on SGA status ($n = 13$), cases with major fetal malformations ($n = 76$) and cases with gestational age at birth < 37 0/7 weeks ($n = 56$), a total of 2299 preterm infants born at < 37 0/7 weeks gestation were included in the analysis, of which 67 (3%) were SGA at birth (Figure 1).

When comparing maternal demographic data between SGA and AGA neonates, there were no significant differences in maternal age, race/ethnicity, education, pre-pregnancy body mass index, parity or smoking between the SGA vs AGA groups (Table 1). In addition, there was no significant difference in the rate of exposure to magnesium sulfate (the planned intervention of the original study) between the groups (52% vs 48%, $P = 0.59$) (Table 1).

When analyzing obstetric outcomes, there were more twin pregnancies (31% vs 17%, $P = 0.003$) and more cesarean deliveries (63% vs 40%, $P < 0.001$) among preterm SGA compared with the AGA group, whereas the AGA group had a higher rate of preterm premature rupture of membranes (87% vs 70% in SGA, $P < 0.001$). The rate of labor induction was similar between the SGA and AGA groups (13% vs 12% in AGA, $P = 0.10$) (Table 2).

At birth, SGA infants had smaller mean birth weights (947 ± 360 vs 1391 ± 510 g, $P < 0.001$), although both groups were delivered at similar gestational ages (30.0 ± 2.6 vs 29.5 ± 2.8 weeks, $P = 0.11$) (Table 3). There was no significant difference in the fetal sex between the SGA and AGA groups. In addition, the frequencies of neonatal sepsis, seizures, mechanical ventilation and bronchopulmonary dysplasia were similar between the SGA and AGA groups (Table 3).

Neurocognitive outcome data at 2 years of corrected age were available for 1855 (81%) neonates. No significant difference was found in the rate of severe or moderate neurocognitive impairment between the preterm SGA and AGA groups (MDI < 70 : 8 (18%) vs 319 (18%), $P = 1.0$; MDI < 85 : 20 (44%) vs 832 (46%), $P = 0.96$; PDI < 70 : 9 (20%) vs 279 (15%), $P = 0.51$; PDI < 85 : 18 (40%) vs 618 (34%), $P = 0.48$). When stratifying by magnesium exposure in this pregnancy, there was no significant difference in the outcomes between the SGA vs AGA groups (MDI or PDI < 70 : 3% in SGA vs 9% in AGA, $P = 0.6$ and MDI or PDI < 85 : 22% in SGA vs 24% in AGA, $P = 0.7$ in the magnesium sulfate exposed group; MDI or PDI < 70 : 14% in SGA vs 9% in AGA, $P = 0.1$; MDI or PDI < 85 : 33% in SGA vs 25% in AGA, $P = 0.6$ in the non-exposed group). There were more fetal or infant deaths in the SGA group (15 (22%) vs 162 (7%), $P < 0.001$) compared with the AGA group. A total of 11 (0.5%) stillbirths occurred in the cohort, of which 2 (3%) were SGA and 9 (0.4%) were AGA ($P < 0.01$). In addition, 132 (6%) neonates died before discharge (10 (15%) SGA vs 122 (5%) AGA, $P < 0.01$). Mortality after discharge (3 (5%) vs 31 (1%), $P = 0.12$) was similar as well. One neonate died after 24 months of corrected age (and before 30 months) but did not undergo BSID-II test.

Multivariable logistic regression models were constructed to determine the independent association of SGA with neurocognitive impairment while adjusting for potential

confounders that were selected based on significance ($P < 0.10$) in the univariable analysis. After adjusting for twin pregnancy, smoking and preterm premature rupture of membranes (collinearity was found between twin pregnancy and mode of delivery), among surviving infants born at preterm gestational ages, no significant association was found between SGA and severe (MDI < 70 or PDI < 70 ; OR = 1.1, 95% CI: 0.4 to 2.6) or moderate (MDI < 85 or PDI < 85 , OR = 1.2, 95% CI: 0.6 to 2.2) neurocognitive impairment at 2 years of age. However, SGA remained significantly associated with fetal or infant death (OR = 3.6, 95% CI: 1.9 to 6.4) when compared with preterm AGA (Table 4).

After adjusting for twin pregnancy, smoking and preterm premature rupture of membranes in a multivariable logistic regression model, we found a significant association between SGA and a composite of death and neurocognitive impairment at 2 years of corrected age (adjusted OR = 3.6, 95% CI: 1.9 to 6.4).

DISCUSSION

In this secondary analysis of the BEAM trial cohort, among surviving infants born at < 37 weeks, SGA was not associated with neurocognitive impairment at 2 years of corrected age compared with AGA. Specifically, there was no association between preterm SGA and MDI or PDI scores < 85 or < 70 , even when adjusting for possible confounders. We found that pregnancies with preterm SGA infants were at increased risk of fetal or infant death compared with AGA infants, and the risk remained after adjusting for twin gestation, smoking and preterm premature rupture of membranes.

There are conflicting data about the association between SGA at preterm gestational ages and neurocognitive outcomes.^{15,16} Previously, in the EPIPAGE (Étude Epidémiologique sur les Petits Ages Gestationnels) study, infants born between 29 to 32 weeks gestation with birth weight less than 10th percentile were at increased risk of cognitive and behavioral difficulties at school age.¹⁷ More recently, a retrospective cohort study by the NICHD Neonatal Network comparing 385 SGA infants with 2586 AGA infants born before 27 weeks gestation found that SGA was associated with increased risk of death or neurocognitive impairment at 18 to 22 months corrected age.³ Both of these studies analyzed data from extremely preterm infants, whereas in our study the median gestational age at birth in both groups was approximately 30 weeks of gestation, which may explain the difference in outcomes. In a recent smaller prospective cohort study by Bickle Graz *et al.*,⁴ no difference was found in neurocognitive impairment at 5 years of life among 342 infants born prior to 32 weeks gestation (16% of whom were SGA at birth). Results of our study are consistent with the outcomes reported by Bickle Graz, although our cohort was almost seven times larger, consisting of 2299 infants. In addition, by including all preterm births between 24 and 37 weeks, and not limiting our analysis to infants born before 32 weeks, our study adds to the literature.

The association between preterm SGA and fetal or infant death has been previously studied. Grobman *et al.*¹⁸ demonstrated, using the BEAM data set, an increased risk of composite outcome of cerebral palsy or death among preterm SGA infants born before 34 weeks gestation compared with preterm AGA infants. In addition, studies by Qiu *et al.* and Sharma

et al. have also found an association between SGA infants and mortality among newborns born before 37 weeks gestation (aOR = 3.1, 95% CI not reported),¹⁹ and 33 weeks gestation (aOR = 2.46, 95% CI: 1.93 to 3.14).²⁰ Although the primary interest of our study was neurocognitive outcome at 2 years of corrected age among survivors, we also found a significant association between SGA and fetal or infant death at preterm gestational ages, which is consistent with prior studies. Given this finding we assessed a composite of death and neurocognitive impairment at 2 years of corrected age and found a significant association between SGA and this composite outcome, likely driven by the strong association between SGA and infant death. The lack of difference in neurocognitive impairment in survivors as measured by BSID-II MDI scores between preterm SGA and AGA infants, with a concurrent increased fetal or infant mortality among preterm SGA infants suggests that factors leading to fetal or infant death in SGA cases may not influence neurocognitive impairment in survivors. However, larger cohorts are necessary to confirm our hypothesis since we may have been underpowered to detect a difference in neurocognitive impairment among survivors.

The strengths of our study include a large prospectively collected cohort of women delivering at preterm gestational ages with the majority of infants (87% follow-up rate) undergoing detailed neonatal evaluations and neurocognitive assessment at 2 years of corrected age. The original study was conducted in 20 academic medical centers with robust geographic and demographic diversity. Discrete maternal demographic, prenatal, intrapartum and neonatal data allowed us to analyze possible confounders appropriately including mode of delivery, twin gestation, fetal gender and chorioamnionitis.

That being said, our study is not without limitations. Prenatal imaging data, including fetal biometric measurements, umbilical or middle cerebral artery Doppler findings, and presence or absence of oligohydramnios were not recorded in the original study, which precluded us from analyzing the potential effect of prenatal placental insufficiency on adverse neonatal outcomes. In addition, the original BEAM trial excluded women with preeclampsia (because magnesium sulfate was the intervention) and most women included (86%) had preterm premature membrane rupture; therefore, the cohort may not be representative of all pathologies leading to prematurity and SGA. This may also be the reason for the lower than expected SGA rate in the cohort (3%). Moreover, the Brenner growth curve is less often used today; however, the Brenner growth curve has been used in other prenatal studies,¹³ and when applying the birth weights from our cohort to a more commonly used Fenton growth curve,¹⁴ the frequency of SGA cases was similar ($n = 74$ (3.2%) vs $n = 67$ (3%) in Brenner). Given the lower rate of SGA and lack of difference in MDI scores we performed a *post hoc* power calculation. We estimated that 143 SGA cases would be needed to detect a 10% difference in MDI scores less than 70 with 80% power at a 5% significance level. Finally, neurocognitive impairment was based on BSID-II evaluations at the time of the BEAM study. The third edition of the Bayley Scales is now in clinical use, making comparison of these data to more recent cohort outcome results challenging.

In conclusion, among surviving infants born at preterm gestational ages we did not find an association between SGA and neurocognitive impairment at 2 years of corrected age. However, preterm SGA was associated with increased risk of fetal or infant death, even

when adjusting for possible confounders. Although our findings need to be confirmed in larger prospective studies using current neonatal growth curves and neurocognitive assessments, we believe they may be useful to clinicians counseling patients with SGA at preterm gestational ages.

Acknowledgments

We acknowledge the assistance of NICHD, the MFMU Network and the Protocol Subcommittee in making the database available on behalf of the project. The contents of this report represent the views of the authors and do not represent the views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network or the National Institutes of Health.

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Figure 1. Flow diagram of the study population. AGA, appropriate-for-gestational age; BEAM, Beneficial Effects of Antenatal Magnesium Sulfate; SGA, small-for-gestational age.

Table 1

Maternal demographic data of preterm small-for-gestational age (SGA) infants compared with preterm appropriate-for-gestational age (AGA) infants

	Preterm SGA <i>N</i> = 67	Preterm AGA <i>N</i> = 2232	<i>P</i> -value ^a
<i>Maternal age</i>			0.63
18–40	66 (99%)	2105 (94%)	
< 18	0 (0.0%)	0 (0.0%)	
> 40	0 (0.0%)	32 (1%)	
Missing	1 (2%)	95 (4%)	
<i>Race</i>			0.89
Caucasian	27 (40%)	832 (37%)	
African American	29 (43%)	961 (43%)	
Hispanic	9 (13%)	391 (18%)	
Asian	1 (2%)	19 (1%)	
Other	1 (2%)	29 (1%)	
Maternal education, years	11.8 (±2.4)	11.9 (±2.6)	0.82
<i>Maternal BMI at pre-pregnancy (kg m⁻²)</i>			0.74
Normal (18.5–24.99)	29 (43%)	892 (40%)	
Underweight (< 18.5)	4 (6%)	128 (6%)	
Overweight (25–29.99)	11 (16%)	469 (21%)	
Obese (≥ 30)	18 (27%)	504 (23%)	
Missing	5 (8%)	239 (11%)	
Nulliparous	23 (34%)	827 (37%)	0.74
Smoking in this pregnancy	25 (37%)	587 (26%)	0.06
Randomized to magnesium sulfate treatment	35 (52%)	1074 (48%)	0.59

Abbreviation: BMI, body mass index.

Data presented as mean (±s.d.) or *n* (%).

^a Comparisons made with χ^2 test or Student's *t*-test.

Table 2

Obstetrical outcomes of pregnancies with preterm small-for-gestational age (SGA) infants compared with preterm appropriate-for-gestational age (AGA) infants

	Preterm SGA <i>N</i> = 67	Preterm AGA <i>N</i> = 2232	<i>P</i> -value ^a
Twin gestations	21 (31%)	370 (17%)	0.003
Preeclampsia	1 (2%)	17 (1%)	1.0
Placental abruption	5 (8%)	170 (8%)	1.0
PPROM	47 (70%)	1934 (87%)	< 0.001
<i>Mode of delivery</i>			0.002
Vaginal	25 (37%)	1350 (61%)	
Cesarean section	42 (63%)	882 (40%)	
<i>Type of labor</i>			0.10
Spontaneous or spontaneous augmented	26 (39%)	1637 (73%)	
Induced	9 (13%)	275 (12%)	

Abbreviation: PPRM, preterm premature rupture of membranes.

Data presented as *n* (%).

^aComparisons performed with χ^2 test.

Table 3

Neonatal outcomes of pregnancies with preterm small-for-gestational age (SGA) infants compared with preterm appropriate-for-gestational age (AGA) infants

	Preterm SGA <i>N</i> = 67	Preterm AGA <i>N</i> = 2232	<i>P</i> -value ^a
<i>Fetal sex</i>			0.21
Male	30 (45%)	1191 (53%)	
Female	37 (55%)	1041 (47%)	
Birth weight (g)	980 (683–1177)	1353 (990–1722)	< 0.001
Gestation at delivery (weeks)	30.6 (28.1–31.7)	29.9 (27.3–31.6)	0.11
Neonatal sepsis	11 (16%)	388 (17%)	1.0
Any mechanical ventilation	35 (52%)	1235 (55%)	0.88
Neonatal seizures	2 (3%)	45 (2%)	0.88
Bronchopulmonary dysplasia	12 (18%)	400 (18%)	1.0
MDI < 70 ^b	8 (18%)	319 (18%)	1.0
MDI < 85 ^b	20 (44%)	832 (46%)	0.96
PDI < 70 ^c	9 (20%)	279 (15%)	0.51
PDI < 85 ^c	18 (40%)	618 (34%)	0.48
Fetal or infant death ^d	15 (22%)	162 (7%)	< 0.001

Abbreviations: MDI, mental developmental index score; PDI, psychomotor developmental index score.

Data presented as median (IQR) or *n* (%).

^a Comparisons made with Wilcoxon test or χ^2 test.

^b 444 infants were missing MDI scores.

^c 426 infants were missing PDI scores.

^d Defined as any of the following: stillbirth, death before discharge or death after discharge (within 30 months after initial discharge).

Table 4

Odds for severe (MDI < 70 or PDI < 70) or moderate (MDI < 85 or PDI < 85) neurocognitive impairment at 2 years, and fetal or infant death among preterm small-for-gestational age (SGA) infants compared with preterm appropriate-for-gestational age (AGA) infants

Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
MDI < 70 or PDI < 70	1.3 (0.4–3.0)	1.1 (0.4–2.6)
MDI < 85 or PDI < 85	1.4 (0.7–2.6)	1.2 (0.6–2.2)
Fetal or infant death	3.6 (1.9–6.4)	3.6 (1.9–6.4)

Abbreviations: MDI, mental developmental index score; PDI, psychomotor developmental index score.

^aModels adjusted for twin gestation (singleton as a reference), smoking during pregnancy (no smoking as a reference) and PPROM (no PPROM as a reference).