

Stunting at 5 Years Among SGA Newborns

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abstract

OBJECTIVE: To compare risk of stunting at 5 years across etiological subgroups of small for gestational age (SGA) newborns.

METHODS: We analyzed data of a subsample ($N = 1100$) of the Early Childhood Longitudinal Study-Birth Cohort. We defined SGA as birth weight <10th percentile, then classified subjects into etiological subgroups by each of 8 risk factors (ie, maternal prepregnancy underweight, short stature, smoking during pregnancy, alcohol use during pregnancy, inadequate gestational weight gain [GWG], hypertension, genital herpes infection, and multiple births) or by cooccurrence of 2 often intertwined risk factors (smoking and inadequate GWG). We defined stunting as 5 years height-for-age z score below -2 . We fitted logistic regression models to test whether the risk of stunting differed across SGA subgroups, adjusting for confounders.

RESULTS: SGA subgroup with maternal short stature (odds ratio [OR] = 3.88; 95% confidence interval [CI] = 2.16–6.96) or inadequate GWG (OR = 2.18; 95% CI = 1.23–3.84) had higher risk of stunting at 5 years, compared with the SGA subgroup without the corresponding risk factor. SGA newborns with both maternal smoking and inadequate GWG during pregnancy had much higher risk of stunting at 5 years (OR = 3.10; 95% CI = 1.21–7.91), compared with SGA newborns without any of these 2 SGA risk factors.

CONCLUSIONS: Etiological subgroups of SGA differed in risk of stunting at 5 years. SGA newborns of inadequate GWG mothers who smoke and SGA newborns of short mothers were at particularly high risk of stunting.



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WHAT'S KNOWN ON THIS SUBJECT: Small for gestational age (SGA) is a risk factor for childhood stunting. Maternal prepregnancy underweight, short stature, smoking and alcohol use during pregnancy, inadequate gestational weight gain, hypertension, infection, and multiple births are 8 well-established risk factors of SGA.

WHAT THIS STUDY ADDS: Etiological subgroups of SGA differed in risk of stunting at 5 years. SGA newborns of inadequate gestational weight gain mothers who smoke and SGA newborns of short mothers were at particularly high risk of stunting.

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Small for gestational age (SGA) refers to birth weight or length below the 10th percentile of reference newborns for a given gestational age. Stunting, often defined as deficit in height or linear growth of 2 SD below normal children,¹ is 1 of a number of significant health problems experienced by SGA newborns.² Evidence suggests that stunting is not only associated with reduced adulthood height but also with neurodevelopmental, mental, and social sequelae in later life.³ However, there is a great deal of heterogeneity in the risk of stunting among SGA newborns, potentially due to different etiologies. Although the majority of SGA newborns experience catch-up growth in length during infancy, some SGA newborns will have persistent disadvantage in height during childhood and adulthood.⁴ Growth hormone therapy is effective to reduce risk of stunting among most SGA cases by improving height growth.⁵ However, there is still debate on the best timing to initiate growth hormone therapy for SGA newborns because many of them will have postnatal “catch-up” growth spontaneously.⁶ Therefore, to find SGA newborns with high risk of stunting by their etiology may inform earlier treatment and reduce stunting risk in later life.⁷

Maternal prepregnancy underweight (BMI <18.5), short stature (<158 cm), smoking during pregnancy, alcohol use during pregnancy, inadequate gestational weight gain (GWG), hypertension, infectious diseases, and multiple births are 8 well-established risk factors of SGA.^{8,9} SGA newborns with maternal prepregnancy underweight, inadequate GWG, and/or hypertension during pregnancy tend to have insufficient supply of nutrition during pregnancy and reduced level of insulin-like growth factor 1 (IGF-1), an important stimulus for fetal linear growth and weight gain.^{10,11} SGA newborns

with maternal short stature may have limited genetic potential of linear growth.¹² SGA newborns with maternal smoking, alcohol use, and infectious diseases during pregnancy may have toxicant-induced epigenetic changes¹³ and growth hormone deficiency due to impaired hypothalamic-pituitary-adrenal axis functions.^{14–17} SGA newborns with maternal smoking and alcohol use during pregnancy are more likely to have poor family dietary habits such as high fat and sugar but low calcium, vitamin D, and protein intake.^{18,19} SGA newborns with maternal smoking and hypertension during pregnancy may undergo insufficient intrauterine supply of oxygen and nutrition related to the restricted umbilical cord blood flow caused by high placental resistance and thus are more likely to experience intrauterine hypoxia,^{20,21} which is related to poor early childhood physical growth. SGA newborns with multiple births may simply lack enough space to grow in utero and are more likely to experience catch-up growth after birth. Furthermore, some SGA risk factors are likely to co-occur. For example, smoking mothers tend to have poorer appetite during pregnancy and gain insufficient weight during pregnancy. It remains unclear how their cooccurrence influences risk of stunting among SGA newborns. In addition, in a recent study, continuous reduced height was observed among innate SGA newborns of constitutional origin (eg, maternal short stature) and without severe fetal growth restriction.²² However, they were metabolically healthy by age 2 years. Lastly, SGA newborns with skeletal dysplasia are at high risk of stunting.

Therefore, it is reasonable to hypothesize that etiological subgroups of SGA newborns have differential genetic potential of linear growth and undergo differential intrauterine and postnatal

environments, which can lead to differential risks of stunting at early childhood. In this study, we tested this hypothesis by using data from a national prospective cohort study with risk of stunting and height-for-age z score at age 5 years as the main outcomes.

METHODS

Study Sample

We analyzed a subsample of the Early Childhood Longitudinal Study-Birth Cohort (ECLS-B) which was a national sample of US children born in 2001.²³ ECLS-B was designed for investigating children’s health, development, and school readiness. The design details of ECLS-B have been published elsewhere.²⁴ Briefly, ~10 700 children were recruited at age 9 months in 2001–2002 and were then followed for physical and cognitive development at ~2 years (retention rate, 92.1%), 4 years (83.2%), 5 years (65.0%), and 6 years (17.8%). ECLS-B oversampled developmentally disadvantaged children such as multiple births (16.2%) and those born with low birth weight (28.4%). In this secondary data analysis, we included 1100 SGA children with complete data on 8 well-established SGA risk factors (ie, maternal prepregnancy underweight, short stature, smoking during pregnancy, alcohol use during pregnancy, inadequate GWG, hypertension, genital herpes infection, and multiple births), height-for-age z score at age 5 years, and potential confounders (discussed subsequently). Figure 1 is the flowchart of the analytic sample. Most sociodemographic and pregnancy characteristics were comparable between excluded ($N = 850$) and included ($N = 1100$) samples of SGA children, except that excluded SGA children were less likely to be breastfed (59.5% vs 62.3%) and had lower mean birth

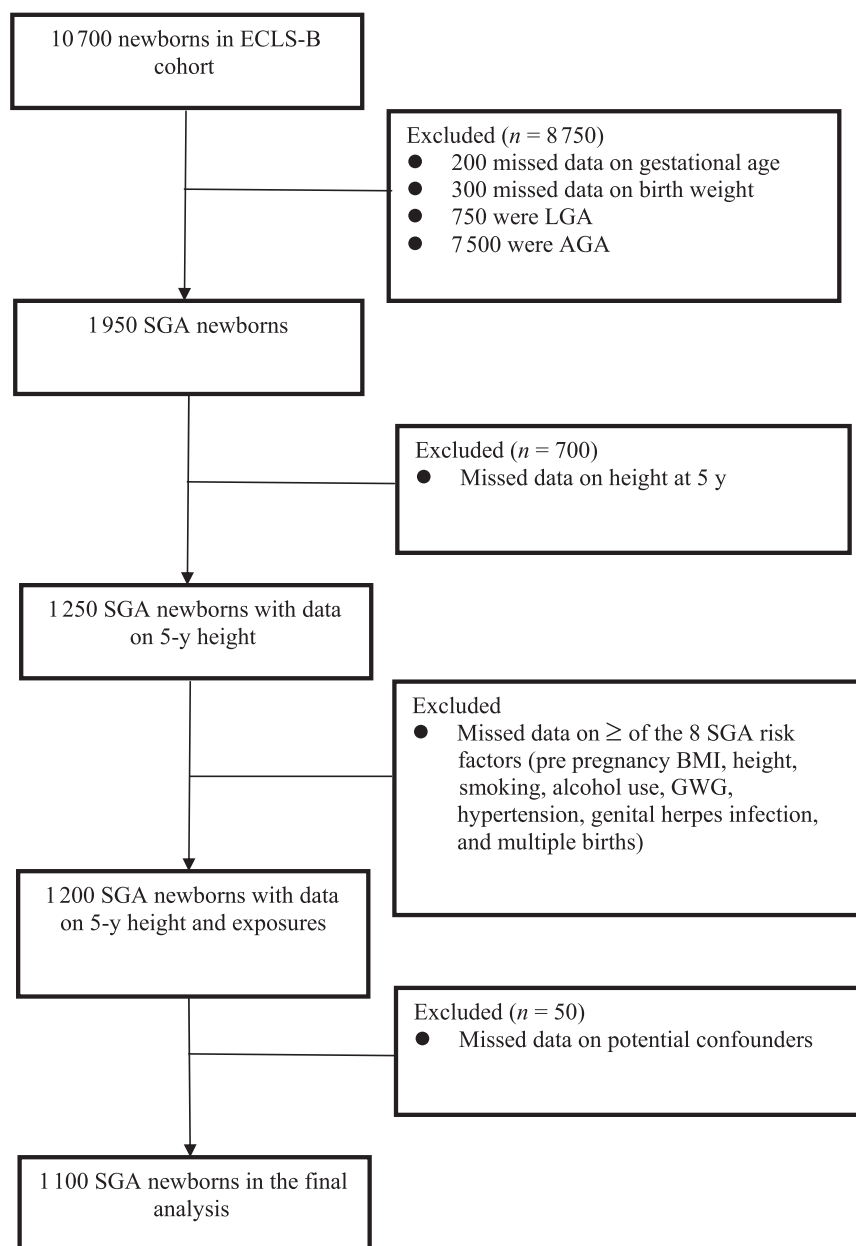


FIGURE 1

Flowchart of the analytic sample. All reported numbers about sample size were rounded to the nearest 50 according to the confidentiality policy of US Department of Education. LGA, large for gestational age.

weight (2164.9 vs 2232.5 g; Table 1).

This secondary data analysis was approved by the Social and Behavioral Sciences Institutional Review Board, University at Buffalo, State University of New York. All reported numbers about sample size had been rounded to the nearest 50 according to

the confidentiality policy of US Department of Education.

SGA Definition

Birth weight and gestational age were obtained by reviewing birth certificates provided by the National Center for Health Statistics' Vital Statistic System. In ECLS-B, gestational age was available for 98% of enrolled

children: 87.4% calculated as the interval between the mother's last menstrual period (LMP) and the child's date of birth, 5.9% imputed from LMP month and year, and 4.7% based on the clinical estimation by the attendant at birth (based on ultrasound and other techniques). High agreement (89.1%) has been reported between LMP- and clinical-estimation-based gestational age in vital statistic system.²⁵ Each newborn's gestational age- and gender-specific birth weight percentile was calculated using reference data of all US singletons.²⁶ We defined SGA as birth weight <10th percentile and appropriate for gestational age (AGA) as birth weight between 10th and 90th percentiles. For the purpose of this analysis, we excluded children born large for gestational age (birth weight >90th percentile).

Etiological Subgroups of SGA Newborns (Exposure)

To define etiological subgroups of SGA, we considered 8 well-established SGA risk factors: maternal prepregnancy underweight, short stature, smoking during pregnancy, alcohol use during pregnancy, inadequate GWG, hypertension, genital herpes infection, and multiple births.^{6,7}

Mothers self-reported their prepregnancy weight and height at 9 months postpartum visit. **Maternal short stature was defined as height ≤ 157.5 cm.**²⁷ Prepregnancy BMI was calculated as prepregnancy weight in kilograms divided by the square of height in meters. Accordingly, we classified mothers into underweight (pregnancy BMI <18.5), normal weight ($18.5 \leq$ BMI <25), overweight ($25 \leq$ BMI <30), and obesity (BMI ≥ 30).²⁸ We obtained GWG mostly from birth certificates (79.1%), and when this information was unavailable (21.9%) on birth certificates, we supplemented it with mothers' retrospectively self-reported GWG at the 9-month postpartum visit.

The correlation between GWG information from birth certificate and that from postpartum retrospective report was fairly high ($r = 0.68$). The mean difference in GWG from these 2 sources was -1.2 kg (SD = 5.7). According to the updated guidelines by the Institute of Medicine in 2009, we defined inadequate GWG for singletons as total GWG <12.5 kg for underweight, 11.5 kg for normal weight, 7 kg for overweight, and 5 kg for obese women, respectively.²⁹ For multiple births, inadequate GWG was defined as total GWG <17 kg for underweight and normal weight, 14 kg for overweight, and 11 kg for obese women, respectively. The information on singleton and multiple births (eg, twins and triplets) was extracted from birth certificates. Although the majority of twins are still naturally conceived, ovulation stimulation is one of the most important reasons for recent rapid increase in rate of multiple births. Thus, we further divided multiple births into those with or without ovulation stimulation based on maternal retrospective recall information at 9 months postpartum interview. Further information on Assisted Reproductive Technology was unavailable in ECLS-B. Maternal smoking (number of cigarettes per day) and alcohol use (yes versus no) information during pregnancy was obtained from birth certificates. If that information was missing, we supplemented it with the data collected from the 9-month postpartum interview. In addition to a binary variable (smoking/nonsmoking), we also classified maternal smoking status during pregnancy as a 4-category variable: never, quit smoking (smoked within 3 months before pregnancy but did not smoke during pregnancy), moderate smoking (1–9 cigarettes/day), and heavy smoking (10+ cigarettes/day). The small percentage (4.3%) of recorded alcohol use during pregnancy did not allow us to examine the dose–response relation of alcohol use during pregnancy with risk of

TABLE 1 Comparison of Characteristics Between Excluded and Included SGA Samples

Variables	Excluded SGA Sample ($n = 850^a$)	Included SGA Sample ($n = 1100^a$)	P^b
Mother			
Age in y, mean (SD)	27.0 (6.5)	27.3 (6.6)	.30
Race, %			
White, non-Hispanic	44.7	48.7	.28
Black, non-Hispanic	25.9	23.5	
Hispanic/multiple races	15.6	14.6	
Asian/Pacific Islander	11.3	9.9	
Native American	2.5	3.4	
Educational level, %			
12th grade or below	23.5	20.0	.08
High school	34.5	32.4	
College	33.8	37.4	
Graduate or above	8.2	10.2	
Married, %	59.1	62.2	.17
Vitamin use within last 3 mo before pregnancy, %	36.1	38.4	.31
Working during last 12 mo before delivery, %	67.9	70.5	.21
Vaginal delivery, %	59.6	56.2	.14
Diabetes during pregnancy, %	3.3	3.8	.55
Primiparity, %	43.4	39.5	.09
Child			
Male gender, %	52.8	49.0	.09
Birth wt, g, mean (SD)	2164.9 (616.9)	2232.5 (589.5)	.01 ^c
Preterm birth, %	31.4	29.4	.33
Gestational age, wk, mean (SD)	37.3 (3.2)	37.5 (3.1)	.27
Timing of solid food introduction, %			
<4 mo	22.5	21.2	.77
4–5 mo	43.2	43.5	
≥ 6 mo	34.3	35.3	
Breastfeeding duration, %			
Never	40.5	37.7	.03 ^c
1–5 mo	43.9	41.9	
6–11 mo	11.3	13.1	
≥ 12 mo	4.3	7.3	

^a Sample size numbers were rounded to the nearest 50 in accordance with US Department of Education guidelines for reporting ECLS-B data.

^b t Tests for continuous variables and χ^2 tests for categorical variables.

^c Significant difference ($P < .05$).

stunting. Hypertensive conditions (ie, chronic hypertension, gestational hypertension, preeclampsia, and eclampsia) and genital herpes infection during pregnancy were extracted from birth certificates.

We classified SGA newborns into etiological subgroups by 1 (Table 2) of the 8 risk factors or by cooccurrence (Table 3) of maternal smoking and inadequate GWG (2 risk factors often cooccurring due to appetite-inhibiting effect of nicotine).

Height Growth Measures (Outcome)

At each wave of data collection, trained ECLS-B research staff

measured child's length/height according to a standardized protocol.^{30–32} Briefly, child's recumbent length was measured by a Seca pediatric measure mat at 9 months visit, and child's standing heights were measured by a stadiometer (Seca Model 214 Road Rod) at 2, 4, 5, and 6 years. Length/height was recorded in centimeters. For each visit, the child's weight and length/height were measured twice and the average was used as the final measure. We decided to use 5-year height as the key outcome in this analysis because it was more correlated to the final adulthood height than earlier

TABLE 2 Risks of Stunting and Mean Height-for-Age z Scores at Age 5 Years of SGA Etiological Subgroups by Single SGA Risk Factor

	Sample Size, n ^a			Risk of Stunting at 5 Years			Height-for-Age z Score at 5 Years		
	(%)	%	Adjusted OR (95% CI) ^b	P	Mean (SD)	Adjusted Mean Difference (95% CI) ^b	P		
All AGA newborns	4400 (100)	2.1	Reference		0.11 (1.04)	Reference			
All SGA newborns	1100 (100)	5.7	3.55 (2.47 to 5.10)	<.001 ^c	-0.36 (1.08)	-0.51 (-0.57 to -0.43)	<.001 ^c		
SGA subgroups by single risk factor									
By pre-pregnancy underweight									
SGA without underweight	1050 (92.5)	5.9	Reference		-0.35 (1.08)	Reference	.75		
SGA with underweight	100 (7.5)	2.4	0.27 (0.07 to 0.99)	.05 ^c	-0.50 (1.01)	-0.03 (-0.25 to 0.18)			
By maternal short stature									
SGA without short stature	750 (65.7)	3.3	Reference		-0.14 (1.06)	Reference	<.001 ^c		
SGA with short stature	400 (34.3)	10.2	3.88 (2.16 to 6.96)	<.001 ^c	-0.77 (1.00)	-0.57 (-0.71 to -0.44)			
By maternal smoking during pregnancy									
SGA without smoking	800 (71.5)	5.3	Reference		-0.32 (1.06)	Reference	.74		
SGA with quit smoking	100 (7.6)	5.9	0.91 (0.30 to 2.79)	.87	-0.40 (1.17)	0.04 (-0.22 to 0.31)	.82		
SGA with moderate smoking (1-9 cigarettes/d)	100 (9.2)	4.9	0.67 (0.24 to 1.90)	.45	-0.36 (1.02)	0.02 (-0.19 to 0.24)	.08 ^c		
SGA with heavy smoking (10+ cigarettes/d)	150 (11.7)	8.5	1.81 (0.73 to 4.47)	.20	-0.57 (1.12)	-0.20 (-0.42 to 0.02)			
By maternal alcohol use during pregnancy									
SGA without alcohol use	1100 (95.7)	5.8	Reference		-0.36 (1.08)	Reference	.66		
SGA with alcohol use	<50 (4.3)	2.1	0.29 (0.03 to 2.89)	.29	-0.35 (1.00)	-0.06 (-0.34 to 0.22)			
By maternal GWG									
SGA with normal GWG	650 (57.5)	3.9	Reference		-0.28 (1.04)	Reference	.01 ^c		
SGA with inadequate GWG	500 (42.5)	8.0	2.18 (1.23 to 3.84)	.007 ^c	-0.46 (1.11)	-0.16 (-0.29 to -0.03)			
By maternal hypertension during pregnancy									
SGA without hypertension	1000 (88.4)	5.3	Reference		-0.36 (1.07)	Reference	.12		
SGA with hypertension	150 (11.6)	8.5	1.01 (0.45 to 2.26)	.99	-0.35 (1.13)	0.16 (-0.04 to 0.36)			
By maternal genital herpes infection during pregnancy									
SGA without genital herpes infection	1100 (88.9)	5.6	Reference		-0.36 (1.08)	Reference	.27		
SGA with genital herpes infection	<50 (1.1)	8.3	1.60 (0.24 to 10.58)	.62	-0.02 (1.19)	0.40 (-0.32 to 1.12)			
By multiple births									
Singleton SGA	750 (65.7)	6.3	Reference		-0.41 (1.09)	Reference	.13		
Multiple-birth SGA without ovulation stimulation	300 (26.7)	4.4	0.92 (0.41 to 2.02)	.83	-0.29 (1.06)	0.13 (-0.04 to 0.29)	.05 ^c		
Multiple-birth SGA with ovulation stimulation	100 (7.6)	4.7	0.79 (0.23 to 2.68)	.70	-0.20 (0.96)	0.27 (0.00 to 0.54)			

^a Sample size numbers were rounded to the nearest 50 in accordance with US Department of Education guidelines for reporting ECLS-B data.

^b Adjusted for maternal age, race, educational level, marital status, delivery method, diabetes during pregnancy, vitamin use within last 3 months before pregnancy, working status during last 12 months before delivery, and gestational age; and child gender; timing of solid food introduction, and breastfeeding duration.

^c Statistically significant ($P < .05$) or marginally significant ($P < .10$) difference.

TABLE 3 Risks of Stunting and Mean Height-for-Age z Scores at Age 5 Years of SGA Etiological Subgroups by Cooccurrence of Maternal Smoking and Inadequate GWG ($N = 1100^a$)

	Smoking	Inadequate GWG	Sample Size, n (%)	Stunting at 5 Years			Height for Age z Score at 5 Years		
				%	Adjusted OR (95% CI) ^b	P	Mean (SD)	Adjusted Mean Difference (95% CI) ^b	P
None	—	—	500 (45.3)	4.0	Reference		−0.25 (1.06)	Reference	
Single factor	+	—	150 (33.9)	3.7	0.77 (0.25 to 2.36)	.64	−0.39 (0.99)	−0.05 (−0.25 to 0.16)	.66
	—	+	400 (12.2)	7.2	1.81 (0.98 to 3.34)	.06 ^c	−0.43 (1.09)	−0.13 (−0.27 to 0.01)	.08 ^c
Two factors	+	+	100 (8.6)	11.5	3.10 (1.21 to 7.91)	.02 ^c	−0.60 (1.19)	−0.32 (−0.57 to −0.07)	.01 ^c

^a Sample size numbers were rounded to the nearest 50 in accordance with US Department of Education guidelines for reporting ECLS-B data.

^b Adjusted for maternal age, race, educational level, marital status, delivery method, diabetes during pregnancy, vitamin use within last 3 months before pregnancy, working status during last 12 months before delivery, and gestational age; and child gender, timing of solid food introduction, and breastfeeding duration.

^c Statistically significant ($P < .05$) or marginally significant ($P < .10$) difference.

ages. We calculated age- and gender-specific height z scores at age 5 years based on the US Centers for Disease Control and Prevention Growth Chart.³³ We defined stunting at age 5 years as height-for-age z score less than -2 .² Although we prefer longer-term follow-up data, we did not include 6-year height as the outcome because of the small (17.8%) and selective sample followed at 6 years in ECLS-B.³²

Confounders

On the basis of the literature and our preliminary analysis, the potential confounders we considered for this analysis included maternal age, race/ethnicity, educational level, marital status, delivery method, diabetes during pregnancy, vitamin use within last 3 months before pregnancy, working status during last 12 months before delivery, and gestational age; and child gender, timing of solid food introduction, and breastfeeding duration.

Statistical Analysis

We used mean and SD to describe continuous variables and percentages to describe categorical variables. Differences in sociodemographic and pregnancy characteristics between the excluded and included SGA samples were examined by t tests and χ^2 tests.

We used multivariable logistic regression models to compare the risk of stunting at age 5 years

between SGA subgroups with and without a specific risk factor (eg, SGA newborns of short mothers versus SGA newborns of normal height mothers). Similarly, mean height-for-age z score at age 5 years was compared with multivariable linear regression models. To examine the cooccurrence of maternal smoking during pregnancy and inadequate GWG, we divided SGA newborns into 4 subgroups: without smoking or inadequate GWG, with smoking only, with inadequate GWG only, with both smoking and inadequate GWG. Then we fitted multivariable logistic regression models to compare the risk of stunting and multivariable linear regression model to compare mean height-for-age z score at age 5 years across these 4 SGA subgroups, respectively. For this step, we collapsed maternal smoking status during pregnancy from the 4 original categories (ie, never, quit, moderate, and heavy smoking) into a binary variable (smoking versus nonsmoking) to ensure enough sample size for each SGA subgroup by smoking and GWG.

All regression models were fitted with generalized estimating equations to control for the correlation between multiple siblings, by specifying exchangeable covariance matrix among siblings. We set .05 as significance level. All the data analyses were performed by SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Sample Characteristics

Among the mothers in the included SGA sample ($n = 1100$), the mean age was 27.3 years ($SD = 6.6$), approximately half (48.7%) were non-Hispanic whites, 47.6% had college or higher education level, and 62.2% were married (Table 1). Among the children, 49.0% were boys, the mean gestational age was 37.5 weeks ($SD = 3.1$), 62.3% were ever breastfed, and 29.4% were preterm birth.

Height of SGA Subgroups by Single Risk Factors

SGA newborns had higher risk of stunting (5.7% vs 2.1%) and lower mean height-for-age z score (-0.36 [$SD = 1.08$] vs 0.11 [$SD = 1.04$]) at 5 years than AGA newborns. Within SGA newborns, the risk of stunting varied substantially across etiological subgroups. SGA subgroup with maternal short stature (adjusted odds ratio [OR] = 3.88, 95% confidence interval [CI] = 2.16 to 6.96) or inadequate GWG (adjusted OR = 2.18, 95% CI = 1.23 to 3.84) had significantly higher risk of stunting at 5 years, compared with SGA newborns without the corresponding risk factor (Table 2). SGA subgroup with maternal heavy smoking during pregnancy had marginally reduced mean height-for-age z score (adjusted mean difference, -0.20 ; 95% CI = -0.42 to 0.02) than SGA subgroup without maternal smoking.

Multiple-birth SGA newborns with ovulation stimulus had marginally higher mean height-for-age z score than singleton SGA newborns (0.27, 95% CI = 0.00 to 0.54).

Our supplemental data analysis showed that 29.4% of included SGA children were born preterm (<37 weeks). The risk of stunting at age 5 years was 8.6% and the mean birth weight was 1588.8 g (SD = 513.2) among the preterm SGA children in the included sample. In addition, 62.1% of the included SGA children were low birth weight (<2500 g), and the risk of stunting at age 5 years was 6.8% among SGA children with low birth weight.

Height of SGA Subgroups by Cooccurrence of Smoking and Inadequate GWG

Table 3 shows the risk of stunting and height-for-age z score differences across SGA etiological subgroups by maternal smoking status during pregnancy and GWG. Compared with SGA subgroup without maternal smoking or inadequate GWG, SGA subgroup with inadequate GWG alone had marginally higher risk of stunting at age 5 years (7.2% vs 4.0%; adjusted OR = 1.81, 95% CI = 0.98 to 3.34), whereas SGA subgroup with both maternal smoking and inadequate GWG had much higher risk of stunting (11.5%; adjusted OR = 3.10, 95% CI = 1.21 to 7.91). To assess the robustness of these findings, we also ran sensitivity analysis by defining SGA as birth weight below 2 SD of the mean birth weight of normal newborns. As expected, this stricter definition led to significant reduction in sample size of SGA children (from 1100 to 350). It yielded similar findings as using 10th percentile but wider CIs. For example, SGA subgroup with cooccurrence of maternal smoking and inadequate GWG had much higher risk of stunting than SGA newborns with single factor only (Supplemental Table 4).

DISCUSSION

In this study, we found that etiological SGA subgroups had differential risks of stunting at age 5 years. SGA subgroups with maternal short stature or with cooccurrence of maternal smoking during pregnancy and inadequate GWG were in particularly high risk of stunting at age 5 years; however, SGA subgroup with maternal prepregnancy underweight had significantly lower risk of stunting at age 5 years. These novel findings had important clinical implications. First, they are helpful in identifying SGA newborns at high risk of stunting at an earlier age and thus informing earlier treatments, which may improve their long-term health and ameliorate their social disadvantage. This earlier prognosis is important because according to the current guidelines, growth hormone is usually held until age 3 years for stunted SGA newborns who do not experience catch-up growth; as a result, some of SGA newborns miss the valuable opportunity for early treatment. Second, our findings can help to reduce unnecessary anxiety of parents and pediatricians about risk of stunting in some SGA etiological subgroups such as due to maternal prepregnancy underweight at least in the United States and possibly other developed countries.

Our finding that SGA subgroup with maternal short stature had higher risk of stunting at age 5 years is consistent with previous studies showing maternal short stature was a risk factor for stunting.³⁴⁻³⁶ A possible reason is that SGA newborns with maternal short stature inherit limited genetic growth potential from their mother.^{35,37} Alternatively, they may share with their mother disadvantaged family environments that inhibit height growth, such as poor diet characterized by low protein, calcium, and vitamin D.³⁵

We found that SGA newborns with maternal inadequate GWG had higher risk of stunting and reduced

mean height-for-age z score at age 5 years compared with SGA newborns without inadequate GWG. GWG is a proxy for maternal nutritional intake or energy balance and placental function during pregnancy. Fetuses with maternal inadequate GWG might have insufficient supply of glucose, vitamin D, calcium, and protein during pregnancy and thus shortened birth length (a predictor for childhood height).³⁸ In addition, intrauterine nutrition shortage can lead to reduced level of circulating IGF-1 in the fetus and thus inhibit fetal linear growth and weight gain.^{12,13}

A novel finding of this study was that SGA newborns with cooccurrence of maternal smoking and inadequate GWG during pregnancy had much higher risk of stunting and lower mean height-for-age z score at age 5 years, while SGA newborns with only 1 of them did not have significantly higher risk of stunting or lower mean height-for-age z score, compared with SGA newborns without these 2 risk factors. It might be explained by the fact that SGA newborns with cooccurrence of these 2 SGA risk factors may undergo “double hits” of linear growth restriction in utero and also that 1 adverse exposure may increase the fetus’s susceptibility to the other. On one hand, maternal smoking may increase the SGA fetus’ susceptibility to height deficit due to inadequate GWG. Specifically, the adverse effect of poor nutrition status reflected by inadequate GWG can be amplified by maternal smoking during pregnancy because smoking is linked to poor appetite, increased energy expenditure, damaged oxidative stress of the placenta, and impaired placenta function.^{39,40} In addition, SGA newborns with maternal smoking during pregnancy are more likely to be exposed to postnatal secondhand smoke, which may prevent them from catch-up linear growth during early childhood. On the other hand, inadequate GWG during pregnancy

may increase fetal susceptibility to height deficit due to maternal smoking. Specifically, smoking during pregnancy likely leads to damage in fetal hypothalamic-pituitary-adrenal axis,¹⁵ which can be worsened by inadequate GWG because fetal brain development relies on glucose and other nutrients from the mother. In addition, maternal smoking during pregnancy and inadequate GWG may both lead to *IGF* gene hypermethylation and thus reduced IGF levels.^{13,41} Therefore, it is even more critical for smoking mothers to gain adequate weight during pregnancy if they cannot quit smoking.

Another novel finding of our study was that SGA subgroup with maternal prepregnancy underweight had similar risk of stunting at age 5 years with AGA children, suggesting that stunting is less of a concern for these SGA children. It seems not that necessary for parents and pediatricians to be anxious about their linear growth.

Our study had several limitations. First, retrospective self-reports of prepregnancy weight and GWG at the 9-month postpartum visit were subject to recall bias. Second, self-reported smoking status during pregnancy might also be subject to bias because it is a socially undesirable behavior. Third, the sample size of SGA subgroup with maternal alcohol use during pregnancy or with genital herpes infection during pregnancy was rather small, and thus our findings for these subgroups need to be interpreted with

caution. Replications are much needed in larger samples. Fourth, ECLS-B data set did not collect information on growth hormone treatment of stunting. Fifth, we could not adjust for maternal birth weight and diet during pregnancy because their information was unavailable in ECLS-B. Sixth, there were no data on birth length available in ECLS-B to better distinguish the impact of prenatal and postnatal factors on linear growth. Seventh, the LMP-based gestational age was subject to errors because of recall bias and irregular menstrual cycle. Eighth, caution is advised in the use of growth hormone therapy at an early age for SGA newborns of inadequate GWG mothers who smoke, given the observational nature of our analysis. Ninth, the considerable attrition rate of SGA sample at 5-year follow-up might limit the generalizability of our findings. Finally, 5-year follow-up is a relatively short portion of childhood. Further research is needed to examine how long our observed differences in height growth across SGA etiological subgroups last.

CONCLUSIONS

Etiological subgroups of SGA largely differed in risk of stunting at age 5 years. SGA newborns of inadequate GWG mothers who smoke and SGA newborns of short mothers were at particularly high risk of stunting. These SGA newborns should be monitored closely for height growth

and receive early intervention if needed. But any benefits of postnatal “catch-up” height growth need to be balanced against its potential contribution to later chronic disease such as diabetes and cardiovascular disease. From prevention perspective, it is critical for smoking mothers to gain adequate weight during pregnancy if they cannot quit, which may protect their child from stunting.

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ABBREVIATIONS

AGA: appropriate for gestational age
 CI: confidence interval
 ECLS-B: Early Childhood Longitudinal Study-Birth Cohort
 GWG: gestational weight gain
 IGF: insulin-like growth factor
 LMP: last menstrual period
 OR: odds ratio
 SGA: small for gestational age

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