



Catch-Up Growth and Neurobehavioral Development among Full-Term, Small-for-Gestational-Age Children: A Nationwide Japanese Population-Based Study

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Objective To examine the relationship between catch-up growth of full-term, small for gestational age (SGA) children and their neurobehavioral development.

Study design Data were obtained from a population-based nationwide Japanese longitudinal survey that started in 2001. Study participants were full-term children with information on height at 2 years of age (n = 32 533). Catch-up growth for SGA infants was defined as achieving a height at 2 years of age of more than -2.0 standard deviations for chronological age. Logistic regression analyses were used to estimate ORs and 95% CIs for the associations of SGA and catch-up growth status with neurobehavioral development at 2.5 and 8 years of age, adjusting for potential infant- and parent-related confounding factors.

Results Fifteen percent of term SGA infants failed to catch up in height. At 2.5 years of age, SGA children without catch-up growth were more likely to be unable to climb stairs (OR, 10.42; 95% CI, 5.55-19.56) and unable to compose a 2-word sentence (OR, 3.58; 95% CI, 1.81-7.08) compared with children with normal growth at birth. Furthermore, SGA children without catch-up growth were at increased risk for aggressive behaviors (OR, 3.85; 95% CI, 1.19-12.47) at 8 years of age.

Conclusions Continuous follow-up for full-term SGA infants with failure of catch-up growth or poor postnatal growth may be beneficial for early detection and intervention for behavioral problems. (*J Pediatr* 2018;192:41-6).

Full-term, small for gestational age (SGA) infants are at increased risk for neurologic problems, such as cerebral palsy and cognitive delay,¹⁻³ as well as neurobehavioral difficulties through 8 years of age.^{4,5} However, term SGA infants are an inhomogeneous group with diverse risk factors, and there is limited evidence to aid in the identification of particularly vulnerable subgroups. This information would be beneficial in assisting pediatricians in providing appropriate long-term developmental follow-up.

Evaluation of catch-up growth or postnatal growth may be useful in stratifying risk for developmental outcomes. A previous study showed that term SGA infants, (defined as a birth weight 2 or SDs below the mean), who caught up to a weight of more than -2 SDs at 1 year of age had favorable cognitive outcomes at 4 years of age compared with those who did not catch up.⁶ However, previous studies examining the relationship between catch-up growth and neurologic development were conducted among mostly preterm children.⁷⁻⁹ Only 2 studies included term SGA children, but they focused only on cognitive function, including the above-mentioned studies.^{6-8,10}

The purpose of this study was to examine the relationship between catch-up growth at 2 years of age and neurobehavioral development at 2.5 and 8 years of age among term SGA children using data from a nationwide population-based survey conducted in Japan.

Methods

The Japanese Ministry of Health, Labour and Welfare has been conducting an annual survey of newborn infants and their parents, the Longitudinal Survey of Babies in the 21st Century, since 2001.^{11,12} Briefly, baseline questionnaires were distributed to all families throughout the country with 6-month-old infants born between January 10 and 17 or between July 10 and 17, 2001. Of 53 575 mailed

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AGA Appropriate for gestational age
GA Gestational age
SGA Small for gestational age

questionnaires, 47 015 were completed and returned (88% response rate). Birth records were also linked to each child included in this survey.

Children were excluded if they did not have information on birth weight and birth length ($n = 152$) or gestational age (GA; $n = 6$). In the present study, we focused on full-term infants and excluded children born before 37 weeks of gestation ($n = 2320$) and after 42 weeks of gestation ($n = 413$), leaving 44 124 children for analysis (Figure; available at www.jpeds.com).

SGA and Catch-Up Growth Status

The Japanese guidelines for growth hormone replacement therapy for SGA-related short stature^{13,14} define SGA as (1) a birth weight below the 10th percentile for GA and birth length below -2.0 SDs for GA, or (2) birth weight below -2.0 SDs for GA and birth length below the 10th percentile for GA. SGA infants were classified based on this definition using the Japanese reference value for birth size according to GA in days from the Committee for Newborns of the Japanese Pediatric Society.^{15,16} Infants who were not SGA at birth were classified as appropriate for GA (AGA).

The Japanese guidelines for growth hormone replacement therapy for SGA-related short stature^{13,14} also were used to define catch-up growth. The guidelines are consistent with the general definition of catch-up growth for SGA infants¹⁷ and define catch-up growth as a height at 2 years of age above -2.0 SDs for age. The report on growth development for children in fiscal 2000¹⁸ was used to calculate SDs for each month at 2 years of age. Finally, SGA children were classified as having catch-up growth or no catch-up growth at 2 years of age. Because height at 2 years of age was queried in the third survey, children were excluded if there was no height information available in the third survey owing to loss to follow-up ($n = 11 444$) or if this information was not provided ($n = 147$), leaving 32 533 children eligible for the final analysis (Figure).

Age-appropriate neurobehavioral outcomes were queried by survey questions at 2.5 (ie, in the third survey) and 8 (ie, in the eighth survey) years of age.^{11,12} The questions at 2.5 years of age were: (1) Can your child walk? (2) Can your child run? (3) Can your child climb stairs? (4) Can your child say words with meaning? (5) Can your child compose 2-word sentences? and (6) Can your child use a spoon to eat? These 6 items were consistent with Denver II.¹⁹ The survey questions at 2.5 years of age were divided into 3 categories dealing with gross motor development, language development, and personal-social development.¹⁹ Most children have these abilities by 2.5 years of age¹⁹; thus, we defined the inability to perform each behavior at 2.5 years of age as developmental delay.

The 7 questions posed at 8 years of age were consistent with the Child Behavior Checklist/4-18 Japanese Edition, designed for children aged 4-18 years.²⁰ Three questions were related to attention problems^{5,21,22}: (1) Does your child interrupt people? (2) Can your child wait his/her turn during play? And (3) Can your child pay attention to surrounding areas when crossing the street? The remaining 4 questions were related to aggressive behaviors^{5,21,22}: 4) Does your child tell lies?

(5) Does your child destroy toys and/or books? (6) Does your child hurt other people? and (7) Does your child cause disturbances in public? We also defined an outcome of “all attention problems” as the existence of all 3 attention problems, and an outcome of “all aggressive behaviors” as the existence of all 4 aggressive behaviors, according to previous studies.^{5,21,22}

Statistical Analyses

Logistic regression models and estimated ORs and 95% CIs were used to evaluate each outcome with AGA children as the reference category. Associations between the SGA and catch-up growth status and behavioral outcomes were evaluated at 2.5 and 8 years of age. Controlling for potential child- and parent-related confounding factors was based on previous studies^{4,5,11,12} and clinical relevance. Child factors included sex, singleton or not, gestational week, and parity. Parental factors included maternal age at delivery, maternal smoking habits, maternal educational attainment, and paternal educational attainment. The child's sex, singleton or not, gestational week, parity, and maternal age at delivery were listed in the birth record. Maternal smoking status was ascertained at the first survey (at 6 months of age). Maternal and paternal educational attainment was obtained from the second survey (at 18 months of age) and classified into 3 categories: high school or less, junior college (2 years) or vocational school, and university (4 years) or higher. We excluded missing and incomplete cases.

In the sensitivity analyses, we excluded children who had visited clinics or hospitals for congenital diseases between 7 and 18 months of age to remove possible selection bias, because children with disabilities might have been born SGA. We had no information on visits made before 6 months of age.

All CIs were calculated at the 95% level. Analyses were performed using Stata statistical software (Stata SE version 14, Stata Corp, College Station, Texas). This study was approved by the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences Institutional Review Board (No. 1506-073).

Results

Table I shows the baseline characteristics of the participants according to SGA and catch-up growth status. Overall, the mean \pm SD birth weight and birth height among the eligible participants were 3074 ± 379 g and 49.1 ± 2.0 cm, respectively. Of the 581 SGA infants, 15% ($n = 86$) did not catch up at 2 years of age. Height was assessed at 30.0 ± 1.0 months. SGA children without catch-up growth (SGA and no catch-up group) were more likely to have more siblings and parents with lower education compared with the other 2 categories (AGA and SGA and catch-up growth, Table I). SGA children with catch-up growth (SGA and catch-up group) were more likely to be girls and to have smoking mothers compared with the other 2 categories (AGA and SGA and no catch-up, Table I). Among the eligible participants (Figure), children without information on behavioral outcomes at 8 years of age were more

Table I. Demographic characteristics of eligible children, separated by SGA and catch-up growth status (n = 32 533)

Characteristics	AGA (n = 31 952)	SGA and catch-up growth (n = 495)	SGA and no catch-up growth (n = 86)
Children			
Sex, n (%) [*]			
Boys	16 559 (51.8)	188 (38.0)	44 (51.2)
Girls	15 393 (48.2)	307 (62.0)	42 (48.8)
Singleton birth, n (%) [*]	31 625 (99.0)	460 (92.9)	81 (94.2)
Multiple birth, n (%) [*]	327 (1.0)	35 (7.1)	5 (5.8)
Mean GA, weeks (SD) [*]	39.1 (1.1)	39.1 (1.2)	38.7 (1.2)
Parity, n (%) [*]			
0	16 121 (50.5)	284 (57.4)	36 (41.9)
≥1	15 831 (49.6)	211 (42.6)	50 (58.1)
Parents			
Mean maternal age at delivery, years (SD) [*]	30.3 (4.4)	29.9 (4.6)	30.4 (4.7)
Maternal smoking status, n (%) [†]			
Nonsmoker	27 162 (85.4)	383 (77.9)	71 (82.6)
Smoker	4642 (14.6)	109 (22.2)	15 (17.4)
Maternal educational attainment, n (%) [‡]			
University or higher	4679 (15.0)	64 (13.3)	9 (10.7)
Junior college	13 243 (42.5)	193 (40.0)	31 (36.9)
Less than or equal to high school	13 206 (42.4)	225 (46.7)	44 (52.4)
Paternal educational attainment, n (%) [‡]			
University or higher	11 790 (38.2)	159 (33.6)	25 (30.5)
Junior college	4931 (16.0)	61 (12.9)	11 (13.4)
Less than or equal to high school	14 117 (45.8)	253 (53.5)	46 (56.1)

There were 151 cases missing on maternal smoking, 839 cases missing on maternal educational attainment, and 1140 cases missing on paternal educational attainment.

^{*}Obtained from the birth record.

[†]Obtained from the first survey (at 6 months of age).

[‡]Obtained from the second survey (at 18 months of age).

likely to be born as SGA infants, and to have mothers who smoke and parents with lower education compared with those included for the analysis at 8 years of age (Table II).

Table III shows the associations between SGA and catch-up growth status and neurobehavioral developmental outcomes at 2.5 years of age. Children in the SGA and no catch-up group were more likely to demonstrate developmental delays in all the behaviors we examined. For example, children in the SGA and no catch-up group were more likely to be unable to climb stairs (OR, 10.42; 95% CI, 5.55-19.56) and compose a 2-word sentence (OR, 3.58; 95% CI, 1.81-7.08) compared with AGA children. Although SGA children with catch-up growth were also at increased risk for abnormal development, the ORs were smaller than those in the SGA and no catch-up group. Even when we excluded 682 children with congenital diseases in the sensitivity analysis, the main findings did not change substantially (Table IV; available at www.jpeds.com).

Table V shows the associations between SGA and catch-up growth status and behavioral outcomes at 8 years of age. Children in the SGA and no catch-up group were at increased risk for 1 aggressive behavioral outcome and were more likely to destroy toys and/or books (OR, 2.47; 95% CI, 1.33-4.61) compared with the AGA group. In addition, the OR for all aggressive behaviors was significantly elevated in the SGA and no catch-up group compared with the AGA group (OR, 3.85; 95% CI, 1.19-12.47). By contrast, the SGA and catch-up group was not at increased risk for attentional problems or aggressive behaviors. Even when we excluded 566 children with congenital diseases in the sensitivity analysis, the main findings did not change substantially (Table VI; available at www.jpeds.com).

Table II. Demographic characteristics of children included and lost to follow-up at age 8 (n = 32 533)

Characteristics	Age 8 years	
	Included (n = 27 485)	Lost to follow-up (n = 5048)
Children		
Sex, n (%) [*]		
Boys	14 218 (51.7)	2573 (51.0)
Girls	13 267 (48.3)	2475 (49.0)
Singleton birth, n (%) [*]	27 184 (98.9)	4982 (98.7)
Multiple birth, n (%) [*]	301 (1.1)	66 (1.3)
Mean GA, weeks (SD) [*]	39.1 (1.1)	39.1 (1.2)
Parity, n (%) [*]		
0	13 859 (50.4)	2582 (51.2)
≥1	13 626 (49.6)	2466 (48.9)
SGA and catch-up growth status		
AGA	27 016 (98.3)	4936 (97.8)
SGA and catch-up growth	403 (1.5)	92 (1.8)
SGA and no catch-up growth	66 (0.2)	20 (0.4)
Parental		
Mean maternal age at delivery, years (SD) [*]	30.4 (4.3)	29.2 (4.7)
Maternal smoking status, n (%) [†]		
Nonsmoker	23 813 (87.0)	3803 (75.9)
Smoker	3560 (13.0)	1206 (24.1)
Maternal educational attainment, n (%) [‡]		
University or higher	4275 (15.8)	477 (10.3)
Junior college	11 784 (43.6)	1683 (36.2)
Less than or equal to high school	10 991 (40.6)	2484 (53.5)
Paternal educational attainment, n (%) [‡]		
University or higher	10 675 (39.8)	1299 (28.5)
Junior college	4291 (16.0)	712 (15.6)
Less than or equal to high school	11 861 (44.2)	2555 (56.0)

There were 151 cases missing on maternal smoking, 839 cases missing on maternal educational attainment, and 1140 cases missing on paternal educational attainment.

^{*}Obtained from the birth record.

[†]Obtained from the first survey (at 6 months of age).

[‡]Obtained from the second survey (at 18 months of age).

Table III. Adjusted* ORs for associations between SGA status and behavioral developments at age 2.5 years

	AGA	SGA and catch-up growth	SGA and no catch-up growth
Age of 2.5 years			
Unable to walk			
n/N	65/31 894	1/494	8/86
OR (95% CI)	1 (ref.)	1.02 (0.14-7.43)	45.84 (20.03-104.88)
Unable to run			
n/N	142/31 892	2/494	10/86
OR (95% CI)	1 (ref.)	0.96 (0.24-3.93)	29.25 (14.18-60.32)
Unable to climb stairs			
n/N	569/31 871	12/493	13/85
OR (95% CI)	1 (ref.)	1.34 (0.73-2.45)	10.42 (5.55-19.56)
Unable to say words with meaning			
n/N	183/31 884	4/494	6/86
OR (95% CI)	1 (ref.)	1.63 (0.6-4.45)	10.39 (4.08-26.43)
Unable to compose a 2-phrase sentence			
n/N	1198/31 868	21/494	11/85
OR (95% CI)	1 (ref.)	1.4 (0.89-2.19)	3.58 (1.81-7.08)
Unable to use a spoon to eat			
n/N	555/31 884	16/494	7/86
OR (95% CI)	1 (ref.)	2.37 (1.41-3.96)	4.81 (2.04-11.31)

*Adjusted for child factors (sex, singleton or not, GA, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Discussion

In this nationwide longitudinal study from Japan, full-term SGA children without catch-up growth were at increased risk for motor, language, and personal-social developmental delays at

2.5 years of age. Furthermore, term SGA children without catch-up growth were at increased risk for aggressive behaviors at school age.

We defined catch-up growth for SGA infants at 2 years of age as a height above -2.0 SDs for age, which is consistent with the general definition for catch-up growth for SGA infants.¹⁷

Table V. Adjusted* ORs for associations between SGA status and behavioral developments at age 8 years

	AGA	SGA and catch-up growth	SGA and no catch-up growth
Attention problems			
Interrupting people			
n/N	10 303/26 681	165/401	21/65
OR (95% CI)	1 (ref.)	1.17 (0.95-1.44)	0.8 (0.47-1.36)
Inability to wait his/her turn during play			
n/N	1597/26 791	21/403	5/65
OR (95% CI)	1 (ref.)	0.65 (0.39-1.08)	1.29 (0.52-3.24)
Failure to pay attention when crossing a street			
n/N	5203/26 776	83/400	15/65
OR (95% CI)	1 (ref.)	1.19 (0.92-1.52)	1.23 (0.69-2.22)
All attention problems			
n/N	429/26 929	7/403	0/65
OR (95% CI)	1 (ref.)	0.96 (0.42-2.18)	NE
Aggressive behaviors			
Lying			
n/N	6496/26 623	97/397	14/65
OR (95% CI)	1 (ref.)	1.01 (0.8-1.28)	0.88 (0.48-1.60)
Destroying toys and/or books			
n/N	2479/26 843	37/401	13/65
OR (95% CI)	1 (ref.)	1.03 (0.72-1.47)	2.47 (1.33-4.61)
Hurting other people			
n/N	2827/26 833	36/399	6/65
OR (95% CI)	1 (ref.)	0.9 (0.63-1.28)	0.86 (0.37-2.00)
Causing disturbances in public			
n/N	5335/26 784	75/400	16/66
OR (95% CI)	1 (ref.)	0.93 (0.71-1.21)	1.19 (0.66-2.14)
All aggressive behaviors			
n/N	314/26 948	3/402	3/65
OR (95% CI)	1 (ref.)	0.6 (0.19-1.89)	3.85 (1.19-12.47)

NE, Not estimatable.

*Adjusted for child factors (sex, singleton or not, GA, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

We found that 15% of term SGA infants did not catch up at 2 years of age. Although we followed the Japanese guidelines for growth hormone replacement therapy for SGA-related short stature, the participants were born in 2001, that is, 7 years before the approval of growth hormone replacement therapy by the Japanese government in 2008.¹⁵ Thus, it is unlikely that the treatment affected the cognitive development of the participants.^{17,23} Although we followed the general definition, previous studies that examined the relationship between catch-up growth or postnatal growth and neurologic development used different definitions (eg, by weight^{6,9,10}), which hampers simple comparison of the findings.

At 2.5 years of age, term SGA children without catch-up growth were more likely to demonstrate developmental delays in gross motor, language, and personal-social development. The ORs for the delays among the term SGA children without catch-up growth at 2 years were higher than those for the term SGA children with catch-up growth (Table III), or those for the term SGA children in total, which we examined in a previous study.⁵ A recent study attempted to examine the association between postnatal weight gain at 6 months of age and gross motor development, defined by cerebral palsy, at 5 years of age among preterm SGA children, but the authors failed to confirm the hypothesis owing to the small number of cases in the study.⁹

Moreover, term SGA children without catch-up growth were more likely to demonstrate aggressive behaviors at 8 years of age in the present study. This finding is consistent with the evidence that term SGA children are more likely to display behavioral development problems (inattention or aggressive behavior) at school age.^{5,24,25} Indeed, our previous study showed that term SGA children were at increased risk for attentional problems and aggressive behaviors,⁵ but effect estimates for aggressive behaviors were lower than those for the SGA and no catch-up children in the present study. The findings of the present study are also consistent with the previous studies that examined the long-term impact of postnatal growth among SGA infants on cognitive function; these studies showed negative impacts of poor postnatal growth in early childhood (defined by weight) on intelligence quotient at 4 or 7 years of age.^{6,10} Only 1 study⁹ conducted among preterm SGA infants examined the impact of poor postnatal weight gain at 6 months of age on inattention-hyperactivity symptoms measured by the Strengths and Difficulties Questionnaire at 5 years of age, or on difficulties in school at 8 years of age. However, the small sample size in this previous study again hampers interpretation.

A strength of our study was that we used a large, nationally representative sample. About 5% of all children born in Japan in 2001 were included in the survey. This allowed for a larger sample of SGA and AGA infants compared with previous studies. In addition, the validity of our findings is strengthened by a high response rate at baseline. Moreover, poor postnatal growth or catch-up growth was defined using the general definition of catch-up growth for SGA infants.¹⁷

This study has several limitations. First, although we used survey questions consistent with Denver-II or the Child Behavior Check List, we were unable to use validated tests to assess

behavioral outcomes such as the Strengths and Difficulties Questionnaire that was used in a previous study.⁹ Some outcome misclassification may have occurred, but the misclassification would be nondifferential, which moves effect estimates toward the null. Second, possible selection bias caused by loss to follow-up may have underestimated effect estimates, because children without information on behavioral outcomes at 8 years of age were more likely to be born as SGA infants and at risk for behavioral problems (ie, smoking mothers and parents with lower education) compared with those included for the analysis at 8 years of age (Table II). Finally, there was a possibility of residual confounding associated with the family environment, although we adjusted for several potential confounders in the analyses, including educational attainment of the parents.

Although long-term neurodevelopmental follow-up of full-term SGA infants may be difficult owing to limited resources, the results of our study suggest that continuous follow-up for those with failure of catch-up growth or poor postnatal growth may be beneficial to detect behavioral problems and provide adequate interventions. ■

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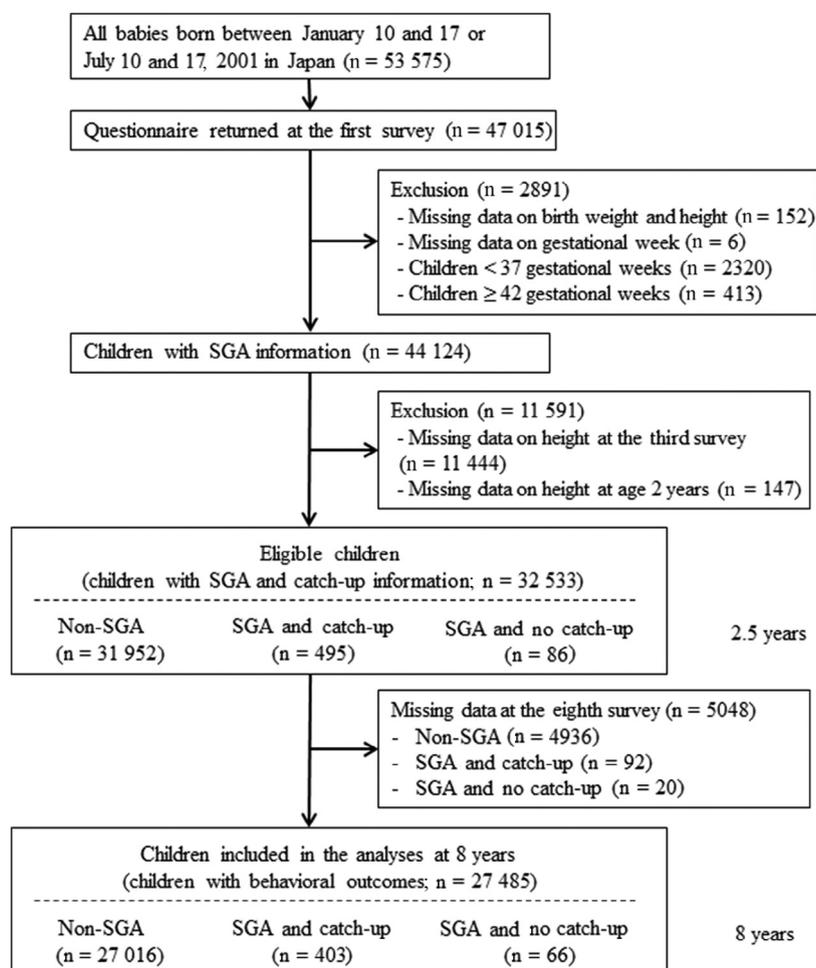


Figure. Study participant flow chart.

Table IV. Adjusted* ORs for associations between SGA status and behavioral developments at age 2.5 years excluding children with congenital disease

	AGA	SGA and catch-up growth	SGA and no catch-up growth
Age of 2.5 years			
Unable to walk			
n/N	32/31 288	0/472	5/74
OR (95% CI)	1 (ref.)	NE	63.35 (21.24-188.94)
Unable to run			
n/N	98/31 287	1/472	6/74
OR (95% CI)	1 (ref.)	0.74 (0.10-5.33)	27.31 (10.58-70.53)
Unable to climb stairs			
n/N	509/31 265	11/472	9/73
OR (95% CI)	1 (ref.)	1.41 (0.75-2.66)	8.94 (4.20-19.05)
Unable to say words with meaning			
n/N	146/31 279	3/472	5/74
OR (95% CI)	1 (ref.)	1.55 (0.49-4.94)	11.74 (4.12-33.49)
Unable to compose a 2-phrase sentence			
n/N	1113/31 263	19/472	7/74
OR (95% CI)	1 (ref.)	1.41 (0.88-2.25)	2.49 (1.06-5.85)
Unable to use a spoon to eat			
n/N	515/31 278	14/472	5/74
OR (95% CI)	1 (ref.)	2.34 (1.35-4.04)	4.04 (1.43-11.39)

*Adjusted for child factors (sex, singleton or not, GA, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Table VI. Adjusted* ORs for associations between SGA status and behavioral developments at age 8 years excluding children with congenital disease

	AGA	SGA and catch-up growth	SGA and no catch-up growth
Attention problems			
Interrupting people			
n/N	10087/26 187	159/383	21/56
OR (95% CI)	1 (ref.)	1.19 (0.96-1.47)	0.99 (0.57-1.72)
Inability to wait his/her turn during play			
n/N	1557/26 292	19/385	4/56
OR (95% CI)	1 (ref.)	0.6 (0.35-1.03)	1.13 (0.41-3.15)
Failure to pay attention when crossing a street			
n/N	5068/26 279	80/382	12/56
OR (95% CI)	1 (ref.)	1.21 (0.94-1.56)	1.12 (0.59-2.13)
All attention problems			
n/N	410/26 428	6/385	0/56
OR (95% CI)	1 (ref.)	0.87 (0.35-2.12)	NE
Aggressive behaviors			
Lying			
n/N	6345/26 129	94/379	14/56
OR (95% CI)	1 (ref.)	1.04 (0.82-1.32)	1.04 (0.56-1.91)
Destroying toys and/or books			
n/N	2410/26 346	36/383	13/56
OR (95% CI)	1 (ref.)	1.07 (0.74-1.53)	2.88 (1.53-5.45)
Hurting other people			
n/N	2746/26 336	34/381	5/56
OR (95% CI)	1 (ref.)	0.9 (0.63-1.29)	0.81 (0.32-2.05)
Causing disturbances in public			
n/N	5211/26 288	73/382	15/57
OR (95% CI)	1 (ref.)	0.95 (0.73-1.24)	1.44 (0.79-2.62)
All aggressive behaviors			
n/N	301/26 447	2/384	3/56
OR (95% CI)	1 (ref.)	0.43 (0.11-1.75)	4.4 (1.35-14.33)

NE, Not estimatable.

*Adjusted for child factors (sex, singleton or not, GA, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).