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Original article

Catch-up growth and behavioral development among preterm, small-for-gestational-age children: A nationwide Japanese population-based study

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Abstract

Objective: To examine the relationship between the catch-up growth of preterm, SGA children and their behavioral development.

Methods: We analyzed data from a large Japanese, nationwide, population-based, longitudinal survey that started in 2001. We restricted the study participants to preterm children with information on height at 2 years of age (n = 1667). Catch-up growth for SGA infants was defined as achieving a height at 2 years of age above −2.0 standard deviations for chronological age. We then used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the associations of SGA/catch-up status with neurobehavioral development both at 5.5 and 8 years of age, adjusting for potential infant- and parent-related confounding factors.

Results: Twenty-six percent of preterm SGA infants failed to catch up. SGA children without catch-up growth were more likely to be unable to listen without fidgeting (OR 2.51, 95% CI: 1.06–5.93) and unable to focus on one task (OR 2.66, 95% CI: 1.09–6.48) compared with non-SGA children at 5.5 years of age. Furthermore, SGA children without catch-up growth were at significant risk for inattention at 8 years of age.

Conclusions: SGA infants with poor postnatal growth were at risk for attention problems throughout preschool-age to school-age among preterm infants. Early detection and intervention for attention problems among these infants is warranted.

Keywords: Attention; Catch-up, postnatal growth; Preterm; Small-for-gestational-age

Abbreviations: SGA, small for gestational age; AGA, appropriate for gestational age; OR, odds ratio; CI, confidence interval; SD, standard deviation; MHLW, Ministry of Health, Labour and Welfare; GHRT, growth hormone replacement therapy; CBCL, Child Behavior Checklist; SDQ, strength and difficulty questionnaire

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1. Introduction

Small-for-gestational age (SGA) is a major concern in current developmental medicine and is comparable with preterm birth [1]. SGA has been shown to increase the risk for developmental delay and behavioral problems including inattention and aggressive behaviors even in full-term infants [1–5]. Moreover, previous studies have shown the relationships between SGA and inattention or attention deficit hyperactivity disorder (ADHD) among premature infants [6–8], although premature birth itself has also been shown to increase the risk of behavioral problems [9,10]. Guellec et al. showed that SGA was a risk factor for inattention-hyperactivity symptoms at 5 years among children born 29 weeks to 32 weeks of gestational age (GA) [6]. Tanis et al. showed that very preterm (less than 32 weeks of gestational age) SGA school-age children had lower functioning selective attention as compared with very preterm appropriate for gestational age (AGA) children [7]. As for an older age group, Strang-Karlsson et al. reported that the SGA group had more executive dysfunctions, which were generally thought to be related to ADHD [11], than the AGA group did among 18- to 27-year-old survivors of very low birth weight (less than 1499 g) [8]. Similarly, our previous study also showed that preterm SGA children were at a slightly increased risk for inattention at preschool age as compared with preterm non-SGA children [1].

In terms of the behavioral development of SGA infants, there has been considerable interest in the relationship between postnatal growth and development. Several studies have shown that postnatal growth affected the neurobehavioral development of term SGA infants [12,13]. Recently, we reported that full-term SGA children without catch-up growth were at increased risk for aggressive behaviors at school age [14]. As for preterm children, there have been a few studies on a similar issue [15–17]. However, the subjects of these studies were very preterm infants or very low birth weight infants (birth weight was less than 1499 g) [15–17]; thus, there was limited information about preterm infants with relatively larger gestational age, who constitute the majority of preterm infants. Therefore, in the present study, we examined the relationship between catch-up growth at 2 years of age and behavioral development both at 5.5 and 8 years of age among all preterm children from a nationwide, population-based survey conducted in Japan.

2. Methods

2.1. Study participants

The Japanese Ministry of Health, Labour and Welfare (MHLW) has been conducting an annual survey of newborn babies and their parents, the Longitudinal Survey of Babies in the 21st Century, since 2001 [9,18]. Briefly, baseline questionnaires were distributed to all families throughout the country with 6-month-old infants born between the 10th and 17th of January or the 10th and 17th of July 2001. Of 53,575 mailed questionnaires, 47,015 were completed and returned (88% response rate). Birth records were also linked to each child included in this survey.

We excluded children without information on birth weight and/or birth length (n = 152) and gestational week (n = 6). In the present study, we focused on preterm infants; therefore, we also excluded children born after 37 weeks (n = 44,537), leaving 2320 children eligible for analysis (Fig. 1).

3. SGA and catch-up growth status

According to the Japanese guidelines for growth hormone replacement therapy (GHRT) for SGA-related short stature [19,20], SGA is defined as 1) birth weight below the 10th percentile for gestational age (GA) and birth length below −2.0 standard deviations (SDs) for GA or 2) birth weight below −2.0 SDs for GA and birth length below the 10th percentile for GA. We classified SGA babies based on this definition using the Japanese reference value for birth size according to GA in days from the Committee for Newborns from the Japanese Pediatric Society [21,22].

We again used the Japanese guidelines for GHRT for SGA-related short stature [19,20] to define catch-up growth, which is consistent with the general definition of catch-up growth for SGA infants [23]. According to the guidelines, catch-up growth for SGA infants is defined as achieving a height at 2 years of age above −2.0 SDs for chronological age. We used the report on growth development for children in the fiscal year of 2000 [24] to calculate SD for each month at 2 years of age. Finally, we combined SGA status with catch-up growth to create a new category named SGA and catch-up growth status (Non-SGA; SGA & Catch-up; and SGA & No Catch-up). Because height at 2 years of age was queried in the third survey, we excluded children for whom height information was not available in the third survey due to loss to follow-up or no information on height in the third survey (n = 653), leaving 1667 children eligible for the final analysis (Fig. 1).

4. Neurobehavioral outcomes

Age-appropriate behavioral outcomes were queried by survey questions at 5.5 (i.e., in the sixth survey) [9,18] and 8 (i.e., in the eighth survey) years of age [9,18]. The questions at 5.5 years of age were as follows: 1) Can your child listen without fidgeting? 2) Can your child focus on one task? 3) Does your child remain

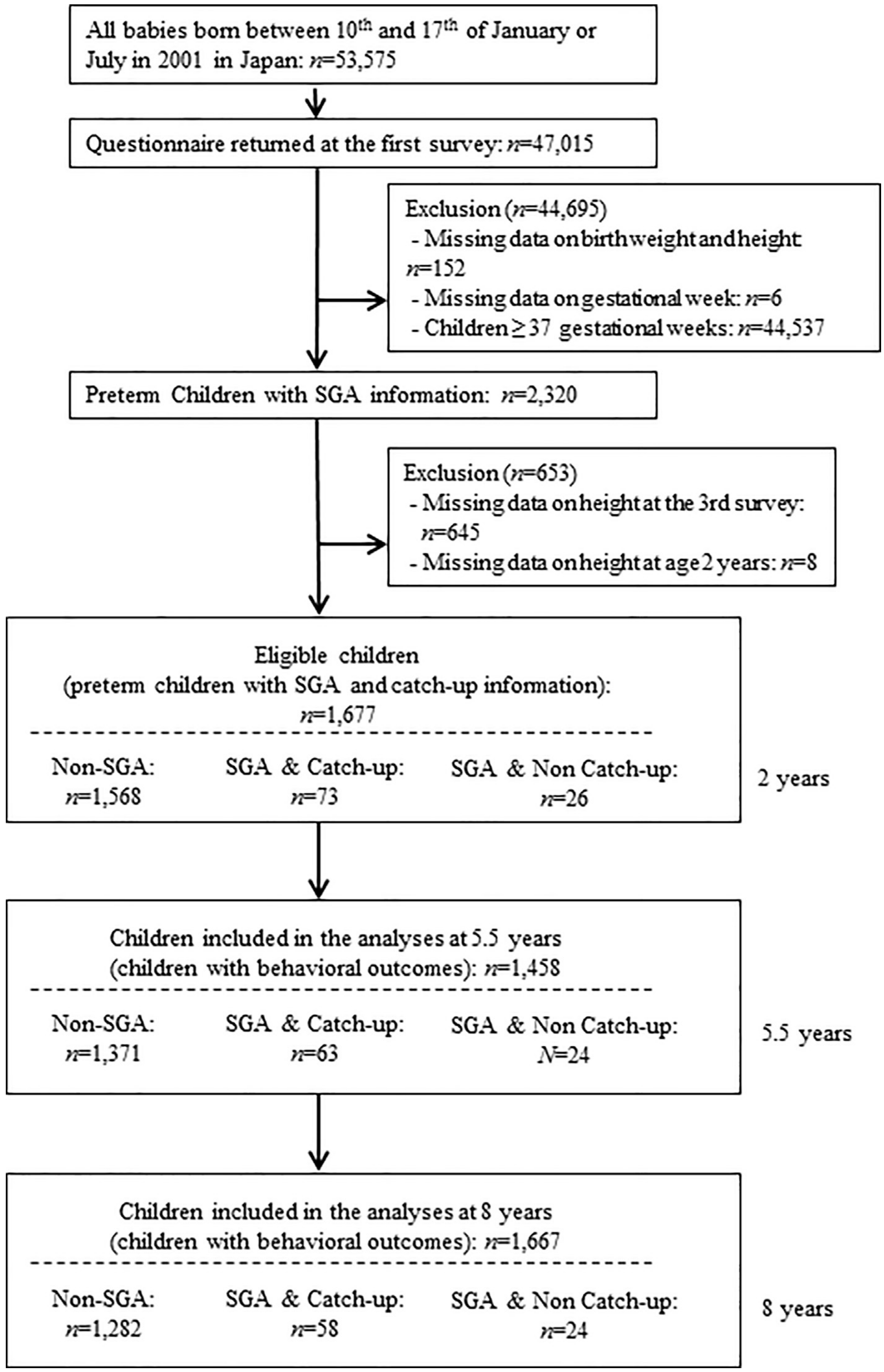

Fig. 1. Study participant flow chart.

patient? 4) Can your child express emotions appropriately? 5) Can your child act with others in a group setting? and 6) Can your child keep promises? According to the MHLW, these questions were developed to capture early signs of behavioral and developmental problems. The Ministry has aimed to track the prevalence of behavioral and developmental problems over the past decade, but we were unable to confirm if these questions have been externally validated.

The seven questions posed at 8 years of age were consistent with the Child Behavior Checklist (CBCL)/4–18 Japanese Edition, designed for children aged 4–18 years [25]. Three questions were related to attention problems [2,10,11,26]: 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 four questions were related to delinquent/aggressive behaviors [2,10,11,26]: 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 three attention problems, and an outcome of "all aggressive behaviors" as the existence of all four delinquent/aggressive behaviors, according to previous studies [2,10,11,26].

5. Statistical analyses

We used logistic regression models and estimated ORs and 95% CIs for each outcome using the non-SGA children as the reference category to examine the associations between the SGA and catch-up status and behavioral outcomes at 5.5 and 8 years of age. We controlled for potential child- and parent-related confounding factors based on previous studies [1,2,9,11,18] and the 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 three categories: ≤high school; 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 45 children with a gestational age less than 28 weeks to remove possible bias, as SGA children with a shorter gestational age tend to be categorized as "No Catch-up."

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

6. Results

Table 1 shows the baseline characteristics of the participants according to SGA and catch-up status. Our cohort included 99 SGA infants, and 26.3% (n = 26) of them did not catch up at 2 years of age. Mean age when each height was assessed was 30 (SD 1.1) months. SGA children without catch-up growth (SGA & No Catch-up group) were more likely to be a multiple birth child and to have more siblings, a smoking mother, a mother with higher education, and a father with lower education compared to the other two categories (non-SGA and SGA & Catch-up, Table 1). Among the eligible participants (Fig. 1), children without information on behavioral outcomes at 8 years of age were more likely to be born as SGA infants and have smoking mothers and parents with lower education compared to those included for the analysis at 8 years of age (Table 2).

Table 3 shows the associations between SGA and catch-up status and neurobehavioral developmental outcomes at 5.5 years of age. Children in the SGA & No Catch-up group were more likely to be unable to listen without fidgeting (OR 2.51, 95% CI: 1.06–5.93) and to focus on one task (OR 2.66, 95% CI: 1.09–6.48) compared with non-SGA children. When we excluded children born before 28 weeks of gestational age, the OR for unable to listen without fidgeting failed to reach significance (Supplemental Table 1).

Table 4 shows the associations between SGA and catch-up status and behavioral outcomes at 8 years of age. Children in the SGA & No Catch-up group were at increased risk for one attention problem and were more likely to fail to pay attention when crossing a street (OR 4.88, 95% CI: 2.08–11.46) compared with children in the non-SGA group. By contrast, the SGA & Catch-up group was not at increased risk for attention problems or delinquent/aggressive behaviors. Also, when we excluded children born before 28 weeks of gestational age, the main findings did not change substantially (Supplemental Table 2).

7. Discussion

To our knowledge, this is the first study to reveal the relationship between failure to catch-up in early childhood and attention problems at preschool age and school age among preterm SGA children. Preterm SGA children without catch-up growth were at increased risk for some behavioral problems. After the exclusion of children born before 28 weeks of gestational age, they were at risk for two behavioral problems, namely "unable to focus on one task" at 5.5 years and "failure to pay attention when crossing a street" at 8 years. Among the survey questions at 5.5 years and the three survey questions related with attention problems at 8 years, "unable to listen without fidgeting", "interrupting people" and "inability to wait his/her turn during play" would rather be related with hyperactivity/impulsivity, while "unable to focus one task" and "failure to pay attention when crossing a street" would rather be related with inattention. Therefore, we thought that preterm SGA children without

Table 1
Demographic characteristics of eligible children, separated by SGA and catch-up status (n = 1667).

	Non-SGA (n=1568)	SGA & Catch-up (n=73)	SGA & Non Catch-up (n=26)
Characteristics of children			
Sex, n (%)[a]			
Boys	937 (59.8)	40 (54.8)	14 (53.9)
Girls	631 (40.2)	33 (45.2)	12 (46.2)
Singleton birth, n (%)[a]	1253 (79.9)	53 (72.6)	16 (61.5)
Multiple birth, n (%)[a]	315 (20.1)	20 (27.4)	10 (38.5)
Mean gestational age, weeks (SD)[a]	34.6 (2.3)	34 (2.4)	32.3 (3.2)
Mean birth weight, gram (SD)[a]	2304.9 (507.4)	1455.2 (374.0)	1180.9 (405.4)
Parity, n (%)[a]			
0	704 (44.9)	47 (64.4)	6 (23.1)
≥1	864 (55.1)	26 (35.6)	20 (76.9)
Parental characteristics			
Mean maternal age at delivery, years (SD)[a]	30.7 (4.6)	31.8 (4.4)	32 (5.4)
Maternal smoking status, n (%)[b]			
Non-smoker	1313 (84.2)	59 (83.1)	21 (80.8)
Smoker	247 (15.8)	12 (16.9)	5 (19.2)
Maternal educational attainment, n (%)[c]			
University or higher	200 (13.2)	11 (15.1)	5 (19.2)
Junior college	632 (41.7)	27 (37)	13 (50)
≤ high school	685 (45.2)	35 (48)	8 (30.8)
Paternal educational attainment, n (%)[c]			
University or higher	566 (37.7)	27 (37)	8 (30.8)
Junior college	225 (15)	13 (17.8)	4 (15.4)
≤High school	709 (47.3)	33 (45.2)	14 (53.9)

There were 10 cases missing on maternal smoking, 51 cases missing on maternal educational attainment, and 68 cases missing on paternal educational attainment.
[a] Obtained from the birth record.
[b] Obtained from the first survey (at the age of 6 months).
[c] Obtained from the second survey (at the age of 18 months).

catch-up growth were at increased risk for inattention in the present study.

In the present study, we defined catch-up growth for SGA infants as achieving a height at 2 years of age above −2.0 SDs for chronological age, which is consistent with the general definition for catch-up growth for SGA infants [23]. We found that 26.3% of preterm SGA infants did not catch up at 2 years of age. Although we followed the Japanese guidelines for GHRT for SGA-related short stature, the participants were born in 2001 (i.e., 7 years before the approval of GHRT by the Japanese government in 2008) [19]. Thus, it is unlikely that the treatment affected the cognitive development of the participants [23,27]. Although we followed the general definition, previous studies that examined the relationship between catch-up growth or postnatal growth and neurological development used different definitions (e.g., by weight [12,13,17]), which hampers a simple comparison of the findings.

As for previous studies on the relationship between postnatal growth and neurodevelopment among preterm SGA children, there were four studies that evaluated cognitive functions [15,16,17,28], including two studies that evaluated both cognitive functions and behavioral difficulties [17,28]. Lappanen et al. showed that head circumference around term age correlated to full scale IQ on Wechsler Preschool and Primary Scales of Intelligence-Revised in SGA very preterm children; however, the weight growth between birth to 2 years of corrected age had no influence [15]. On the other hand, Latal-Hajnal et al. showed very preterm SGA children without catch-up growth of weight had lower Psychomotor Development Index of Bayley Scale of Infant Development at 2 years of age than SGA children with catch-up growth did [16].

Casey et al. studied cognitive functions and behavioral problems of AGA and SGA children with or without failure to thrive (FTT). No differences were found across the 4 groups (namely, AGA, SGA, AGA/FTT and SGA/FTT) in CBCL at 8 years of age [28]. Guellec et al. [17] also studied cognitive functions and behavioral difficulties at 5 years. Behavioral difficulties were assessed by the Strength and Difficulties Questionnaire. The subjects were divided into SGA and AGA groups according to the SD of birth weight, and SGA children without catch-up growth of weight at 6 months of age

Table 2
Demographic characteristics of children included and those lost to follow-up at age 8 (n = 1667).

	Age 8 years	
	Included (n = 1364)	Lost to follow-up (n = 303)
Characteristics of children		
Sex, n (%)[a]		
Boys	807 (59.2)	184 (60.7)
Girls	557 (40.8)	119 (39.3)
Singleton birth, n (%)[a]	1084 (79.5)	238 (78.6)
Multiple birth, n (%)[a]	280 (20.5)	65 (21.5)
Mean gestational age, weeks (SD)[a]	34.5 (2.3)	34.4 (2.4)
Parity, n (%)[a]		
0	617 (45.2)	140 (46.2)
≥1	747 (54.8)	163 (53.8)
SGA and catch-up status		
Non-SGA	1282 (94)	286 (94.4)
SGA & Catch-up	58 (4.3)	15 (5)
SGA & Non Catch-up	24 (1.8)	2 (0.7)
Parental characteristics		
Mean maternal age at delivery, years (SD)[a]	30.9 (4.6)	29.9 (4.9)
Maternal smoking status, n (%)[b]		
Non-smoker	1166 (86.1)	227 (75.2)
Smoker	189 (14)	75 (24.8)
Maternal educational attainment, n (%)[c]		
University or higher	182 (13.7)	34 (12)
Junior college	580 (43.5)	92 (32.5)
≤High school	571 (42.8)	157 (55.5)
Paternal educational attainment, n (%)[c]		
University or higher	515 (39)	86 (30.9)
Junior college	204 (15.4)	38 (13.7)
≤High school	602 (45.6)	154 (55.4)

There were 10 cases missing on maternal smoking, 51 cases missing on maternal educational attainment, and 68 cases missing on paternal educational attainment.

[a] Obtained from the birth record.
[b] Obtained from the first survey (at the age of 6 months).
[c] Obtained from the second survey (at the age of 18 months).

Table 3
Adjusted [a] ORs for associations between SGA status and behavioral developments at age 5.5 years among preterm births.

	Non-SGA	SGA & Catch-up	SGA & Non Catch-up
Age of 5.5 years			
Unable to listen without fidgeting			
N *cases*/N	304/1357	10/63	10/24
OR (95% CI)	1 (ref.)	0.63 (0.31–1.28)	2.51 (1.06–5.94)
Unable to Focus on One Task			
N *cases*/N	195/1362	11/63	8/24
OR (95% CI)	1 (ref.)	1.06 (0.52–2.15)	2.66 (1.09–6.48)
Unable to Remain Patient			
N *cases*/N	360/1353	19/62	10/24
OR (95% CI)	1 (ref.)	1.29 (0.72–2.29)	1.97 (0.84–4.61)
Unable to Express Emotions			
N *cases*/N	337/1355	14/62	8/24
OR (95% CI)	1 (ref.)	0.74 (0.4–1.4)	1.51 (0.63–3.64)
Unable to Act in a Group			
N *cases*/N	107/1359	6/63	3/24
OR (95% CI)	1 (ref.)	0.95 (0.36–2.48)	1.11 (0.31–4)
Unable to Keep Promises			
N *cases*/N	299/1346	7/62	7/23
OR (95% CI)	1 (ref.)	0.31 (0.12–0.78)	1.42 (0.56–3.57)

CI, confidence interval; OR, odds ratio; SGA, small for gestational age.
[a] Adjusted for child factors (sex, singleton or not, gestational age, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

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Table 4
Adjusted [a] ORs for associations between SGA status and behavioral developments at age 8 years among preterm births.

	Non-SGA	SGA & Catch-up	SGA & Non Catch-up
Attention problems			
Interrupting people			
N *cases*/N	533/1273	23/57	10/24
OR (95% CI)	1 (ref.)	0.94 (0.53–1.65)	0.98 (0.42–2.29)
Inability to wait his/her turn during play			
N *cases*/N	128/1275	3/58	2/23
OR (95% CI)	1 (ref.)	0.48 (0.15–1.59)	0.59 (0.13–2.71)
Failure to pay attention when crossing a street			
N *cases*/N	278/1273	9/58	14/24
OR (95% CI)	1 (ref.)	0.7 (0.33–1.46)	4.88 (2.08–11.46)
All attention problems			
N *cases*/N	44/1279	1/58	1/24
OR (95% CI)	1 (ref.)	0.54 (0.07–4.13)	0.99 (0.12–8.3)
Aggressive behaviors			
Lying	357/1263	10/58	9/24
N *cases*/N	1 (ref.)	0.54 (0.27–1.1)	1.33 (0.56–3.14)
OR (95% CI)			
Destroying toys and/or books	175/1273	6/58	4/23
N *cases*/N	1 (ref.)	0.78 (0.32–1.89)	1.11 (0.36–3.44)
OR (95% CI)			
Hurting other people	167/1274	5/58	2/24
N *cases*/N	1 (ref.)	0.59 (0.23–1.53)	0.4 (0.09–1.8)
OR (95% CI)			
Causing disturbances in public			
N *cases*/N	330/1268	11/58	4/24
OR (95% CI)	1 (ref.)	0.68 (0.34–1.34)	0.51 (0.17–1.53)
All aggressive behaviors			
N *cases*/N	28/1279	0/58	1/24
OR (95% CI)	1 (ref.)	NE	1.17 (0.13–10.63)

CI, confidence interval; NE, not estimable; OR, odds ratio; SGA, small for gestational age
[a] Adjusted for child factors (sex, singleton or not, gestational age, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

were at increased risk not for inattention-hyperactivity symptoms but for cognitive deficiency at 5 years of age compared with AGA children with good postnatal growth. These results differed from our findings. However, there were some differences in methodology between these studies and the present study (e.g. number of subjects, gestational age of subjects, and definition of catch-up growth or failure to thrive).

Two possible reasons would explain the present finding that failure to catch-up growth among SGA infants has negative impacts on behavioral development. One reason is undernutrition of brain due to poor postnatal growth. The other is impaired brain environment in utero due to severe fetal growth restriction and severe SGA infants at birth have few chances to achieve height above −2.0SD until 2 years of age even with appropriate postnatal growth. Indeed, Sucksdorff et al. previously showed that the smaller the SD of birthweight was, the greater the risk for ADHD at school age among preterm and term children was [29]. Although it is unclear which mechanism more affected the behavioral problems of SGA & No catch-up children, further investigation is needed about this issue.

A major strength of the present study is that we used a large, nationally representative sample. About 5% of all children born in Japan in 2001 were included in the survey. We were therefore able to increase the number of SGA and non-SGA infants compared with previous studies. In addition, the validity of our findings is strengthened by a very high response rate at baseline. Moreover, we could define poor postnatal growth or catch-up growth following the general definition for catch-up growth for the SGA infants [23].

By contrast, this study has several limitations. First, we were unable to use validated tests to assess the behavioral outcomes such as the SDQ used in a previous study [17], although we did use survey questions consistent with the CBCL at 8 years. Some outcome misclassification may be likely, but the misclassification would be non-differential, which moves effect estimates toward

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the null. Second, a 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 (i.e., smoking mothers and parents with lower education) compared to those included for the analysis at 8 years of age (Table 2). Third, there was a possibility of residual confounding factors associated with the family environment, although we adjusted for several potential confounders in the analyses, including the educational attainment of parents. Finally, we did not confirm whether "No catch-up" to −2 SD of height was caused by poor postnatal growth or severely low SD of birthweight with decent postnatal growth.

8. Conclusions

In summary, in this large, nationwide, longitudinal study in Japan, preterm SGA children without catch-up growth were at increased risk for behavioral problems, including inattention symptoms, from pre-school age to school age. Long-term developmental follow-up for the preterm, even relatively larger gestational age, SGA infants with failure of catch-up growth is needed, and it would be beneficial to detect behavioral problems that became apparent after admission to kindergarten or elementary school and to provide adequate intervention.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.12.004.

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