Associations of Birth Weight for Gestational Age with Child Health and Neurodevelopment among Term Infants: A Nationwide Japanese Population-Based Study

Kei Tamai, MD[1,2], Takashi Yorifuji, MD, PhD[3], Akihito Takeuchi, MD, PhD[2], Yu Fukushima, MD[2], Makoto Nakamura, MD, PhD[2], Naomi Matsumoto, MD, PhD[3], Yosuke Washio, MD, PhD[1], Misao Kageyama, MD[2], and Hirokazu Tsukahara, MD, PhD[1]

Objective To examine the association of specific Z-score categories of birth weight for gestational age with child health and neurodevelopment using a large nationwide survey in Japan, focusing on term infants.

Study design We included 36 321 children born in 2010. Hospitalization up to 66 months of age was used as an indicator of health status, and responses to questions about age-appropriate behaviors at 30 and 66 months of age were used to indicate neurobehavioral development. We conducted binomial log-linear regression analyses, controlling for child and parental variables. A restricted cubic spline function was used to model the relationship.

Results Compared with children with birth weight appropriate for gestational age (−1.28 to 1.28 SDs of expected birthweight for gestational age), children who were small for gestational age (SGA) (<−1.28 SD) had higher risks of hospitalization and unfavorable neurobehavioral development, and the risks increased as SGA status became more severe. Compared with the appropriate for gestational age group, the adjusted risk ratios for hospitalization for all causes were 2.5 (95% CI, 1.7-3.6), 1.3 (95% CI, 1.1-1.6), and 1.1 (95% CI, 1.0-1.2) for children who were severely, moderately, and mildly SGA and 1.0 (95% CI, 0.9-1.1), 1.1 (95% CI, 0.9-1.2), and 1.4 (95% CI, 0.9-2.1) for children who were mildly, moderately, and severely large for gestational age, respectively. Severely large for gestational age children also had higher risks of unfavorable neurobehavioral development. These results were supported by spline analyses.

Conclusions Among term infants, the risks of unfavorable child health and neurodevelopment increased with the severity of SGA. *(J Pediatr 2020;226:135-41)*.

Abnormal birth weight for gestational age is reported to be a risk factor for neonatal outcomes, child health, and child neurodevelopment.[1-3] For example, compared with children with birth weight appropriate for gestational age (AGA), children who are small for gestational age (SGA), defined as a birth weight of less than the 10th percentile for gestational age, have increased risks of unfavorable child health and neurodevelopmental delay.[4-10] Most studies have dichotomized birth weight and less is known about the impact of severity of birth weights that are small or large for gestational age on child health and neurodevelopment.

Several studies have examined the association between child health and neurodevelopment and the magnitude of deviation from the mean in birth weight for gestational age. For example, a population-based cohort study in Sweden examined the association between birth weight Z-scores and asthma and showed that the incidence of asthma treatment increased with increasing severity of SGA.[11] In addition, 2 population-based studies showed that the risk of cognitive impairment during adolescence increased with increasing severity of SGA.[12,13] These previous studies also noted several adverse effects of birth weights that were large for gestational age (LGA). However, few studies have examined the association between specific birth weight Z-score categories and the risk of hospitalization and behavioral development among children born full term.

In the present study, we examined the association of specific birth weight Z-score categories with child health and behavioral development using a large nationwide survey in Japan, focusing on term infants.

Methods

The Japanese Ministry of Health, Labour, and Welfare implemented a nationally representative longitudinal survey to follow infants born throughout the country between May 10 and 24, 2010, called the Longitudinal Survey of Newborns in the 21st Century (2010 Cohort).[14-17] Baseline questionnaires were sent to all families

AGA	Appropriate for gestational age
LGA	Large for gestational age
SGA	Small for gestational age

From the [1]Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; [2]Division of Neonatology, Okayama Medical Center, National Hospital Organization; and the [3]Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Supported in part by a Grant for Strategies for Efficient Operation of our University (2007030201). The sponsor had no involvement in the study design; the collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit the paper for publication. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.06.075

when the infants born during the study period were 6 months old. Of the 43 767 questionnaires mailed, 38 554 were completed and returned (88.1% response rate). Follow-up questionnaires were sent to all participants who initially responded each year (at 18, 30, 42, 54, and 66 months). The sixth survey was completed in 2015. Birth record data from the Vital Statistics system such as birth weight, gestational age, singleton or multiple birth, sex, parity, and parental age at delivery were also obtained for each child included in this survey.

Children were excluded if they did not have information on birth weight (n = 7) or gestational age (n = 3). In the present study, we focused on term infants and thus excluded children born before 37 weeks of gestation (n = 2096) and after 42 weeks of gestation (n = 127), resulting in inclusion of 36 321 children in the analysis. Follow-up rates were 83.2% at 1.5 years of age and 68.9% at 5.5 years of age (**Figure 1**; available at www.jpeds.com). Although follow-up rates were not largely different between birth weight categories, severely SGA and severely LGA tended to be lost to follow-up.

To express the magnitude of differences in birth weight for gestational age, we used the SD of birth weight for gestational age from the Committee for Newborns of the Japanese Pediatric Society to classify the participants.[18] Using conventional medical terms, participants were categorized as follows (from lighter to heavier): severely SGA (<−3.0 SD of expected birth weight for gestational age); moderately SGA (−3.0 to −2.0 SD); mildly SGA (−2.0 to −1.28 SD); AGA (−1.28 to 1.28 SD reflecting the 10th-90th percentiles); mildly LGA (1.28 to 2.0 SD); moderately LGA (2.0 to <3.0 SD); and severely LGA (≥3.0 SD).

Child Health and Behavioral Development Outcomes

To examine the impact of the magnitude of differences in birth weight for gestational age on long-term morbidity, we used overnight hospitalizations in early childhood (up to 66 months of age) as an indicator of health status. The survey obtained information on whether the child had been hospitalized during the previous 12 months for any reason and asked respondents to provide further details if the hospitalization resulted from one of several common diseases. The same question was asked in each survey from age 18 to 66 months. In this study, we focused on hospitalizations that occurred during early childhood before enrolling in elementary school (ie, 7-66 months of age). We targeted hospitalizations resulting from all causes, as well as those specifically caused by respiratory infection or gastrointestinal infection because these are the most common causes of hospitalization during early childhood.

The survey queried behavioral development at 30 and 66 months of age. We assessed the impact of birth weight categories on neurodevelopment status using behavioral development at both of these ages. In the survey, the parents were asked to provide a "yes" or "no" response according to whether children had reached various age-appropriate motor, language, and behavioral milestones. The questions used have not been officially validated or taken from an established scale, but they have been used in previous studies to assess risk factors for unfavorable development.[8,14,15,19-22]

Statistical Analyses

We first conducted a descriptive analysis of children categorized by birth weight: less than −3 SD of expected birth weight for gestational age; −3 to −2 SD; −2 to −1.28 SD; −1.28 to 1.28 SD (10th-90th percentiles); +1.28 to +2 SD; +2 to less than +3 SD; and +3 SD or greater. We then conducted a binomial log-linear regression analysis to evaluate the relationship of the birth weight categories defined above with overnight hospitalizations from 7 to 66 months of age and behavioral development at 30 and 66 months of age. When overnight hospitalizations were used as an outcome, generalized estimating equation analysis was conducted to account for the longitudinal nature of the surveys. We estimated the risk ratio and 95% CI for the main outcomes using the AGA category (ie, −1.28 to 1.28 SD, 10th-90th percentiles for gestational age) as a reference and adjusted for child and parental factors.

We selected the potential confounders based on previous studies (**Table I**).[8,19-21] Data regarding infant sex, singleton or multiple birth, parity, and maternal age at delivery were obtained from the birth record. Maternal smoking status was ascertained from the first survey (at infant age of 6 months). Parental educational level was obtained from the second survey (at child age of 18 months). We classified the educational level into three categories as follows: high school or less, junior college (2 years) or vocational school, and university (4 years) or higher.

To evaluate the shape of the association of birth weight for gestational age with the risk of overnight hospitalizations and unfavorable behavioral development, we conducted a restricted cubic spline analysis with 4 knots for SD of birth weight for gestational age and predicted the association. In this analysis, we used the crude value of the SD rather than the categories defined elsewhere in this article.

In the sensitivity analyses, we excluded children who had visited clinics or hospitals for congenital disease at 7-18 months of age to remove possible selection bias, because children with congenital disease might have been born SGA or LGA. Because the questionnaire at 18 months of age queried whether the child had visited clinics or hospitals for any congenital disease and the definition of the congenital disease was not specific, we did not adjust for the congenital disease in the primary analyses.

Stata SE version 15 statistical software (StataCorp, College Station, Texas) was used for all analyses. This study was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences Institutional Review Board (No. 1506-073).

Results

The baseline characteristics of the eligible children and their parents are shown in **Table I**. Compared with AGA or LGA children, SGA children were more likely to be born from a

Table I. Demographic characteristics of eligible children, separated by birth weight category (n = 36 321)

Characteristics	Birth weight category						
	<−3 SD (n = 59)	−3 to −2 SD (n = 572)	−2 to −1.28 SD (n = 2241)	−1.28 to 1.28 SD (n = 29 725)	+1.28 to +2 SD (n = 2748)	+2 to < +3 SD (n = 878)	≥+3 SD (n = 98)
Characteristics of children							
Sex, n (%)*							
Boys	32 (54.2)	294 (51.4)	1094 (48.8)	15 192 (51.1)	1407 (51.2)	484 (55.1)	59 (60.2)
Girls	27 (45.8)	278 (48.6)	1147 (51.2)	14 533 (48.9)	1341 (48.8)	394 (44.9)	39 (39.8)
Singleton birth or not, n (%)*							
Singleton birth	55 (93.2)	538 (94.1)	2175 (97.1)	29 500 (99.2)	2745 (99.9)	878 (100)	98 (100)
Multiple birth	4 (6.8)	34 (5.9)	66 (3)	225 (0.8)	3 (0.1)	0 (0)	0 (0)
Parity, n (%)*							
0	28 (47.5)	252 (44.1)	1035 (46.2)	13 875 (46.7)	1383 (50.3)	446 (50.8)	49 (50)
≥1	31 (52.5)	320 (55.9)	1206 (53.8)	15 850 (53.3)	1365 (49.7)	432 (49.2)	49 (50)
Mean birthweight, g (SD)*	1993 (197.5)	2276.2 (197.2)	2527.5 (179.3)	3031.5 (276.4)	3580.8 (196.8)	3856.7 (207.2)	4257.1 (280.9)
Parental characteristics							
Mean maternal age at delivery, years (SD)*	33 (5.5)	31.6 (4.9)	31.5 (4.8)	31.4 (4.9)	31.4 (4.9)	31.8 (5.1)	32.1 (5.1)
Maternal smoking status, n (%)†							
Nonsmoker	53 (89.8)	491 (85.8)	2019 (90.4)	27 634 (93.2)	2594 (94.5)	831 (95)	89 (90.8)
Smoker	6 (10.2)	81 (14.2)	215 (9.6)	2002 (6.8)	150 (5.5)	44 (5)	9 (9.2)
Maternal educational attainment, n (%)‡							
University or higher	10 (19.6)	116 (23.7)	505 (26.3)	6866 (26.7)	637 (26.8)	187 (24.9)	13 (17.6)
Junior college	23 (45.1)	209 (42.7)	770 (40)	10 591 (41.1)	946 (39.8)	333 (44.3)	36 (48.7)
Less than high school	18 (35.3)	165 (33.7)	649 (33.7)	8285 (32.2)	794 (33.4)	232 (30.9)	25 (33.8)
Paternal educational attainment, n (%)‡							
University or higher	16 (33.3)	209 (43.4)	823 (43.6)	11 144 (44)	1074 (45.8)	337 (45.4)	27 (38)
Junior college	10 (20.8)	91 (18.9)	370 (19.6)	4663 (18.4)	404 (17.2)	130 (17.5)	14 (19.7)
Less than high school	22 (45.8)	182 (37.8)	693 (36.7)	9502 (37.5)	866 (37)	275 (37.1)	30 (42.3)

There were 103 cases missing for maternal smoking, 4911 cases missing for maternal educational attainment, and 5439 cases missing for paternal educational attainment.
*Obtained from the birth record.
†Obtained from the first survey (at the age of 6 months).
‡Obtained from the second survey (at the age of 18 months).

multiple gestation, have a lower mean birth weight, and have smoking mothers.

The number of participants who were hospitalized in each category and the relative risks for birth weight categories and hospitalization are shown in **Table II** (available at www.jpeds.com). Compared with the AGA group (−1.28 to +1.28 SD), children born severely, moderately, and mildly SGA had higher risks of hospitalization. Although the CI was wide, children born severely LGA also had slightly higher risks of hospitalization (risk ratio, 1.4; 95% CI, 0.9-2.1). Elevated risks for children born SGA were also observed for hospitalizations for respiratory and gastrointestinal infections. The restricted cubic spline analysis for overnight hospitalizations supported these findings (**Figure 2**). Although U-shaped associations were observed for hospitalization because of all causes and respiratory infection in the restricted cubic spline analysis, the association seemed to be linear for hospitalizations because of gastrointestinal infection.

Table III (available at www.jpeds.com) shows the association between birth weight category and behavioral outcomes at 2.5 years. Children born severely, moderately, and mildly SGA and children born severely LGA had higher risks of unfavorable behavioral development. For example, children born severely, moderately, and mildly SGA and children born severely LGA were more likely to be unable to say meaningful words than children with AGA. However, children born mildly LGA tended to have favorable development compared with children born AGA, with, for example, a risk ratio of 0.4 (95% CI, 0.2-0.9) of being unable to say meaningful words. The restricted cubic spline analysis for behavioral development outcomes at 2.5 years of age supported the findings (**Figure 3**). Children with a birth weight Z-score of +1 SD seemed to have the most favorable behavioral outcomes at 2.5 years old of being unable to run, unable to say meaningful words, and unable to say his or her own name.

The results for neurodevelopment at 5.5 years of age are shown in **Table IV** (available at www.jpeds.com). Although the tendency of favorable neurodevelopment among children born mildly LGA was not observed at this age, children born SGA and children born severely LGA still had higher risks of unfavorable behavioral development, and the risks increased as the SGA status became more severe. The restricted cubic spline analysis for behavioral development outcomes at 5.5 years of age supported the findings (**Figure 4**).

When 560 children with congenital disease were excluded in the sensitivity analyses, the main findings for children born SGA did not change substantially (**Tables V**, **VI**, and **VII**; available at www.jpeds.com). However, the risks of severe LGA status disappeared in hospitalization (**Table V**) and

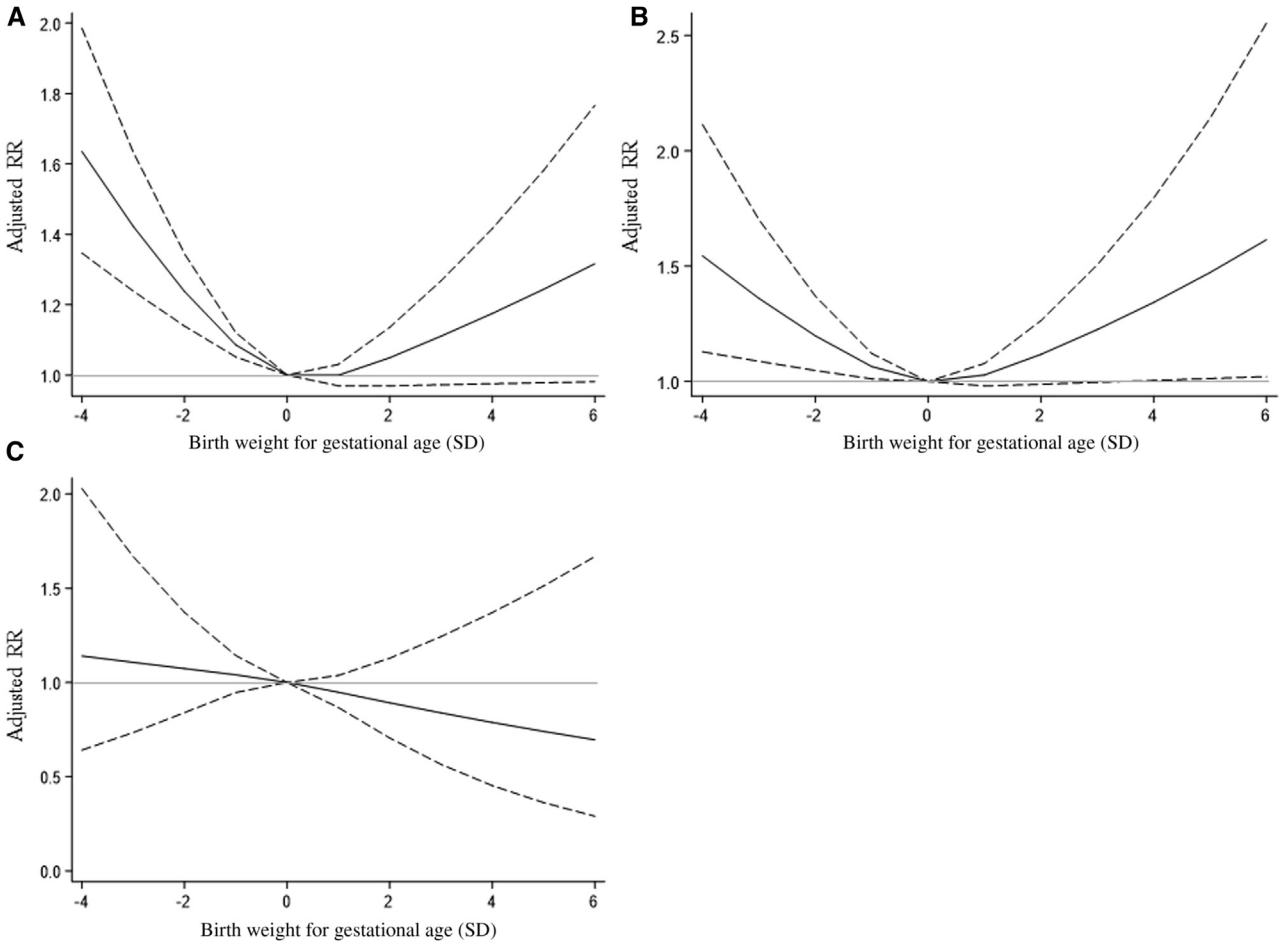

Figure 2. Adjusted risk ratios and 95% CIs for the associations between SD scores of birth weight for gestational age and hospitalizations from 6 to 66 months of age for, **A,** all causes, **B,** respiratory infection, and **C,** gastrointestinal infection.

were found only in some of the behavioral development outcomes assessed (Table VI and Table VII) in the sensitivity analysis.

Discussion

The purpose of the present study was to examine the association of detailed birth weight Z-score categories with child health and behavioral development using a large nationwide survey in Japan, with a focus on term births. Compared with children with AGA birth weights, children born SGA had higher risks of hospitalization and unfavorable behavioral development, and the risks increased as SGA status became more severe. Children born LGA also had higher risks of unfavorable neurobehavioral development. The association of birth weight Z-score with unfavorable behavioral development was U-shaped, with AGA and mildly LGA children having the lowest risk. The spline analyses supported the findings.

A cohort study in Sweden showed that the risk of asthma at 2-9 years of age increased as SGA or LGA status became more severe among children born from 39 to 41 gestational weeks.[11] Other studies have demonstrated that the risks of learning difficulties, attention problems, unfavorable school performance, decreased intellectual performance, or attention deficit hyperactivity disorder increased as SGA or LGA status became more severe.[12,13,23,24] Consistent with these previous studies, and supplementing them with detailed categories of birth weight Z-scores, we observed several negative impacts of the magnitude of differences in birth weight for gestational age on child health and behavioral outcomes in term children. Moreover, children born severely SGA had the highest risks of negative impacts on these outcomes compared with other groups; thus, clinicians need to pay further attention to children born severely SGA, even among term infants.

The spline analyses further supported our findings regarding hospitalization, but the association differed for specific causes of hospitalization; that is, although U-shaped associations were observed for hospitalization for all causes and respiratory infection, the association seemed to be linear for hospitalization because of gastrointestinal infection. This

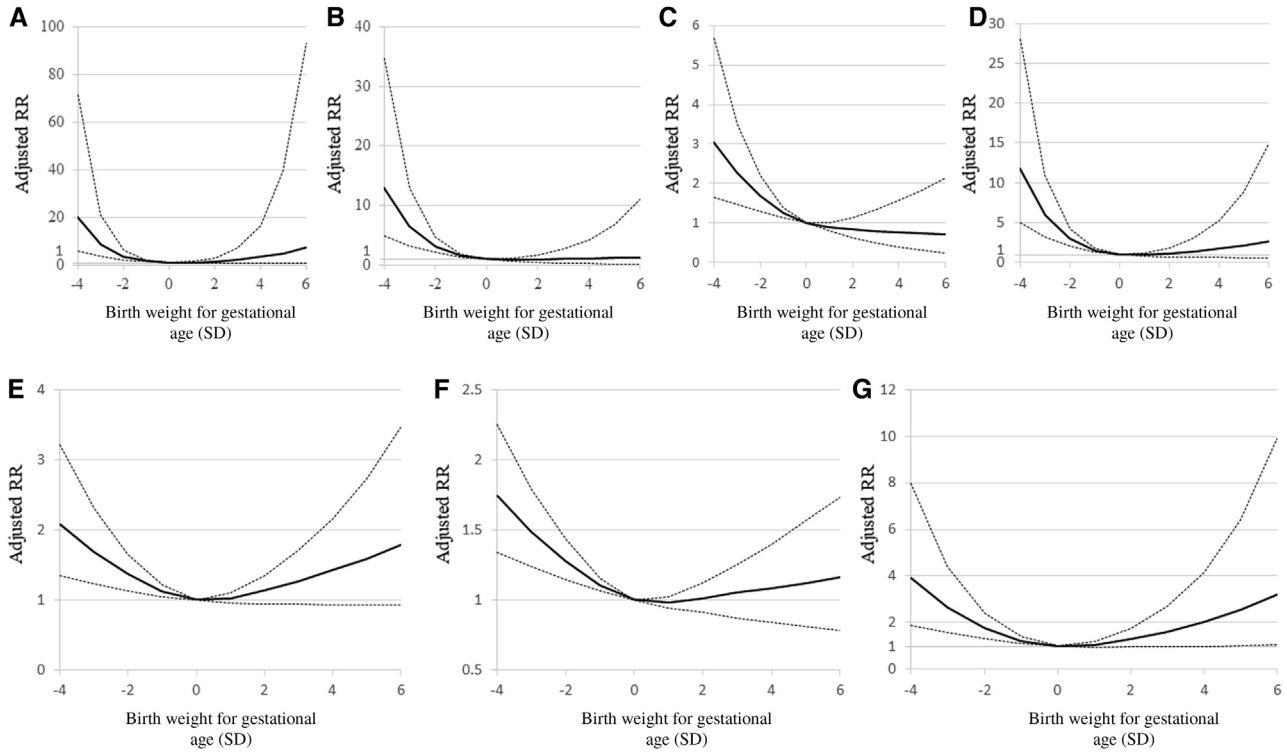

Figure 3. Adjusted risk ratios and 95% CIs for the associations between SD scores of birth weight for gestational age and behavioral development outcomes at 2.5 years old of being, **A,** unable to walk, **B,** unable to run, **C,** unable to climb stairs, **D,** unable to say meaningful words, **E,** unable to compose a 2-phrase sentence, **F,** unable to say his or her own name, and **G,** unable to use a spoon to eat.

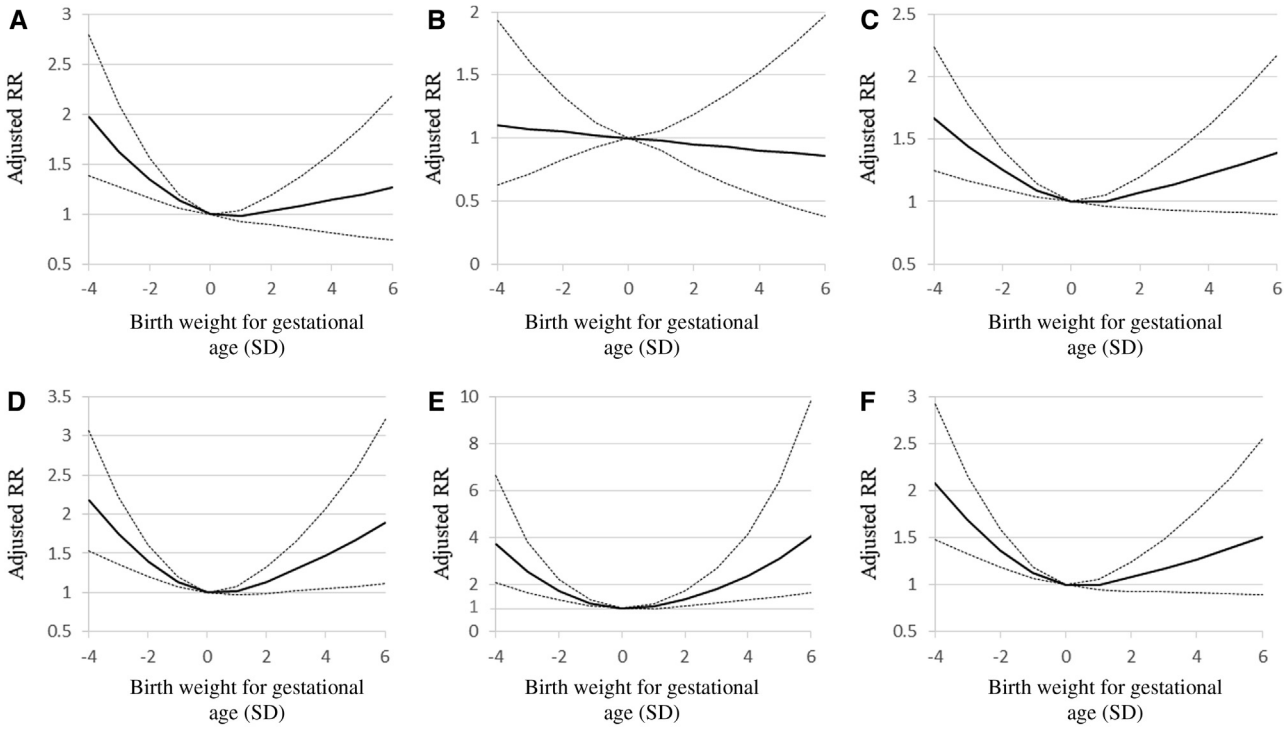

Figure 4. Adjusted risk ratios and 95% CIs for the associations between SD scores of birth weight for gestational age and behavioral development outcomes at 5.5 years old of being, **A,** unable to listen carefully, **B,** unable to focus on one task, **C,** unable to remain patient, **D,** unable to express emotions, **E,** unable to participate in a group, and **F,** unable to keep promises.

observation is consistent with previous studies that demonstrated that infants born SGA and LGA had a higher risk of neonatal respiratory morbidity, which could be related to morbidity during early childhood.[3,25-27] In contrast, only SGA children were reported to have a higher risk of hospitalization for gastrointestinal infection during childhood than children born AGA,[7] and no study has demonstrated an association between children born LGA and gastrointestinal infection.

In the present study, although children born mildly LGA had favorable neurodevelopmental outcomes at 2.5 years of age, children born severely LGA had higher risks of hospitalization and unfavorable behavioral development. Previous findings in term infants on the association of LGA status, defined as a birth weight of greater than the 90th percentile for gestational age, with child health and neurodevelopmental delay are inconsistent.[28-31] For example, a population-based cohort study in Australia demonstrated that, although infants born LGA suffered greater complications at birth, such as respiratory distress, cerebral hemorrhage, the need for mechanical ventilation, the need for blood transfusion, brachial plexus palsy, and other birth trauma, these complications did not persist into later life, and children born LGA showed better school performance than AGA children.[31] However, the present findings suggest that clinicians need to follow-up with children born SGA and severely LGA.

The present study has some strengths. The large sample size allowed us to estimate the impact of specific birth weight Z-score categories on child health and neurodevelopment. Moreover, the validity of our findings was reinforced by a very high response rate at baseline.

Some limitations of this study should be acknowledged. The questions used to assess behavioral outcomes were not externally validated. However, as noted, the questions were used in previous studies, and unfavorable outcomes have been associated with gestational age, SGA status, or breastfeeding in an anticipated manner.[8,19-21] Even if misclassifications occurred, they would have a nondifferential effect of shifting estimates toward the null condition. Moreover, there was loss to follow-up and children born severely SGA and severely LGA tended to be lost (**Figure 1**), which may have underestimated the adverse effects of several SGA or LGA. Finally, because we could not adjust for congenital disease in the main analysis, we conducted the sensitivity analyses excluding those with congenital disease.

In conclusion, we found that the risks of unfavorable child health and neurodevelopmental delay increased with the severity of SGA status. Moreover, the association of birth weight for gestational age with neurodevelopmental delay was U-shaped, with children born AGA and mildly LGA having the lowest risk. ■

We thank Dr Mariko Hattori, Dr Shigehiro Mori, and Dr Kazue Nakamura for their valuable comments. We also thank Saori Irie for data collection. We thank Lisa Kreiner, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/) for editing a draft of this article.

Submitted for publication Feb 25, 2020; last revision received Jun 24, 2020; accepted Jun 25, 2020.

Reprint requests: Kei Tamai, MD, Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata, Kita-ku, Okayama 700-8558, Japan. E-mail: gmd501041@s.okayama-u.ac.jp

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Weissmann-Brenner A, Simchen MJ, Zilberberg E, Kalter A, Weisz B, Achiron R, et al. Maternal and neonatal outcomes of large for gestational age pregnancies. Acta Obstet Gynecol Scand 2012;91:844-9.
2. ACOG Practice Bulletin No. 204. Fetal Growth Restriction. Obstet Gynecol 2019;133:e97-109.
3. Mendez-Figueroa H, Truong VTT, Pedroza C, Khan AM, Chauhan SP. Small-for-gestational-age infants among uncomplicated pregnancies at term: a secondary analysis of 9 Maternal-Fetal Medicine Units Network studies. Am J Obstet Gynecol 2016;215:628.e1-7.
4. Simmons R. Abnormalities of fetal growth. In: Gleason CA, Juul SE, eds. Avery's diseases of the newborn. 10th ed. Philadelphia: Elsevier Saunders; 2018;p. 61-9.
5. Paranjothy S, Dunstan F, Watkins WJ, Hyatt M, Demmler JC, Lyons RA, et al. Gestational age, birth weight, and risk of respiratory hospital admission in childhood. Pediatrics 2013;132:e1562-9.
6. Á Rogvi R, Forman JL, Greisen G. Prematurity, smallness-for-gestational age and later hospital admissions: a nation-wide registry study. Early Hum Dev 2015;91:299-306.
7. Yoshimoto J, Yorifuji T, Washio Y, Okamura T, Watanabe H, Doi H, et al. Population-based longitudinal study showed that children born small for gestational age faced a higher risk of hospitalisation during early childhood. Acta Paediatr 2019;108:473-8.
8. Takeuchi A, Yorifuji T, Takahashi K, Nakamura M, Kageyama M, Kubo T, et al. Neurodevelopment in full-term small for gestational age infants: a nationwide Japanese population-based study. Brain Dev 2016;38:529-37.
9. Takeuchi A, Yorifuji T, Takahashi K, Nakamura M, Kageyama M, Kubo T, et al. Behavioral outcomes of school-aged full-term small-for-gestational-age infants: a nationwide Japanese population-based study. Brain Dev 2017;39:101-6.
10. Løhaugen GCC, Ostgård HF, Andreassen S, Jacobsen GW, Vik T, Brubakk AM, et al. Small for gestational age and intrauterine growth restriction decreases cognitive function in young adults. J Pediatr 2013;163:447-54.
11. Källén B, Finnstrom O, Nygren KG, Olausson PO. Association between preterm birth and intrauterine growth retardation and child asthma. Eur Respir J 2013;41:671-6.
12. Lindström L, Wikström A-K, Bergman E, Lundgren M. Born small for gestational age and poor school performance – how small is too small? Horm Res Paediatr 2017;88:215-23.
13. Eide MG, Øyen N, SkjÆrven R, Bjerkedal T. Associations of birth size, gestational age, and adult size with intellectual performance: evidence from a cohort of Norwegian men. Pediatr Res 2007;62:636-42.
14. Yorifuji T, Tsukahara H, Kashima S, Doi H. Intrauterine and early postnatal exposure to particulate air pollution and Kawasaki disease: a nationwide longitudinal survey in Japan. J Pediatr 2018;193:147-54.
15. Yorifuji T, Tsukahara H, Doi H. Early childhood exposure to maternal smoking and Kawasaki disease: a longitudinal survey in Japan. Sci Total Environ 2019;655:141-6.
16. Yorifuji T, Tsukahara H, Doi H. Breastfeeding and risk of Kawasaki disease: a nationwide longitudinal survey in Japan. Pediatrics 2016;137:e20153919.

17. Nakahara Y, Yorifuji T, Kubo T, Doi H. Maternal smoking as a risk factor for childhood intussusception. Arch Environ Occup Heal 2018;73:96-101.
18. Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. Pediatr Int 2014;56:702-8.
19. Kato T, Yorifuji T, Inoue S, Yamakawa M, Doi H, Kawachi I. Associations of preterm births with child health and development: Japanese population-based study. J Pediatr 2013;163:1578-84.e4.
20. Yorifuji T, Kubo T, Yamakawa M, Kato T, Inoue S, Tokinobu A, et al. Breastfeeding and behavioral development: a nationwide longitudinal survey in Japan. J Pediatr 2014;164:1019-25.e3.
21. Tamai K, Yorifuji T, Takeuchi A, Nakamura M, Washio Y, Tsukahara H, et al. Associations of gestational age with child health and neurodevelopment among twins: a nationwide Japanese population-based study. Early Hum Dev 2019;128:41-7.
22. Higa Diez M, Yorifuji T, Kado Y, Sanada S, Doi H. Preterm birth and behavioural outcomes at 8 years of age: a nationwide survey in Japan. Arch Dis Child 2016;101:338-43.
23. O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. Pediatrics 2003;112:301-7.
24. Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, et al. Preterm birth and poor fetal growth as risk factors of attention-deficit/hyperactivity disorder. Pediatrics 2015;136:e599-608.
25. Mendez-Figueroa H, Truong VTT, Pedroza C, Chauhan SP. Large for gestational age infants and adverse outcomes among uncomplicated pregnancies at term. Am J Perinatol 2017;34:655-62.
26. Szabo SM, Gooch KL, Korol EE, Bradt P, Vo P, Levy AR. Respiratory distress syndrome at birth is a risk factor for hospitalization for lower respiratory tract infections in infancy. Pediatr Infect Dis J 2012;31:1245-51.
27. Betts KS, Soares Magalhães RJ, Alati R. The role of neonatal pulmonary morbidity in the longitudinal patterns of hospitalisation for respiratory infection during the first year of life. Epidemiol Infect 2018;146:1130-7.
28. Lei X, Zhao D, Huang L, Luo Z, Zhang J, Yu X, et al. Childhood health outcomes in term, large-for-gestational-age babies with different postnatal growth patterns. Am J Epidemiol 2018;187:507-14.
29. Frank CE, Speechley KN, Macnab JJ, Campbell MK. Infants born large for gestational age and developmental attainment in early childhood. Int J Pediatr 2018;2018:1-7.
30. Pinto LA, Guerra S, Anto JM, Postma D, Koppelman GH, de Jongste JC, et al. Increased risk of asthma in overweight children born large for gestational age. Clin Exp Allergy 2017;47:1050-6.
31. Khambalia AZ, Algert CS, Bowen JR, Collie RJ, Roberts CL. Long-term outcomes for large for gestational age infants born at term. J Paediatr Child Health 2017;53:876-81.

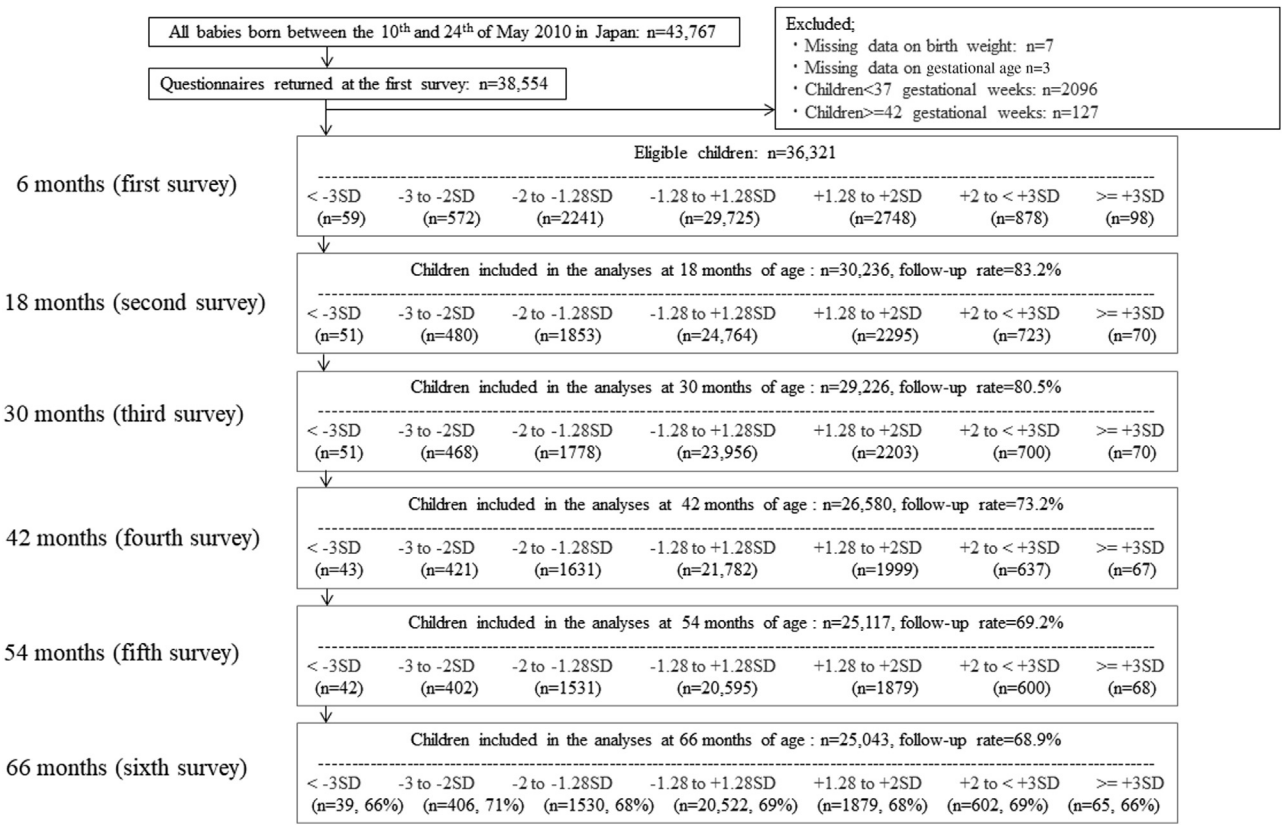

Figure 1. Study participant flow chart.

Table II. Adjusted* RRs for associations between birth weight category and all-cause and cause-specific admission from 6 to 66 months of age

	Birth weight category						
Associations	**<−3 SD**	**−3 to −2 SD**	**−2 to −1.28 SD**	**−1.28 to 1.28 SD**	**+1.28 to +2 SD**	**+2 to < +3 SD**	**≥+3 SD**
All-cause admission	39/226	189/2177	587/8323	7193/111 619	629/10 255	215/3262	32/340
RR (95% CI)*	2.5 (1.7-3.6)	1.3 (1.1-1.6)	1.1 (1-1.2)	1 (ref.)	1 (0.9-1.1)	1.1 (0.9-1.2)	1.4 (0.9-2.1)
Respiratory infection admission	16/226	68/2177	213/8323	2739/111 619	253/10 255	88/3262	9/340
RR (95% CI)*	2.6 (1.4-4.7)	1.3 (1-1.7)	1.1 (0.9-1.3)	1 (ref.)	1 (0.9-1.2)	1.1 (0.9-1.4)	1 (0.4-2.2)
Gastrointestinal infection admission	5/226	20/2177	65/8323	857/111 619	72/10 255	16/3262	4/340
RR (95% CI)*	3.1 (1.2-8)	1.3 (0.8-2)	1 (0.8-1.4)	1 (ref.)	0.9 (0.7-1.2)	0.6 (0.4-1.1)	0.8 (0.2-3.8)

RR, risk ratio.
Data are presented as the raw numbers and adjusted RR (95% CI).
*Adjusted for child factors (sex, singleton, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Table III. Adjusted* RRs for associations between birth weight category and behavioral developments at age of 2.5

	Birth weight category						
Associations	**<−3 SD**	**−3 to −2 SD**	**−2 to −1.28 SD**	**−1.28 to 1.28 SD**	**+1.28 to +2 SD**	**+2 to < +3 SD**	**≥+3 SD**
Age of 2.5 years							
Unable to walk	2/51	3/487	11/1862	54/25 019	2/2302	3/732	1/72
RR (95% CI)*	18.5 (4.5-75.7)	2.2 (0.5-8.9)	2.9 (1.4-5.7)	1 (ref.)	0.5 (0.1-1.9)	2.1 (0.7-6.8)	7.1 (1.0-50.9)
Unable to run	3/51	8/487	19/1865	110/25 015	5/2302	2/733	1/72
RR (95% CI)*	14.6 (4.8-44.7)	3.2 (1.4-7.3)	2.5 (1.5-4.1)	1 (ref.)	0.5 (0.2-1.3)	0.7 (0.2-2.8)	3.6 (0.5-25.6)
Unable to climb stairs	2/51	17/487	48/1865	452/25 008	31/2302	14/733	1/72
RR (95% CI)*	2.2 (0.6-8.7)	1.7 (1.0-2.8)	1.5 (1.1-2.0)	1 (ref.)	0.7 (0.5-1.1)	1.1 (0.7-1.9)	0.9 (0.1-6.0)
Unable to say meaningful words	4/51	6/487	21/1863	152/25 017	6/2302	4/734	4/72
RR (95% CI)*	12.2 (4.7-31.5)	2.3 (1.0-5.2)	1.8 (1.1-3.0)	1 (ref.)	0.4 (0.2-0.9)	0.9 (0.3-2.5)	10 (3.8-26)
Unable to compose a 2-phrase sentence	7/51	20/487	87/1863	973/25 011	97/2301	27/733	9/72
RR (95% CI)*	2.7 (1.3-5.6)	0.9 (0.6-1.5)	1.2 (1.0-1.5)	1 (ref.)	1.1 (0.9-1.4)	0.9 (0.6-1.3)	3.5 (1.9-6.3)
Unable to say his or her own name	17/51	69/486	224/1863	2711/24 972	232/2297	67/733	14/72
RR (95% CI)*	2.6 (1.7-3.8)	1.3 (1.0-1.6)	1.1 (1.0-1.3)	1 (ref.)	0.9 (0.8-1.1)	0.8 (0.6-1)	1.9 (1.2-3)
Unable to use a spoon to eat	4/51	11/486	30/1862	315/25 015	25/2301	8/733	4/72
RR (95% CI)*	4.4 (1.5-13.2)	1.5 (0.7-3)	1.3 (0.9-2)	1 (ref.)	0.9 (0.6-1.3)	0.9 (0.4-1.7)	4.8 (1.9-12.3)

Data are presented as the raw numbers and adjusted RR (95% CI).
*Adjusted for child factors (sex, singleton, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Table IV. Adjusted* RRs for associations between birth weight category and behavioral developments at age of 5.5

	Birth weight category						
Associations	**<−3 SD**	**−3 to −2 SD**	**−2 to −1.28 SD**	**−1.28 to 1.28 SD**	**+1.28 to +2 SD**	**+2 to < +3 SD**	**≥+3 SD**
Age of 5.5 years							
Unable to listen carefully	7/41	40/419	146/1600	1476/21 357	142/1956	37/617	4/67
RR (95% CI)*	2.5 (1.3-4.8)	1.4 (1.0-1.9)	1.3 (1.1-1.6)	1 (ref.)	1.1 (0.9-1.3)	0.9 (0.6-1.2)	0.7 (0.2-2.1)
Unable to focus on one task	2/41	19/420	68/1602	738/21 361	70/1958	17/619	0/67
RR (95% CI)*	1.4 (0.4-5.5)	1.3 (0.8-2)	1.2 (0.9-1.5)	1 (ref.)	1 (0.8-1.3)	0.8 (0.5-1.3)	NE
Unable to remain patient	9/41	58/420	185/1600	2160/21 341	187/1957	71/617	4/67
RR (95% CI)*	2.1 (1.2-3.7)	1.3 (1.0-1.7)	1.1 (1.0-1.3)	1 (ref.)	1 (0.8-1.1)	1.1 (0.9-1.4)	0.6 (0.2-1.6)
Unable to express emotions	9/40	45/419	128/1602	1457/21 334	136/1955	44/617	7/67
RR (95% CI)*	2.8 (1.5-5.2)	1.6 (1.2-2.1)	1.2 (1.0-1.4)	1 (ref.)	1 (0.8-1.2)	1 (0.8-1.4)	1.6 (0.8-3.3)
Unable to act in group	7/41	16/419	48/1601	463/21 355	40/1958	17/616	3/67
RR (95% CI)*	6.6 (3.2-13.5)	1.8 (1.1-3.0)	1.3 (1.0-1.8)	1 (ref.)	0.9 (0.7-1.3)	1.2 (0.7-2.0)	2.1 (0.7-6.4)
Unable to keep promises	10/41	41/419	156/1600	1584/21 332	142/1957	40/618	8/67
RR (95% CI)*	3 (1.7-5.2)	1.3 (0.9-1.8)	1.3 (1.1-1.5)	1 (ref.)	1 (0.8-1.1)	0.9 (0.7-1.2)	1.7 (0.9-3.2)

NE, not estimable.
Data are presented as the raw numbers and adjusted RR (95% CI).
*Adjusted for child factors (sex, singleton, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Table V. Adjusted* RRs for associations between birth weight category and all-cause and cause-specific admission from 6 to 66 months of age excluding children with congenital disease

	Birth weight category						
Associations	**<−3 SD**	**−3 to −2 SD**	**−2 to −1.28 SD**	**−1.28 to 1.28 SD**	**+1.28 to +2 SD**	**+2 to < +3 SD**	**≥+3 SD**
All-cause admission	35/213	154/1997	511/7671	6435/103 624	573/9579	194/3035	20/284
RR (95% CI)*	2.4 (1.7-3.6)	1.2 (1.0-1.5)	1.1 (1.0-1.2)	1 (ref.)	1 (0.9-1.1)	1.1 (0.9-1.2)	1.1 (0.6-1.8)
Respiratory infection admission	13/213	59/1997	190/7671	2520/103 624	235/9579	84/3035	5/284
RR (95% CI)*	2.2 (1.1-4.2)	1.2 (0.9-1.6)	1 (0.9-1.2)	1 (ref.)	1 (0.9-1.2)	1.2 (0.9-1.5)	0.5 (0.1-1.6)
Gastrointestinal infection admission	5/213	15/1997	58/7671	783/103 624	64/9579	15/3035	2/284
RR (95% CI)*	3.3 (1.3-8.6)	1 (0.6-1.7)	1 (0.7-1.3)	1 (ref.)	0.9 (0.7-1.2)	0.7 (0.4-1.2)	1 (0.2-4.3)

Data are presented as the raw numbers and adjusted RR (95% CI).
*Adjusted for child factors (sex, singleton, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Table VI. Adjusted* RRs for associations between birth weight category and behavioral developments at age of 2.5 years excluding children with congenital disease

	Birth weight category						
Associations	**<−3 SD**	**−3 to −2 SD**	**−2 to −1.28 SD**	**−1.28 to 1.28 SD**	**+1.28 to +2 SD**	**+2 to < +3 SD**	**≥+3 SD**
Age of 2.5 years							
Unable to walk	2/47	1/433	6/1644	27/22 327	0/2069	2/652	0/55
RR (95% CI)*	34.6 (8.0-149.6)	2 (0.3-14.9)	3.3 (1.4-8.1)	1 (ref.)	NE	2.8 (0.7-11.7)	NE
Unable to run	3/47	4/433	12/1646	56/22 324	2/2069	1/653	0/55
RR (95% CI)*	25.4 (8.1-79.3)	3.8 (1.4-10.5)	3.1 (1.6-5.7)	1 (ref.)	0.4 (0.1-1.6)	0.6 (0.1-4.5)	NE
Unable to climb stairs	2/47	10/433	38/1646	358/22 317	23/2069	12/653	0/55
RR (95% CI)*	2.7 (0.7-10.4)	1.5 (0.8-2.8)	1.5 (1.1-2.0)	1 (ref.)	0.7 (0.5-1.1)	1.1 (0.6-2.0)	NE
Unable to say meaningful words	3/47	4/433	13/1644	109/22 324	4/2069	4/653	1/55
RR (95% CI)*	11.2 (3.7-33.6)	1.9 (0.7-5.1)	1.7 (1.0-3.0)	1 (ref.)	0.4 (0.1-1.1)	1.2 (0.4-3.2)	3.7 (0.5-25.5)
Unable to compose a 2-phrase sentence	5/47	14/433	71/1644	816/22 320	87/2068	25/653	6/55
RR (95% CI)*	2 (0.8-5.1)	0.9 (0.5-1.5)	1.2 (1.0-1.6)	1 (ref.)	1.1 (0.9-1.4)	1 (0.6-1.4)	3.1 (1.5-6.5)
Unable to say his or her own name	14/47	55/432	195/1644	2380/22 284	207/2064	59/653	10/55
RR (95% CI)*	2.3 (1.5-3.6)	1.2 (1.0-1.6)	1.1 (1.0-1.3)	1 (ref.)	0.9 (0.8-1.1)	0.8 (0.6-1.0)	1.7 (1.0-2.9)
Unable to use a spoon to eat	4/47	5/432	23/1643	253/22 324	20/2068	8/653	3/55
RR (95% CI)*	5.3 (1.8-15.8)	1.1 (0.5-2.6)	1.3 (0.9-2.0)	1 (ref.)	0.8 (0.5-1.3)	1 (0.5-2.0)	4.9 (1.7-14.4)

Data are presented as the raw numbers and adjusted RR (95% CI).
*Adjusted for child factors (sex, singleton, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).

Table VII. Adjusted* RRs for associations between birth weight category and behavioral developments at age of 5.5 years excluding children with congenital disease

	Birth weight category						
Associations	**<−3 SD**	**−3 to −2 SD**	**−2 to −1.28 SD**	**−1.28 to 1.28 SD**	**+1.28 to +2 SD**	**+2 to < +3 SD**	**≥+3 SD**
Age of 5.5 years							
Unable to listen carefully	5/38	33/383	127/1460	1330/19 578	130/1808	36/569	3/56
RR (95% CI)*	2 (0.9-4.4)	1.3 (1.0-1.9)	1.3 (1.1-1.6)	1 (ref.)	1.1 (0.9-1.3)	0.9 (0.7-1.3)	0.5 (0.1-2.1)
Unable to focus on one task	2/38	15/384	59/1463	654/19 585	62/1811	17/570	0/56
RR (95% CI)*	1.6 (0.4-6.2)	1.2 (0.7-2.0)	1.2 (0.9-1.6)	1 (ref.)	1 (0.8-1.3)	0.9 (0.6-1.4)	NE
Unable to remain patient	8/38	51/384	166/1460	1960/19 565	174/1810	63/569	3/56
RR (95% CI)*	2.1 (1.2-3.8)	1.3 (1.0-1.7)	1.1 (1.0-1.3)	1 (ref.)	1 (0.8-1.1)	1.1 (0.9-1.4)	0.5 (0.2-1.6)
Unable to express emotions	9/38	38/383	118/1461	1325/19 561	125/1808	38/569	6/56
RR (95% CI)*	3.1 (1.7-5.7)	1.5 (1.1-2.0)	1.2 (1.0-1.5)	1 (ref.)	1 (0.8-1.2)	1 (0.7-1.4)	1.6 (0.8-3.4)
Unable to act in group	7/38	13/383	42/1460	416/19 577	35/1810	15/568	2/56
RR (95% CI)*	7.7 (3.8-15.6)	1.7 (1.0-2.9)	1.4 (1.0-1.9)	1 (ref.)	0.9 (0.7-1.3)	1.2 (0.7-2.0)	1.7 (0.4-6.4)
Unable to keep promises	9/38	34/383	135/1461	1432/19 558	129/1811	38/569	6/56
RR (95% CI)*	3 (1.7-5.5)	1.2 (0.8-1.7)	1.3 (1.1-1.5)	1 (ref.)	0.9 (0.8-1.1)	0.9 (0.7-1.2)	1.4 (0.7-3.0)

Data are presented as the raw numbers and adjusted RR (95% CI).
*Adjusted for child factors (sex, singleton, and parity) as well as parental factors (maternal age at delivery, maternal smoking status, maternal educational attainment, and paternal educational attainment).