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Intrauterine growth restriction affects z-scores of anthropometric parameters during the first 6 years in very low-birth-weight-children born at less than 30 weeks of gestation

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Original Article

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Abstract

Objective: Little is known about physical constitution outcomes for very preterm infants. Here, we compare z-scores of anthropometric parameters up to 6 years of age in children born with very low birth weight (VLBW) at less than 30 weeks of gestation, with or without intrauterine growth restriction (IUGR). **Design:** Participants were divided into four subgroups: male (M), small for gestational age (SGA) ($n = 30$); M, appropriate for gestational age (AGA) ($n = 59$); female (F), SGA ($n = 24$); and F, AGA ($n = 61$). z-Scores of body weight (BW), body length (BL), and body mass index (BMI) were assessed at birth, 1 year corrected age, 3 years of age, and 6 years of age. **Results:** For boys, BW and BMI were significantly lower among SGA children than among AGA children at all assessments, but there was no difference in BL at 3 or 6 years. For girls, BW and BL were significantly lower among SGA children than among AGA children at all assessments, but no difference was detected in BMI after 1.5 years. No significant variation in the z-score of BW or BMI in either SGA group was observed after 1 year. BL z-score in all groups gradually increased until 6 years of age. **Conclusion:** IUGR affects BW and BMI in boys and BW and BL in girls during the first 6 years in VLBW children born at less than 30 weeks of gestation. SGA children did not catch up in BW or BMI from 1 to 6 years of age.

Key Notes

- There are limited longitudinal cohort studies examining the trajectory of anthropometric parameters in early life among children born very preterm.
- We compared z-scores of anthropometric parameters up to 6 years in children born with very low birth weight at less than 30 weeks of gestation, with or without intrauterine growth restriction.
- Intrauterine growth restriction affected the z-scores of body weight and body mass index for boys and of body weight and body length for girls during the first 6 years of life among children born with very low birth weight at less than 30 weeks of gestation.
- We did not observe any catch-up in body weight or body mass index among children who were small for gestational age between 1 year corrected age and 6 years of age.

Introduction

In recent decades, advances in neonatal intensive care have brought about dramatic improvements in the prognosis of preterm infants – especially those with very low birth weight (VLBW, <1500 g) and those who are born very preterm (<32 completed weeks of gestation).[1] Nonetheless, concern continues regarding the long-term effects of prematurity.[2] The intrauterine environment and pattern of growth during early childhood are now generally accepted as important determinants of the risk of disease in later life. Placental insufficiency and malnutrition during pregnancy induce intrauterine growth restriction (IUGR) of the fetus and are the primary causes of infants being small for gestational age (SGA).[3,4]

Low birth weight can result from IUGR and/or preterm birth, but, when followed by adequate postnatal nutrition, catch-up growth typically occurs during infancy. Although this process has potential advantages for preterm infants in terms of short-term survival and later cognitive outcomes, rapid catch-up growth may increase the risk of metabolic disease later in life.[5] Moreover, postnatal growth in very preterm and/or VLBW infants has been associated with a variety of short- and long-term outcomes, including cognitive functioning,[6,7] motor performance,[7] and body composition.[8] Although the majority of VLBW and very preterm infants exhibit late postnatal catch-up growth, they often remain short and thin during childhood and adolescence.[9]

Several recent longitudinal studies have tried to identify and characterize distinct trajectories of body mass index (BMI) in pediatric populations of term-birth infants to improve the identification of relationships between growth and health outcomes.[10,11] In contrast, there are limited longitudinal cohort studies examining the trajectory of anthropometric parameters in children with VLBW and/or very preterm birth early in life, especially in Japan.

The aim of the present study was to evaluate trajectories of the z-scores of body weight (BW), body length (BL), and BMI during the first 6 years of life in VLBW infants born at less than 30 completed weeks of gestation, with or without IUGR.

Method

Study population

We conducted a retrospective, multi-center study that included preterm infants admitted to neonatal intensive care units (NICUs) in the three affiliated hospitals of Juntendo University (Juntendo University Hospital in Tokyo, Juntendo University Urayasu Hospital in Chiba, and Juntendo University Shizuoka Hospital in Shizuoka) from January 2007 to December 2011. The inclusion criteria for preterm infants were birth weight <1500 g, gestational age (GA) <30 weeks, and Japanese parentage. GA was determined based on mother's last menstrual period and first-trimester ultrasonogram. Basic characteristics including GA and sex were collected from medical records. BW and BL at birth, 1 year corrected age (CA), 3 years of age, and 6 years of age were also collected from medical records, and BMI (kg/m2) was subsequently calculated. Sex- and GA-independent z-scores and percentiles for anthropometric parameters at birth were calculated according to the Japanese standard curve, which was estimated using 2003–2005 data from the Japan Society of Obstetrics and Gynecology registry database.[12] Based on the curve, SGA was defined as birth weight below the 10th percentile, and appropriate for gestational age (AGA) was defined as birth weight in the 10th to 90th percentile.

The exclusion criteria for preterm infants were the presence of congenital diseases; chromosomal abnormalities; or severe cardiac, renal endocrine, brain, and/or gastrointestinal diseases. Infants whose birth weight were over the 90th percentile and children who received growth hormone therapy were also excluded.

z-Scores of BW, BL, and BMI at birth, 1 year CA, 3 years of age, and 6 years of age were also calculated according to the standard growth chart for children from a 2000 national survey.[13] Excel-based software has been developed for both standard curves by the Japanese Society for Pediatric Endocrinology; this software is available on their website.[14] The software can calculate z-scores based on sex-specific standards for BW by GA or height and BMI by age for a Japanese population. The z-scores of height and BMI were adjusted by age- and sex-specific standards for comparisons at different ages. Participants were divided into four subgroups based on sex and IUGR as follows: male (M), SGA; M, AGA; female (F), SGA; and F, AGA.

This study was carried out by the opt-out method of the hospital website, and it was approved by the institutional review boards of the three hospitals (17-094, 2017-059, and rin-541).

Statistical analysis

Results are presented as mean ± SD. Between-group differences were analyzed with the Mann–Whitney *U*-test. Differences within groups were analyzed using an ANOVA, followed by the Tukey–Kramer multiple comparison test. A *p*-value <0.05 was considered statistically significant. All statistical analyses were conducted with JMP statistical software, version 12.0 (SAS Institute Inc., Cary, NC).

Results

There were 479 preterm infants with VLBW and GA <30 weeks born in the three NICUs during the study period, and 468 infants met the inclusion criteria at birth. Of these infants, 374 were discharged from the NICU. We collected anthropometric data up to 6 years of age for 183 children. We excluded nine children (six SGA and three AGA) because they received growth hormone therapy and another four because their birth weight was higher than the 90th percentile. Of the 174 remaining children, 30 were categorized in the M/SGA group, 59 in the M/AGA group, 24 in the F/SGA group, and 61 in the F/AGA group.

Table 1 presents the clinical characteristics and anthropometric indices of the participants. There was no difference in GA by sex. Anthropometric data at birth and 1 year CA were significantly different between the groups for both sexes ($p < 0.05$). For boys, the z-scores of BW and BMI were significantly lower among SGA children than among AGA children at all time points, but no difference was observed in BL z-score at 3 or 6 years. For girls, the z-scores of BW and BL were significantly lower among SGA children than among AGA children at all time points, but no difference was observed in BMI z-score after 1.5 years CA (Fig. 1). No significant variation in the z-score of BW or BMI was observed in the SGA groups after 1 year CA. BL z-score in all groups gradually increased until 6 years of age (Fig. 1).

Discussion

To the best of our knowledge, this is the first study to assess the influence of IUGR on anthropometric outcomes using z-scores during the first 6 years of life among Japanese VLBW infants born at less than 30 weeks of gestation. It has previously been reported that individuals who are born preterm often exhibit substantial growth failure in the early postnatal period, usually followed by catch-up growth over the subsequent 2 years.[9] However, recent studies have observed that children born with VLBW or born very preterm remained short in stature, irrespective of whether they were SGA or of average size at birth.[15,16] Other studies have also reported that children born with VLBW or extremely low birth weight experience significant growth failure in early childhood.[17,18] These results indicate that both unfavorable intrauterine environments and adverse postnatal circumstances in the NICU could lead to permanent alterations that prevent catch-up growth. In a study of infants born at ≤25 weeks of gestation in 1995 in the United Kingdom and Ireland, children had the same mean BMI z-score (−0.9 ± 1.3) at a median age of 6 years as did the participants in our study.[19]

Our results indicated that VLBW children with IUGR are not only lighter but also leaner for boys and shorter for girls during early childhood compared with those without IUGR. Hack *et al.*[20] previously reported catch-up growth in weight, height, and BMI among VLBW girls aged 8–20 years, but this was not

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Table 1. General characteristics of very-low-birth-weight children born at less than 30 weeks of gestation

		Male		Female	
		SGA	AGA	SGA	AGA
	n	30	59	24	61
At birth	Gestational age (weeks)	27.4 ± 1.8	27.1 ± 1.8	27.0 ± 1.8	26.2 ± 2.3
	BW (g)	715 ± 192	987 ± 235**	612 ± 193	852 ± 261**
	BW z-score[1]	−5.8 ± 0.6	−5.0 ± 0.7**	−6.3 ± 0.6	−5.5 ± 0.8**
	BW z-score[2]	−2.3 ± 0.8	−0.3 ± 0.6**	−2.7 ± 0.8	−0.1 ± 0.6**
	BL (cm)	31.9 ± 3.2	35.0 ± 3.0**	30.4 ± 3.5	33.3 ± 3.7**
	BL z-score[1]	−8.0 ± 1.5	−6.5 ± 1.4**	−9.2 ± 1.4	−7.2 ± 1.8**
	BL z-score[2]	−1.5 ± 1.0	0.1 ± 0.6**	−2.0 ± 0.8	−0.1 ± 0.7**
	BMI (kg/m^2)	6.9 ± 0.8	7.9 ± 0.8**	6.5 ± 0.8	7.5 ± 0.8**
	BMI SDS[1]	−5.6 ± 0.9	−4.5 ± 0.8**	−6.3 ± 0.6	−4.8 ± 0.8**
At 1 year corrected age	Age (months)	15.6 ± 1.8	15.6 ± 2.6	14.9 ± 1.4	15.9 ± 2.2*
	BL (cm)	72.0 ± 3.5	73.4 ± 4.0**	68.2 ± 4.9	71.9 ± 3.2**
	BL z-score[1]	−2.4 ± 1.1	−1.8 ± 1.1**	−3.1 ± 1.8	−2.0 ± 1.1*
	BW (kg)	7.8 ± 1.2	8.7 ± 1.3**	6.8 ± 1.4	8.0 ± 1.1**
	BW z-score[1]	−2.6 ± 1.4	−1.5 ± 1.4**	−3.6 ± 2.7	−1.8 ± 1.4**
	BMI (kg/m^2)	15.1 ± 1.4	16.0 ± 1.4**	14.8 ± 1.4	15.4± 1.4*
	BMI z-score[1]	−1.0 ± 1.2	−0.3 ± 1.0**	−0.9 ± 1.1	−0.4 ± 1.1*
At 3 years	Age (months)	37.2 ± 1.5	37.3 ± 2.4	37.2 ± 1.3	37.1 ± 2.2
	BL (cm)	89.0 ± 3.5	90.2 ± 3.9	86.4 ± 4.3	89.1 ± 3.7**
	BL z-score[1]	−1.5 ± 0.9	−1.1 ± 1.0	−2.1 ± 2.0	−1.1 ± 1.0**
	BW (kg)	11.6 ± 1.7	12.7 ± 1.6**	10.7 ± 1.8	11.9 ± 1.7**
	BW z-score[1]	−1.7 ± 1.4	−0.8 ± 1.1**	−2.1 ± 2.0	−1.1 ± 1.3**
	BMI (kg/m^2)	14.6 ± 1.5	15.6 ± 1.1**	14.4 ± 1.4	15.0 ± 1.5
	BMI SDS[1]	−0.9 ± 1.5	0.1 ± 1.0**	−0.9 ± 1.3	−0.4 ± 1.2
At 6 years	Age (months)	72.8 ± 4.1	72.9 ± 4.2	72.7 ± 3.2	71.9 ± 8.4
	BL (cm)	108.3 ± 5.3	110.2 ± 4.9	105.1 ± 6.6	109.3 ± 4.9*
	BL z-score[1]	−1.2 ± 0.8	−0.7 ± 1.0	−1.7 ± 1.4	−0.9 ± 1.1*
	BW (kg)	16.4 ± 2.6	18.2 ± 2.9**	15.5 ± 2.8	17.3 ± 2.5*
	BW z-score[1]	−1.7 ± 1.3	−0.8 ± 1.3**	−2.2 ± 2.0	−1.2 ± 1.3*
	BMI (kg/m^2)	14.0 ± 1.5	14.9 ± 1.4**	13.9 ± 1.2	14.4 ± 1.4
	BMI z-score[1]	−1.4 ± 1.5	−0.6 ± 1.3**	−1.2 ± 1.0	−0.8 ± 1.1

SGA, small for gestational age; AGA, appropriate for gestational age; BW, body weight; BL, body length; BMI, body mass index.
*$p < 0.05$, **$p < 0.01$, compared with the intrauterine growth restriction group. Data are presented as means ± SDs. SDS[1] were calculated based on the Japanese growth curve.[13] SDS[2] were calculated based on the Japanese neonatal anthropometric charts for gestational age at birth.[12]

the case for boys who remained significantly smaller than their normal-birth-weight counterparts at 20 years of age. In contrast, Makhoul *et al.*[21] showed that the z-score of childhood weight among VLBW, premature infants was not associated with sex. Further research is needed to clarify the sex differences in anthropometric parameters among preterm Japanese children.

Although SGA children in this study appeared to have low BMI during infancy and early childhood, some may be at risk for obesity in later childhood and adulthood. Gaskins *et al.* reported that SGA children born at <33 weeks of gestation are at risk of being overweight at 11 years of age.[22] It has also recently been reported that early timing (<4 years of age) of adiposity rebound (the period when BMI begins to increase from its nadir) is associated with future obesity among term infants.[23,24] In the present study, 81 children (46.6%, 24 SGA) showed an increase in BMI from 1.5 to 3 years of age, but there were no obese children at 6 years of age (BMI z-score >2). Further studies are needed to confirm the relationship between adiposity rebound and later obesity among preterm children born at <30 weeks of gestation.

It has been hypothesized that, in children with low birth weight, altered body composition may be a key factor in increasing susceptibility to a diabetogenic environment, although the mechanisms

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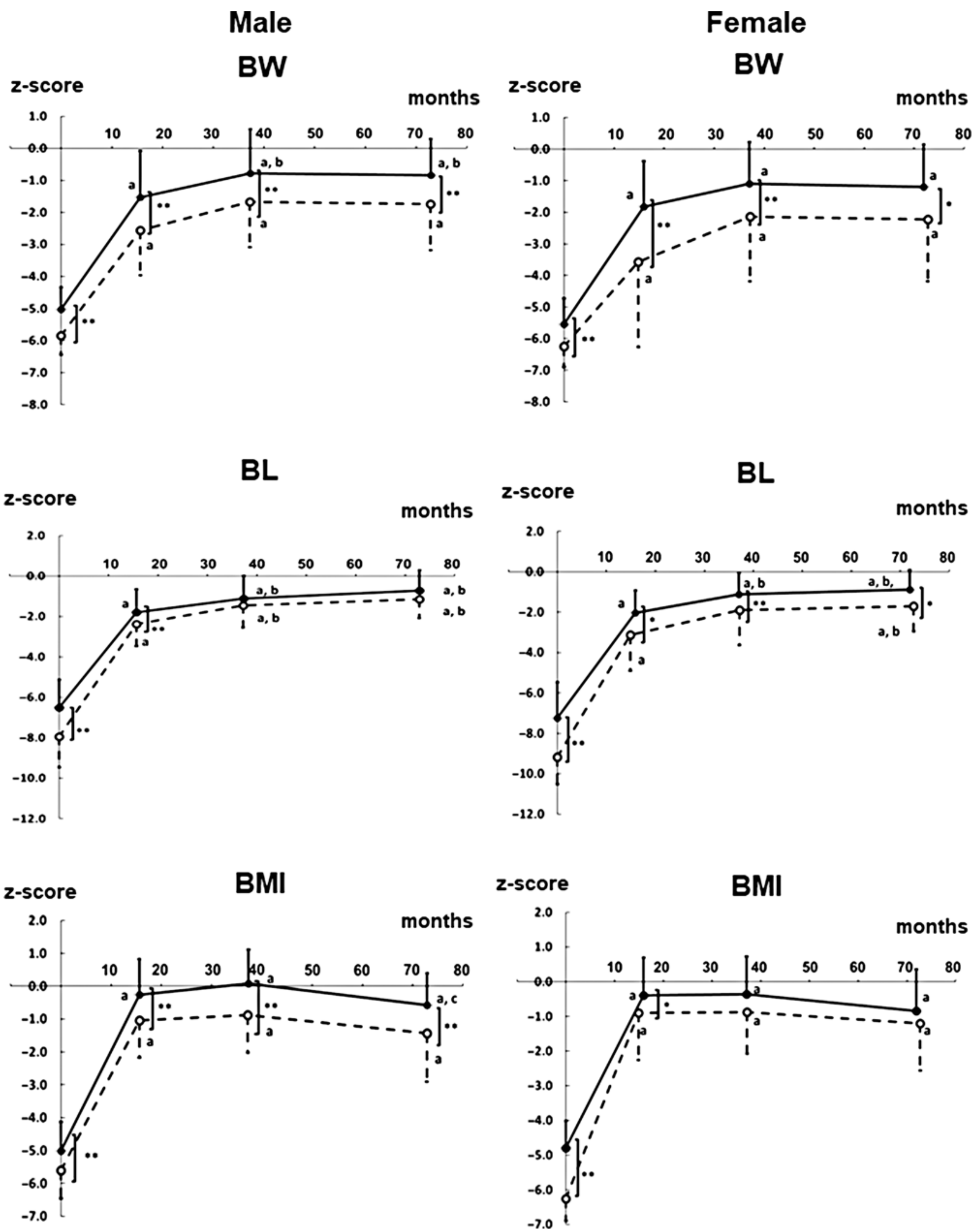

Fig. 1. z-Score trajectories (left, boys; right, girls) at birth, 1 year corrected age, 3 years of age, and 6 years of age in very-low-birth-weight children born at less than 30 weeks of gestation. Black circles, appropriate-for-gestational-age groups; white circles, small-for-gestational-age groups. BW, body weight; BL, body length; BMI, body mass index. Data are presented as means – SDs. *$p < 0.05$, **$p < 0.01$ between groups. [a]$p < 0.05$ compared to birth; [b]$p < 0.05$ compared to 1 year corrected age; [c]$p < 0.05$ compared to 3 years corrected age.

leading to metabolic reprogramming remain unclear.[25] Studies of young adults born preterm with VLBW or born very preterm suggest that these individuals have decreased insulin sensitivity, as assessed by fasting insulin, the homeostasis model assessment-estimated insulin resistance index,[26] or the hyperinsulinemic–euglycemic clamp.[27] Moreover, some have speculated that skeletal muscle alterations caused by IUGR are implicated in the pathogenesis of insulin resistance.[28] Physicians who provide follow-up care to SGA preterm children should consider monitoring these children's insulin resistance before adulthood.

Our study had several limitations. The sample size was small, the rate of follow-up was quite low, the policy for starting growth hormone therapy was not unified across the three hospitals, the information of feeding method and nutritional management during postnatal period was not evaluated, and we were unable to examine the body composition of the participants. Ranke *et al.*[29] recently reported that there were no differences between 43 SGA and 98 AGA preterm children (mean GA = 29.2 weeks, 8.3 years of age) in BMI, fat-free mass (measured by bioelectrical impedance analysis), or total fat mass (measured by dual-energy X-ray absorptiometry). Additionally, Darendeliler *et al.*[30] studied 30 SGA and 63 AGA preterm children (mean GA = 32.6 weeks, 4.7 years of age), finding no difference between the groups in body composition parameters measured by dual-energy X-ray absorptiometry. The subjects of these studies had longer GA, compared with the children in our study, and further studies are needed to evaluate the body composition of preterm children born at less than 30 weeks of gestation.

In conclusion, boys born at VLBW with IUGR were relatively lean, and girls born at VLBW with IUGR were smaller at school age, compared with those without IUGR. IUGR affects the z-scores of BW and BMI in boys and of BW and BL in girls during the first 6 years of life among VLBW children born at less than 30 weeks of gestation. We did not observe any catch-up in BW or BMI among SGA children between 1 year CA and 6 years of age.

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Conflicts of interest. None

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