Tohoku J. Exp. Med., 2014, **232**, 27-33

Learning Disability in 10- to 16-Year-Old Adolescents with Very Low Birth Weight in Japan

Keiko Tanabe,[1, 2] Koji Tamakoshi,[2] Saya Kikuchi[3] and Jun Murotsuki[4,5]

[1]Tohoku University Hospital, Sendai, Miyagi, Japan
[2]Department of Nursing for Developmental Health, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[3]Department of Psychiatry, Tohoku University Hospital, Sendai, Miyagi, Japan
[4]Department of Advanced Fetal and Developmental Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[5]Department of Maternal and Fetal Medicine, Miyagi Children's Hospital, Sendai, Miyagi, Japan

In recent years, there has been an increase in the number of infants with very low birth weight (VLBW, i.e., weight less than 1,500 g) in Japan. However, the effect of VLBW on subsequent behavioral development and mental health remains unknown. Subjects enrolled were 57 individuals (13.4 ± 1.9 years old) with VLBW (VLBW group), including 23 small-for-gestational-age (SGA) infants (i.e., the SGA/VLBW group) and 34 appropriate-for-gestational-age (AGA) infants (the AGA/VLBW group). The control group was 29 individuals born AGA at term. We used the questionnaires, the Pupil Rating Scale Revised (PRS) to screen for learning disabilities and the Children's Depression Inventory (CDI) to examine the presence of depression. The PRS score in the VLBW group was significantly lower than that of the control group ($p <$ 0.001). Suspected learning disabilities (LD, defined by a score below 65 points on the PRS) were found in 6 out of the 56 subjects in the VLBW group (10.7%), whereas none were found in the 29 control subjects ($p = 0.074$). The frequency of suspected LD children was higher in the SGA/VLBW group (4 out of 22 evaluated infants, 18.2%) than that in the AGA/VLBW group (2/34, 5.9%). The frequency of suspected LD in the non-verbal field was significantly higher ($p = 0.02$) in the SGA/VLBW group (18.2%) than in the AGA/VLBW group (0%). However, CDI score did not significantly differ between groups. These findings suggest that VLBW and fetal growth restriction may pose a risk for LD among adolescents with VLBW.

Keywords: adolescence; depression; learning disabilities; small for gestational age; very low birth weight
Tohoku J. Exp. Med., 2014 January, **232** (1), 27-33.

Introduction

In recent years, there has been a decline in the number of births in Japan and an increase in the number of infants with low birth weight. In 2011, 9.6% of all infants born in Japan had birth weights below 2,500 g, and 0.8% had very low birth weight (VLBW, defined as a birth weight below 1,500 g; Maternal and Child Health Statistics of Japan 2011). Improvements in perinatal and neonatal care have resulted in the survival of an increasing number of VLBW infants, and these individuals constitute a substantial minority of Japan's future population.

Recent epidemiological studies and animal experiments have shown that nutritional disorders and environmental factors from the fetal period to infancy lead to not only morphological defects such as physical malformations, but also the occurrence of lifestyle-related diseases such as hypertension, diabetes mellitus, and cardiovascular events later in life (de Boo and Harding 2006; Rice et al. 2006; Tanabe et al. 2011). According to this evidence, the concept of developmental origins of health and disease (DOHaD) has been defined as the process through which the environment encountered before birth, or in infancy, shapes the long-term control of tissue physiology and homeostasis (Gluckman and Hanson 2004; Gluckman et al. 2005).

By contrast, the effect of intrauterine nutritional disorders on subsequent behavioral development or mental health remains to be established. According to a descriptive epidemiologic study by Hunt et al. (1988), 18 (16.7%) of 108 eight-year-olds who had VLBW were diagnosed with learning disabilities (LD) using the Wechsler Intelligence Scale for Children (WISC) and the Wide Range Achievement Test (WRAT). In Japan, Kanazawa et al. (1997) investigated 33 VLBW infants using Myklebust's Pediatrics Rating Scale and found that 27.3% were sus-

Received October 30, 2013; revised and accepted December 27, 2013. Published online January 28, 2014; doi: 10.1620/tjem.232.27.
Correspondence: Keiko Tanabe, R.N., N.M., Ph.D., Department of Nursing for Developmental Health, Graduate School of Medicine, Nagoya University, 1-1-20 Daiko-minami, Higashi-ku, Nagoya, Aichi 461-8673, Japan.
e-mail: tanabe@met.nagoya-u.ac.jp

pected to have LD. These findings suggest a correlation between prematurity or intrauterine nutritional disorders and LD. However, few previous studies compared same-age children with VLBW and those born at 37 weeks or more of gestation with appropriate-for-gestational-age (AGA) weight (Strang-Karlsson et al. 2008). Additionally, little is known about the proportion of LD between children with VLBW who were small for their gestational age (SGA) and those with VLBW who were AGA (Räikkönen et al. 2008).

Some studies have examined the association between poor nutrition during the fetal period and depression later in adulthood (Thompson et al. 2001; Gale and Martyn 2004; Rice et al. 2006; Räikkönen et al. 2008). Some (Gale and Martyn 2004; Räikkönen et al. 2008) reported a positive association, but others (Vasiliadis et al. 2008) reported no association, indicating that no conclusion has yet been reached as to whether a link exists. To our knowledge, no study has examined the association between intrauterine environment and depression during the school age period.

We conducted a follow-up survey on infants with VLBW who were discharged from neonatal intensive care units (NICU) between 1994 and 2000 and term infants born during the same period. In this study, we selected subjects aged 10 years or over who were enrolled in our survey and examined their growth, behavioral development, and mental health. The World Health Organization (WHO) identifies adolescence as the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19 (UNFPA 1998). The purpose of this study is to compare growth, behavioral development, and mental health between children with VLBW and those born AGA at term, and then to elucidate the epidemiological effects of intrauterine environment on growth, behavioral development, and mental health in adolescence.

Materials and Methods

Subjects, design, and study variables

Our follow-up study started in 2000. There were three groups defined according to the physical standard value from gestation at birth established by Japan Pediatric Society Neonatal Committee (1994) (i.e., SGA weight below the 10^{th} percentile, or −1.28 standard deviations from the mean; Ogawa et al. 1998). There were 60 SGA infants weighing less than 1,500 g (SGA in VLBW group, hereafter denoted as the SGA/VLBW group), 89 AGA infants weighing less than 1,500 g at birth (the AGA in VLBW group, hereafter denoted as the AGA/VLBW group) with less than 32 weeks of gestation, and 96 term AGA infants (control group) with more than 37 weeks of gestation. Every infant was born in the Tohoku University Hospital from January 1994 to December 2000. In 2010, 39 SGA/VLBW subjects, 57 AGA/VLBW subjects, and 49 control subjects participated in the growth, development, and health evaluations. Self-report questionnaires were sent to each subject by mail. Data for 23 SGA/VLBW subjects, 34 AGA/VLBW subjects, and 29 control subjects were available for the present study.

This study was approved by the Ethics Review Committee of the Graduate School of Medicine, Tohoku University School of Medicine. All subjects gave their consent to participate in this study.

Self-report questionnaires

The items of the self-report questionnaire included assessments of the subjects' conditions at birth and their physical development values. Parents were asked about their own physical condition, education, employment at childbirth, and annual income. We used the Japanese version (Morinaga et al. 1992) of the Pupil Rating Scale Revised (PRS), developed by Myklebust (1981), to test for LD. The PRS is comprised of five subscales, including auditory comprehension and memory, spoken language, orientation, motor coordination, and personal-social behavior. There are 24 items in total, each rated on a 5-point Likert-type scale. This screening tool has been extremely accurate in identifying possible learning problems in children. We evaluated individual scores according to Myklebust (1981) criteria. The children who scored below 20 points on verbal items, 40 points on non-verbal items, and 65 points in total were suspected to be verbal LD children, non-verbal LD children, and LD children, respectively. We also used the Children's Depression Inventory (CDI) to examine the presence of depression (Kovacs 1981). The CDI is a 27-item questionnaire used to assess depressive symptoms in children between the ages of 6 and 17. We purchased the translated Japanese version from Multi-Health Systems (North Tonawanda, NY). According to a study by Kovacs (1981), the mean CDI score in healthy children is 9, while the cut-off point for depression is 19. In Japanese infants and school-aged children, Murata et al. (1989) suggested that a cut-off point of 22 was suitable, so we used it in the present study. The CDI was administered to the child subjects, whereas the self-report questionnaire and PRS were administered to his/her parents.

Statistical analysis

The questionnaire items and scores on the PRS and CDI were compared as follows: (1) the entire VLBW group versus the control group, (2) SGA/VLBW group versus control group, (3) AGA/VLBW group versus control group, and (4) SGA/VLBW group versus AGA/VLBW group.

For the statistical analysis, χ^2 tests were used to conduct between-group comparisons on qualitative variables, whereas the quantitative variables were analyzed using *t*-tests. Adjustment for confounding factors was performed by using analyses of covariance. SPSS for Windows (version 18) was used for statistical analysis. The significance threshold was set at 5%.

Results

Characteristics of the subjects

The characteristics of the VLBW group (SGA and AGA) and the control group are shown in Table 1. Mothers of the VLBW group had a significantly higher percentage of pregnancy-induced hypertension compared with mothers of the control group. Furthermore, between the VLBW groups, the mothers of the SGA group had a significantly higher percentage of pregnancy-induced hypertension compared with those of the AGA group. In terms of social conditions, the percentages of fathers and mothers who had graduated with a four-year university education were significantly lower in the VLBW group (mother: 5.4%; father: 15.7%) compared with the control group (mother: 24.1%,

Table 1. Characteristics of very Low-Birth-Weight (VLBW) Infants Born Small for Gestational Age (SGA) and Appropriate for Gestational Age (AGA) and of Term Control Subjects.

Characteristics	VLBW	VLBW		Control	vs. Control			VLBW
		SGA	AGA					
	$n = 57$	$n = 23$	$n = 34$	$n = 29$	p^1	p^2	p^3	p^4
<Infants>		Perinatal						
Boys/Girls	30/27	10/13	20/14	14/15	0.498	0.475	0.280	0.193
Multiple birth, twin or triplet	twin7, triplet2	twin1	twin6, triplet2	0				
Gestational age (week)	30.3 ± 3.0	32.2 ± 3.2	28.9 ± 1.9	39.9 ± 1.0	< 0.001	< 0.001	< 0.001	< 0.001
Birth weight (g)	1,108.5 ± 266.3	1,078.7 ± 287.1	1,128.7 ± 253.7	3,119.8 ± 301.0	< 0.001	< 0.001	< 0.001	0.491
Standardized birth weight	−1.1 ± 1.2	−2.24 ± 0.8	−0.36 ± 0.7	−0.01 ± 0.6	< 0.001	< 0.001	0.027	< 0.001
Body height at birth (cm)	35.8 ± 3.5	36.1 ± 3.6	35.6 ± 3.4	49.6 ± 1.8	< 0.001	< 0.001	< 0.001	0.619
Head circumference at birth (cm)	26.1 ± 2.0	26.2 ± 2.3	26.0 ± 1.8	33.7 ± 1.2	< 0.001	< 0.001	< 0.001	0.689
Apgar score at 1 minute	5.5 ± 2.7	5.8 ± 2.7	5.4 ± 2.7	8.0 ± 1.1	< 0.001	< 0.001	< 0.001	0.586
Apgar score at 5 minutes	7.6 ± 1.9	8.3 ± 1.8	7.2 ± 1.9	9.0 ± 0.4	< 0.001	0.114	< 0.001	0.030
Caesarean delivery (%)	46 (80.7)	22 (95.7)	24 (70.1)	3 (10.0)	< 0.001	< 0.001	< 0.001	0.018
Age at delivery (year)	30.4 ± 3.9	31.8 ± 3.9	29.5 ± 3.6	32.5 ± 3.8	0.021	0.501	0.002	0.030
Mother's height (cm)	156.3 ± 5.7	157.2 ± 5.8	155. 7 ± 5.6	157.7 ± 4.6	0.237	0.691	0.123	0.341
Weight without pregnancy (kg)	51.5 ± 8.7	52.3 ± 7.5	51.0 ± 9.5	51.1 ± 6.6	0.816	0.534	0.955	0.570
BMI (kg/m^2)	21.0 ± 3.2	21.2 ± 2.8	21.0 ± 3.5	20.6 ± 2.7	0.445	0.389	0.584	0.799
Primipara/Multipara	33/24	14/9	19/15	14/15	0.268	0.267	0.363	0.461
pregnancy induced hypertension (%)	10 (17.5)	9 (39.1)	1 (2.9)	0 (0)	0.012	< 0.001	0.540	0.001
Employment status: presence of job (including maternity leave) (%)	28 (49.1)	11 (47.8)	17 (50.0)	13 (44.8)	0.203	0.238	213.000	0.750
Father's height (cm)	170.8 ± 5.2	170.1 ± 4.9	171.3 ± 5.4	172.6 ± 6.5	0.207	0.165	0.446	0.430
Employment status: full-time/ self-employed/house-husband	46/5/1	20/3/0	26/2/1	27/2/0	0.683	0.662	0.601	0.520
<Mother>		Parental						
Age at evaluation	44.1 ± 4.5	45.8 ± 4.1	42.9 ± 4.4	45.3 ± 4.7	0.245	0.676	0.042	0.015
Highest education					0.117	0.231	0.192	0.615
Junior high school	1 (1.8)	0 (0)	1 (2.9)	0 (0)				
Senior high school	30 (53.5)	9 (41.0)	21 (61.8)	12 (41.4)				
College or technical school	22 (39.3)	12 (54.5)	10 (29.4)	10 (34.5)	0.016	0.061	0.044	0.661
Undergraduate	3 (5.4)	1 (4.5)	2 (5.9)	6 (20.7)				
Graduate	0 (0)	0 (0)	0 (0)	1 (3.4)				
<Father>								
Age at evaluation	46.8 ± 5.8	48.6 ± 5.0	45.5 ± 6.1	48.1 ± 5.3	0.331	0.740	0.086	0.057
Highest education					0.001	0.074	< 0.001	0.178
Junior high school	3 (5.9)	1 (4.5)	2 (6.7)	1 (3.5)				
Senior high school	30 (58.8)	11 (50.0)	19 (65.5)	5 (17.2)				
College or technical school	10 (19.6)	5 (22.7)	5 (16.7)	6 (20.7)	< 0.001	0.011	< 0.001	0.207
Undergraduate	6 (11.8)	5 (22.7)	1 (3.5)	15 (51.7)				
Graduate	2 (3.9)	0 (0)	2 (6.9)	2 (6.9)				
<Family>		Family						
Annual income					0.162	0.174	0.153	0.478
less than 2 million	2 (4.4)	1 (6.7)	1 (3.3)	0 (0)				
2-4 million	7 (15.6)	0 (0)	7 (22.3)	3 (12.0)				
4-6 million	11 (24.4)	4 (26.7)	7 (22.3)	9 (36.0)				
6-8 million	13 (28.9)	5 (33.3)	8 (26.7)	2 (8.0)	0.113	0.372	0.091	0.355
8-10 million	8 (17.8)	3 (20.0)	5 (16.7)	5 (20.0)				
more than 10 million	4 (8.9)	2 (13.3)	2 (6.7)	6 (24.0)				
<Age composition>		Child						
Age at evaluation	13.4 ± 1.9	13.7 ± 1.9	13.2 ± 1.9	12.3 ± 2.0	0.015	0.017	0.062	0.421
10 years	2 (0/2)	0 (0/0)	2 (0/2)	7 (4/3)				
11 years	9 (6/3)	4 (3/1)	5 (3/2)	4 (1/3)				
12 years	11 (7/4)	5 (3/2)	6 (4/2)	6 (2/4)				
13 years	9 (5/4)	1 (1/0)	8 (4/4)	5 (3/2)				
14 years	6 (2/4)	4 (1/3)	2 (1/1)	2 (1/1)				
15 years	8 (3/5)	3 (1/2)	5 (2/3)	2 (1/1)				
16 years	12 (7/5)	6 (1/5)	6 (6/0)	3 (2/1)				

Data are given as mean (S.D.) or as number (percentage).
A two-group comparison was carried out using Student's *t*-test.
IUGR infants: 3 sets of twin, AFD infants: 6 sets of twin, 2 sets of fetus.
Employment status was the status at delivery.
p^1: VLBW child and term controls.
p^2: VLBW child born SGA and term controls.
p^3: VLBW child born AGA and term controls.
p^4: VLBW group between those born SGA and those born AGA.
Education and annual income were dichotomized and were compared.

father: 58.6%; mother: $p = 0.016$, father: $p < 0.001$). The percentage of those with income more than 8,000,000 yen was lower in the VLBW group (26.7%) than in the control group (44.0%), but this difference was not statistically significant ($p = 0.113$).

PRS score

The PRS and CDI scores of the subjects are shown in Table 2. The PRS score of one subject and the CDI scores of two subjects were not available; namely, the data on PRS and CDI were available in 56 subjects and 55 subjects, respectively. The total PRS score was significantly lower in the VLBW group compared with the control group. Scores of the verbal field and the non-verbal field were also significantly lower in the VLBW group. Furthermore, the VLBW group scored significantly lower than did the control group on each of the subscales, including auditory understanding and memory, spoken language, orientation, motor coordination, and social behavior. Further, six out of the 56 subjects in the VLBW group (10.7%) had suspected LD (a total PRS score of less than 65), but none of the 29 control subjects did. This difference was not statistically significant ($p = 0.074$). More specifically, four out of the 22 SGA subjects were found to have suspected LD (18.2%; SGA vs. control: $p = 0.029$). The results of the above comparison of PRS scores did not change even after adjusting for age at evaluation, sex, and parents' highest level of education.

Next, we compared the percentages of suspected LDs in the verbal and non-verbal fields, and in total, between the SGA/VLBW and AGA/VLBW groups. The percentages were as follows: in the SGA/VLBW group, the values were 1/22 (4.5%), 4/22 (18.2%), and 4/22 (18.2%), respectively; in the AGA/VLBW group, the values were 1/34 (2.9%), 0/34 (0%), and 2/34 (5.9%), respectively. Thus, more suspected LD children were present in the SGA/VLBW group. The percentage of suspected LD in the non-verbal field was significantly higher in the SGA/VLBW group than in the AGA/VLBW group ($p = 0.02$).

CDI score

The mean scores of the CDI in both the SGA/VLBW group (12.5 ± 5.7 points) and the AGA/VLBW group (10.9 ± 6.8 points) were higher compared to the control group (10.0 ± 6.1 points), but no significant differences were found. A CDI score of more than 22 points was obtained by one adolescent from the SGA/VLBW group (4.5%), 3 adolescents from the AGA/VLBW group (9.1%), and 2 adolescents from the control group (6.9%). None of these comparisons were significant.

Discussion

This is the first study, to our knowledge, to evaluate the development and mental health of adolescents with VLBW compared to those born AGA at term (control group) in Japan. The results revealed that the PRS scores of VLBW infants were significantly lower in each subscale (auditory comprehension and memory, spoken language, orientation, motor coordination, and personal-social behavior) compared to those of the control group. The percentage of suspected LD based on PRS score was significantly higher in the VLBW group than in the control group. Furthermore, more LD subjects were found in the SGA/VLBW group than in the AGA/VLBW group. There were no significant differences in CDI scores between the SGA/VLBW, AGA/VLBW, and control groups.

Our findings on LD were consistent with findings from previous studies. Aarnoudse-Moens et al. (2009) conducted a quantitative meta-analysis of studies published between 1998 and 2008 on academic achievement (14 studies), behavioral functioning (9 studies), and executive function (12 studies), which compared a total of 4,125 very preterm and/or VLBW children with 3,197 term-born controls. They reported that very preterm and/or VLBW children have moderate-to-severe deficits in academic achievement, attention problems, internalizing behavioral problems, and poor executive function.

Previously, only the Helsinki Study of Very-Low-Birth-Weight Adults examined whether the effects of VLBW on development differ between VLBW adults who were SGA and those who were AGA (Strang-Karlsson et al. 2008). VLBW adults in the SGA subgroup (mean age: 22.2 years old) scored significantly higher on the executive dysfunction and emotional instability subscales of the Adult Problem Questionnaire (a measure of attention deficit hyperactivity disorder [ADHD] behavioral symptoms), than did those in the AGA subgroup (mean age: 22.5 years old) and the term comparison group (mean age: 22.5 years old; Strang-Karlsson et al. 2008). ADHD is known to be related to LD, and studies have reported that VLBW infants had a higher risk for ADHD and LD when they reached school age compared with a normal term group (Aarnoudse-Moens et al. 2009). The Helsinki Study proposed new evidence that VLBW-SGA individuals had excessive ADHD-related behaviors. We also found more excessive LD-related symptoms in the non-verbal field in VLBW-SGA individuals than in VLBW-AGA individuals.

Our findings suggest that intrauterine growth retardation, for which SGA serves as a proxy, and prematurity, for which VLBW serves as a proxy, predict later LD-related behavioral characteristics. The underlying mechanisms may be biological and psychosocial. Biological programming of the developing brain caused by an unsuitable intrauterine environment or prematurity-associated illness in the postnatal period may disturb neuronal organization and modify later psychological characteristics. In animal experiments, malnutrition during the fetal period has been shown to cause a reduction in essential proteins (MeCP2) for normal epigenetic regulation of gene expression in the brain (Lillycrop et al. 2008). The psychosocial environment may also affect the development of the VLBW individual because having a VLBW child can give rise to maternal psychological distress (Singer et al. 1999). In our study, a

Table 2. The Pupil Rating Scale revised (PRS) score and Children's Depression Inventory (CDI) score of Very low birth weight (VLBW) individuals either small for geatational age (SGA) or appropriate for gestational age (AGA) and of the term comparison group.

	VLBW	VLBW		Control	vs. Control			VLBW
		SGA	AGA		p^1	p^2	p^3	p^4
	n = 56	*n* = 22	*n* = 34	*n* = 29				
Boys/Girls	30/26	10/12[a]	20/14	14/15	0.663	0.442	1	0.404
Age at evaluation	13.4 ± 1.9	13.6 ± 1.9	13.2 ± 1.9	12.3 ± 2.0	0.019	0.029	0.062	0.552
<PRS>								
Subscale scores								
Auditory comprehension and memory	13.7 ± 2.7	13.5 ± 3.3	13.8 ± 2.3	16.3 ± 2.2	<.001	0.001	<.001	0.741
Spoken language	15.3 ± 3.3	15.8 ± 4.7	15.0 ± 1.9	17.1 ± 2.4	0.011	0.241	<.001	0.464
Orientation	12.5 ± 2.3	12.5 ± 2.8	12.6 ± 1.9	14.8 ± 2.1	<.001	0.001	<.001	0.869
Motor coordination	9.6 ± 2.2	9.0 ± 2.0	10.0 ± 2.2	11.2 ± 2.0	0.001	<.001	0.024	0.088
Personal-social behavior	26.5 ± 5.3	25.7 ± 6.6	27.0 ± 4.2	30.3 ± 3.8	0.001	0.003	0.002	0.393
Verbal field	28.5 ± 5.4	28.9 ± 7.5	28.1 ± 3.5	33.5 ± 4.1	<.001	0.014	<.001	0.750
Suspected LD in verbal field (less than 20 points)	2 (3.6)	1 (4.5)	1 (2.9)	0 (0)	0.431	0.431	0.540	0.636
Non-verbal field	48.6 ± 8.7	47.1 ± 10.8	49.6 ± 7.2	56.6 ± 6.7	<.001	0.001	0.001	0.240
Suspected LD in non-verbal field (less than 40 points)	4 (7.1)	4 (18.2)	0 (0)	0 (0)	0.181	0.029	1	0.020
Total score	77.2 ± 13.6	76.0 ± 17.7	78.0 ± 10.6	90.1 ± 9.8	<.001	0.001	<.001	0.290
Score range	29-115	29-108	63-115	74-107				
Suspected LD in total (less than 65 points)	6 (10.7)	4 (18.2)	2 (5.9)	0 (0)	0.074	0.029	0.287	0.156
	n = 55	*n* = 22	*n* = 33	*n* = 29				
Boys/Girls	30/25	10/12[a]	20/13[b]	14/15	0.437	0.442	0.540	0.648
Age at evaluation	13.4 ± 1.9	13.6 ± 1.9	13.2 ± 1.9	12.3 ± 2.0	0.020	0.025	0.073	0.478
<CDI>								
Total score	11.6 ± 6.4	12.5 ± 5.7	10.9 ± 6.8	10.0 ± 6.1	0.282	0.142	0.572	0.381
Score range	2-31	2-22	2-31	0-23				
Depression tendency (22 points and over)	4 (7.3)	1 (4.5)	3 (9.1)	2 (6.9)	0.660	0.604	0.562	0.472

Data are given as mean ± standard deviation or as number (percentage).
Between comparison was carried out using student's *t*-test.
p^1: VLBW vs. controls.
p^2: VLBW child born SGA vs. controls.
p^3: VLBW child born AGA vs. controls.
p^4: VLBW group between those born SGA vs. those born AGA.
[a]Data unavailable from one subject.
[b]Data unavailable from one subject.

difference in academic background and income was observed between the VLBW group and the control group. However, even after adjustment for academic background and income, PRS scores were significantly lower in the VLBW group than in the control group.

Two studies have examined the effect of intrauterine environment on mental health later in life (Gale and Martyn 2004; Alati et al. 2007). However, these studies were conducted on subjects with low birth weight (LBW, i.e., weight less than 2,500 g), and data on mental health outcomes of VLBW young adults are scant and inconsistent. Hack et al. (2004) sought to examine gender-specific behavioral outcomes and evidence of psychopathology in a cohort of 241 VLBW young adults at 20 years of age. Parents of VLBW women reported significantly higher scores for their daughters on the anxious/depressed, withdrawn, and attention problem subscales compared with control parents. Moreover, according to the Helsinki study, VLBW adults in the SGA subgroup (22.2 ± 2.1 years old) scored higher on the emotional instability subscale of the Adult Problem Questionnaire than did those in the AGA subgroup (22.5 ± 2.1 years old) and the term comparison group (22.5 ± 2.2

years old). This finding indicates that rather than VLBW per se, intrauterine growth retardation, as reflected by SGA status in the VLBW subjects, confers a risk for emotional adversity in young adulthood. On the other hand, Cooke (2004) reported no difference in self-reported anxiety and depression between 138 subjects aged 19-20 years with VLBW and 163 term control subjects. In our study, individuals in the VLBW group were more likely to have higher CDI scores [11.6 ± 6.4 (SGA/VLBW group: 12.5 ± 5.7, AGA/VLBW group: 10.9 ± 6.8)] compared with term control group individuals (10.1 ± 6.1), though no statistical difference was observed. Further follow-up studies are needed.

There are both strengths and limitations in our study. A strength is that we divided the VLBW group into AGA and SGA subgroups. Few previous studies the effect of VLBW on development in later life while considering intrauterine growth retardation (Räikkönen et al. 2008). Another strength is that data were collected on many kinds of factors known or suspected to modify the development of infants, such as parents' educational backgrounds and family income. Therefore, we could elucidate the independent effect of VLBW by multivariate adjustment. Several limitations of this study also deserve mention. First, the number of subjects in our study was smaller than that in previous Western studies on the development of VLBW infants. Therefore, we could not determine gender differences in learning disability or depression in this study. Second, our study subjects were recruited from a local area in Japan, making it difficult to generalize our findings. Third, in recent years, psychological stress during pregnancy, such as anxiety and depression, has been shown to have adverse effects on infant development during the fetal period and after birth, including premature delivery, reduced infant weight at birth, and impaired behavioral and emotional development in the child. However, data on psychological status during pregnancy were not available in our study. Moreover, we could not collect medical histories of psychological disease from the parents. Finally, unfortunately, we were able to collect the current data on LD and depression symptoms only from a portion of the originally enrolled infants. We could not identify the reasons for attrition.

In conclusion, consistent with previous findings in VLBW children, we found evidence of increased LD symptoms in all subscales of the PRS (auditory comprehension and memory, spoken language, orientation, motor coordination, and personal-social behavior) among the adolescents with VLBW. Moreover, more LD-related symptoms in the non-verbal field were observed in SGA/VLBW teens compared with AGA/VLBW teens. Therefore, not only VLBW per se, but also intrauterine growth retardation may pose a risk for LD among adolescents. In contrast, we found no evidence of increased symptoms of depression among the adolescents with VLBW.

The purpose of our original follow-up survey on VLBW infants was to support their growth and development after discharge from the NICU. The epidemiological evidence described in the long-term follow-up study on VLBW infants from the fetal period to adulthood must be able to serve as a reference to provide proper support for each infant's growth and development. It is also necessary to elucidate the pathophysiological and neuropsychological mechanisms underlying them.

Acknowledgements

This study was funded by Grants-in-Aid for Scientific Research 2010-2012 (Task No. 22592481).

Conflict of Interest

The authors declare no conflict of interest.

References

Aarnoudse-Moens, C.S.H., Weisglas-Kuperus, N., van Goudoever J.B. & Oosterlaan, J. (2009) Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics*, **124**, 717-728.

Alati, R., Lawlor, D.A., Mamun, A.A., Williams, G.M., Najman, J.M., O'Callaghan, M. & Bor, W. (2007) Is there a fetal origin of depression? Evidence from the Mater University Study of Pregnancy and its outcomes. *Am. J. Epidemiol.*, **165**, 575-582.

Cooke, R.W. (2004) Health, lifestyle, and quality of life for young adults born very preterm. *Arch. Dis. Child.*, **89**, 201-206.

de Boo, H.A. & Harding, H.E. (2006) The developmental origins of adult disease (Barker) hypothesis. *Aust. N. Z. J. Obstet. Gynaecol.*, **46**, 4-14.

Gale, C.R. & Martyn, C.N. (2004) Birth weight and later risk of depression in a national birth cohort. *Br. J. Psychiatry*, **184**, 28-33.

Gluckman, P.D. & Hanson, M.A. (2004) Living with the past: evolution, development, and patterns of disease. *Science*, **305**, 1733-1736.

Gluckman, P.D., Hanson, M.A., Spencer, H.G. & Bateson, P. (2005) Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proc. Biol. Sci.*, **272**, 671-677.

Hack, M., Youngstrom, E.A., Cartar, L., Schluchter, M., Taylor, H.G., Flannery, D., Klein, N. & Borawski, E. (2004) Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. *Pediatrics*, **114**, 932-940.

Hunt, J.V., Cooper, B.A. & Tooley, W.H. (1988) Very low birth weight infants at 8 and 11 years of age: role of neonatal illness and family status. *Pediatrics*, **82**, 596-603.

Japan Pediatric Society Neonatal Committee (1994) Recommendations on terminology for neonates. *J. Jpn. Pediatr. Soc.*, **98**, 1946-1950 (in Japanese).

Kanazawa, T., Shimizu, S., Kamada, J., Tanabe, H. & Itoigawa, N. (1997) Intelligence and learning disabilities in 6- to 8-year-old children weighing under 1000 grams at birth. *Int. J. Behav. Dev.*, **20**, 179-188.

Kovacs, M. (1981) Rating scales to assess depression in school-aged children. *Acta Paedopsychiatr.*, **46**, 305-315.

Lillycrop, K.A., Phillips, E.S., Torrens, C., Hanson, M.A., Jackson, A.A. & Burdge, G.C. (2008) Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPARα promoter of the offspring. *Br. J. Nutr.*, **100**, 278-282.

Maternal and Child Health Statistics of Japan (2011) Boshi Hoken Jigyodan, Tokyo (in Japanese).

Morinaga, R. & Oki, T. (1992) Manual for the pupil rating scale revised: screening for learning disabilities (Translated and standardized in Japan), edited by Hermer, R. Myklebust. Bunkyo Shiryo Kyokai, Co. LTD., Tokyo, Japan (in Japanese).

Murata, T., Tutumi, T., Sarada, Y., Nakaniwa, Y. & Kobayashi, R. (1989) A clinical study on childhood and adolescent depression II. An investigation using the CDI. Study on the etiology and treatment of childhood and adolescent mental disorders commissioned by the Ministry of Welfare, 'Mental-neural disorders research program'. Study Reports 1988, 69-76 (in Japanese).

Myklebust, H.R. (1981) *The pupil rating scale revised: screening for learning disabilities*, Grune & Stratton, New York.

Ogawa, Y., Iwamura, T., Kuriya, N., Nishida, H., Takeuchi, H., Takada, M., Itabashi, K., Imura, S. & Isobe, K. (1998) Birth size standards by gestational age for Japanese neonates. *J. Jpn. Soc. Neonatal Med.*, **34**, 624-632 (in Japanese).

Räikkönen, K., Pesonen, A.K., Heinonen, K., Kajantie, E., Hovi, P., Järvenpää, A.L., Eriksson, J.G. & Andersson, S. (2008) Depression in young adults with very low birth weight: the Helsinki study of very low-birth-weight adults. *Arch. Gen. Psychiatry*, **65**, 290-296.

Rice, F., Harold, G.T. & Thapar, A. (2006) The effect of birthweight with genetic susceptibility on depressive symptoms in childhood and adolescence. *Eur. Child Adolesc. Psychiatry*, **15**, 383-391.

Singer, L.T., Salvator, A., Guo, S., Collin, M., Lilien, L. & Baley, J. (1999) Maternal psychological distress and parenting stress after the birth of a very low-birth-weight infant. *JAMA*, **281**, 799-805.

Strang-Karlsson, S., Räikkönen, K., Pesonen, A.K., Kajantie, E., Paavonen, E.J., Lahti, J., Hovi, P., Heinonen, K., Järvenpää, A.L., Eriksson, J.G. & Andersson, S. (2008) Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. *Am. J. Psychiatry*, **165**, 1345-1353.

Tanabe, K., Tamakoshi, K. & Murotsuki, J. (2011) Association of women's birth weight with their blood pressure during pregnancy and with the body size of their babies. *Tohoku J. Exp. Med*., **224**, 287-292.

Thompson, C., Syddall, H., Rodin, I., Osmond, C. & Barker, D.J.P. (2001) Birth weight and the risk of depressive disorder in late life. *Br. J. Psychiatry*, **179**, 450-455.

UNFPA (1998) The Sexual and Reproductive Health of Adolescents: A Review of UNFPA Assistance. Technical Report, 43, New York, UNFPA.

Vasiliadis, H.M., Gilman, S.E. & Buka, S.L. (2008) Fetal growth restriction and the development of major depression. *Acta Psychiatr. Scand.*, **117**, 306-312.