

Body mass index
in
children born between
23 and 28 weeks of gestational age

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1. Introduction

1.1. Trends in perinatal survival

The survival rate of premature infants has improved dramatically during past decades as neonatology has developed[1]. Figure 1 shows the trend in neonatal mortality in Japan over the past 70 years, with key developments in neonatology.

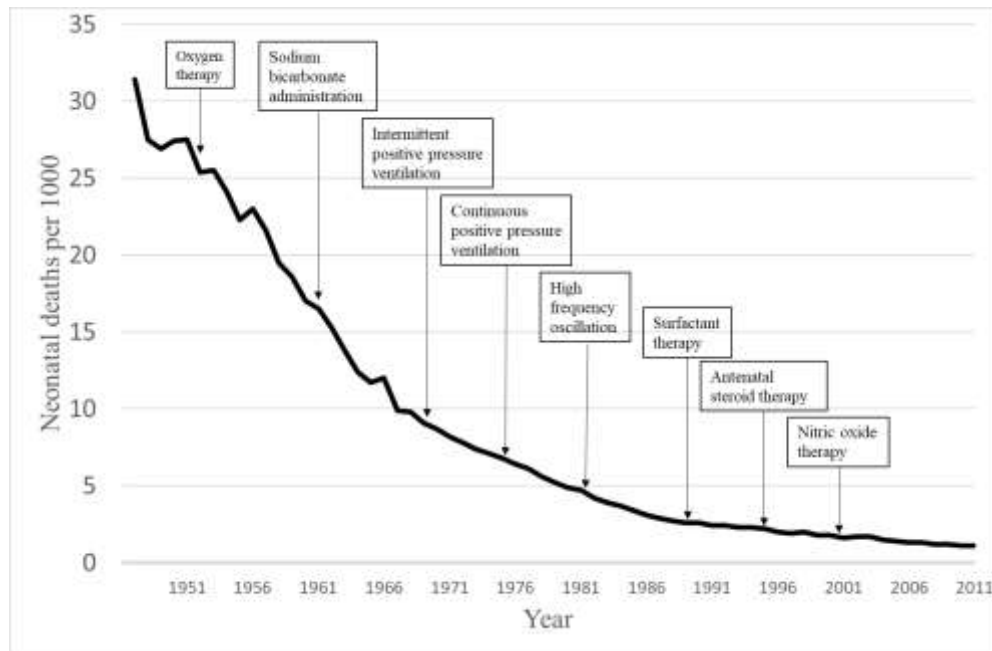


Figure 1-1: Development of neonatology and the Japanese neonatal mortality rate, 1948 - 2012

As shown in Figure 1-1, around the 1960s, premature infants with respiratory disorders were treated with oxygen. In 1963, Usher reported “Usher’s regime” that added administration of sodium bicarbonate and brought further improvements in respiratory disorder in premature infants[2]. Their respiratory distress was known to arise from lack of pulmonary surfactant, but this chemical was only developed in the 1980s and clinical use began at this time. Since then, more infants have been able to

survive from respiratory distress[3] and its prophylactic use changed their clinical course[4].

Simultaneously with these developments in medical interventions for respiratory-distressed premature neonates, ventilation techniques also progressed. It was in the 1970s that the continuous positive pressure ventilation machine was invented, followed by intermittent positive pressure ventilation and high frequency oscillation. Ventilation techniques continue to develop, leading to continual improvements in lung-protective ventilation techniques[5].

Other therapies like antenatal glucocorticoid therapy, aggressive nutrition policies[1], and appropriate oxygen supplementation[6] are also still in progress. As a result of these developments, the survival rate of premature infants improved; in 1985, 95% of US infants born between 1200 and 1500g survived[7] and in 2010, 90% of very preterm infants (birth weight under 1500g) in Germany survived[8]. In 18 European countries, declines in stillbirth and neonatal mortality rates between 2004 and 2010 were reported[9]. The latest study from Hungary reported on a care protocol for infants weighing under 500 grams that improved their survival rate from 30.8% to 70.8%[10]. All these reports suggest that more and more premature infants are surviving their neonatal period.

1.2. Developmental origins of health and disease

As a result of these developments in neonatology, more premature infants are surviving their neonatal period[6] and their long-term health outcomes have become a matter of much concern. The most popular concept is the theory of the developmental origins of health and disease (DOHaD).

Concern about long-term health and development outcomes in infants born small was first reported in 1986 as an association between neonatal environment and cardiovascular diseases[11]. Since then, many studies have reported an association between poor early life environment and adverse health effects in later life, and now metabolic syndromes like obesity, hypertension, diabetes are reported to have an association with neonatal environment[12]. In the 1980s, infants born between 1200 and 1500 g had a survival rate exceeding 95%, but survival in infants born 500 to 550 g was very low[7]. This means that the DoHAD theory was developed only in infants born over 1200 g. Furthermore, at that time the studies only used low birth weight, and gestational age was not considered[1]. Accordingly, the concept of DOHaD covers immature infants who survived in the past few decades, but in more premature infants who only became able to survive their neonatal period recently, the extent and nature of health problems related to premature birth remains poorly understood[13]. To reveal their future outcome is becomingly increasingly urgent[14] because they are growing and their developmental outcomes will begin to be revealed.

1.3. The development of neonatology and extremely premature neonates in Japan

Japan is one of the leading countries in neonatology and as shown in Figure 1, has seen a dramatic decrease in the neonatal death rate. Japanese studies report mortality rates among very low birth weight infants at discharge improved from 10.8 to 8.7 % between 2003 and 2008[15], with the greatest improvement seen in infants born between 501 and 750 g. Their mortality rate improved from 25.6 to 17.7 % during the study period. There has been a similar decline in in-hospital mortality of extremely low birth weight infants from 17.7 % in 2000 to 13.0 % in 2005, and a reduction in mortality

in infants weighing less than 400g from 67.7% to 53.3% during this period in Japan[16]. These trends in Japan are one of the most developed trends in neonatology in the world. In Japan, the neonatal mortality rate is 1.1 per 1000, as low as Sweden and Finland and almost as low as the lowest European rates, which are 1.0 per 1000 live births in Iceland and the Czech Republic.

These infants are now growing and there are studies from Japan about the relationship between those born low birth weight and adult disease. There are reports about hypertension and poor intrauterine environment[17], birth weight and cardiovascular disease[18], and obesity[19] from Japan and future complications in infants born low birth weight are garnering attention now.

1.4. Previous body composition research

Among many possible long-term outcomes in premature infants, body composition is a major concern. Table 1-1 summarizes the results of previous studies about body composition in premature infants.

Table 1-1: Previous studies of body composition in premature infants

Number of patients	Gestational age	Born before 30 weeks	Evaluation age	IUGR or not	Outcome	Publication year
2385	< 35	Yes	3-60 months	No	BMI	2017[20]
1320	29.1 \pm 2.1	NA	6 years	Yes	Height	2007[21]
81	28.3 \pm 3.6	NA	24 months	Yes	Weight	2017[22]
998	< 32	NA	2, 5, 19 years	Yes	Height	2017[1]
61	27.2	NA	9.5 years	No	DXA	2017[23]
143	29.2 \pm 2.6	NA	8 years	Yes	BMI	2016[24]
63	30 \pm 2	NA	5 years	No	Fat-free mass	2015[25]
985	< 35	NA	3-8 years	No	Weight	2012[26]
123	31.5 \pm 2.7	NA	3-4 months	No	Fat-free mass	2011[27]
312	< 32	NA	11 years	Yes	BMI	2010[28]
85	< 34	NA	5 years	No	BMI, DXA	2008[29]
403	29.7 \pm 1.5	NA	19 years	No	BMI	2005[30]

DXA: dual-energy x-ray absorptiometry

The sample size of previous studies was at most 2385 and the population characteristics are not uniform. The largest sample size in a uniform sample was 1320. The mean gestational age of all samples was at least 28 weeks. There was little information about infants born less than 30 weeks of gestational age, who may not be affected by the DOHaD theory. Moreover, infants with intrauterine growth retardation (IUGR) were not separately analyzed in some studies. IUGR results from uteroplacental insufficiency and causes chronic hypoxia and delay in all aspects of the growth process[31], and infants with IUGR are a high risk population not only during hospital

stay[32] but also in their later lives, with higher risk of a wide range of health problems including neurodevelopmental outcomes[33], high blood pressure, abnormal lipid profiles, mental illness and cancer[34]. Moreover, as many of the studies to date have been single center studies, the results may be affected by unmeasured center-specific factors[35].

1.5. Objectives

A large multi-center study with a larger population of infants born less than 28 weeks of gestational age is needed to properly understand the long-term health consequences of extreme prematurity. This study will:

- Collect data from the NRNJ database, which is a multi-center database of infants born between 23 and 28 weeks of gestational age.
- Describe demographic and natal characteristics of this unique sample of very preterm births
- Analyze the relationship between BMI at 18 and 36 months and gestational age, IUGR and birth outcomes

This study will shed new light on long-term body composition outcomes in younger gestational age samples.

2. Methods

2.1. Data source

Data on premature births between January 1, 2003 and December 31, 2012 was extracted from the Neonatal Research Network of Japan (NRNJ) database.

The NRNJ database was established in 2003 for clinical study by the Japan society of neonatal health and development. The number of participating institutions of each level is shown in Table 2-1 by year. The NRNJ Database covers level 2 and level 3 NICUs. A level 3 NICU is capable of caring for very small or very sick infants and a level 2 NICU provide less care and targets infants who weigh between 1200 and 1800g or were born between 30 and 34 weeks of gestational age.

Table 2-1: **Number of institutions participating the NRNJ database by year**

Year	Level 3 NICU	Level 2 NICU	Others	Total
2003	35	2	3	40
2004	44	3	3	50
2005	54	3	5	62
2006	58	3	7	68
2007	65	13	10	88
2008	71	13	6	90
2009	75	22	4	101
2010	80	91	8	179
2011	84	105	6	195
2012	87	99	6	192

Every infant born alive and whose birth weight was less than 1500g and/or was born before 32 weeks of gestational age was registered and each participating NICU filled in a common questionnaire, which is show in the Appendix.

All infants born between 23 and 28 weeks of gestational age were eligible for this study. Infants were excluded from the study if they met any of the following exclusion criteria:

- Died during hospital stay or follow up period
- Unknown gender (both no information of gender and gender were not able to choose)
- Congenital anomaly

2.2.Data collection

Information about birthweight, gestational age, death, parity, maternal complications during pregnancy (multiple pregnancy, hypertension), complications during infants' hospital stay (congenital anomaly, chronic lung disease (CLD), late circulatory collapse (LCC), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC)), and body weight and height at 18 and 36 months were extracted.

All infants' body length and body weight were measured at birth, 18 and 36 months. Although there are no instructions about how to measure body composition in the NRNJ database, commonly, both body length and body weight are measured using a scale for children without any clothing and shoes. Body length is measured lying until 18-months and at 36-months, it is measured standing.

BMI was calculated as $\text{body weight (kg)} / (\text{body length (m)})^2$. I excluded extremely large or small data of body length and body weight before calculating BMI. I excluded infants with BMI more than 30 or less than 10.

2.3. Ethical considerations

This study protocol was approved by the ethical committee of Juntendo university (approval number: 17-314).

2.4. Statistical Analysis

First, I analyzed the characteristics between infants with BMI data available at 18- or 36-months (those who were included in study sample) and those with missing data at both 18- and 36-months (those who dropped out) to compare characteristics of these two groups. I used t-tests for gestational age, birth weight, body length at birth, and maternal age, and chi-square tests for IUGR proportion and gender proportion. Then, I performed the same analysis for infants with missing data at either the 18-months follow up point or the 36- months follow up point separately. These analyses were performed to examine differences between those who dropped out and those who were analyzed.

Second, because some of the multiple pregnancies were achieved by in vitro fertilization[36] and in these cases both BMI and prognosis differs from single pregnancies [37], I divided the sample into two groups: Single pregnancy and multiple pregnancy. Then, I analyzed their basic characteristics using the same tests and also compared their number of complications during pregnancy and the neonatal period.

Third, I compared BMI by number of births and presence of IUGR, separately by gender because their prognosis differs[38, 39], using t-tests.

Finally, I regressed BMI at 18- and 36-months against gestational age in weeks, with an interaction term for gestational age and IUGR. In this regression, non-IUGR was set as the reference category. Gestational age was rescaled so that a value of 0 corresponded to 23 weeks of gestational age, so that the intercept term measured the BMI for an infant born non-IUGR at 23 weeks. Parity, complications during pregnancy, and complications during hospital stay were included as covariates. Linear regression analysis was conducted. R-squared statistics were reported to show the goodness-of-fit

of the model. The analysis was performed using the R statistical software package.

3. Results

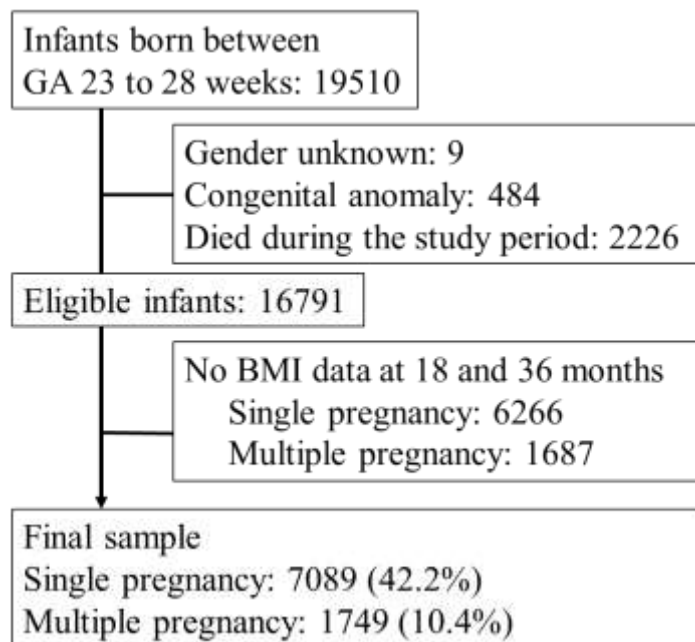
3.1. Study protocol

There were 40806 infants included in the NRNJ database. A total of 19510 infants were born between 23 to 28 weeks of gestational age and eligible for this study. Among these, a further 2719 infants were excluded due to unknown gender, death during the study period, or congenital anomaly, leaving 16791 infants included in this study.

Among these 16791 eligible infants, there were no data available at 18 months and 36 months in 7953 (47.3 %) infants. Finally, 8838 (52.6 %) infants were included in the sample, including 7089 infants from single pregnancies (80.2 % of the study sample) and 1749 (19.7 % of the study sample) from multiple pregnancies.

The study protocol is shown in Figure 3-1.

Figure 3-1: Study protocol



3.2. Comparison of missing and follow up samples

I compared basic characteristics of infants with data on BMI at either 18 or 36 months and infants with no data at both these time points. The result is shown in Table 3-1.

Table 3-1: Comparison of characteristics of infants with and without BMI data at 18 and 36 months

Variable	18- or 36-month data available (8838)	Neither 18- nor 36-month data available (7952)	P
Gestational age (weeks)	26.1 ± 1.58	26.2 ± 1.59	< 0.05
Birth weight at birth (g)	850.2 ± 226.1	869.8 ± 229.7	< 0.05
Body length at birth (cm)	33.2 ± 3.3	33.4 ± 3.2	< 0.05
IUGR (%)	1956 (22.1)	1607 (20.8)	< 0.05
Maternal age	31.3 ± 5.3	30.9 ± 5.5	< 0.05
Multiple pregnancy (%)	1749 (19.8)	1686 (21.2)	< 0.05

Gestational age, birth weight, body length, maternal age: t-test

IUGR, multiple pregnancy: chi-square test

In infants with follow up data, gestational age was significantly shorter, birth weight and body length at birth were significantly smaller, and IUGR proportion was significantly larger, which suggest that this sample group infants had more severe prematurity and birth complications.

I compared infants with BMI data and without BMI data at the 18 months follow up point. The comparison is shown in Table 3-2.

Table 3-2: Comparison of characteristics of infants with and without BMI data at 18-months

Variable	18-month data available (4671)	18-month data not available (12119)	P
Gestational age (weeks)	26.1 ± 1.57	26.1 ± 1.59	0.55
Birth weight (g)	857.9 ± 228.7	860.1 ± 227.8	0.95
Body length at birth (cm)	33.2 ± 3.4	33.2 ± 3.4	0.08
IUGR (%)	1068 (22.9)	2495 (20.6)	< 0.05
Maternal age	31.6 ± 5.3	31.0 ± 5.4	< 0.05
Multiple pregnancy (%)	888 (19.0)	2547 (21.0)	< 0.05

Gestational age, body weight, body length at birth, maternal age: t-test

IUGR, multiple pregnancy: chi-square test

There was no difference in gestational age, birth weight, body length at birth. However, the proportion of IUGR was significantly different.

The results of the comparison of infants with BMI data and without BMI data at 36 months are shown in Table 3-3.

Table 3-3: Comparison of characteristics of infants with and without BMI data at 36-months

Variable	36-month data available (8978)	36-month data not available (7812)	P
Gestational age (weeks)	26.1 ± 1.58	26.2 ± 1.59	< 0.05
Birth weight (g)	844.5 ± 224.0	872.5 ± 230.7	< 0.05
Body length at birth (cm)	33.1 ± 3.3	33.5 ± 3.3	< 0.05
IUGR (%)	1752 (22.4%)	1811 (20.2)	< 0.05
Maternal age	31.3 ± 5.3	30.9 ± 5.5	< 0.05
Multiple pregnancy (%)	1554 (19.9)	1881 (21.0)	0.24

Gestational age, body weight, body length at birth, maternal age: t-test

IUGR, multiple pregnancy: chi-square test

Compared to the 18 months follow up data, there were significant differences in gestational age, birth weight, and body length at birth.

3.3. Comparison of characteristics in study sample

Table 3-4 shows the result of characteristics compared by single pregnancy and multiple pregnancy.

Table 3-4: Characteristics by single and multiple pregnancy in study sample

Variable	Single pregnancy (7089)	Multiple pregnancy (1749)	P
Gestational age (weeks)	26.0 \pm 1.6	26.3 \pm 1.5	< 0.05
Birth weight (g)	847.7 \pm 228.1	860.4 \pm 217.3	< 0.05
Body length at birth (cm)	33.1 \pm 3.3	33.5 \pm 3.2	< 0.05
18 months BMI available (%)	3783 (53.3)	888 (50.7)	0.15
36 months BMI available (%)	6258 (88.2)	1554 (88.9)	0.79
Gender (boy/girl)	3769/ 3320	903/ 846	0.25
IUGR (%)	1538 (21.6)	418 (24.0)	0.13
Maternal age (year-old)	31.5 \pm 5.4	30.9 \pm 5.0	< 0.05

Gestational age, birth weight, body length at birth, maternal age: t-test

Rate of BMI available, gender, IUGR: chi-square test

In single pregnancy, gestational age, birth weight, body length at birth were significantly larger. There were no differences in gender and IUGR proportion.

Table 3-5 shows the number and proportion of complications during pregnancy and the neonatal period.

Table 3-5: Complications during pregnancy and neonatal period

Variable	Single pregnancy		Multiple pregnancy	
	Boy	Girl	Boy	Girl
Parity (more than 1) (%)	1942 (51.8)	1652 (50.1)	304 (33.7)	297 (35.3)
PIH (%)	465 (12.3)	581 (17.6)	47 (5.2)	59 (7.0)
CLD (%)	2399 (64.0)	1960 (59.3)	539 (60.0)	459 (54.3)
LCC (%)	588 (15.8)	418 (12.7)	131 (14.8)	115 (13.7)
IVH (%)	170 (4.5)	141 (4.3)	56 (6.6)	42 (5.0)
NEC (%)	63 (1.7)	31 (0.9)	13 (1.5)	9 (1.1)

Maternal complication: PIH (pregnancy induced hypertension)

Complication during hospital stay: CLD (chronic lung disease), IVH (intraventricular hemorrhage), LCC (late circulatory collapse), NEC (necrotizing enterocolitis)

CLD (chronic lung disease) was the most frequent complication during the neonatal period, followed by IVH (intraventricular hemorrhage). NEC (necrotizing enterocolitis) had the lowest rate.

BMI in single and multiple pregnancies are shown in Table 3-6.

Table 3-6: Comparison of BMI score by presence of multiple pregnancy

	Single pregnancy	Multiple pregnancy	P value*
18 months			
Boy	15.5 ± 1.4	15.6 ± 1.3	< 0.05
Girl	15.1 ± 1.3	15.2 ± 1.4	< 0.05
36-months			
Boy	15.1 ± 1.4	15.1 ± 1.3	< 0.05
Girl	14.9 ± 1.4	14.8 ± 1.3	< 0.05

*t-test

In both 18- and 36-months, BMI was higher in single pregnancy.

BMI scores by presence of IUGR are shown in Table 3-7.

Table 3-7: Comparison of BMI score by presence of IUGR

	IUGR	Non-IUGR	P value*
18 months			
Boy	15.0 ± 1.3	15.6 ± 1.3	< 0.05
Girl	14.6 ± 1.3	15.4 ± 1.4	< 0.05
36 months			
Boy	14.5 ± 1.2	15.2 ± 1.3	< 0.05
Girl	14.3 ± 1.4	15.1 ± 1.3	< 0.05

*t-test

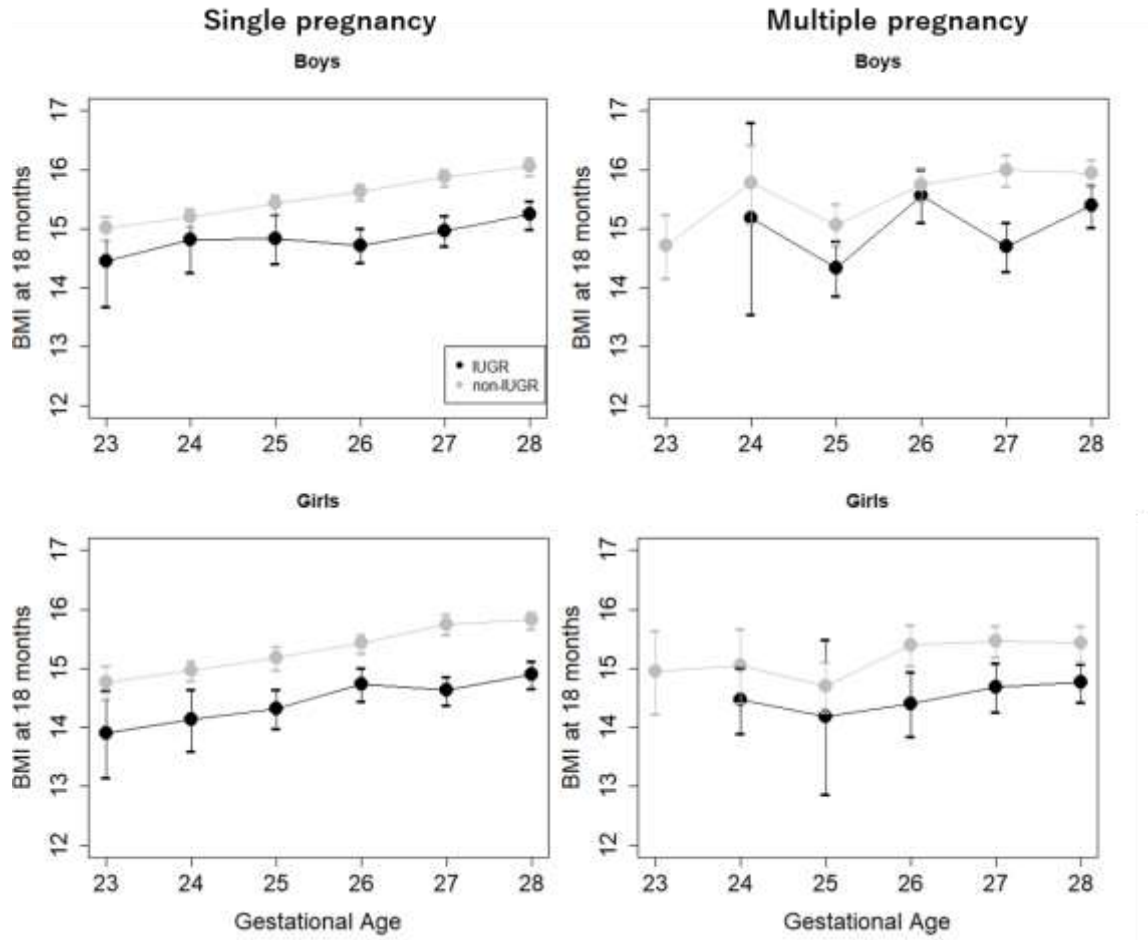
At both 18 and 36 months, BMI was higher in non-IUGR infants.

3.4. BMI score at each gestational age

Mean BMI was plotted for each gestational age with 95% confidence interval (CI) separately for boys and girls.

Figure 3-2 shows BMI at 18-months.

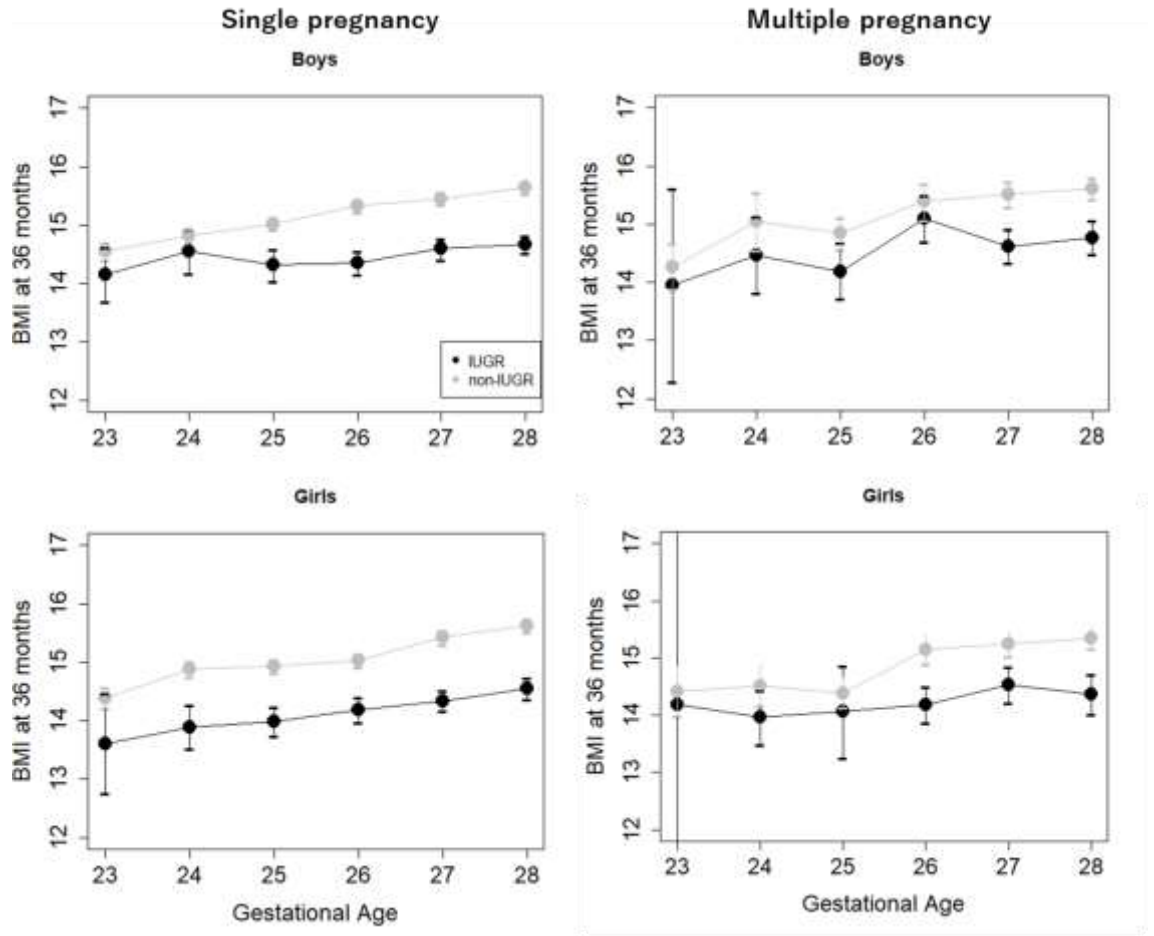
Figure 3-2: BMI at 18-months by gender and multiplicity



In single pregnancies, BMI of IUGR infants is smaller than those without IUGR throughout every gestational age with an increasing trend by gestational age. However, this tendency is not present in multiple pregnancies.

Figure 3-3 shows BMI for each gestational age with 95 % CI separately for boys and girls at 36-months by sex and multiplicity.

Figure 3-3: BMI at 36-months by gender and multiplicity



In single pregnancies, BMI of IUGR infants was smaller than those without IUGR throughout every gestational age with an increasing trend by gestational age. However, this tendency was not present in multiple pregnancies.

I regressed BMI against gestational age in weeks with an interaction term for gestational age and IUGR in single pregnancy with linear regression analysis. Parity, complications during pregnancy and hospital stay are included as covariates. The coefficients, 95 % CI, and p-value of this model are shown in Table 3-8.

Table 3-8: Linear regression analysis on BMIs by gender and IUGR in single pregnancies

		Coefficients	95% CI	P values	Model R-squared
18 months					
Boys	IUGR	-0.591	-0.954 – -0.228	< 0.05	0.0962
	GA	0.207	0.167 – 0.247	< 0.05	
	IVH	-0.472	-0.731 – -0.214	< 0.05	
	IUGR and GA	-0.061	-0.159 – 0.036	n.s.	
Girls	IUGR	-0.753	-1.114 – -0.392	< 0.05	0.1232
	GA	0.204	0.150 – 0.250	< 0.05	
	LCC	-0.242	-0.420 – -0.063	< 0.05	
	IVH	-0.422	-0.711 – -0.132	< 0.05	
	IUGR and GA	-0.047	-0.146 – 0.052	n.s.	
36 months					
Boys	IUGR	-0.443	-0.178 – -0.167	< 0.05	0.1123
	GA	0.210	0.180 – 0.239	< 0.05	
	IVH	-0.530	-0.737 – -0.324	< 0.05	
	IUGR and GA	-0.120	-0.194 – -0.045	< 0.05	
Girls	IUGR	-0.836	-1.123 – -0.549	< 0.05	0.1333
	GA	0.209	0.175 – 0.242	< 0.05	
	LCC	-0.231	-0.376 – -0.086	< 0.05	
	IVH	-0.307	-0.543 – -0.071	< 0.05	
	IUGR and GA	-0.049	-0.127 – 0.029	n.s.	

The effect of both IUGR and gestational age, and their interaction were seen in BMI score at 36 months in boys. However, no interaction between IUGR and gestational age was seen in girls. In 18-months BMI, there was no interaction between gestational age in either boys or girls.

Table 3-9 shows the results of regressing BMI against gestational age with an interaction term for gestational age and IUGR in multiple pregnancy. Parity, complications during pregnancy and hospital stay are included as covariates.

Table 3-9: Linear regression analysis on BMIs by gender and IUGR in multiple pregnancies

		Coefficients	95% CI	P values	Model R-squared
18 months					
Boys	IUGR	-0.590	-1.388 – 0.209	n.s	0.1084
	GA	0.169	0.083 – 0.255	< 0.05	
	IVH	-0.970	-1.438 – -0.502	< 0.05	
	IUGR and GA	-0.061	-0.159 – 0.036	n.s.	
Girls	IUGR	-0.712	-1.675 – 0.251	n.s.	0.0703
	GA	0.121	0.027 – 0.216	< 0.05	
	IVH	-0.705	-1.257 – -0.153	< 0.05	
	IUGR and GA	-0.005	-0.246 – 0.237	n.s.	
36 months					
Boys	IUGR	-0.320	-0.907 – 0.268	n.s.	0.1324
	GA	0.180	0.109 – 0.251	< 0.05	
	LCC	-0.422	-0.689 – -0.154	< 0.05	
	IVH	-1.017	-1.399 – -0.636	< 0.05	
	NEC	-0.968	-1.717 – -0.219	< 0.05	
	IUGR and GA	-0.111	-0.264 – 0.042	n.s.	
Girls	IUGR	-0.753	-0.951 – -0.224	n.s.	0.1109
	GA	0.205	0.137 – 0.268	< 0.05	
	LCC	-0.242	-0.548 – -0.020	< 0.05	
	IVH	-0.422	-0.845 – -0.023	< 0.05	
	IUGR and GA	-0.047	-0.271 – 0.039	n.s.	

In 18-months BMI, gestational age and IVH had significant effect. At 36 months there were effect of gestational age, LCC, IVH, and NEC were associated with BMI. In girls, gestational age had a significant effect on BMI at both 18 and 36 months. There was also a significant effect of IVH on BMI at 18 months and LCC and IVH on BMI at 36 months.

4. Discussion

In this study I collected data on infants born between 23 and 28 weeks of gestational age from the NRNJ database. This is the largest database of infants hospitalized in NICU in Japan that is suitable for research. I performed regression analysis of the association between BMI at 18 and 36 months and gestational age and presence of IUGR in these highly pre-term infants, adjusted for complications during pregnancy and the neonatal period. To the best of my knowledge, I could not find study about long-term outcome of body composition in premature infants in Japan and this is the first study on long-term body composition in Japanese infants.

Until recently ponderal index was used for this purpose, but BMI has been reported to be a useful measurement in preterm infants[40] and it is also reported to be a useful predictor of overweight in future[41], and to better reflect metabolic health outcome[42, 43]. Furthermore, BMI curves of preterm infants were published recently, and BMI has established its reliability in this field[44]. Since the goal of this study was to inform long term metabolic health outcomes in very premature infants, I chose to use BMI as the measure of growth. In several previous studies, body composition was evaluated using fat-free mass or dual-energy X-ray absorptiometry (DXA), which are said to reflect body composition more appropriately, but BMI can be calculated easily. This is an important consideration in health check-ups, because complex measurements of body composition such as DXA are not usually performed. By studying BMI, I ensured that my research results are consistent with the practical measurements taken during health check-ups for children.

I showed that that BMI at 18 and 36 months is strongly dependent on gestational age in both single and multiple pregnancies, except at 36 months in multiple pregnancies. For example, in boys from single pregnancies, every one week increase in gestational age is associated with an increase in BMI of 0.207 kg/m^2 (95% CI: $0.167 - 0.247$) at 18 months, and 0.210 kg/m^2 (95% CI: $0.180 - 0.239$) at 36 months. However, if the boy suffered IUGR, the BMI gain with each week of gestational age is reduced by 0.061 kg/m^2 (95% CI: $0.036 - 0.159$) at 18 months and 0.120 kg/m^2 (95% CI: $0.045 - 0.194$) at 36 months. The BMI relationships reported here are adjusted for confounding due to complications during pregnancy and the neonatal period, which have been reported to have an association with body composition in previous studies. This analysis shows that IVH had a significant effect on BMI in every sample. This may be because infants with IVH often have motor disfunction that results in failure to thrive.

In previous studies about body composition of premature infants, the premature population was defined as less than 32 weeks of gestational age[30] and 35 weeks of gestational age, which is more mature than our target population. Some studies did not describe growth by gestational age, but only by birth weight[1], but this study shows that IUGR can have a large impact on body composition and it is no longer reasonable to discuss body composition without both gestational age and body weight information. Even in the studies that described the sample by gestational age, the authors often divided the sample by gestational age into broad categories of less than 32 weeks and between 32 weeks and 36 weeks[28], which is not sufficiently detailed to explore the specific effect of decreased gestational age on future body composition. Studies based on birthweight only divided the study samples into birthweight increments of 500 grams[26]. To evaluate premature infants only by birth weight and ignore gestational

age is no longer reasonable, because being born preterm or low birth weight can have a different prognosis[1], and very low birth weights and gestational ages are becoming increasingly common as infant survival improves.

In contrast to these previous studies, our study collected data on a large sample of premature infants and analyzed the effect of gestational age and IUGR in detail, adjusting for confounding factors from pregnancy complications. Our results suggest that gestational age has a large and significant effect on BMI, especially in non-IUGR infants.

In modern studies of premature infants, it is important to analyze samples separately by presence of multiple pregnancy, because their prognosis is different[45]. Previous studies did not describe multiple pregnancy, or analyzed them together with singleton births. Moreover, distinguishing infants with IUGR from those without IUGR is very important because they have many complications and the pathology is different[46], and it has been reported that there is growth failure in IUGR infants[22]. This study was able to consider both multiple pregnancy and IUGR because of the large sample size and to the best of my knowledge, this is the first study to study the effects on BMI of gestational age by multiple pregnancy and IUGR at the same time.

There are some limitations in this study. The first is that the number of infants with no data available is large. I compared the characteristics of infants with and without BMI data and those who dropped out of the study had longer gestational age and lower prevalence of IUGR. This could be because those who had good prognosis stopped coming to the hospital for 18- and 36-month checkups. This means that our study may not be generalizable to all preterm infants or may only accurately describe the growth patterns of the highest-risk infants. However, pediatricians need information

about the infants who had the worst outcomes, and our study likely informs specifically on this population. Among infants with BMI at 18 months and 36 months, 88% had data on BMI at 36 months, compared to only 50% with data available at 18 months. It is therefore likely that 36 months data is more generalizable. The reason for poor follow-up at 18 months is unclear, as both 18 and 36 months are key ages for follow up, and caution should be shown in generalizing the 18-month results found here. The second limitation is that nutrition status is not mentioned in this study. Aggressive nutrition policies are recommended for good neurocognitive outcome and motor function[47, 48], but these policies may increase the risk of metabolic disease[49], and their use is still controversial. We were unable to draw any conclusions about their role in growth in this study, and further research on their impact is needed.

The third limitation is that follow up period is shorter than some studies. In previous studies, the authors analyzed the body composition until school age[29], 11-years-old[28], and young adulthood[30]. However, interventions are easier in older children, and our population likely includes those infants having the most difficulty in weight gain and thus requiring more medical intervention. Moreover, this study revealed that BMI is affected within 18 months of birth, and indicates that intervention should be considered shortly after discharge, long before the interventions recommended by studies with longer follow-up times. The fourth limitation is that there was only a small number of infants with small gestational age, especially in multiple pregnancies. For example, there were only 52 infants from multiple pregnancies who were born at 23 weeks, compared to 847 single pregnancy infants born at 28 weeks. This small number may be the cause of survivor bias in some findings.

Long-term impact on infants discharged from NICU are reported to be important, but most studies mainly focus on neurological or developmental outcomes[14, 50-52]. Moreover, according to DOHaD theory, premature infants are believed to be at high risk of weight gain and parents are taught to be careful to prevent this. However, my study results contradict this impression for very premature infants, and suggest that gestational age, IUGR, and other neonatal factors should be considered during follow up, rather than a simple risk assessment based on prematurity alone. My study also suggests that the DOHaD theory may not apply in the same way to very premature infants, and in particular that failure to thrive is a greater concern than overweight in this population. According to the follow up policy of the Japan Neonatal Follow-up Study Group, caregivers should evaluate body weight and body length, but there are no guidelines regarding the balance between them. Moreover, they only suggest checking them and give no instructions on the proper interpretation or application of the results of measurement. Information from this study should be used to provide guidelines for caregivers on identifying whether their child's growth is consistent with that of other children with the same background, and instructions in the response to infants who are not growing.

In my study, IVH was also found to affect BMI, consistent with a previous study that found IVH affects not only neurological but also growth outcomes[53]. IVH causes both cerebral palsy, disability, and cognitive impairment[54]. Cerebral palsy is a risk of feeding disorders, and moreover, if there are complications of cerebral palsy like gastroesophageal reflux and oropharyngeal dysfunction, they have more difficulty in weight gain[55]. Disabilities such as motor dysfunction and mental disorders also have an

impact on malnutrition[56]. Nutritional interventions have been studied in premature infants with IVH who are at risk of neurodevelopmental impairment[57], and our study shows that this is of particular concern in very premature infants. Similar to previous interventions, pediatricians should focus more on BMI in infants with IVH.

4.1. Conclusion

As more premature infants are surviving their perinatal period and their survival rate continues to improve[15], it is important to know their long-term outcome. Japan is at the forefront of neonatology[16] and to reveal the future features of infants born premature in this country will contribute to neonatology in other countries. This study revealed that in preterm infants born under 28 weeks of gestational age, gestational age is an important factor in future BMI, and presence of IUGR is important in single pregnancy infants. When we follow them, we should be aware of their base line characteristics and be conscious of the difficulty in gaining weight in this high-risk population. As more infants survive at younger gestational ages, policy developed based on the findings of this study will ensure they are able to thrive to adulthood, and enjoy the full benefits of their miraculous survival.

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Appendix: NRNJ database questionnaire

Facility data

Facility ID

Informed date,

Facility class

Facility provide,

Number of beds (total, NICU, MFICU)

Number of staff (doctor, nurse, psychologist)

Accept surgery: Yes/ No

Accept cardio-surgery: Yes/ No

Accept neurosurgery: Yes/ No

Accept ophthalmology: Yes/ No

Follow up out-patients: Yes/ No

Number of patients born under 1500g

Patient and maternal data

Patient ID

Age

Gravida

Parity

Comorbidity

Number of fetus: if multiple pregnancy, birth order, plurality

Complications during pregnancy

Diabetes: Yes/ No

Hypertension: Yes/ No

CAM (clinical, pathological): Yes/ No

If Yes, grade of CAM

Delivery data

PROM Yes/ No

Antenatal steroid Yes/ No

NRFS Yes/ No

Fetal position

Delivery mode: Normal/ Caesarian section

Feto-maternal transfusion: Yes/ No

Cord blood transfusion: Yes/ No

Infant data

Admission day

Sex

Out born: Yes/ No

If No, mother emergency transport: Yes/ No

Gestational age

Confirmed by ultrasonic exam in early pregnancy period: Yes/ No

APGAR score (1 minute, 5 minutes)

Resuscitation oxygen use: Yes/ No, intubation: Yes/ No

Birth weight, length, Head circumference

Livebirth: Yes/ No

Cord blood gas sample: Yes/ No

If Yes, pH, pO₂, pCO₂, BE

Gas sample at admission: Yes/ No, artery/ vein

If Yes, pH, pO₂, pCO₂, BE

Respiratory diseases

RDS: Yes/ No

Air leak: Yes/ No

Pulmonary hemorrhage: Yes/ No

PPHN: Yes/ No

Length of oxygen supply (day)

Length of CPAP (day)

Length of MV (day)

HFO use: Yes/ No

Number of surfactant use

Length of NO (day)

CLD: Yes/ No

If Yes, type, steroid therapy: Yes/ No, steroid inhalation therapy: Yes/ No

Oxygen supply at CA 36w Yes/ No, if Yes % of oxygen

Cardiovascular diseases

Symptomatic PDA: Yes/ No

If Yes, indomethacin use: Yes/ No, surgery: Yes/ No

Steroid therapy for LCC: Yes/ No

Neurologic diseases

Seizure: Yes/ No

IVH: Yes/ No

If Yes, grade, hydrocephalus: Yes/ No

PVL: Yes/ No

HIE: Yes/ No

Infectious diseases

Intrauterine infection: Yes/ No

Sepsis: Yes/ No

If Yes, onset is before day 7: Yes/ No

Antibiotics use: Yes/ No

Gastrointestinal diseases

Hyperalimentation: Yes/ No

NEC: Yes/ No

Perforation: Yes/ No

Hearing and eyesight

Hearing screening result: Normal/ Abnormal/ Not performed

Retinopathy of premature: Yes/ No

If Yes, therapy: Yes/ No, therapy with anti-VEGF: Yes/ No

Congenital Anomalies

Congenital anomalies: Yes/ No

Surgery: Yes/ No

Others

Feeding exceed 100ml/ kg/ day

Blood transfusion: Yes/ No

If Yes, EPO use: Yes/ No

Discharge information

Transfer: Yes/ No

If Yes, reason and date of readmission

Discharge day, discharge death: Yes/ No

If Yes, cause of death, autopsy: Yes/ No

Discharge to home: Yes/ No

Oxygen use at discharge: Yes/ No

Tracheostomy at discharge: Yes/ No

Discharge body weight, body length, head circumference

Motor disability: Yes/ No

Visual disability: Yes/ No

18 to 24 month outcomes

Health check-up data available: Yes/ No, if Yes, corrected age, if No, reason of drop out

Death after discharge: Yes/ No, if Yes, cause of death

Body weight, body length, head circumference

Oxygen use: Yes/ No, if Yes, duration of oxygen use

Visual disability: Yes/ No

Cerebral palsy: Yes/ No, if Yes, type and grade of cerebral palsy, and its cause

DQ results

Hearing loss: Yes/ No, if Yes, use of aid: Yes/ No

Asthma: Yes/ No

Epilepsy: Yes/ No

Home health care: Yes/ No

Respirator use: Yes/ No

Tracheostomy: Yes/ No

Tube feeding: Yes/ No

VP shunt: Yes/ No

Educational training: Yes/ No

36 month outcomes

Health check-up data available: Yes/ No, if Yes, corrected age, if No, reason of drop out

Death after discharge: Yes/ No, if Yes, cause of death

Body weight, body length, head circumference

Oxygen use: Yes/ No, if Yes, duration of oxygen use

Visual disability: Yes/ No

Cerebral palsy: Yes/ No, if Yes, type and grade of cerebral palsy, and its cause

DQ results

Hearing loss: Yes/ No, if Yes, use of aid: Yes/ No

Asthma: Yes/ No

Epilepsy: Yes/ No, if Yes, medication: Yes/ No

Home health care: Yes/ No

Respirator use: Yes/ No

Tracheostomy: Yes/ No

Tube feeding: Yes/ No

VP shunt: Yes/ No

Educational training: Yes/ No

Abnormal behavior: Yes/ No, if Yes, type of abnormal behavior

Blood pressure

Urine test: OB, Pro, Glu

Family: Father, Mother, Brother, Sister, Grandfather, Grandmother, others

Father and mother education (over 12 years or not)

Maltreatment: Yes/ No

Nursery: Yes/ No

Walking: Yes/ Yes with help/ No

Standing: Yes/ Yes with help/ No

Sitting: Yes/ Yes with help/ No

Muscle tone: Normal/ Hypertonia/ Hypotonia

Fine motor: Normal/ Border line/ Abnormal

Motor disability: Normal/ Border line/ Abnormal

Cerebral palsy: Yes/ Border line/ No, if Yes, type of CP and its cause

CT/MRI: Yes/ No, if Yes, result: PVL, Enlarged ventricles, others