

# The Impact of Neonatal Morbidities on Child Growth and Developmental Outcome in Very Low Birth Weight Infants: Nationwide Cohort Study

**Jung Ho Han**

Yonsei University

**So Jin Yoon**

Yonsei University

**Joo Hee Lim**

Yonsei University

**Jeong Eun Shin**

Yonsei University

**Ho Seon Eun**

Yonsei University

**Min Soo Park**

Yonsei University

**Kook In Park**

Yonsei University

**Soon Min Lee** (✉ [smlee@yuhs.ac](mailto:smlee@yuhs.ac))

Yonsei University <https://orcid.org/0000-0003-0174-1065>

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## Original Article

**Keywords:** growth, very low birth weight, morbidities, neurodevelopmental outcomes

**Posted Date:** February 8th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-168031/v1>

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**Version of Record:** A version of this preprint was published at European Journal of Pediatrics on July 8th, 2021. See the published version at <https://doi.org/10.1007/s00431-021-04177-x>.

# Abstract

## Introduction

Growth in preterm infants has long-term implications for neurodevelopmental outcomes. We aimed to estimate the nationwide growth outcomes from birth to 5 years in infants born under 1,500 g and to analyze the effects of major morbidities of preterm infants on growth.

## Methods

Total 2,961 children with birth weight under 1,500 g who were born in 2013 and examined the Infant Health Check-up between 2013 and 2018 from the National Health Insurance Service database were included. Check-ups were at 4-6, 9-12, 18-24, 30-36, 42-48, and 54-60 months of age. Information was obtained by the International Classification of Diseases-10 codes or by the questionnaire in the check-up program.

## Results

At 60 months of age, mean percentiles of weight, height, and head circumference showed only 30 – 40<sup>th</sup> percentile of normal growth for their ages. About 30% had growth parameters below the 10<sup>th</sup> percentile and showed worse neurodevelopmental outcomes. Using multiple logistic regression, infants with bronchopulmonary dysplasia showed significantly higher incidence of growth restriction in all three categories, weight (odds ratio [OR] 1.50), height (OR 1.33), and head circumference (OR 1.36) at 60 months. Sepsis was associated with growth restriction in weight (OR 1.43) and head circumference (OR 1.33). Periventricular leukomalacia infants had relatively small head circumferences (OR 1.91) and poor developmental screening results (OR 2.89).

## Conclusion

Catch-up growth remains a major issue in infants born under 1,500 g, especially those with some morbidities of preterm birth. Regular check-ups to monitor and early intervention for their normal growth is essential.

## What Is Known

Growth in preterm infants has long-term implications for neurodevelopmental and cardiometabolic outcomes.

There is lack of data about the effects of preterm morbidities on long-term growth outcomes.

## What Is New

All growth parameters of VLBW infants including weight, height, and head circumference showed only 30 – 40<sup>th</sup> percentile of normal growth for their ages at 60 months of age, which means catch-up growth of them remains still an unsolved issue.

VLBW infants with major preterm morbidities including BPD, PVL, sepsis were hard to achieve normal catch-up growth and neurodevelopment at 60 months of age.

## Introduction

Recent improvements in preterm survival resulted in shifting of the focus for preterm infants toward improving quality of life through monitoring parameters such as growth and developmental status [1]. Growth represents an increase in body size and is a complex process that is influenced by genetic, hormonal, and environmental factors [2]. Infants born with very low birth weight (VLBW) have a higher risk of postnatal growth failure [3, 4]. Differences in postnatal growth patterns by gestational age in the first 3 months in infants developing morbidities were reported [5]. In addition, preterm morbidities including patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and late-onset sepsis influence growth to different degrees depending on the morbidity [6].

Many studies have reported close relationships between postnatal growth and neurodevelopmental outcomes in preterm infants [4, 7-9]. Linear growth may be more relevant to neonatal brain development than weight gain which cannot differentiate the development of organs from an increase of adipose tissue [10]. Growth-restricted extremely preterm infants with postnatal head sparing showed better neurodevelopmental outcomes than those without it, especially in motor function [11]. Overall, it is important to assess the current health status of infants born prematurely using all three growth parameters comprehensively. However, to date, few studies have dealt with the effects of preterm morbidities on long-term growth outcomes.

The catch-up growth patterns of preterm infants have been a matter of debate. Most preterm infants tended to have catch-up growth generally starting early in the first months of life and often achieved within the first 2 years of life [12]. However, many studies have reported that catch-up growth can continue after infancy, even into adolescence [13-15]. Various complications of preterm birth may make catch-up growth and normal neurodevelopment difficult.

Growth is often assessed by comparing weight, length, and head circumference (HC) to normal growth references of a given society. This study aimed to estimate the nationwide long term growth outcomes of infants born under 1,500 g from a population-based surveillance system and to compare those with term infants. Furthermore, we aimed to analyze the effects of major morbidities of preterm birth on growth outcomes.

## Methods

### *Patients and data source*

We initially identified 430,541 infants who were born in 2013 and examined the Infant Health Check-up between 2013 and 2018 from the National Health Insurance Service (NHIS) database. Healthcare claims such as diagnostic codes, costs of diagnostic tests and procedures of almost all Korean residents were linked to a health check-up database. The information about birth weight was obtained by the International Classification of Diseases-10 (ICD-10) codes inputted by the hospital or by the questionnaire of the Infant Health Screening Program. Extremely low birth weight (ELBW) infants were defined as infants born under 1,000 g and VLBW infants were defined as infants with birth weights between 1,000 and 1,499 g. We used birth certificate data from Statistics Korea to estimate the examination rate of the National Health Screening Program in preterm infants.

The National Health Screening Program for infants and children in Korea was launched in 2007 to monitor current health issues and has been successfully implemented as one of the primary clinical services. The program is a type of population surveillance system which includes taking medical history, physical examination, anthropometric measurements, screening for visual acuity, developmental screening by Korean Developmental Screening Test (K-DST), oral examination, and questionnaires with anticipatory guidance. The study population involved had the 1<sup>st</sup> visits at 4-6 months of age, 2<sup>nd</sup> at 9-12 months, 3<sup>rd</sup> at 18-24 months, 4<sup>th</sup> at 30-36 months, 5<sup>th</sup> at 42-48 months, and 6<sup>th</sup> at 54-60 months. The K-DST is a screening test which verifies whether infants have normal neurodevelopmental status in the domains of gross/fine motor, cognition, communication, social interaction, and self-control. Tests are administered according to the child's corrected age at the time of the clinic visit. Results are categorized into 4 groups: further evaluation, follow-up test, peer-level, and high-level groups. Children who score below -1 standard deviation of their age are categorized as the follow-up test group, and short-term check-ups are recommended for re-evaluation. We consider any additional positive questions as red flags for clinically important neurodevelopmental diseases, such as cerebral palsy, language delay, and autism spectrum disorders [16] and the involved infants/children should be referred to medical specialists for further evaluation [17]. Preterm morbidities including BPD, sepsis, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and intraventricular hemorrhage (IVH) were identified using ICD-10 codes inputted by the hospital.

### *Statistical analyses*

Baseline subject characteristics are expressed as means and standard deviations for continuous variables and as percentages for categorical variables. The cohort was stratified according to birth weight group and the time checking the screening program. Growth parameters were analyzed by the year or according to birth weight group using one-way ANOVA or Chi-square test. Univariate and multiple logistic regression models were used to determine the independently associated factors between preterm infants and their growth with odds ratios (OR) and 95% confidence intervals (CI). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). *P*-values <0.05 were considered statistically significant.

### *Ethics statement*

This study used NHIS-NSC data (NHIS-2020-1-543) made by NHIS. The authors declare no conflict of interest with NHIS. In this study, all identifiable variables, including claim-, individual-, and organizational-level identification numbers, were randomly re-generated by the NHIS database to protect patient privacy. The study protocol was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No. 3-2019-0147). Informed consent was waived due to the nature of the study.

## Result

From the Birth Statistics, the number of live infants born under 1,500 g in 2013 was 2,961. The numbers of infants who received the Health Check-up at ages 6 to 60 months were as follows: 1<sup>st</sup> visit 830 (28%) infants, 2<sup>nd</sup> 1,015 (34%), 3<sup>rd</sup> 1,690 (57%), 4<sup>th</sup> 2,602 (88%), 5<sup>th</sup> 2,031 (69%), and 6<sup>th</sup> 1,836 (62%). Mean percentiles of growth parameters at ages 6 to 60 months are shown in Figure 1. Mean growth percentiles of ELBW and VLBW infants were significantly lower than those of the control group. Mean weight percentile was the highest at age 36 months (33.1), mean height percentile at 36 months (38.9), and mean head circumference at 24 months (33.0).

The incidences of the infants having poor growth parameters in the less than 10<sup>th</sup> percentile of age norms at each visit are shown in Figure 2. VLBW and ELBW infants showed clearly higher incidences of poor growth than infants with normal birth weight from birth to 60 months of age. For the comparison between ELBW and VLBW infants, significant differences in the incidence of infants below 10<sup>th</sup> percentile in growth parameters were noted until 36 months of age; however, it became similar after 48 months.

In ELBW and VLBW infants, hyaline membrane disease (HMD), PDA, IVH, sepsis, and BPD significantly increased the risk for having weights less than the 10<sup>th</sup> percentile of normal at 60 months old by univariate logistic regression analysis. HMD, sepsis, BPD, and PVL were associated with a risk for having height below the 10<sup>th</sup> percentile at 60 months. HMD, PDA, IVH, sepsis, BPD, and PVL were the significant risk factors for having head circumference less than the 10<sup>th</sup> percentile for age at 60 months old (Table 1).

Multiple regression analysis with preterm morbidities adjusted by sex and birth weight was performed to determine the independent risk factors for growth restriction (having growth parameters less than 10<sup>th</sup> percentile for age at 60 months of age). BPD (OR 1.50; 95%CI 1.16-1.94) and sepsis (OR 1.43; 95%CI 1.14-1.79) were confirmed as independent risk factors for growth restriction in weight, and BPD (OR 1.33; 95%CI 1.02-1.73) was the only risk factor for growth restriction in height. BPD (OR 1.36; 95%CI 1.04-1.78), sepsis (OR 1.33; 95%CI 1.02-1.73), and PVL (OR 1.91 95%CI 1.27-2.88) were risk factors for growth restriction in head circumference (Table 2).

Figure 3 shows the serial comparison of mean growth percentiles at ages 12 to 60 months among ELBW and VLBW infants with and without BPD/PVL. All three growth parameters showed significant differences between the infants with and without BPD/PVL.

Among ELBW and VLBW infants, the infants with growth restriction in any growth parameter at 60 months of age showed significantly poor outcomes by developmental screening compared to those who did not have growth restriction (Fig. 4). As a result of multiple regression analysis with preterm morbidities and growth parameters as risks for poor developmental outcomes at the age of 60 months, PVL (OR 2.89; 95%CI 1.68-4.99), growth restriction in head circumference (OR 2.36; 95% CI 1.46-3.80) and height (OR 2.42; 95% CI 1.57-3.74) were confirmed as independent risk factors for the further evaluation.

## Discussion

Postnatal growth of preterm infants can be an excellent indicator for identifying their current health condition and predicting developmental outcomes. Several studies have shown the relationship between impaired extra-uterine growth and poor long-term performances in preterm infants [4, 7, 8]. Our study confirmed the negative effect of postnatal growth failure on neurodevelopmental outcomes as well as the morbidities affecting the growth outcomes until 5 years of age in infants born under 1,500 g.

In Korea, the National Health Screening Program for infants and children has enabled us to obtain a vast amount of data on postnatal growth patterns of preterm infants. We found the screening rates of ELBW and VLBW infants were lower at the 1<sup>st</sup> (28.0%) and 2<sup>nd</sup> (34.3%) check-up, and increased over time to around 70%. It is important for neonatologists to encourage caregivers of these infants to schedule regular screening check-ups to monitor proper and continuous catch-up growth.

All three growth parameters of ELBW and VLBW infants tended to gradually approach normal growth rates over time. However, only 30 to 40<sup>th</sup> percentile of norm reference ages at 60 months of age were noted. In addition, about 30% of the preterm infants showed growth restriction under the 10<sup>th</sup> percentile of normal reference in all three parameters at the age of 48 and 60 months and showed worse neurodevelopmental outcomes at 60 months, as has been reported by many other studies [4, 7-9, 18, 19]. Similarly, very-preterm-born and small-for-gestational age-born infants in Denmark, showed a catch-up growth in weight and height at 6 years of age, however, reached a significantly lower mean z score than appropriate for gestational age (AGA) children. AGA infants also did not achieve catch-up growth completely at 6 years of age [20]. Clinicians should carefully monitor these infants with extended follow-up after discharge and seek more ways to assist catch-up growth. It is widely known that postnatal head growth appears to be spared relative to weight and height [10, 11, 19]. In our study, head growth seemed to be similarly spared when compared with the other two parameters at the 1<sup>st</sup> check-up, yet with time the proportion at which growth restriction occurred became similar in all three groups (around 30% at 48 and 60 months). It can be assumed that failure to achieve catch-up growth after an extended period of time will eventually lead to the disappearance of the sparing effects of head growth. Catch-up growth of premature babies after discharge should be monitored and addressed as soon as possible.

Growth is influenced by various factors including co-morbidities and sex [9, 21]. In our study, infants with BPD showed significant long-term growth restrictions in all three growth parameters. Furthermore, even with adjustment of other morbidities, it was the only meaningful factor that was associated with growth

restrictions in all three categories. BPD happens through complex mechanisms and has long term effects from infancy to even young adults [22, 23]. Repetitive hypoxic insults, increased respiratory efforts, use of postnatal steroids, undernutrition due to fluid restriction and feeding difficulty, and frequent infections are the factors associated with growth restriction in BPD infants [18, 24, 25]. Prevention of BPD is not just beneficial for lung function of premature infants, but is also important for overall health conditions and neurodevelopmental outcomes.

In a previous large-scale cohort study, infection in ELBW infants affected growth failure in weight and head circumference at both 36 weeks and 18 to 22 months of corrected gestational age [26]. We found that both ELBW and VLBW infants with sepsis were more likely to experience delayed growth, especially in weight gain (OR, 1.43) and head growth (OR, 1.33). Infection in the neonatal period affects long-term growth, even into pre-school age. Inflammation-induced white matter injury is already a widely known phenomenon in both experimental and clinical models [27-29], and delay in head growth in premature infants with sepsis may be associated with this inflammation. Our data suggests that once the brain is damaged due to sepsis and associated inflammation, recovery is difficult, and the inflammation may cause continued failure in brain growth and loss of brain function. Premature infants are vulnerable to infection and have a relatively higher incidence of sepsis. Therefore, efforts to prevent and treat for sepsis in preterm infants is of paramount importance in preventing such issues that could affect neurodevelopmental outcomes.

Our research has some strengths. First, with the data from the National Health Insurance Corporation of Korea, we were able to analyze a nationwide database of preterm infants longitudinally with higher accuracy and reliability. Second, because the data were based on a common set time, comparative analysis was possible for specific times. Finally, prior to our study, there were few studies about the relationship between morbidities caused by prematurity and poor long-term postnatal growth. Our results can help neonatologists focus on preterm infants with certain morbidities in terms of postnatal growth, thereby minimizing growth failure and neurodevelopmental disabilities. On the other hand, we also had some limitations. First, this was a retrospective and observational study, therefore can have an unavoidable limit. Second, not all the infants received check-ups at each of the investigated times. Lastly, there are diversities of treatment protocols between NICU units; this might have affected the postnatal growth of preterm infants.

## Conclusions

Despite recent improvements in nutritional supports and treatments of preterm infants, growth failure is still an unresolved problem in infants born weighing under 1,500 g. Moreover, it is associated with poor neurodevelopmental outcomes. Infants with major morbidities resulting from preterm birth, such as BPD, sepsis, and PVL, are more likely to have growth restrictions. Neonatologists and pediatricians should complete regular check-ups of preterm infants for many years and seek to monitor for and treat issues with catch-up growth and neurodevelopment.

# Declarations

**Funding Sources:** None

**Conflict of Interest/Competing interests:** The authors have no conflicts of interest to declare.

## **Ethics approval and consent to participate**

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and the study protocol was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No. 3-2019-0147). Informed consent was waived due to the nature of this study.

**Consent to publication:** N/A

## **Availability of data and material**

There are ethical restrictions on sharing a deidentified data set unless permitted by the National Health Insurance Service (NHIS) of Korea. Data availability was subjected to the Act on Bioethics and Safety [Law No. 1518, article 18 (Provision of Personal Information)]. Contact for sharing the data or access the data can be possible only through the committee of NHIS and after permitted by the NHIS of Korea.

**Code availability:** N/A

## **Author Contributions:**

Conceptualization: Jung Ho Han, Soon Min Lee

Methodology: Jung Ho Han, Jeong Eun Shin

Software: Jung Ho Han, Soon Min Lee

Validation: Min Soo Park

Writing – original draft: Jung Ho Han, Soon Min Lee

Writing-reviewing & editing: Ho Seon Eun, Min Soo Park, Kook In Park

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## Tables

**Table 1. Univariate Analysis of Preterm Morbidities as Risk Factors for Poor Growth at 60 Months of Age**

	Weight < 10 percentile N=663 (36.1%)	Height < 10 percentile N=534 (29.1%)	Head Circumference < 10 percentile N=555 (30.2%)
HMD	1.33 (1.10-1.61)	1.39 (1.13-1.71)	1.65 (1.34-2.02)
PDA	1.36 (1.10-1.68)	1.25 (1.00-1.56)	1.57 (1.26-1.95)
IVH	1.28 (1.00-1.63)	1.12 (0.87-1.45)	1.58 (1.23-2.02)
Sepsis	1.60 (1.30-1.97)	1.34 (1.08-1.67)	1.82 (1.47-2.26)
ROP	1.23 (0.52-2.89)	0.91 (0.36-2.35)	1.08 (0.44-2.66)
BPD	1.59 (1.31-1.93)	1.47 (1.20-1.80)	1.85 (1.51-2.27)
PVL	1.39 (0.94-2.06)	1.67 (1.12-2.49)	2.45 (1.66-3.62)

+ data is shown as odds ratio (95% confidence interval)

HMD; hyaline membrane disease, PDA; patent ductus arteriosus, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity, BPD; bronchopulmonary dysplasia, PVL; periventricular leukomalacia

**Table 2. Multivariate Analysis of Preterm Morbidities as Risk Factors for Poor Growth at 60 Months of Age**

	Weight < 10 percentile N=663 (36.1%)	Height < 10 percentile N=534 (29.1%)	Head Circumference < 10 percentile N=555 (30.2%)
HMD	NS	NS	NS
PDA	NS	NS	NS
IVH	NS	NS	NS
Sepsis	1.43 (1.14-1.79)	NS	1.33 (1.02-1.73)
ROP	NS	NS	NS
BPD	1.50 (1.16-1.94)	1.33 (1.02-1.73)	1.36 (1.04-1.78)
PVL	NS	NS	1.91 (1.27-2.88)

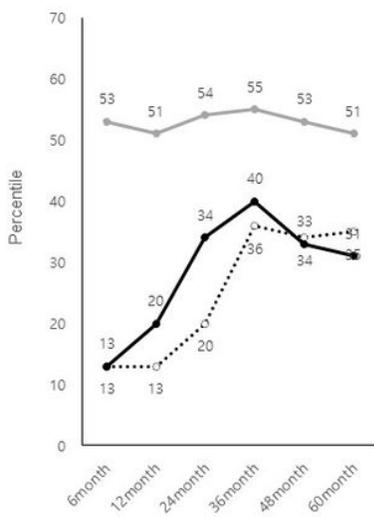
+data is shown as odds ratio (95% confidence interval)

\*NS; not significant

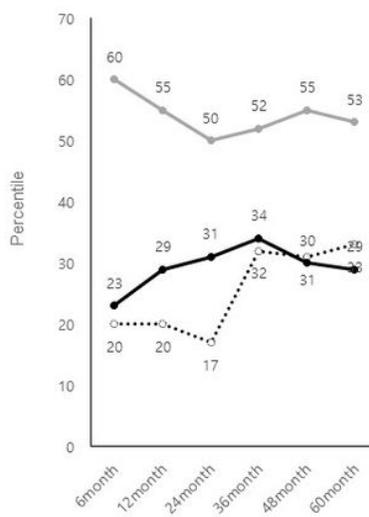
HMD; hyaline membrane disease, PDA; patent ductus arteriosus, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity, BPD; bronchopulmonary dysplasia, PVL; periventricular leukomalacia

## Figures

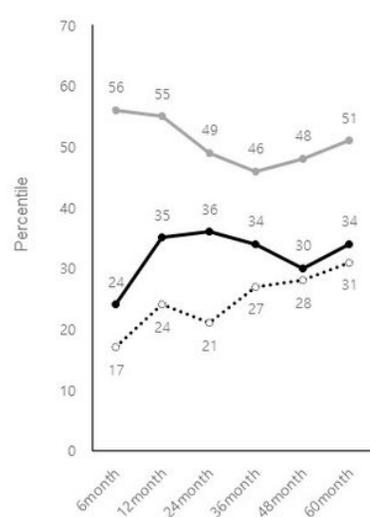
A Height Percentile



B Weight Percentile



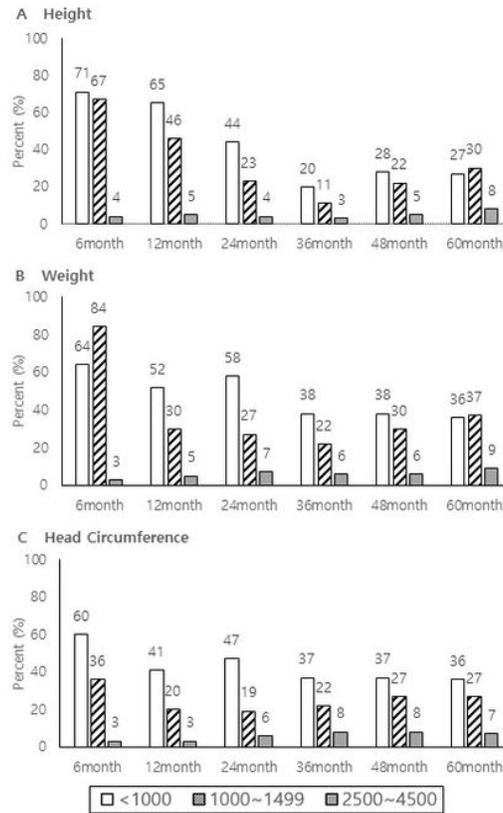
C Head Circumference Percentile



<1000      1000~1499      2500~4500

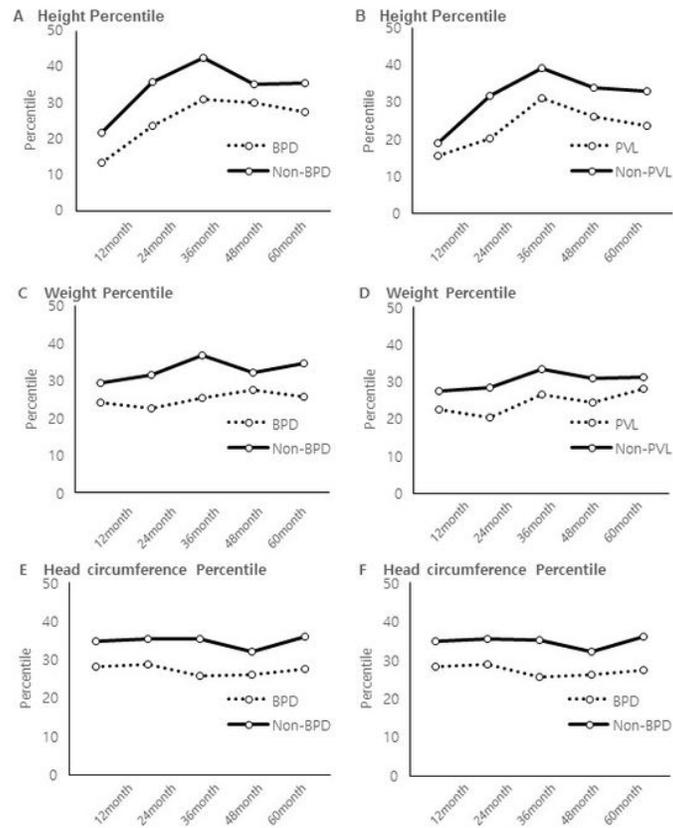
## Figure 1

Mean percentiles of growth parameters of three different birth weight groups: ELBW, VLBW, and infants with birth weight of 2,500-4,500g. (A) Height percentile (B) Weight percentile (C) Head circumference percentile ELBW; extremely low birth weight, VLBW; very low birth weight



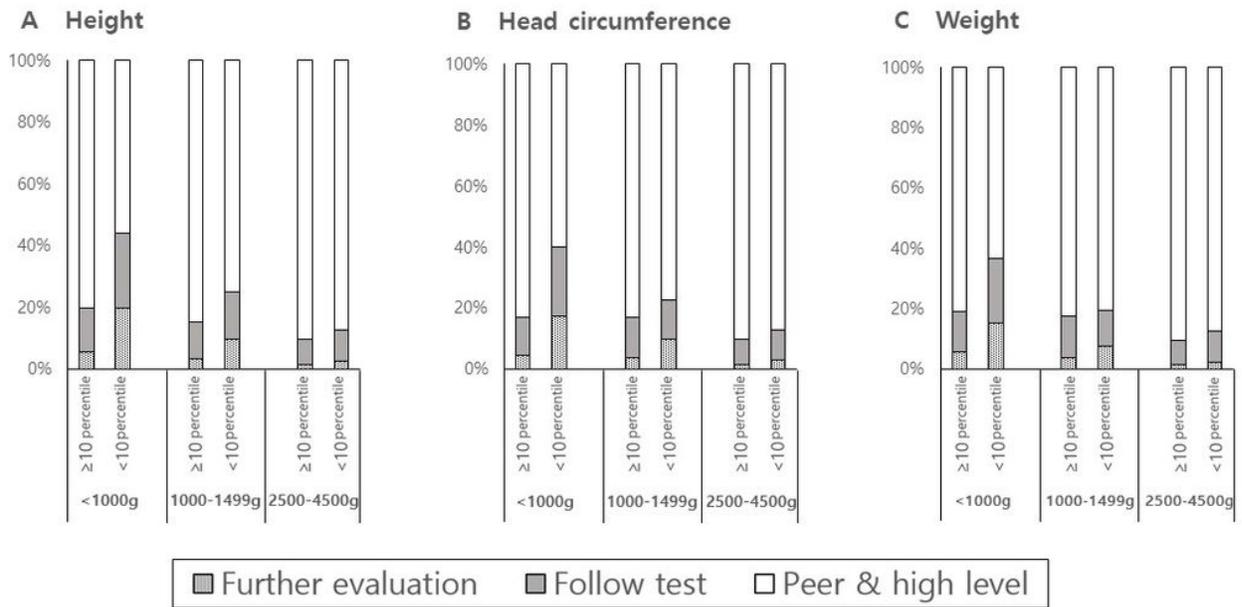
## Figure 2

The incidences of infants having growth parameters less than 10th percentile of their age among three birth weight groups: ELBW, VLBW and Infants with birth weight of 2,500-4,500g. (A) Height (B) Weight (C) Head circumference ELBW; extremely low birth weight, VLBW; very low birth weight



**Figure 3**

The effects of BPD and PVL on long term growth outcomes (A) Height percentile of BPD and non-BPD infants (B) Height percentile of PVL and non-PVL Infants (C) Weight percentile of BPD and non-BPD infants (D) Weight percentile of PVL and non-PVL infants (E) Head circumference percentile of BPD and non-BPD infants (F) Head circumference percentile of PVL and non-PVL infants BPD; bronchopulmonary dysplasia, PVL; periventricular leukomalacia



**Figure 4**

The results of the developmental screening test at 60 months of age among three birth weight groups; ELBW, VLBW, and the control. (A) Height (B) Head circumference (C) Weight ELBW; extremely low birth weight, VLBW; very low birth weight