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Analysis of Patterns and Determinants of Postneonatal Growth in Very Low Birth Weight Infants Using Modelling Procedures

by

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ABSTRACT

Objectives: To describe growth patterns and to determine factors that are associated with postneonatal growth in VLBW infants from Southern Alberta.

Study sample: Five hundred and fourteen VLBW infants born between 1977-1992 were selected from the Alberta Children's Hospital Perinatal Follow-Up Program data base.

Methods: Growth measurements of length and weight were obtained at 4, 8, 12, 18, and 36 months adjusted age. The growth level of VLBW was compared with the National Center for Health Statistics (NCHS)/WHO and the Canadian growth references. Demographic and perinatal factors were examined for their potential relationship to postneonatal growth using mixed effects models. The factors that were predictive of subnormal growth were determined using a generalized estimating equation approach.

Results:

1. The mean growth level of VLBW infants remained significantly lower than those of references. Catch-up growth occurred during infancy for length compared to either the NCHS/WHO or the Canadian reference. For weight, no catch-up was found in the first year compared to the NCHS/WHO reference while catch-up growth was found compared to the Canadian reference.
2. Mixed effects models revealed that various factors were associated with postneonatal growth in VLBW infants. The factors that were positively associated with body length were: larger birth weight, taller mid-parental height, and male gender. The

factors that were negatively associated with body length were the presence of bronchopulmonary dysplasia (BPD), cerebral palsy (CP) and necrotizing enterocolitis, young maternal age, and longer gestational age given birth weight. Except for the presence of CP that was not significantly associated with body weight, all other variables had the same direction of association with body weight as they did with length.

3. Mid-parental height, birth weight, gestational age, maternal age and necrotizing enterocolitis were found to be predictive of subnormal length, and mid-parental height, birth weight, gestational age, maternal age and BPD to be predictive of subnormal weight.

Conclusions: Models were developed describing detailed associations between perinatal and parental factors and VLBW infants growth in length and weight. Variables with significant impacts on length or weight are birth weight, mid-parental height, gestational age, maternal age CP, BPD, NEC and gender.

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LIST OF ABREVIATIONS

1. ACH: Alberta Children's Hospital
2. AGA: Appropriate for gestational age
3. BPD: Bronchopulmonary dysplasia
4. BW: Birth weight
5. CP: Cerebral palsy
6. FGR: Fetal growth ratio
7. GA: Gestational age
8. GEE: Generalized estimating equations
9. IGUR: Intrauterine growth retardation
10. IPPV: Intermittent positive pressure ventilation
11. MPH: Mid-parent height
12. NCHS: National Center for Health Statistics
13. NEC: Necrotizing enterocolitis
14. NICU: Neonatal Intensive Care Unit
15. PDA: Patent ductus arteriosus
16. PI: Ponderal index
17. RDS: Respiratory distress syndrome
18. RMLR: Restricted maximum likelihood ratio
19. SD: Standard deviation
20. SES: Socioeconomic status
21. SEI: Socioeconomic Index
22. SGA: Small for gestational age
23. TPN: Total parenteral nutrition
24. VLBW: Very low birth weight infants
25. WHO: World Health Organization

CHAPTER ONE: BRIEF OVERVIEW OF THE STUDY

1.1 INTRODUCTION TO THE RESEARCH PROBLEMS

Very low birth weight (VLBW) infants are infants who weigh less than 1,500 grams at birth. Reports from several countries show that children with VLBW often grow poorly in early childhood,[1-9] but the growth patterns of VLBW infants have not been well described. Findings on the growth outcomes in VLBW infants in the literature vary. Some studies have shown that there is no or little catch-up growth,[4,7,10] while others have found some catch-up growth[1,8] or satisfactory catch-up growth.[11] Lack of understanding of normal growth patterns of very low birth weight (VLBW) infants makes it difficult to assess an individual or a group of individuals' growth status among this population and to provide nutritional or anticipatory guidance for parents.

In order to assess the growth status of VLBW infants, it is important to select an appropriate growth reference which represents the "optimal" growth of the population. Several growth references are now available.[12,13] Although the National Center for Health Statistics growth reference, referred as the NCHS/WHO reference, has been used widely in the literature, the validity of this reference has been questioned.[14] It is unknown whether different growth outcomes would be obtained if different growth references were used for the same individual and the same group of individuals of VLBW infants. Since most VLBW infants are premature at birth with gestation less than 37 weeks, age adjustment for prematurity is crucial in the assessment of their growth. Very few studies

have explored the necessary period of age adjustment for prematurity in VLBW infants.[11,15]

Various factors may influence the postneonatal growth of VLBW infants; such as 1) the maturity and growth status at birth which can be stated in terms of birthweight, gestational age and intrauterine growth retardation(IUGR); 2) Perinatal clinical conditions: bronchopulmonary dysplasia, necrotizing enterocolitis, cerebral palsy, hypertension during pregnancy, and maternal smoking; 3) social economical factors: maternal education and family social economical status; 4) genetic background: mid-parental height and maternal race; and 5) feeding practices and feeding problems. The understanding of the association between these factors and postneonatal growth is important for assessing, predicting and preventing growth problems in VLBW infants. However, the associations between those factors and postneonatal growth in VLBW infants have not been well described. Studies in the literature suffer from several methodological problems, such as 1) long time intervals between repeated measurements,[2-4,6,16-19] 2) analyzing longitudinal data with cross-sectional statistical methods,[1-3,8] and 3) small sample size[20-23].

1.2 Resources for the present study

Longitudinal growth data have been collected in the Alberta Children's Hospital (ACH) Perinatal Follow-Up Program for two decades, providing a unique opportunity to study the growth patterns and determinants of growth in VLBW infants. The growth data

from the ACH Perinatal Follow-Up Program are population-based in Southern Alberta. Since infants were routinely measured 5 times during 4 and 36 month adjusted ages, the change of growth status over time and the factors that might affect the change could be investigated.

The statistical analysis of longitudinal data presents special opportunities and challenges. Longitudinal growth data tend to have the following characteristics: a) The serial growth measurements within an individual are likely to be correlated with each other; b) the measurements are unequally spaced; and c) missing data and attrition are unavoidable. Because of these characteristics of the follow-up growth data, standard multivariate procedures are usually not applicable to the population-based longitudinal growth data.[24,25] Modelling methods for longitudinal data have recently become available to researchers. [26-30]

1.3 Study Objectives

The objectives of this study were to describe the postneonatal growth patterns of VLBW infants and to identify the determinants of growth in VLBW infants. To fulfill the objectives, attempts were made to answer the following questions: 1) How do the growth levels of VLBW infants, relative to the growth references, change during infancy? 2) How does the prevalence of subnormal growth change during infancy (increase or decrease)? 3) Do the growth levels and the change of the growth levels depend on the perinatal and social environmental characteristics of infants? 4) What factors are

associated with the growth levels and the change of growth levels? 5) What are the expected growth levels of VLBW infants free from adverse clinical conditions? and 6) Who will be more likely to be "subnormal" in growth?

1.4 STUDY SAMPLE

The longitudinal growth data of 514 VLBW infants was analyzed in this study. The study sample were selected from 1007 infants who were born during January 1977 and May 1992, weighed 1250 grams or less at birth and survived to discharge from NICU. To be consistent with the current cutoff point in the ACH perinatal follow-up program, the birth weight of 1250 grams was used to define VLBW in this study. The infants were routinely followed up at 4±1, 8±1, 12±2, 18±3, and 36±6 months of adjusted age. Only infants with four or five of five sets of the follow-up growth measurements were included in this study. Infants with noticeable congenital anomalies were excluded. Compared with infants who were not included in this study, the infants of the study sample represent those with lower birth weight, shorter gestational age, and more frequent adverse clinical conditions. Mothers of the infants in the study sample appeared to be older with higher education and social economic status (SES) than mothers of infants who were not selected.

1.5 Statistical analysis

The growth measurements were compared with three growth references: the NCHS/WHO, the Canadian, and the growth reference for breast fed infants. Three modelling procedures, (1) mixed effects models, (2) the Generalized estimating equations (GEE) approach and (3) logistic regressions, were conducted to assess the associations between potential factors and postneonatal growth.

1.6 Major findings

The average growth levels of VLBW infants were found to be substantially lower than the median of reference data. Growth status of VLBW infants in both length and weight improved with age during infancy when compared with the Canadian reference. Catch-up growth in VLBW infants was found for both length and weight relative to the Canadian reference. When compared with the NCHS/WHO reference, catch-up growth was found for length but not for weight in the first year of life. Although a trend to catch-up was found, the average growth levels of VLBW infants remained significantly lower than the median of reference data by the end of the observation.

Various factors were found to be associated with postneonatal growth by fitting mixed effects models to growth parameters in this population. The presence of some adverse clinical conditions had negative impacts on the postneonatal growth. BPD, NEC and CP were found to be associated with length, and BPD and NEC with weight. Birth weight, gestational age, mid-parental height, gender and maternal age were also

associated with postneonatal growth in both weight and length. Larger birth weight infants remained longer and heavier during infancy than infants with a lower birth weight, but the difference in length between infants of different birth weights became smaller because lower birth weight infants showed slightly faster growth than larger birth weight infants. Infants with longer gestational age appeared to be shorter and lighter than infants with shorter gestational age. Since birth weight was included in the model, the gestational age here was an indicator of intrauterine growth status rather than a measurement of the maturation of neonates. For the same birth weight infants, the longer the gestational age was, the more severe was the intrauterine growth retardation (IUGR). The infants of taller parents were not substantially longer and heavier than the infants of shorter parents at early months of life, but they grew much faster than infants of shorter parents. The infants of mothers who were 20 years old or younger were shorter and lighter, and grew slower than infants of mothers older than 20 years of age. Even for infants who were free from BPD, NEC and CP; five perinatal characteristics, birth weight, gestational age, gender, mid-parental height and maternal age, were important predictors of the postneonatal growth in VLBW infants.

Some factors such as intrauterine growth retardation (IUGR) and body proportionality which were found to be associated with growth status in the preliminary analysis were not associated significantly with postneonatal growth in the mixed effects growth models. It may be due to the fact that the information provided by IUGR and body proportionality have been captured by including birth weight and gestational age in

the models. The diagnosis of IUGR is based on the birth weight and gestational age of infants. The body proportionality of neonates was found to be associated with the severity of IUGR. Given birth weight and gestational age, including either indicators of IUGR and body proportionality did not provide extra predictive values for postneonatal growth in VLBW infants.

The factors related to subnormal growth were identified using the GEE approach and logistic regressions. Mid-parental height, birth weight, gestational age, maternal age and necrotizing enterocolitis were found to be predictive of subnormal length, and mid-parental height, birth weight, gestational age, maternal age and BPD to be predictive of subnormal weight. The predictive value of necrotizing enterocolitis for subnormal length decreased, and the predictive value of mid-parental height for subnormal weight increased as infants grew.

1.7 Implications

The growth patterns described in this study are helpful to health professionals in understanding the growth process of VLBW infants. Growth models established in this study can be used as a tool to predict growth status of VLBW infants with specific characteristics. Predicted values may serve as a reference for growth assessment of VLBW infants.

Findings on the differences in growth outcomes if different references are applied to the same population warns health professionals that the growth references being used

may influence the estimated growth outcomes. The necessity for developing an appropriate growth reference for VLBW infants is suggested.

Findings on the determinants of growth in this study have important implications for preventing occurrence of subnormal growth in VLBW infants. Different analytic approaches have been used for the present study. The modelling procedures for longitudinal data have been shown to be powerful statistical techniques for analyzing follow-up growth data.

CHAPTER TWO: LITERATURE REVIEW

2.1 VLBW INFANTS

2.1.1 Terms in classification of birth weight and gestational age[31]

Low birth weight: birth weight<2500 grams

Very low birth weight: birth weight <1500 grams

Extremely low birth weight: birth weight <1000 grams

Preterm birth: gestational age <37 weeks

Very preterm birth: gestational age < 32 weeks

2.1.2 Intrauterine growth status

It is now clear that the determinants of poor fetal growth differ from those of preterm delivery.[11,32-35] Intrauterine growth impaired infants are more likely to have other adverse consequences in infancy and childhood in terms of mortality, morbidity, and poor growth than unimpaired infants[8,11,23,36-39] Therefore, it is important to distinguish the different intrauterine growth patterns of VLBW infants. The body size at birth is determined by two factors: gestation and average intrauterine growth rate. Various definitions have been used to describe intrauterine growth status.[11] Infants with poor intrauterine growth have been referred to as small for gestational age (SGA) or as having

intrauterine growth retardation or intrauterine growth restriction (IUGR) by different ways:

- Birth weight below 10th percentile of intrauterine growth reference[1,22,23,36,40-45]
- Birth weight below -2SD relative to the intrauterine growth reference mean or median.[8,46-51] or birth weight below the 3rd percentile.[52]
- Fetal growth ratio (FGR) less than 0.85.[32,41,53]

These cut-off points are arbitrary. While the 10th percentile is similar to 0.85 FGR (9th percentile) for term infants, the -2SD criterion is more stringent. The former is important as a screen for neonatal problems, and the later is important to identify those who need to be most closely observed and followed[36]. Regardless of which cutoff point is used, the classification of a newborn as SGA may have implications for diagnosis, prognosis, surveillance and treatment.

Many investigators have proposed growth reference data for the assessment of fetal growth by clinicians, public health practitioners, and researchers.[45,51,54-58] Perhaps the most widely used reference is that of Lubchenco et al,[45,54] which is derived from a single hospital and constructed for weights, lengths and Ponderal indices of liveborn Caucasian infants of white and Hispanic mothers of predominantly low socio-economic status living at moderately high altitude near Denver, Colorado, USA. Gestational ages are based on the last normal menstrual period (LMP). Despite the recognition that the Lubchenco curves are considerably lower than other references because of the low socioeconomic status of the reference sample and the fetal growth-restricting effect of high altitude, they

continue to be used by many clinicians and researchers. Usher and McLean based their reference curves on liveborn, singleton, white infants at a single hospital in Montreal, Canada. Gestational age to the nearest week was estimated on the basis of LMP.[51] A more recent birth weight reference has been published based on the birth weights of over one million births in Canada from 1986 to 1988.[59,60] Gestational ages in completed weeks were reported by mothers or by the attending physicians, and thus reflect ultrasound and other obstetric estimates as well as LMP. This is the most recent birth weight reference, but there are irregularities in extreme percentiles at low gestational ages because no smoothing technique was used.[59] Despite the many differences in calendar times, population characteristics, and methods of estimating gestational age, the similarities among the various references are more striking than their differences.[61] Birth weights in the recent Canadian[59,60] reference do not exceed those of the other references until term. Recently, Robertson et al[62] have developed a local intrauterine growth reference based on birth weight data from 1985-1995 in the province of Alberta, Canada. This reference perhaps is the most appropriate one for assessing intrauterine growth of newborns in the province of Alberta because the data were locally collected in the most recent years.

The assessment of intrauterine growth status is based on birth weights at given gestational ages. Birth weight is a continuous variable. There are no dividing lines to separate newborns into distinct groups. To measure the severity of intrauterine growth retardation, Kramer et al.[32,41,53] classified SGA infants into three different groups according to the magnitude of fetal growth ratios (FGR), which conveys more

information on the intrauterine growth status of newborns. Tenovuo et al. measured the severity of intrauterine growth retardation by the different percentiles of birth weight given gestational age.[63]

The body size at birth like body sizes at any other times of life, is the cumulative result of the impacts of multiple factors. The diagnosis of SGA is based on an arbitrary cut-off point on a continuous variable, the birth weight given gestational age. It may be hypothesized that, even within a group of AGA or SGA infants, the lower birth weight newborns might have been exposed to more adverse prenatal factors than those with higher birthweight. Therefore, actual birth weight given gestational age rather than classifying infants into different groups may capture more information on etiology and prognosis of VLBW birth. Using model procedures, birth weight given gestational age can be taken as a continuous variable.

2.1.3 Body proportionality at birth

Many authors consider intrauterine growth retardation to be a heterogeneous entity comprising two distinct patterns of growth in fetal body proportions[42,44,53,64-69]: symmetric (proportionate) and asymmetric (non-proportionate). Different approaches have been used in the literature to define asymmetric retardation. The most commonly used of these is based on Rohrer's ponderal index.[42,44,53,64-69] Newborns with a ponderal index less than a cut-off point, usually the 10th percentile of the reference, are considered as "asymmetric." The body proportionality at birth may capture information about the

timing of growth retardation as well as the nutritional status of newborns. Symmetric retardation is believed to result from factors present throughout the pregnancy. Asymmetric retardation is believed to arise in the third trimester. Findings on the association between body proportionality and postneonatal outcomes are inconsistent. Some researchers find a higher mortality and morbidity in the symmetric group, [70-73] while others find the asymmetric group to be at greater risk.[74,75] Some studies show that classification of symmetrically or asymmetrically growth retarded using the neonatal ponderal index has no prognostic significance.[66,76] For the outcomes of growth, asymmetrically retarded infants were found to have a more favorable growth outcome than those who are symmetrically retarded by some researchers.[42,46,77] Contrary to the general belief, Kramer et al.[53] report that proportionality is associated with the severity of intrauterine growth retardation in newborns, and that asymmetric IUGR infants tend to be more severely growth retarded than their symmetric counterparts. Once the severity of retardation has been controlled, the body proportionality appears to be of little if any etiologic[41] or prognostic importance.[78]

However, the association between body proportion and severity of IUGR in VLBW is still not clear. If body proportionality is associated with the severity of IUGR, it may still be a valuable indicator for the postneonatal prognosis, especially when gestational age is not available and the severity of IUGR can not be assessed. It is also interesting to know if body proportionality can provide extra information for growth prognosis in VLBW infants given the severity of IUGR.

2.2 Growth assessment in VLBW infants

2.2.1 Growth references

A growth "reference" and a "standard" are different.[61] A growth reference is defined as a tool for grouping and analyzing data and provides a common basis for comparing growth status among populations; no inferences should be made about the meaning of observed differences. A standard, on the other hand, embraces the notion of a norm or desirable target, and thus involves a value judgment[61]. To assess the growth status and to identify subnormal growth of VLBW infants in clinical settings, a growth reference which can be taken as a "standard" representing the optimal growth of VLBW infants is required. Various sets of reference data for height and weight have been developed.[12,79-87] The differences in growth references from different populations have been realized in the literature.[12,61,86,88-91] A WHO working group[92] stated that "for practical purposes they (the differences) are not considered large enough to invalidate the general use of the NCHS (National Centers for Health Statistics) population both as reference and a standard." However, there is no study to validate this statement in VLBW infants. The American NCHS chart, adopted for international use by WHO is referred to as the NCHS/WHO growth reference in this study.

The proper assessment of growth can lead to an appropriate action to improve health and nutritional status in VLBW infants. Growth charts are an essential tool in the surveillance of infants growth.[86,89,93] Among several growth references which are

available to health professional workers and parents, the NCHS/WHO growth reference[85,94-96] perhaps is the most widely used reference even though the WHO expert committee pointed out concerns that the current NCHS/WHO reference is inadequate and therefore recommended the development of a new reference for infants.[61] Based on data of seven studies from 6 developed countries, a growth reference for breast-fed infants has been developed recently.[61,97] For assessing growth of Canadian infants, Guo et al.[12] have developed a growth reference based on longitudinal data of Canadian infants. Growth data were collected in two cities, Montreal and Toronto.[12,98] The Canadian reference data were collected in 1977 and 1978 while the NCHS/WHO reference data for infants were collected between 1929 and 1975.[61] Some efforts have been made to establish growth references for specific groups of infants or conditional growth references. Growth references for low birth weight (LBW) infants were developed based on growth data of LBW infants.[7,99,100] However, the application of these references may be limited without clear understanding of normal growth pattern of LBW infants. It is not clear which reference should be used for assessing growth of VLBW infants in Canada. By using different growth references to assess growth status of VLBW infants, could we get substantial differences in the assessed growth outcomes in VLBW infants? If there are differences in growth outcomes determined using different references, the selection of an appropriate growth reference is important in the growth assessment in both clinical settings and community based surveillance.

Some growth references in which certain characteristics are taken into account have been developed, such as parent-height specific references [83,101,102], disease-specific charts[103-106], and a multifactoral growth model[107]. Parent-height specific references are important to distinguish infants of genetically small size from those of non-genetically (illness or malnutrition) small size. Disease-specific references and multifactoral growth models are useful for predicting future growth and identifying secondary growth retardation.

2.2.2 Expression of Growth measurements

Three different systems are commonly used to express the growth status of an individual or population: Z-scores, percentiles, and percent of median values.

The Z-score system expresses an anthropometric value as a number of standard deviations below or above the reference mean or median value.

- Z-score or SD score= [(Observed value)-(Median reference value)]/(SD of reference population)

A fixed Z-score interval implies a fixed height or weight difference for children of a given age. A major advantage of this system is that, for population-based applications, it allows the mean and standard deviation to be calculated for a group of Z-scores.

A percentile refers to the rank position of an individual on a given reference distribution. It means what percentage of the group equals or exceeds the growth level of this individual. Percentiles are commonly used in clinical settings because their

interpretations are straightforward. However, statistical calculations, such as means and standard deviations, are inappropriate for percentile values since the same unit in percentile corresponds to different growth measurement at different part of the distribution. Towards the extremes of the reference distribution a little change in percentile values means a substantial change in weight or length status.

Anthropometric measurements can also be expressed as a percentage of the median value of a reference, which is the ratio of a measured value of an individual to the median value of the reference data, expressed as a percentage. This is the only approach that can be used when only the median value of the reference is available and the distribution of the reference population is unknown. The main disadvantage of this system is the lack of correspondence with a fixed point of the distribution across age. For example, depending on the child's age, 80% of median weight for age might be above or below -2 Z-score. In terms of health, this would result in different classification of risk.

The advantage and limits of three reporting systems have been summarized[61,92] The Z-score system 1) adheres to the reference distribution; 2) permits summary statistics; 3) allows uniform criteria across indices; and 4) is useful for detection of changes at extremes of the distributions.[61,108] Also, if the distribution of reference values follows a normal distribution, percentiles and Z-scores are related through a mathematical transformation. The commonly used -3, -2, and -1 Z-scores are, respectively the 0.13th, 2.28th, and 15.8th percentiles. It can be seen that the 3rd percentile and the -2 Z-score are very close to each other. Because of the strengths above, the Z-score system is preferred

for analysis and presentation. For population-based assessment, the WHO expert committee recommended two ways to report the anthropometry-based results.[61] One is the commonly used cut-off-based prevalence. The other is the summary statistics of the Z-score – mean, median and SD.

2.2.3 Reporting population growth outcomes

2.2.3.1 Prevalence reporting

To estimate the proportion of those who might be considered to have poor growth, it is conventional to use cut-off points to define subnormal growth. In previous studies in the literature, different cut-off points have been used: 3rd centile,[109] 5th centile,[1,4,110] 10th centile,[1,20,111] and mean minus 2SD or Z-score of -2.[8,46,47,112] The cut-off should be chosen at the point most appropriate for the particular purpose in view and the growth reference being used. More children will be considered at risk by using the 10th percentile as the cut-off point than the 3rd, 5th, and -2 Z-score, which may be important for screening purposes. In general, subnormal growth is statistically defined as a growth measurement value below -2 standard deviations or Z-scores <-2 .[61] The use of -2 Z-score as a cut-off ensures that 2.3% of the reference population will be classified as having "subnormal" growth. Therefore, 2.3% can be regarded as a baseline or expected prevalence. It should be noted that this does not truly define the "normal" range from the point of view of health and nutrition; rather, it should be used as a guide to facilitate clinical screening or population-

based surveillance. For this reason, proper assessment of the prevalence of a condition requires the subtraction of the baseline prevalence from the observed prevalence.

2.2.3.2 Mean Z-score based reporting

The growth status of a population can also be expressed by the mean and SD of Z-scores. Although this reporting is less commonly used, it has the advantage of describing the nutritional status of the entire population directly, without resorting to a subset of individuals below a cut-off. The mean Z-score significantly lower than zero usually means that the entire distribution has shifted downward, suggesting a larger proportion of infants than expected have been affected. Plotting the entire distribution of Z-scores against the reference distribution is helpful in representing the nutritional status of a population.[61]

For assessing the change of growth status in VLBW infants, mean Z-scores can be compared among different age groups. This property is useful for exploring the important concept of catch-up growth in VLBW infants.

2.2.4 Age adjustment for prematurity

Recent studies assessing growth of preterm infants have utilized age adjusted for prematurity.[1-4,6-8,10,40,111,113] It appears to be an intuitively correct concept. Although it is a common practice, there are few studies to assess the necessary period of age adjustment

and what difference the adjustment will make in the assessment of growth outcomes in VLBW infants. Brandt[11] studied appropriate for gestational age (AGA) infants, most of whom had birthweight <1500 grams, in Germany. She concluded that the age adjustment for prematurity became unnecessary after 24 months of age for weight and 3.5 years for length. Karniski et al. reported that different growth patterns could be obtained if age was unadjusted.[10] In a recent study, Elliman et al.[15] reported that the correction for gestational age continued to make a difference in the height SD score (Z-score) to the age of seven years in very preterm babies with birth weight 2000 g or less.

2.3 Growth in VLBW infants

2.3.1 Short term postnatal growth in very low birth weight infants

Lack of understanding of the normal growth patterns in very low birth weight (VLBW) infants makes it difficult to assess an individual or a group of individuals' growth status among this population. For short term growth, considerable emphasis has been placed on the growth of the fetus *in utero* as a standard reference to assess the postnatal growth in VLBW preterm infants.[114,115] There are no sufficient biological reasons for supposing that the extra-uterine growth is the same as the fetus' normal growth *in utero*.[116] New born infants are in a totally different environment from the fetus *in utero*. Few studies focus on directly comparing short term postnatal growth patterns with intrauterine growth curves. Brandt compared the postnatal growth of preterm infants with six different intrauterine growth references, and found that the postnatal

growth measurements in both weight and length are lower than any of those intrauterine growth references.[11]

Several efforts have been made to describe the growth of VLBW infants and establish growth grids for VLBW infants.[117-122] The postnatal weight growth patterns in VLBW infants in the first month of life, described in these studies, are different from intrauterine growth patterns.[16,45,51] An initial period of weight loss occurs before a period of weight gain. Bauer et al. [123] found that such weight loss was due to loss of total water but that loss of lean body tissue did not occur. The maximum weight loss occurred at about 1 week of life (range from 3 to 9 days). There are differences in the amount of weight loss in different studies, ranging from 6.4 to 14.5 percent of birth weight. Some studies showed that the postnatal weight loss depended on the birthweight, that the infants with lower birth weight had higher percentage of weight loss[117-119,122]. No particular patterns of weight loss have been found in other studies.[120,121] After reaching minimum weight, body weight increased and the birthweight was usually regained at about 2 weeks. Differences in postnatal weight change among those studies may be due to the different characteristics of study samples. Since the optimal growth of VLBW infants before term is still unknown, the postnatal growth curves reported in previous studies can only serve as a description of growth in VLBW infants with specific characteristics rather than as a "standard" to identify growth problems. However, those curves may be helpful to identify those with severe growth retardation and who need to be paid special attention to their growth status.

2.3.2 Long term postneonatal growth in very low birth weight infants

After term (40 weeks postneonatal gestational age), the growth status in VLBW infants can be assessed by comparing their growth with a reference of normal term infants. The growth of normal term infants has been taken as optimal growth for VLBW infants. These growth references can be established based on growth data of normal term infants from local geographic area (local growth references) or established based on infants who are considered to live in optimal living conditions (international growth references). An important issue on the growth of VLBW infants is whether those infants show catch-up growth during infancy.

Catch-up growth in VLBW infants

Catch-up growth is an important concept in describing the growth status of VLBW infants. In a classic publication by Prader et al,[124] catch-up growth was defined as follows: "at the end of a period of growth retardation ... the child grows more rapidly than usual so that he catches up toward or onto his original growth curve."[124] However, the individual original growth curve is usually unknown. In the literature on growth of low birth weight infants, some operational definitions of catch-up growth have been used based on the way of presenting and analysing growth data:

- The infant has "subnormal" growth (<-2SD, 3rd, 5th or 10th percentiles as a cut-off point) at birth or previous measures, and reaches the "normal" range after a period of

significantly more rapid growth velocity than occurs in control or reference infants.[1,8,109,112]

- The average growth velocity of VLBW children during a certain period or at a certain point of time is greater than that of normal term infants.[2,7]
- The mean differences in growth measurements between VLBW infants and normal term peers decreases during certain period.[1,40,109,112]

Also, the term "incomplete catch-up growth" is used to describe those who have some "acceleration" of growth after birth but not reaching the expected percentile.[11] At the population level, the existence of catch-up growth will be considered if the prevalence of subnormal growth decreases or the mean Z-score of a growth measurement increases with age.

A pattern of diminishing numbers of infants below certain cut-off points was found as VLBW children grew older in the studies observing the change of the prevalence of subnormal growth in length and weight.[2,8,109,110] Evidence of catch-up growth was found in these studies. However, the findings from the studies observing the change in the average levels of growth distances or velocities in VLBW infants are inconsistent. There are reports of no catch-up growth.[4,7,10,99] Kimble et al. found that growth for VLBW infants proceeded below, but roughly parallel to the mean of NCHS (National Center for Health Statistics) growth norms between 1 and 3 years of age.[4] Casey et al. reported that the growth levels of VLBW infants were lower than NCHS/WHO growth reference and there were no

significant differences in weight growth velocity between VLBW and heavier birth weight infants in the first 3 years of life[7].

There are some reports of catch-up growth in VLBW infants. As in Binkin et al's study, children with lower birth weights appeared to undergo greater weight gain during the first 2 years of life than those with heavier birth weights, although they remained shorter and lighter thereafter.[112] Catch-up growth in length was found by Tammela between age of 6 months and 1 year, during which the mean standard deviation score of length was from -2 SD to -1 SD.[125] Casey et al. also found that growth velocity for VLBW infants was significantly greater than that of heavier birth weight infants at the age of 12 months in length; while growth rates of head circumference were significantly lower than those of heavier birth weight infants, directly the opposite of what would be expected in catch-up growth.[7] Brandt reported that the AGA infants could catch up to term infants in first two months of adjusted age in weight; first 21 months in length.[11]

The discrepancies in previous studies might be, in part, attributable to the differences in the methods of presenting and analysing growth data. For example, in a study by Kitchen et al,[2] the average annual increments in weight and height were computed during 3-year intervals between 2 and 5 years and 5 and 8 years. The growth rates for VLBW children were lower than those of normal birth weight children. Between 2 and 5 years, the differences were not statistically significant, but between 5 and 8 years, the VLBW children grew at significantly lower rates than did the normal birth weight children. It was suggested that "VLBW children as a group not only do not catch up to their normal-birth-weight peers

by 8 years, but also may fall further behind between ages 5 and 8 years." However, in the same study, VLBW children with a weight or height under the 10th percentile at age 2 years, only approximately one half of them were found to be below the 10th percentile of the reference for the corresponding measurement at age 8 years, which suggested a catch-up growth during the observed period. The conflicted findings might be due to the diversity of individual growth patterns. As Kitchen et al. pointed out that "there are individual exceptions to the average."[2]

The timing of catch-up growth varied among different studies. Obvious catch-up growth usually occurred in the first two years of life.[8,40,46,112] However, a continuing catch-up growth in VLBW infants during 2 to 5 years of age and 5 to 8 years of age was also found.[1,2] Even in the studies in which catch-up growth was demonstrated, there were still more than expected numbers of infants remaining subnormal in physical growth.[1,2] The determinants of poor catch-up growth are still poorly understood, even though some efforts have been made to identify them.[1-3,8] Hack et al.[8] reported that significant correlates of poor catch-up growth in the AGA infants were birth weight, gestational age, severity of neonatal complications, poor neonatal head growth and chronic physical and neurologic sequelae. In the infants of the SGA group, the correlates of poor catch-up growth were birth weight, multiple birth, and social class. Kitchen et al.[2] found that the only variable significantly associated with a weight below the 10th percentile at age 8 years was birth weight. The only variable significantly associated with a height below the 10th percentile at age 8 years was the maternal height. Qvigstad et al.[1] reported that the parental level of education, total

parental height, sex, hypertension during pregnancy, and some early measures contributed to the prediction of length classification (smaller/larger than 10th percentile).

In studies by Brandt[126] and Karniski et al,[10] the mean Z-scores of growth measurements at different ages were presented. The change of growth status in VLBW infants could be observed. A satisfactory catch-up growth was found in the former study and little catch-up growth were found in the later one. However, in the most recent large sample studies,[3,4,7,100] the mean growth measurements were compared directly with growth references. They concluded that VLBW infants grew poorer than reference population, and little catch-up growth was found in VLBW infants. Such a direct comparison of mean growth measurements with growth references is not appropriate for assessing the change of growth status over age in VLBW infants, because the mean values of growth measurements and variances among population increase with age.

2.4 Growth models

Models are often fitted to growth data to derive a smooth curve that will summarize the information provided by an individual child. Thus, replacing large numbers of observations collected over time on an individual by a few parameters leads to an efficient method for comparison of growth under different conditions such as different diets, diseases or environments.[127] It is more efficient to compare these parameters than to compare mean values at many time points.[128] From such a smooth curve, growth velocity and acceleration can be estimated directly at any time-point within the observed age

range. Desirable features of a growth model were outlined by Berkey.[129] They include (i) simplicity of the fitting procedure, (ii) biological interpretation and (iii) model parsimony. Various models have been studied and utilized in the analysis of growth in both term and preterm infants.[12,127,130-134] The repeated measurements can be distilled into a few parameters from those growth models.

The simplest function is the polynomial in age. It is easy to fit, and the degree of complexity can be extended indefinitely by increasing the order of the polynomial. However, polynomials have their limits. They are restricted in the shape of curve they can model, their behaviour at the extremes of the data is unpredictable, and the addition of higher-order terms does not guarantee a suitable curve. The growth process is essentially smooth and gradual, and exponential functions are generally more suitable than polynomials for modelling it. The mathematical models from literature are presented in Table 2-1.

Table 2-1 Mathematical models from the literature

Model	Equation
Jenss & Bayley (1937)[133]	$y=a+bt-\exp(c+dt)+e$
Count (1943)[130]	$y=a+bt+c\log(t)+e$
Kouchi et al.(1985)[135]	$y=a+bt^c+e$
Berkey & Reed(1987)[136]	$y=a+bt+c\log(t)+d/t+e/t^2+..+e$
Karlberg (1987)[131]	
Infancy component	$y=a+b[1-\exp(-ct)]+e$
Childhood component	$y=a+bt+ct^2$
Guo et al. (1990)[12]	$y=a+b\sqrt{t}-\exp(c+dt)+e$

y represents length, weight, or other growth measurements

t represents age in months

a, b, c, d and e represent parameters to be estimated

e represents errors.

Simondon et al.[137] compared the Count, Reed, Karlberg, and Kouchi models for weight during infancy, and found that the Karlberg model was the best fitting 3-parameter model, while the 4-parameter Reed model was the best overall. However, they pointed out that their conclusions probably did not apply generally.

Peerson et al.[132] applied nine mathematical models to 24-month length, weight, and head circumference growth curves of 39 breastfed and 31 formula-fed infants. Count,

Reed first-order, Reed second-order, Karlberg, Guo, Jenss and three polynomial models were included in their study. For both breast-fed and formula-fed infants, the Karlberg model best described the relationship between body length and age and the Jenss model best described the relation between head circumference and age. For formula-fed infants several models appropriately described the relationship between weight and age. None of the models suitably described the shape of the weight curve for breast-fed infants.

There are many factors that affect the fit of a model - the measurement, the age range and the children's characteristics. Therefore, different models are likely to be optimal in different situations.[129,138] However, no previous study examined the best model to describe the relationship between age and postneonatal growth in VLBW infants.

The early growth models mainly focused on describing growth patterns and the change of growth measurement over age.[12,127,130-134] The growth model has been extended in various ways. One early extension was to allow separate models for subgroups or equivalently, to allow the parameters to depend upon individual characteristics or covariates.[139,140] The data for this analysis required that each subject is measured at certain times which are the same for all subjects and that there are no missing values. These requirements limit the ability to analyze the longitudinal growth data since it is impractical to keep measurements at the same age for all infants. The loss to follow up is often unavoidable. A major breakthrough in the analysis of longitudinal data is to adopt the conventional regression tools, which relate the response variables to the explanatory variables while the within-subjects correlation is accounted for.[25] One

approach is to shift the fixed effects models to the models including random effects.[26,28] The overall model is called a mixed effects model with population parameters fixed and individual effects random.[140] Mixed effects models are currently in the developing stage but they have become increasingly available to researchers.[29,141-143] The advantages of mixed effects models will be discussed in the section of "summary of methodological issues" (page 38) in this chapter. Another approach is an extension of generalized linear models, the generalized estimating equations (GEE) in which the regression and within-subject correlation are modelled separately.[25,30,144] Regression coefficients from GEE approaches have the same interpretation as coefficients from a cross-sectional analysis.

2.5 Factors Related to Postneonatal Growth

Growth is the result of a complex set of interrelated factors, including perinatal, genetic and environmental factors, modified by the presence and severity of illness. Various factors have been studied in the literature. The findings in the literature will be discussed below.

2.5.1 Birth weight

In normal infants, there is a diminishing positive association between birth weight and body weight at three months (r=0.55), to six months (r=0.46), one year (r=0.39), and two years (r=0.27), with the coefficient of correlation being greater for boys than girls.[145] During the early months of age in low birth weight infants, body weight remains lower in

infants of lower birth weight categories.[118,120,121] Although in some studies low birth weight children appear to have accelerated growth in weight and length during the first 2 years of life when compared with their normal birth weight counterparts, low birth weight children remain shorter and lighter.[112] Such differences were found throughout early childhood.[2,7,112] Growth appears to be more affected by birth weight in early childhood than in later childhood, and weight is more affected by birth weight than is the height or length[20,47,112], while head circumference is the least affected by birth weight.[8,109] However, since infants with lower birth weight tend to have a greater frequency of other adverse conditions,[9] the impact of birth weight on growth might be confounded by those factors. Intrauterine growth status and body proportionality may also influence the postneonatal growth in VLBW infants.

2.5.2 Intrauterine growth retardation (IUGR)

Previous studies have shown that IUGR has adverse effects on the growth of term infants.[42,49,69,135,146] However, controversy exists regarding the impact of IUGR on the growth of premature infants. There are reports of no catch-up growth or less catch-up growth of SGA infants [8,10,22,23,147] to AGA infants. Also, there are reports of satisfactory growth for weight and height in comparison with premature infants with appropriate size for gestational age.[148] The confusion in interpreting the results may,[23,149,150] in part, be due to the use of differently matched (birth weight and gestational age) controls for comparison and the small sample size. Sung et al. compared the growth status of SGA

VLBW infants with that of two control groups of AGA infants: birth weight matched (AGA-BW) and gestational age matched groups (AGA-GA). SGA infants were shorter and lighter than AGA controls. Differences between SGA and AGA-GA control group in growth measurements were larger than the difference between SGA and AGA-BW controls. Most previous studies do not take differences in perinatal characteristics between SGA and AGA into account.[43] To determine the effect of intrauterine growth retardation on the outcome of the premature infant, Pena et al.[38] also compared a group of 35 premature, small-for-gestational-age (SGA) infants with two groups of premature, appropriate-for-gestational-age (AGA) infants: one with similar birth weight (AGA-BW group) and the other with similar gestational age (AGA-GA group). Groups were matched by year of birth, race, gender, and socioeconomic status. Infants were free of major congenital anomalies and intrauterine infection. The infants were evaluated at term, at 20 and 40 weeks, and at 1 year adjusted ages. The SGA infants had significantly smaller body dimensions at birth, more nursery complications, and a higher incidence of major neurologic problems than their AGA-GA matches but were comparable to the AGA-BW matches. Both studies showed the importance of birth weight on postneonatal outcomes since there is no or little difference between SGA infants and AGA-BW controls. Robertson et al. reported that no statistical significant differences were found in height and weight between SGA and AGA-BW or AGA-GA controls at 8 years age.[151] However, their data showed the trend that SGA children were shorter and lighter than

AGA children and the differences between SGA and AGA-GA controls were larger than those between SGA and AGA-BW controls.

2.5.3 Body proportionality at birth

Since body proportionality at birth may capture information about the timing of growth retardation as well as the nutritional status of newborns, it can be considered as a potential determinant of postneonatal growth. As discussed previously, body proportionality at birth was found to be associated with the severity of IUGR and asymmetric IUGR infants tend to be more severely growth retarded than their symmetric counterparts by Kramer et al.[53] However, the growth status of asymmetric IUGR infants tend to be better than that of symmetric infants,[42,46,77] which conflicts with the Kramer et al's finding. Once the severity of growth retardation has been controlled, the body proportionality appears to be of little if any etiologic[41] or prognostic importance.[78] Further studies are required to investigate if the body proportionality at birth is, independent of intrauterine growth retardation, associated with postneonatal growth.

2.5.4 Parental height

The hereditary background of a child has a great influence on the growth pattern and final size.[11,101] "Mid-parent stature (or height), the average of the stature of two parents, is used frequently for studies of parent-child stature relationships because it summarises the genetic contributions of the parents, and because the statistical and genetic assumptions

involved are appropriate".[101] In a study of discriminant function of variables predicting small height (<10th percentile) at 5 years of age by Qvigstad et al,[t] it was found that total (or mid) parental height contributed most to the discriminant function. In a longitudinal follow-up study of growth in SGA children in Sweden, the parental heights of children who did not exhibit catch-up growth were 0.9 SD below the mean of the Swedish population.[47] However, since parental height may be associated with infants birth weight, further analysis is necessary to determine if the association of parental height and postneonatal growth is independent of birth weight.

2.5.5 Sex

Like normal term infants, preterm VLBW boys tend to be heavier and taller (or longer) than girls during infancy.[4,7,11] Growth velocities were found not to differ significantly between girls and boys.[7,11] However, when compared with normal term infants, boys are more likely to have "subnormal" growth than girls. Kimble et al. reported that, at 3 years of age, 19% of boys versus 12% of girls in weight, and 23% versus 17% in length were below 5th percentile of the NCHS reference.[4]

2.5.6 Bronchopulmonary dysplasia (BPD)

BPD is a frequent sequela of lung injury in low birth weight infants, with about 20-40% incidence in VLBW infants in published surveys.[125,152,153] Poor growth has been found in infants with BPD.[110,154,155] It has been suggested that this poor growth may be due to the

elevated resting metabolic expenditure and increased work involved in breathing. The supplying of enough energy to patients with BPD has proved to be a problem since they frequently experience feeding problems.[153,156] Compared with normal term reference infants, BPD infants were found to have poorer growth.[109,155] When infants with BPD were compared with preterm infants without BPD, the results were variable. Some studies reported poorer growth in BPD infants;[20,110,157,158] while others found that the growth pattern for infants with BPD did not significantly differ from other preterm infants.[125,154] Since BPD is associated with other developmental problems and medical complications,[110,155,157] it is difficult to assess the specific contribution of BPD to growth without controlling confounding effects of other variables. Most studies have not controlled for birth weight or other differences between infants with and without BPD. Bozynski et al. found that after adjustment for birth weight, BPD did not explain the growth pattern.[159] Sell and Vaucher reported that birth weight (not BPD) explained 70-85% of the variance in subsequent weight prior to 8 months of age.[157] A small sample analysis published by Kurzner et al. suggested that both birth weight and severity of BPD are important.[160] The relationship among BPD, postneonatal growth, birth weight and other factors and their contributions to the postneonatal growth need to be explored further.

2.5.7 Antenatal steroids

Steroid therapies may affect growth in either directions.[161-165] Significant reductions in the incidence of respiratory distress syndrome (RDS), mortality, and NEC were

observed in premature infants born of mothers who received antenatal steroid therapy in a series of randomized trials assessed by meta-analysis.[166,167] Recently, studies on the outcomes of antenatal steroid administration consistently showed that antenatal steroid therapy reduced mortality and morbidity in low birth weight and VLBW infants.[168-172] Therefore, antenatal steroid therapy may be associated with better postneonatal growth in VLBW infants because of reduction in the incidence of BPD, RDS and NEC which may affect growth. Doyie et al. reported that antenatal steroid therapy was associated with a significant improvement in growth of VLBW infants at 2 years of age.[173] For the subgroup of their study sample, the extremely low birth weight (<1000 grams) infants, no significant improved growth was found at 5 years of age in antenatally treated infants.[161] The reason for such a discrepancy is unknown. It may be because the effect of steroid therapy depends on birth weights, or it may be due to the small sample size of extremely low birth weight infants. Follow-up data have been published on physical growth and development from three large trials. None of these studies indicates that antenatal steroids therapy has any effect on growth parameters.[162,164,165] In another study by Doyle et al, the weight and height at 5 years were greater in infants of the steroid group than those of the control infants although it was not statistically significant.[161] A collaborative group on antenatal steroid therapy[162] also found that the infants in the steroid treatment group were slightly heavier and taller than the infants of placebo group.

The antenatal steroid therapy can have beneficial effects on preventing adverse clinical conditions, and these conditions may be associated with the postneonatal growth

of VLBW infants. No studies have been found to investigate the independent association between the antenatal steroid therapy and postneonatal growth of VLBW infants.

2.5.8 Feedings

Feeding practices have been found to be associated with postneonatal growth.[90,174-179] The findings on the effects of breastfeeding on growth are inconsistent. Some studies showed that infants who were formula fed gained more weight during infancy than infants who were exclusively breastfed.[174-176,180] Other studies found that breastfed infants were heavier than formula fed infants.[181,182] Whether different growth of the exclusively breast-fed infants from that of formula-fed infants represents appropriate physiological growth is not known. Feeding practices should be considered as a determinant of postneonatal growth in VLBW infants.

2.5.9 Other factors

Maternal factors that may influence the growth achievement of VLBW infants include social class, maternal education and hypertension during pregnancy.[1,50,183] Management and care of preterm infants may also influence future growth, although this remains controversial.[19,49] Later growth depends on adequate nutrition to ensure postneonatal weight gain[184] as well as feeding practices and feeding problems.[40,156] Necrotizing enterocolitis forces nutrition management to parenteral nutrition for bowel rest.[156] Neonatal sepsis and suspected sepsis will result in withholding all enteral feeds until it is established that the

infant is stable.[156] General health status is another predictor of growth outcome. Duration of hospital stay which reflect the seriousness of postneonatal illness may be a determinant of energy intake[40] and growth achievement.[1] The factors affecting growth of high risk infants have been listed for growth assessment.[36,185] Nutritional and dietary factors, social demographic factors and some other medical complications may also have important impacts on postneonatal growth.[156]

2.6 Summary of methodological issues

2.6.1 Long time intervals

Many previous studies have used long intervals between measurements.[2-4,6,16-19] The change of growth status in VLBW infants cannot be accurately described with long time intervals. During infancy, the growth velocity decreases with age. The accurate growth rate cannot be obtained using data with long time intervals.

Also, the change of growth status with age should be observed by comparing positions in growth measurements relative to the reference distribution. The direct comparison of observed differences between study sample and the mean of a reference at different ages is not appropriate to describe the change of growth status with age since the same difference does not have the same clinical and statistical meaning at different ages. Unfortunately, in most of the longitudinal studies in the literature, the mean values of growth measurements or growth rates were compared directly with the means or medians of a reference.[4,7,100]

2.6.2 Confounding effects and statistical methods

In VLBW infants, it is possible that factors affecting growth are associated with each other. Lower birth weight infants or intrauterine growth retarded infants are more likely to have other adverse clinical conditions.[23,40] Therefore, when assessing the association of a factor and postneonatal growth, confounding effects should be taken into account in design and/or data analysis stages.

The growth rate and growth pattern of VLBW infants can only be described through longitudinal growth data, in which each individual is measured at different ages. In the literature on determining factors associated with postneonatal growth, the longitudinal data were often analyzed by cross sectional statistical methods. For example, Kitchen et al.[2] used logistic regression to determine the variables that might predict poor growth (below 10th percentile of reference data) for weight or height at age 8 years. Qvigstad et al.[1] and Kitchen et al.[3] used another multivariate statistical method, discriminant analysis, to obtain predictors of growth measurements under the 10th percentile at 5 years of age. In those studies, only one (the last one) of the repeated measurements was taken as the dependent variable in the multivariate analysis, in which the detailed relationship between a factor and growth process cannot be assessed. The important information on the change of growth status provided by longitudinal data is lost by only picking up one of the serial measurements for the analysis. In Bozynski et al's study,[159] the growth rate for each infant was estimated by the Count model;[130] and the association between explanatory

variables and growth rates were assessed by multiple regression techniques. However, only a small number of variables which might affect postneonatal growth in VLBW infants were included in their study.

Satisfactory methods of analyzing longitudinal data are only recently becoming available. The objectives for statistical models of longitudinal data are 1) to adopt the conventional regression tools, which relate the response variables to the explanatory variables; and 2) to account for the within subject correlation. The detailed association between a factor and postneonatal growth can be explored by using mixed effects models.[26-29]

In the mixed-effects models for longitudinal data analysis, the regression coefficients of fixed effects represent the average responses to the change of an independent variable in the outcome of interest in population. Generally, the fixed effect of a factor is the average change in outcome caused by per unit change of the factor in the population. The regression coefficient(s) for each factor provides information on how this factor is associated with the outcome of interest while confounding effects of other factors are taken into account. Although the nature of this correlation is often of secondary interest, it is essential to account for the within-subject correlation because the repeated outcomes for one individual, which are part of longitudinal data, tend to be correlated with one another. In mixed effects models, the within-subject correlation is accounted for by including random effects in the models. The random effects represent natural heterogeneity among individuals. The mixed effects model assumes that the correlation

among the repeated measurements of an individual is due to some latent characteristic that gives an individual a higher or lower than the average intercept and slope. For example, some infants may be heavier or longer than others at the beginning of the observation period.

The mixed effects models provide the flexibility for researchers to study determinants of growth process, allowing for unbalanced designs, incomplete data and within subject correlations.[26,144] However, no reports have been found using this method to study the determinants of growth in VLBW infants.

CHAPTER THREE: METHODS

3.1 OBJECTIVES

The objectives of this study were to 1) describe the postneonatal growth patterns of VLBW infants and to 2) identify the determinants of postneonatal growth in VLBW infants from Southern Alberta.

To fulfill these objectives, attempts were made to answer the following questions: 1) How do the growth levels of VLBW infants, relative to growth references, change during infancy? 2) How does the prevalence of subnormal growth change during infancy (increase or decrease)? 3) Do the growth levels and the change of growth levels depend on the perinatal and social environmental characteristics of infants? 4) How are perinatal and demographic factors associated with growth levels and the change of growth levels? 5) What are the expected growth levels for VLBW infants free from adverse clinical conditions? and 6) Who will be more likely to be "subnormal" in growth?

3.2 STUDY SAMPLE

The study sample was selected from the Alberta Children's Hospital (ACH) Perinatal Follow-Up Program which included infants from Southern Alberta and Southeast British Columbia. The ACH Perinatal Follow-Up Program is a unique resource for rapidly assessing postneonatal outcomes of VLBW infants because of the availability of longitudinal data collected from repeated examinations over two decades. Eligibility was

restricted to those infants who were born during January 1977 and May 1992, with birth weights of 1250 grams or less and who were discharged alive from the NICU. There were 1007 infants who met the above criteria. In the Follow-Up Program, these infants were routinely followed up at 4±1, 8±1, 12±1, 18±3, and 36±6 months adjusted ages. Adjusted age was calculated by subtracting the expected date of delivery from the date of assessment; and recorded as the number of nearest month. Fourteen days or less was not considered a month while 15 days or more was. The study sample is a subset of the cohort whose selection was based on the availability of growth assessment at follow-up visits. Only infants with 4 or 5 sets of measurements were included in this study since growth patterns could not be accurately described with smaller number of repeated measurements. Five hundred and fourteen (514) infants with growth data in length and weight available on 4 or 5 visits were included, which consisted of 51% of total VLBW survivors discharged from the NICU. Of 514 infants, 477 (93%) were examined at 4±1 months, 491 (96%) at 8±1 months, 442 (86%) at 12±1 months, 483 (94%) at 18±3 months and 447 (87%) at 36±6 months adjusted age, see Figure 3-1.

The detailed description of the study sample will be given in the chapter on results (page 60). The representativeness of the study sample to the population of VLBW infants in ACH Perinatal Follow-Up Program was assessed by comparing the characteristics between the study sample and infants who were not included in the study sample. To assess the generalizability of the growth models developed in this study, the growth models were used to predict the growth of infants who were not included in the study

sample. The residuals which were the differences between observed and predicted values were checked.

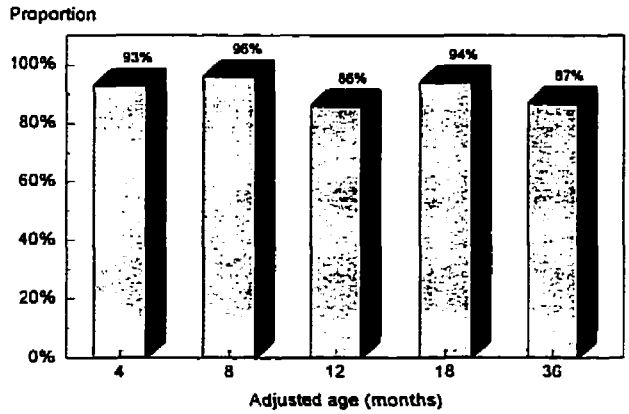


Figure 3-1 Proportions of infants with growth measurements available in the study sample at different visits

3.3 MEASUREMENTS

A broad range of clinical research information of the study sample was gathered from mothers' and infants' health records, physical examinations and parent interviews during the nursery stay and follow-up visits following the standard protocols of the Alberta Children's Hospital (ACH) Perinatal Follow-up Program.

3.3.1 Weight and Length

Weight and **length** were measured in a standardized fashion[186] by two trained volunteers at each visit. Infants were weighed undressed on a calibrated infants balance

scale. Length was measured in the supine position on standardized infant measurement boards.[186]

3.3.2 Perinatal factors

Birth weight was measured by clinical staff to the nearest 10 grams. **Gestational age** was assessed based on a best estimate derived from the maternal last normal menstrual period, clinical assessments and antenatal ultrasound examinations. **Adjusted ages** for prematurity were generated by subtracting the time between the actual and expected date of 40 week full term birth from the chronological age of the infant.

The intrauterine growth status was measured in two ways. First, based on birth weight and gestational age, infants were categorized into two groups: **small for gestational age (SGA)** and appropriate for gestational age (AGA). Infants with birth weight less than the 10th percentile of Lubchenco's intrauterine growth reference[45] were classified as SGA and infants with birthweights at the 10th percentile or higher as AGA. Second, intrauterine growth was characterized on the basis of fetal growth ratio, defined by Kramer et al[53] as the ratio of the observed birth weight to the mean or median of the reference population. The mean values of Lubchenco's intrauterine growth data were used as the reference in this study to calculate the **fetal growth ratio (FGR)** for each infant. The approach of measuring the severity of intrauterine growth retardation described by Kramer et al[53] was adopted in this study. Infants were divided into different groups according to the severity of IUGR based on the FGR. However, cutoff points were

shifted from those presented in their original paper,[41] because the distribution of FGR in the study sample was different from that of term infants.

Body proportionality was determined based on a Ponderal index (PI), which was calculated as *birth weight (g) × 100/birth length (cm)*^{3}. PI less than the 10th percentile of Lubchenco's reference data[54] was defined as "asymmetric" or "disproportionate" and PI at the 10th percentile or higher as "symmetric" or "proportionate".

The **feeding practices** during the NICU stay were classified by the duration of feeding type. Infants who were fed with breast milk longer than 50% of their NICU stay were classified as "**primarily breastfed**", otherwise as "**formula-fed.**" The use of **Antenatal steroids** was recorded if any steroids were used before delivery.

The presence of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), apnea, patent ductus arteriosus (PDA), neonatal sepsis, jaundice or cerebral palsy (CP) was determined by clinical examinations.

BPD: The infant was diagnosed as having BPD if he or she required additional oxygen at 36 weeks' corrected postconceptional age[187] and met the criteria described by Bancalari et al.[188] Therefore, the criteria for BPD in this study were (i) mechanical ventilation for respiratory distress in the first week of life; (ii) required supplemental oxygen 0.25 or greater to maintain Pao_2 or transcutaneous Pao_2 equal or greater than 55 mm Hg for more than 28 days and 36 weeks' corrected post-natal gestational age; (iii)clinical signs of chronic respiratory distress for more than 28 days of age; and (iv) Characteristics of chest radiograph of BPD.[110,187,188]

Necrotizing enterocolitis (NEC): NEC was diagnosed if x-ray reports indicated one or more of the following:

- pneumatosis intestinalis;
- portal venous gas;
- peritoneal air;
- presence of unchanging or persistent bowel loops with a thickened wall on sequential x-ray confirmation;

usually accompanied by significant abdominal distention, tenderness and/or blood in stools.

Neonatal sepsis: If a positive blood or cerebrospinal fluid culture was found at any time during NICU stay, the infant would be considered to have sepsis.

Apnea: Apnea was considered "present" if there were three or more episodes (15 seconds of breathing stopping in each episode) per day for more than one day of apnea or bradycardia requiring stimulation.

Patent ductus arteriosus (PDA): The presence of PDA was diagnosed by a physician and confirmed by x-ray or echocardiogram. Those which were surgically ligated or treated with drugs such as Indocid and Lasix were coded as present.

Cerebral palsy (CP) was diagnosed by an experienced pediatrician and a physiotherapist based on muscle tone, reflex and flexibility. CP was determined in follow-up examinations[189] while other conditions were diagnosed before the discharge from the NICU.

Apgar score at 5 minutes was classified into two groups: less than 6 and ≥6. The duration of acute NICU stay was measured by the total days in the acute NICU before their first discharge from the unit. Total days on intermittent positive pressure ventilation (IPPV) and the duration of total parenteral nutrition (TPN) were determined by subtracting the date of commencement of the treatment from the date of the termination of the treatment. Since the change of neonatal intensive care practices over time might have impacts on the infants' growth, the **year of birth** was taken as a proxy of the change in neonatal intensive care practice and the change of infants characteristics during the period of data collection.

3.3.3 Parental characteristics

Mid-parental height is the average height of both natural parents in centimeters. **Maternal education** was measured using the total school years of the natural mother, which was categorized into two groups: less than 12 years and 12 years or more. **Socioeconomic status (SES)** was measured based on the occupation of sociological father using the socio-economic index (SEI) developed by Blishen and McRoberts for occupations in Canada.[190] SES was grouped into two groups: low (SEI<30) and median or high (SEI≥30). The information on **Maternal race** was obtained from the hospital records. Since the majority of mothers were Caucasian, the maternal race was only categorized into two groups: Caucasian and non-Caucasian.

3.4 DATA MANAGEMENT

The data for this study were in two files in the ACH Perinatal Follow Up Program database: 1) the perinatal data which were collected from mothers' and infants' health records before infants were discharged from NICU, and 2) the follow-up data which were collected at each follow-up visit. Since each infant was identified by the same unique identification number in both files, the two files were linked to form a data set for the present analyses.

The extreme values were identified for growth measurements and potential contributing factors. Original records were checked if unreasonable values were found by examining the observed range of values for each variable and the scatter plots of growth measurements against age and other measurements. Corrections were made if a value in the data set was found to be different from that in the original record.

The variables are coded as following:

For the variables of clinical conditions such as BPD, NEC, CP, neonatal apnea, sepsis, SGA and PDA, the presence of the condition was coded 1 and absence was 0. Maternal age 20 years or younger was coded 1, otherwise 0. Blishen and McRoberts index below 30 was coded 1, otherwise 0. The original measurements were used for the variables of birth weight, gestational age and mid-parental height. For gender, boys were coded 1 and girls were coded 0. For the exploring purpose, the continuous variables such as birth weight, mid-parental height, FGR, maternal age, number of days of acute NICU stay and year of birth were categorized into different groups, see Chapter 4 for details.

3.5 Data analyses

3.5.1 Outline of the analyses

Step 1: Basic descriptive analysis

- Characteristics of VLBW survivors
- Comparison between study sample and VLBW infants who were not selected
- Relations among the potential contributing factors

Step 2: Average growth levels of the study sample

- Mean Z-scores relative to different references
- Prevalence of subnormal growth relative to different growth references
- Mean Z-score based on adjusted and unadjusted ages
- Prevalence of subnormal growth based on adjusted and unadjusted ages

Step 3: Exploratory analysis of the determinants of growth in VLBW infants

Step 4: Mixed effects models

- Basic models
- Gender specific growth models
- Models including covariates

Step 5: Predicting growth of infants who were not included in the present study

Step 6: Predictors of subnormal growth at three years of age

- Comparison of levels or frequency of potential determinants between subnormal and normal infants.

- Logistic regression models.

Step 7: Predictors of subnormal growth during the observed period: Generalized estimating equation (GEE) approach.

3.5.2 Basic descriptive analyses

The Characteristics of the study sample were compared with those of infants who were not selected for the present study. For continuous variables, 95% confidence intervals of the differences between the study sample and the infants who were not selected were calculated. The Chi square tests were conducted to test the differences between two groups for categorical variables.

3.5.3 Average growth status

In order to describe the growth status of VLBW infants at different ages, Z-score transformations were made. A Z-score (standard deviation score) is the deviation of an individual's value from the median value of a reference population, divided by the standard deviation in the reference population:

Z-score= (observed value)-(median reference value)/(standard deviation of reference population)

A fixed Z-score implies a fixed height or weight difference for children of a given age. For population-based applications, a major advantage of Z-score transformation is that it allows the mean and standard deviation to be calculated for a group of Z-scores. A mean Z-score represents the average difference of growth measurements of VLBW population

and the median of the reference population in the unit of standard deviation. Therefore, the change of mean Z-score over age allows us to assess the change of growth status of VLBW infants over age during the observational period. Two reference populations were used for the present study. One was the NCHS/WHO growth data, since it has been recommended as a reference for international comparisons by WHO Expert Committee.[61] Also this reference has been used in some clinical settings to identify growth problems in infants. The other one was the growth reference based on Canadian data,[12] since it might be more comparable to the study sample in terms of social demographic characteristics than the NCHS/WHO growth data. The differences between these two growth references are discussed in Chapter 5.

An anthropometrical package Epi Nut in Epi Info[191] was used to make the Z-score transformation against the NCHS/WHO reference. The growth indices for the present analysis were weight-for-age and length-for-age. Length-for-age reflects achieved linear growth and its deficits indicate long-term, cumulative inadequacies of health or nutrition. Low length-for-age is described as "Shortness" or "Stunting". Weight-for-age reflects body mass relative to age. "Lightness" and "underweight" have been used as descriptive terms for low weight-for-age. Shortness and lightness imply nothing about the reason for an individual's being "low"; while stunting and underweight imply that the "low" is pathological. The cutoff point of less than -2 SD (or Z-score less than -2) was used to calculate proportions of infants with low length-for-age and low weight-for-age.

The Z-score transformations against Canadian growth data was only done up to 18 months of age, since the maximum age in the reference data was 18 months. The mean Z-score values for age groups were calculated and plotted against age. The growth outcomes of study sample assessed using different growth references were compared.

In addition to the NCHS/WHO and the Canadian growth references, the WHO "growth reference for breastfed infants" was also used for the purpose of comparisons. Because the age range in this reference is only up to 12 months, the growth outcomes assessed using this reference cannot be obtained for infants older than 12 months of age.

The above analyses were based on the adjusted age (adjusting for prematurity) of preterm infants. To assess the necessary period for age adjustment, the mean Z-scores of growth measurements and the proportions of subnormal growth were also calculated based on chronological ages. The growth outcomes assessed with adjusted and unadjusted ages were compared. The mean Z-scores and proportions of subnormal growth were compared between two outcomes estimated using adjusted and unadjusted ages.

3.5.4 Associations between potential factors, growth level and growth rate

3.5.4.1 Exploratory analysis

Infants were categorized into different groups according to the level of each of factors such as birthweight, intrauterine growth status, parental height, maternal age, maternal education, the presence of BPD, CP or NEC and so on. The mean Z-scores of growth measurements were calculated for each group. These mean Z-scores and their

95% confidence intervals were presented graphically. No statistical tests were made and no attempts were made to consider the confounding effects of other factors. Since infants were grouped by a single variable and no statistical tests were made in this analysis, the associations observed might be attributable to the confounding effects of other factors (confounders) or simply to random errors. The information provided in this analysis was important for further modelling procedures.

3.5.4.2 Mixed effects growth models

Mixed effects models were fitted to assess the effects of perinatal and parental factors on postneonatal growth, while the effects of covariates were taken into consideration. First, basic models were fitted to describe the average growth patterns of VLBW infants. Second, mixed effects growth models including gender were fitted to compare the average growth patterns of VLBW infants with those of growth references, which were gender specific. Also, the relations between gender and the postneonatal growth in length and weight were described in these models. Third, the mixed effects models, each including only one variable besides age and sex, were fitted to determine how each factor was associated with postneonatal growth while no confounding effects of other factors except gender were considered. This analysis should be able to replicate the results from previous exploratory analyses but provide more objective results on the relation between a factor and the postneonatal growth. Since over 20 variables were explored in this study, only the variables which were suspected to be associated with

postneonatal growth from the results of the previous exploratory analyses were included. Finally, the detailed relationship between a potential factor and postneonatal growth was described while the confounding effects of other factors were considered in the analysis. The interaction terms among potential factors were tested in the model to examine the assumption of the independence, that is that the effect of a factor on postneonatal growth does not depend on the values of other factors.

3.5.4.2.1 Basic growth models

A mathematical formula expressing the relation between age and growth was established for VLBW infants as a group. Although several attempts had been made to apply mathematical models to human growth in the literature,[12,129-132] they mainly focused on the growth of normal term infants. It was unknown which model was appropriate to describe the growth of VLBW infants in this study. Karlberg's growth model for infants includes two components: the infant component and the childhood component. The age at which the growth model shifts from the infant component to the childhood component occurs between 4 and 12 months of age.[131] Since the intervals of measurements were relatively wide in this study, the age of change from the infant component to the childhood component could not be identified. Therefore, Karlberg's model was not used for this study. The components in Table 2-1 were used to build the basic models. Each component was considered as a candidate component to enter into the model. Based on the likelihood ratio tests in the mixed effects models,[28,29] the basic

models that were developed to express the relationship between age and postneonatal growth.

In order to compare findings with growth references, which were sex specific, an indicator of gender was incorporated into the basic models. The gender specific growth curves predicted from basic growth models represented the estimated average growth level of boys and girls in the study sample. These growth curves were compared with both the NCHS/WHO and Canadian growth references.

3.5.4.2.2 Linear mixed effects models including determinants (covariates)

The details of fitting and analyzing mixed effects models have been described in the literature.[25-28] Based on the basic models, each potential determinant of growth was incorporated into the models. Selection of factors depended on the results from the previous bivariate analyses. To consider the confounding effects of other factors, a model was fitted for each growth measurement including explanatory variables which had significant contributions to the postneonatal growth while the confounding effects of other factors were taken into consideration.

An example of the mixed effects model for the data can be written as

$$Weight_{it} = (\beta_0+\beta_{01} Sex +\beta_{02} BW + \beta_{03} MPH + \beta_{04} BPD+ \beta_{05} CP + ...+ b_{i0})+ (\beta_1 + \beta_{11} Sex +\beta_{12} BW + \beta_{13} MPH + \beta_{14} BPD+ \beta_{15} CP + ...+ b_{i1})* Age_t + (\beta_2 + \beta_{21}Sex +\beta_{22}BW + \beta_{23} MPH + \beta_{24} BPD+ \beta_{25} CP + ...)*log(Age_t) + e_{it}$$

Where the dependent variable is the growth measurement for an individual *i* at a certain age *t*. The βs are fixed effects which provide estimates of the average response to independent variables. The "b"s are random effects which allow individuals to have different growth curves. The "e" is within subject error. Those interaction terms between age and factors are included to allow different groups of infants to have different growth curves or growth rates.

Estimation of the parameters in the model was carried out using a restricted maximum likelihood (REML) estimation procedure described by Linstrom and Bates.[28]The use of REML allows for the unbiased estimation of all the effects in the model, even though individuals may have different numbers of repeated observations. To explore if the effects of one factor depend on the level of the other factors, various second degree interaction terms were tested in the model. Tests of significance of individual covariates in the model were obtained by likelihood ratio tests. Inclusion of a variable and its interaction term with other variables in the model depended on the P values of the Likelihood Ratio test (the drop of deviance). Variables with P values less than 0.05 remained in the final model. If an interaction term of two variables was included in the model, both main effect terms would be included.

The appropriateness of the model was assessed by examining the distribution of the residuals and the estimates of random-effects components from the model. Plots of the residuals versus the fitted values and observed values versus fitted values were used to identify single outlier observations.

3.5.5 Predictors of subnormal growth

Of particular interest to clinicians is the outcome of the shortest and lightest infants. To determine the variables that might predict whether a VLBW infant would be subnormal in growth at age 3 years, infants were divided into two groups: subnormal and normal in growth measurements. The characteristics of infants were compared between two groups to explore the relations between factors and subnormal growth. The relation between each factor and subnormal growth were further analyzed with logistic regressions. In the logistic regression model, the dependent variable was an indicator of subnormal growth at 3 years. Inclusion of a variable into the model depended upon the change of the residual deviance by adding the variable in the model.

Both fitting procedures of mixed effects models and logistic regression models were performed using statistical software S plus version 3.3 in the SUN UNIX system at the Department of Community Health Sciences, the University of Calgary. Epi Info Version 6.04 was used for data management and Z-score transformations.

To assess the associations between potential factors and subnormal growth during the observational period, the GEE (generalized estimating equations) approach, a generalized linear model for dependent data,[30] was used to estimate the odds ratios of subnormal growth based on all the data available in the study sample. The logit link function was used. Different correlation structures were utilized. No substantial different coefficients were obtained using different correlation structures. The results of using the

"exchangeable" correlation structure were presented. The regression coefficients of GEE approach in this study have the same interpretation as coefficients from a logistical regression for cross-sectional data. The change of the association between factors and subnormal growth with age could be explored.

CHAPTER FOUR: RESULTS

4.1 DESCRIPTION OF THE STUDY SAMPLE

4.1.1 Perinatal characteristics of the study sample

Characteristics of the total 1007 VLBW infants who survived to discharge from NICU during January 1977 to May 1992 are presented in Table 4-1 to Table 4-3. The characteristics of the study sample compared with those of infants who were not included in this study, are listed in Table 4-4 to Table 4-6.

Table 4-1 The characteristics of total VLBW infants discharged from NICU: Means

	Mean	SD	Infants with data available (%)
Birthweight, (g)	979.1	185.5	1007 (100)
Gestational age (wk.)	28.1	2.4	1007 (100)
Ponderal index	2.14	0.26	983 (97.6)
Maternal age (yr.)	26.4	5.4	1005 (99.8)
Maternal school (yr.)	12.8	2.6	723 (71.8)
Blishen index	43.3	15.5	770 (76.5)
Acute NICU stay (days)	45.0	34.1	1006(99.9)
Total hospital stay (days)	81.6	43.6	996 (98.9)
Mid-parental height (cm)	170.3	5.6	639 (63.5)

Table 4-2 The characteristics of total VLBW infants discharged from NICU: Proportions

	Proportions %	95% CI	Infants with data available (%)
Male	49.2	46.0, 52.3	1007 (100)
Apgar score less than 6:			
at 1 minutes	75.2	72.4, 77.9	984 (97.7)
at 5 minutes	21.2	18.8, 24.0	994 (98.7)
Race, Non-Caucasian	13.5	11.9, 16.4	970 (96.3)
SGA	25.1	22.4, 27.9	1007 (100)
Asymmetric (PI<10th centile)	14.9	12.7, 17.2	983 (97.6)
Multiple birth	21.1	18.6, 23.7	1007 (100)
Antenatal steroids used	53.3	50.2, 56.5	992 (98.5)
Primarily breastfed at NICU	58.1	55.0, 61.2	1007 (100)
BPD	29.1	27.0, 32.8	982 (97.5)
Jaundice	98.9	98.2, 99.5	1006 (99.9)
Necrotizing enterocolitis	17.7	15.4, 21.2	1001 (99.4)
PDA	36.8	33.8, 39.8	1006 (99.9)
RDS	67.2	64.2, 70.1	1006 (99.9)
Sepsis	17.2	14.9, 19.7	1006 (99.9)
Seizures	3.1	2.1, 4.3	1007 (100)
Apnea	69.4	66.0, 71.8	1006 (99.9)
Low SES (SEI < 30)	26.6	23.5, 29.9	770 (76.5)
Maternal education (< 12 yr.)	23.8	20.7, 27.1	723 (71.8)
Maternal education (< 12 yr.)[a]	17.9	15.0, 21.0	626 (62.2)
Born during 87-92	40.7	42.4, 48.6	1007 (100)

a: Based mothers who were older than 20 yr.

Table 4-3 The characteristics of total VLBW infants discharged from NICU: Medians

	Median	Infants with data available (%)
TPN (days)	8	1006 (99.9)
Days on O_2	36	1004 (99.7)
IPPV (days)	10	989 (98.2)
Acute NICU stay (days)	39	1006 (99.9)
Total hospital stay (days)	76.5	996 (98.9)

Table 4-4 Characteristics of the study sample compared with infants who were not included in the study: Means and medians

	Study sample			Unselected infants			
Total number of infants		514			493		
	Mean	SD	No.	Mean	SD	No.	95% CI of difference
Birthweight, (g)	954.6	185.9	514	1004.6	187.7	493	-73.1, -26.9
Gestational age (wk.)	27.7	2.3	514	28.4	2.4	493	-0.9, -0.4
Ponderal index	2.14	0.26	501	2.14	0.27	482	-0.03, 0.04
Maternal age (yr.)	27.6	5.2	514	25.2	5.2	491	1.8, 3.1
Maternal school (yr.)	13.1	2.4	475	12.1	2.8	248	0.6, 1.4
Blishen index	44.9	16.0	462	40.8	14.4	308	1.9, 6.4
Total birthweight loss (g)	133.9	61.5	513	130.0	65.6	493	-4.1, 11.6
Acute NICU stay (days)	45.6	32.85	514	44.5	35.4	492	-3.1, 5.4
Total hospital stay (days)	87.3	35.9	512	75.5	49.7	484	6.5, 17.3
Mid-parental height	170.4	6.1	430	170.1	5.6	209	-0.7, 1.3

Table 4-5 Characteristics of the study sample compared with infants who were not included in the study: Proportions

	Study sample		Unselected		
	Proportion %	No.	Proportions %	No.	P value[a]
Male	48.1	514	50.3	493	0.47
Apgar score less than 6:					
at 1 minutes	73.6	504	76.9	480	0.26
at 5 minutes	20.6	509	21.9	485	0.64
Race, Non-Caucasian	11.5	505	16.8	465	0.018
SGA	23.4	514	26.8	491	0.21
Asymmetric at birth	14.0	501	15.8	482	0.43
Multiple birth	21.4	514	20.7	493	0.78
BPD	32.7	502	26.9	480	0.047
Jaundice	98.8	513	99.2	493	0.75
Necrotizing enterocolitis	15.0	512	20.4	489	0.025
PDA	42.2	514	31.1	492	0.0003
RDS	69.1	514	65.4	492	0.22
CP	7.8	513	-	-	-
Sepsis	19.3	514	15.0	492	0.076
Seizures	3.3	514	2.8	493	0.67
Apnea	71.4	514	66.5	492	0.09
Low SES (SEI <30)	23.2	462	31.8	308	0.0078
Primarily breastfed[b]	61.1	514	55.0	493	0.049
Antenatal Steroid use	55.8	509	50.7	483	0.11
Maternal educ. (< 12 yr.)	16.6	475	37.5	248	<0.00001
Maternal educ. (<12 yr.)[c]	12.8	429	28.9	197	<0.00001
Born during 87-92	56.8	514	33.7	493	<0.00001

a: P values of Chi square test or Fisher's exact test. b: Primarily breastfed at during the NICU stay. c: Based mothers who were older than 20 yr.

Table 4-6 Characteristics of the study sample compared with infants who were not included in the study: Medians

	Study sample		Unselected	
	Median	No.	Median	No.
TPN (days)	9.0	514	7.0	492
Days on O_2	43.0	513	26.0	491
IPPV (days)	15.0	510	7.0	479
Acute NICU stay (days)	39	514	39	492
Total hospital stay (days)	83.5	512	69.0	484

Compared with infants who were not selected for the present study, the study sample represents VLBW infants with lower birth weights, shorter gestational ages, and longer duration of hospital stay and longer duration of other treatments such as total parenteral nutrition (TPN), intermittent positive pressure ventilation (IPPV) and Oxygen therapy. Infants selected for the present study have a higher prevalence of BPD and PDA, and a lower prevalence of NEC than infants who were not selected. The mothers of infants in the study sample tend to be older with higher education and a higher social-economic status.

4.1.2 Intrauterine growth status

The relations among birthweight, gestational age and IUGR were explored, see Figure 4-1. Since the study population only included infants with birthweight 1,250 grams or less, all the infants with gestational age 32 weeks or longer were classified as

small for gestational age (SGA). When studying the association of IUGR and postneonatal outcomes, the outcomes of AGA and SGA infants are usually compared in the literature. What we actually do in a population of VLBW infants is to compare a group of infants with another group of infants who have different gestational ages and different birth weights. The interpretations of results from such direct comparisons are not straight forward, since the effects of intrauterine growth status and maturation are mixed together. Various epidemiological and statistical techniques can be used to control for the confounding effects. For example, a stratified analysis can be done to compare the growth outcomes of SGA and AGA infants with the same gestational age or with the same birth weight.[23]

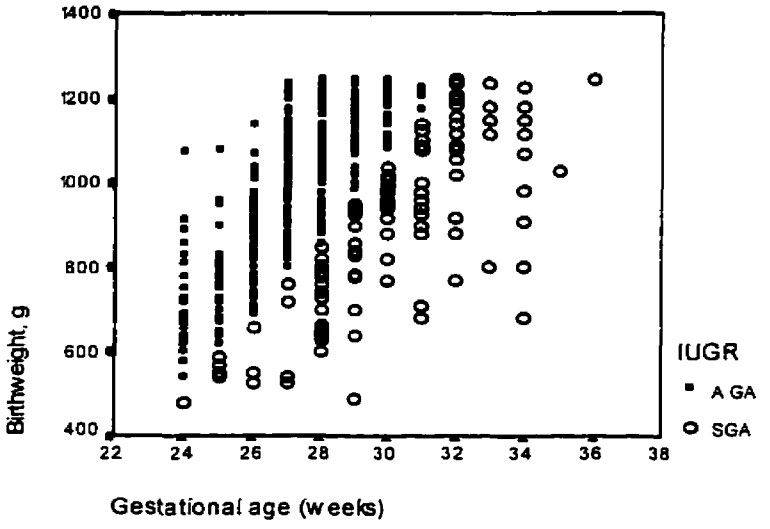


Figure 4-1 Birth weight, gestational age and intrauterine growth status

As shown in Figure 4-1, the birth weight, a continuous variable, is used to divide infants into two groups arbitrarily by a single cutoff point of each gestation. It is obvious

that birth weights vary a lot within each group. The classification by one cut-off point may not be able to capture the complete information of the intrauterine growth status in VLBW infants.

To measure the severity of intrauterine growth retardation, the fetal growth ratio (FGR), birth weight over the median of the reference, was calculated. The distribution of FGR was close to normal, see Figure 4-2. No evidence of bimodality or the existence of two distinct groups of infants were seen. According to Kramer's classification,[53,192] the infants with 0.80-<0.85 of FGR are defined as mildly retarded, 0.75-<0.80 moderately and <0.75 severely retarded growth. Although 0.85 of FGR is similar to the 10th percentile of the intrauterine growth reference for term infants,[53] for VLBW infants in this study this cut-off point represents a much higher percentile. Using the 10th percentile of Lubchenco intrauterine growth curves as cut-off point, 23.4% infants were classified as SGA, while 60.2% infants would be classified as SGA by using 0.85 of FGR as the cut-off, see Table 4-7. Therefore, different cutoff points from Kramer's study were used in the present study to categorize the severity of IUGR. FGR 0.60-<0.70 was defined as mild, 0.50-<0.60 as moderate and <0.50 as severe intrauterine growth retardation. The mean birth weights and gestational ages for each group of infants according to the severity of IUGR are shown in Table 4-8. The more severe the IUGR of an infant is, the longer the gestational age is. Birth weight also has a tendency to decrease with the severity of IUGR.

Table 4-7 Distribution of severity of IUGR in VLBW infants based on Kramer et al.'s classification[53]

FGR*	Severity of IUGR	Frequency	Percent	Cum. Percent
<0.75	Severe	174	34.0	34.0
0.75-<0.80	Moderate	61	11.9	45.9
0.80-<0.85	Mild	73	14.3	60.2
0.85+	Normal	204	39.8	100.0

* FGR: Fetal growth ratio

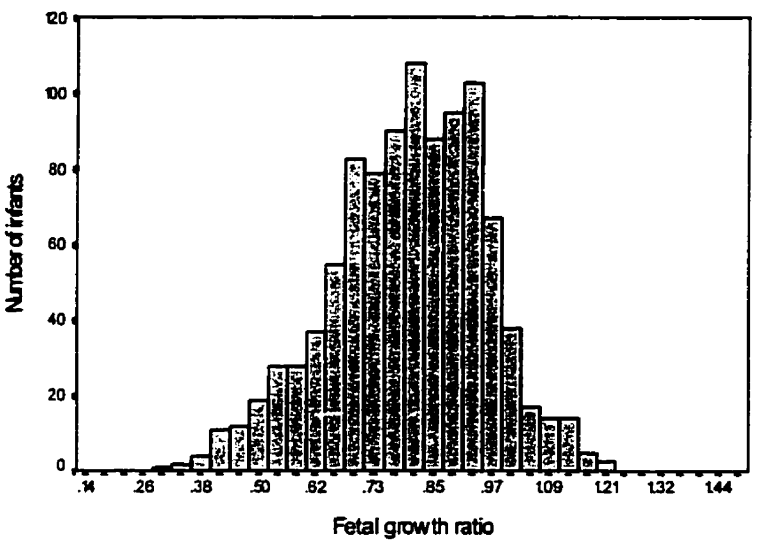


Figure 4-2 Distribution of fetal growth ratio in VLBW infants

Table 4-8 Distribution of severity of IUGR in VLBW infants based on fetal growth ratios (FGR)

FGR	Severity	Frequency (%)	Birthweight, g Mean (SD)	Gestational age, wk. Mean (SD)
<0.50	Severe	39 (3.9)	853.0 (262.7)	32.3(3.2)
0.50-<0.60	Moderate	71 (7.1)	844.9 (221.2)	30.0(3.0)
0.60-<0.70	Mild	141 (14.1)	881.4 (197.7)	28.7(2.7)
0.70+	Normal	750 (74.9)	1019.8 (158.1)	27.6(1.7)

4.1.3 Body proportionality

Infants were classified into two groups according to their body proportionality at birth. About 28.9% of SGA infants were asymmetric (below 10th percentile of ponderal index in Lubchenco's data) and 10.3% of AGA infants were asymmetric, see Table 4-9. The proportion of asymmetric infants increased with severity of intrauterine growth retardation Table 4-10.

Table 4-9 Body proportionality and IUGR in VLBW infants*

IUGR	Asymmetric No. (%)	Symmetric No. (%)	No. of infants
SGA	70 (28.9%)	172 (71.1%)	242
AGA	76 (10.3%)	659 (89.7%)	735

* P value of Chi square test for the differences between SGA and AGA is less than 0.0001.

Table 4-10 Body proportionality and severity of IUGR in VLBW infants

IUGR	Body proportionality at birth		No. of infants
	Asymmetric No. (%)	Symmetric No. (%)	
Severe	14(37.8%)	23 (62.2%)	37
Moderate	23(33.8%)	45 (66.2%)	68
Mild	30(21.7%)	108(78.3%)	138
Normal	79(10.8%)	655(89.2%)	734

The relations between body proportionality and birth weight, birth length and gestational age are presented in Table 4-11. The asymmetric infants are heavier, longer and more mature than symmetric infants in both SGA and AGA groups. The body proportionality is associated with the intrauterine growth status and maturation of neonates. Whether body proportionality provides extra information which is not provided by birth weight and gestational age for predicting postneonatal growth outcomes of VLBW infants needs to be determined by modeling procedures, in which the effects of birth weight and gestational age could be controlled.

Table 4-11 Birth weight, birth length, gestational age and body proportionality in VLBW infants

	Asymmetric			Symmetric			
	Mean	SD	No.	Mean	SD	No.	P value*
Birth weight							
SGA	964.5	214.7	70	894.3	204.0	172	0.018
AGA	1081.6	150.5	76	996.0	172.3	659	<0.001
Birth length							
SGA	37.5	3.0	70	34.3	2.8	172	<0.001
AGA	39.4	2.0	76	35.6	2.4	659	<0.001
Gestational age							
SGA	31.0	2.8	70	29.9	2.5	172	0.003
AGA	28.4	1.7	76	27.3	1.7	659	<0.001

* Two tail t-test for the differences between asymmetric and symmetric infants.

4.1.4 Relations among the potential factors

To explore the associations among the potential influencing factors, two examples were given: relations between 1) the presence of BPD and 2) antenatal steroids with other factors.

4.1.4.1 Relations between BPD and other clinical conditions

The proportions of clinical conditions and other characteristics of infants with BPD and without BPD are presented in Figure 4-3, the comparisons of mean values are in Table 4-12. The BPD infants are more likely to have other adverse clinical conditions.

They also tend to be lighter and more premature at birth. Therefore, when exploring the impact of BPD on postneonatal growth, we should take the confounding effects of other factors into account by modeling procedures.

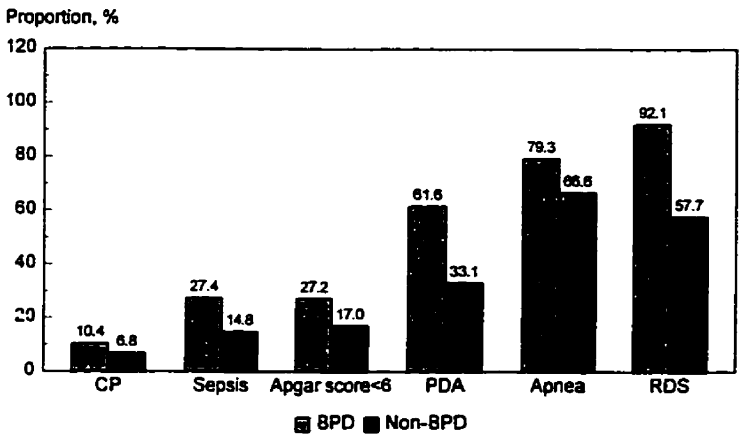


Figure 4-3 Proportion of clinical conditions among infants with and without BPD

Table 4-12 Characteristics of VLBW infants with and without BPD

	BPD infants		Non-BPD infants		P value
	Mean	SD	Mean	SD	
Birth weight, g	847.9	191.1	1007.1	160.8	<0.001
Gestational age, wk.	26.7	2.0	28.3	2.3	<0.001
Ponderal index	2.17	0.26	2.13	0.26	0.06
Maternal age	27.7	5.2	27.5	5.1	0.70
Acute ICU stay, days	71.9	29.8	32.4	25.0	<0.001
Mid-parental height, cm	169.8	4.8	170.7	6.6	0.15
Number of infants	164		338		

4.1.4.2 Relations between antenatal steroid therapy and other factors

Infants with antenatal steroid therapy were found to have significantly higher birth weight than infants without antenatal therapy, see Table 4-13. The use of antenatal steroids was found to be associated with maternal age. The mothers who were younger than 21 years old were less likely to receive antenatal steroids than the mothers who were older than 20 years. Infants who received antenatal steroid therapy had a significantly lower prevalence of BPD than those without the use of antenatal steroids. Infants with the use of antenatal steroids had a slightly lower prevalence of CP and NEC but the differences had no statistical significance, see Table 4-14.

Table 4-13 Characteristics of infants with and without antenatal steroid therapy: means

	Infants with antenatal steroids			Infants without antenatal steroids			
	Mean	SD	No.	Mean	SD	No.	95% CI of Difference
Birthweight, (g)	970.4	176.7	284	932.1	195.9	225	5.7, 70.7
Gestational age (wk.)	27.9	2.1	284	27.6	2.5	225	-0.1, 0.7
Mid-parental height, cm	170.3	5.7	244	170.5	6.5	182	-1.3, 1.0

Table 4-14 Characteristics of infants with the antenatal steroid therapy: prevalence %

	Infants with antenatal steroids	No.	Infants without antenatal steroids	No.	P value [a]
Male	49.3	284	47.1	225	0.62
Maternal age <21	7.4	284	12.9	225	0.038
CP	6.3	284	9.4	225	0.20
BPD	26.6	278	40.2	219	0.0013
NEC	14.4	284	15.7	223	0.69

a: P values of chi square test or Fisher exact test.

4.2 Description of growth status for VLBW infants

4.2.1 Mean Z-scores relative to NCHS/WHO and Canadian growth references

The mean Z-scores and 95% confidence intervals relative to the NCHS/WHO and the Canadian references at each age group were calculated. Using the NCHS/WHO reference, the mean Z-scores increased with age for length and decreased from 4 to 12 months of age and increased afterward for weight. Using the Canadian reference, mean Z-scores for both length and weight increased with age, see Figure 4-4 and Figure 4-5. Throughout the observational period, the Z-scores were lower than 0, indicating that the average growth levels were lower than the mean levels of either growth reference.

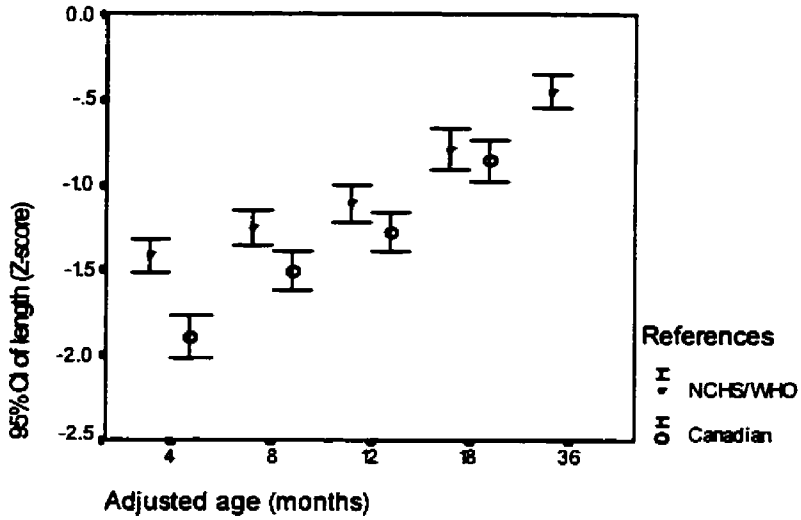


Figure 4-4. Mean Z-scores of growth measurements in VLBW infants, relative to different references: Length

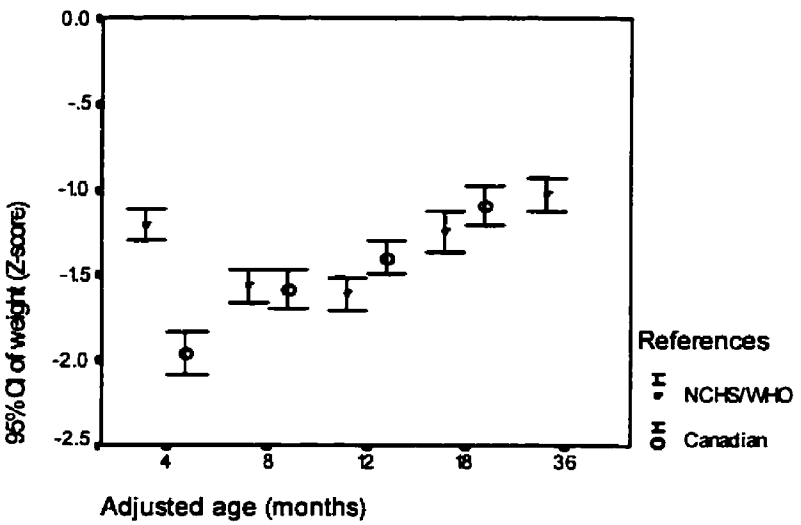


Figure 4-5 Mean Z-score of growth measurements in VLBW infants, relative to different references: Weight

4.2.2 Mean Z-scores relative to growth references for VLBW infants

To compare growth status of the study sample with those of VLBW infants in USA, the mean Z-scores relative to the reference for VLBW infants reported by Casey et al[7] were also calculated, see Figure 4-6. Mean Z-scores relative to the reference for VLBW infants is slightly lower than zero. The average growth level of the study sample was lower than that of the reference population from eight centers in USA.

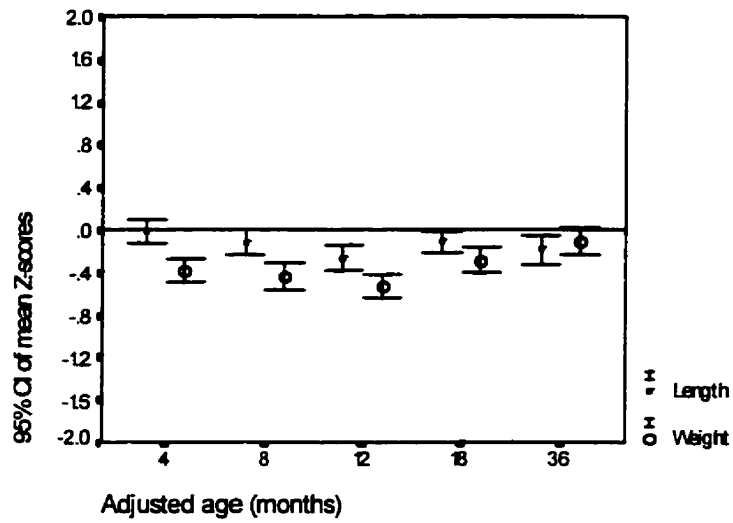


Figure 4-6 Mean Z-scores relative to growth reference for VLBW infants[7]

4.2.3 Prevalence of subnormal growth in VLBW infants

The prevalence of subnormal growth defined by a growth measurement less than the median minus 2 SD of the growth references or Z-score less than -2 is presented in Figure 4-7. Since the Canadian growth reference data are only available until 18 months and the

WHO reference for breastfed infants until 12 months, the estimation of growth status using these references were not made after the above periods.

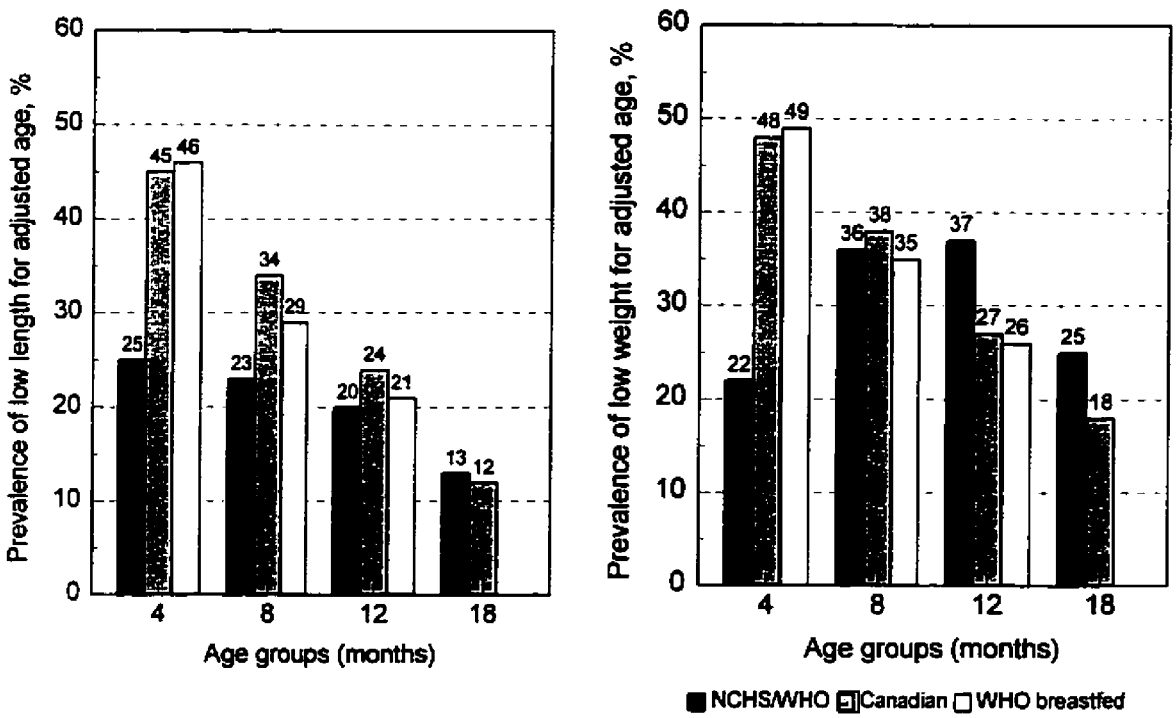


Figure 4-7 Prevalence of subnormal growth in VLBW infants estimated by using different growth references

There were no significant differences between the estimated prevalence of subnormal growth determined using the Canadian reference and WHO reference for breastfed infants. The estimated prevalence by the NCHS/WHO reference was lower than that estimated by either of the other two references at 4 months for underweight and at 4 and 8 months for stunted, with statistical significance ($p<0.05$ based on Chi square test). There were no statistically significant differences in estimated prevalence of stunted growth

between using the Canadian reference and the NCHS/WHO reference at 12 and 18 months of adjusted age. More infants were identified as underweight at 12 and 18 months of age using the NCHS/WHO reference than using the Canadian reference, with $p < 0.05$ based on Chi square tests.

4.2.4 Age adjustment for prematurity and growth assessment

4.2.4.1 Mean Z-scores based on chronological age and adjusted age

The NCHS/WHO reference was used for comparing the growth status of VLBW infants assessed by using chronological and adjusted ages, since it covers the age range of the present study sample. The mean Z-scores and 95% confidence intervals based on chronological and adjusted ages are presented in Figure 4-8. The mean Z-scores based on adjusted age were always closer to zero, the average level of the reference population, than were scores based on chronological age. The adjusted estimate of Z-score was higher than the unadjusted estimate at every age group in both length and weight. Although the difference became smaller as infants grew older, it remained statistically significant up to 36 months adjusted age (p values based on t-tests were <0.001).

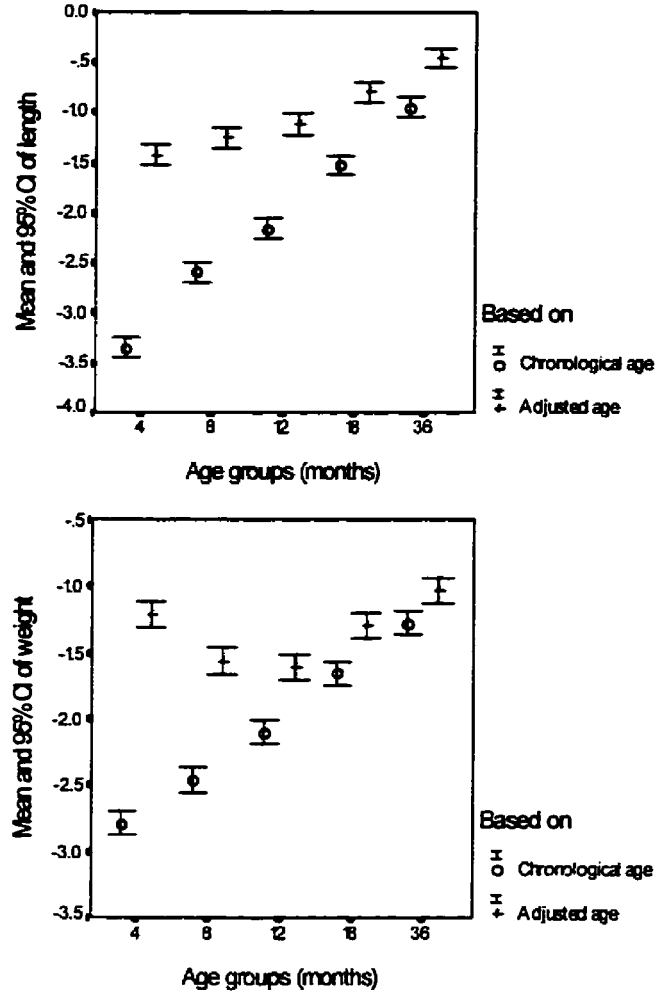


Figure 4-8 Mean Z-scores based on chronological and adjusted ages in VLBW infants

4.2.4.2 Prevalence of subnormal growth based on chronological age and adjusted age

The prevalence of subnormal growth estimated using both adjusted and unadjusted age is shown in Figure 4-9. A substantially higher proportion of infants were labeled as "subnormal growth" (<-2SD of median) when assessed based on the chronological age than on the adjusted age, especially in early age groups for both length and weight. For length, about 91% vs. 25%, 73% vs. 23%, 53% vs. 20, 31% vs. 13%, and 14% vs. 7% of

infants were labeled as stunted based on chronological age vs. adjusted age at 4, 8, 12, 18, and 36 months adjusted ages, respectively; and the corresponding values for underweight were 79% vs. 23%, 71% vs. 36%, 55% vs. 38%, 40% vs. 26%, and 26% vs. 16%. The difference between adjusted and unadjusted prevalence of either stunted or underweight had statistical significance with p values < 0.001 at each age group based on Chi square test.

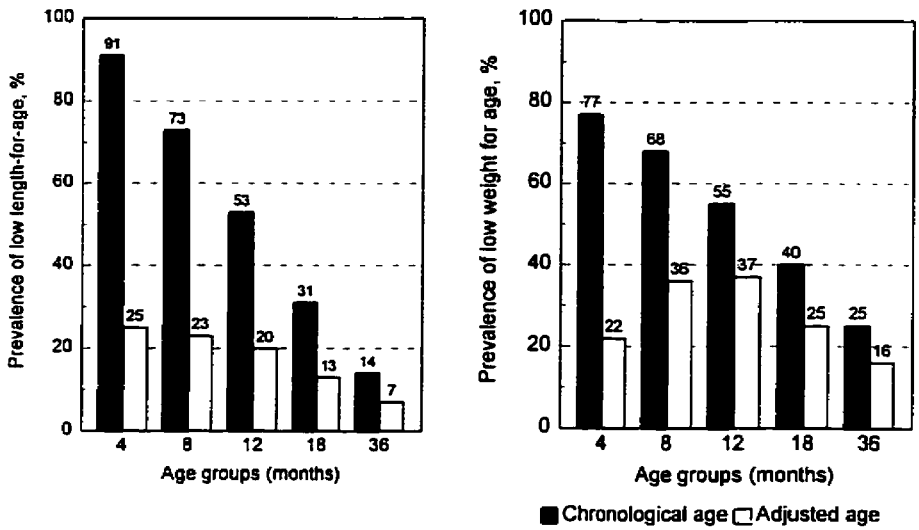


Figure 4-9 Prevalence of subnormal growth based on chronological and adjusted age in VLBW infants

4.3 EXPLORATORY ANALYSIS OF DETERMINANTS OF POSTNEONATAL GROWTH

Bivariate relations between potential determinants and postneonatal growth (Mean Z-scores) were explored graphically. These graphs were only preliminary analyses, in which no statistical significance tests were made and no confounding effects were taken into account. In these analyses, the crude associations between potential factors and

postneonatal growth were explored. The results provide information for the further analyses of modelling procedures.

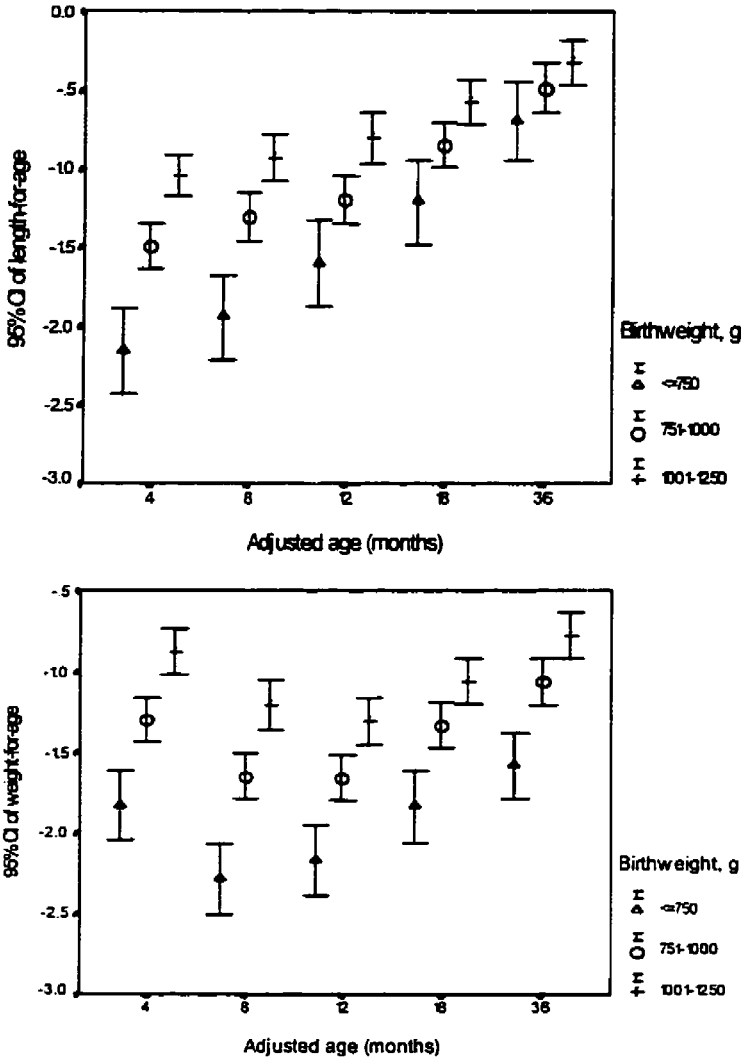


Figure 4-10 Birthweight and Z-scores for length and weight in VLBW infants

4.3.1 Birth weight

Mean Z-scores of weight and length were calculated for infants in different categories of birth weight, see Figure 4-10. Infants with lower birth weights tend to be

shorter and lighter during infancy than infants with higher birth weights. However, the differences in length among different birth weight groups become smaller as infants grow.

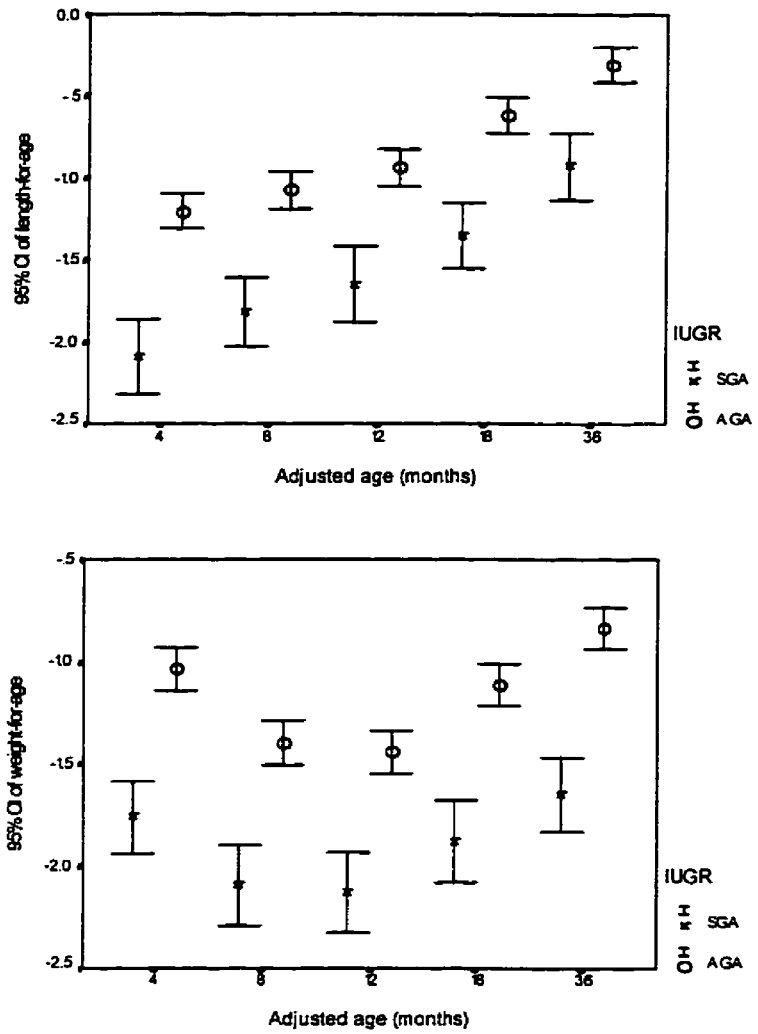


Figure 4-11 Intrauterine growth retardation and Z-scores for length and weight in VLBW infants

4.3.2 Intrauterine growth status and body proportionality at birth

The average level of SGA infants in either length or weight was found to be lower than that of AGA, see Figure 4-11. The postneonatal growth and severity of IUGR expressed by the FGR are presented in Figure 4-12.

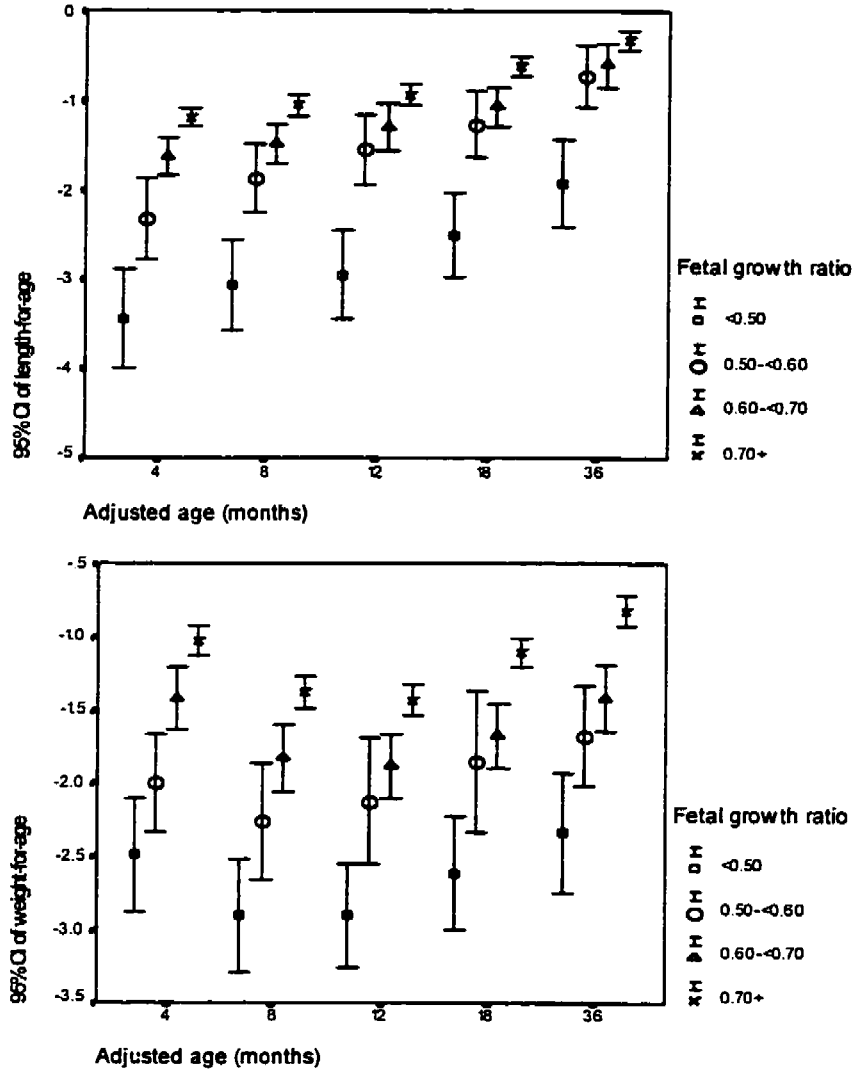


Figure 4-12 Severity of intrauterine growth retardation and Z-scores for length and weight in VLBW infants

The postneonatal growth status appears to depend on the severity of intrauterine growth retardation. The most severely retarded infants have the lowest mean Z-scores in both length and weight. For both SGA and AGA infants, those infants with asymmetrical body shape at birth were taller and heavier than their symmetrical counterparts, see Figure 4-13.

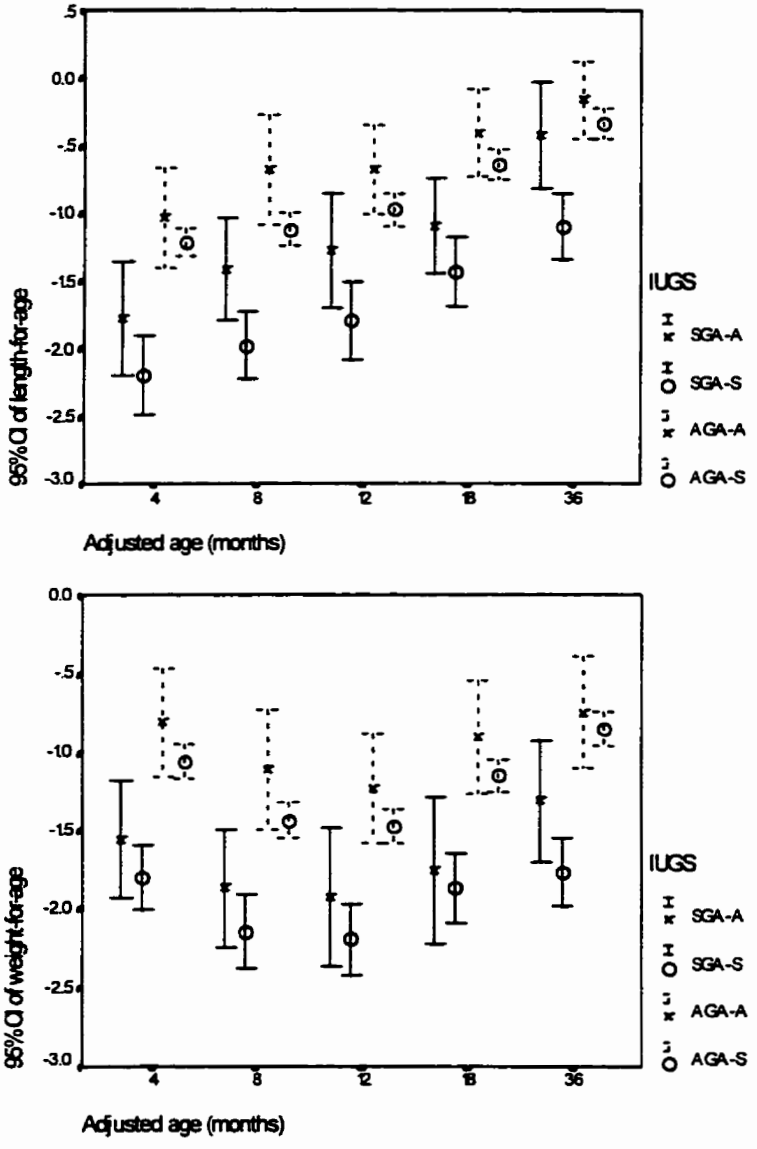


Figure 4-13 Body proportionality and Z-scores for length and weight in VLBW infants

4.3.3 Parental height

Infants were classified into three groups according to their mid-parental heights. Infants in the higher mid-parental height group were taller and heavier than those in the shorter mid-parental height groups. The differences became more obvious as infant grew for both length and weight, see Figure 4-14.

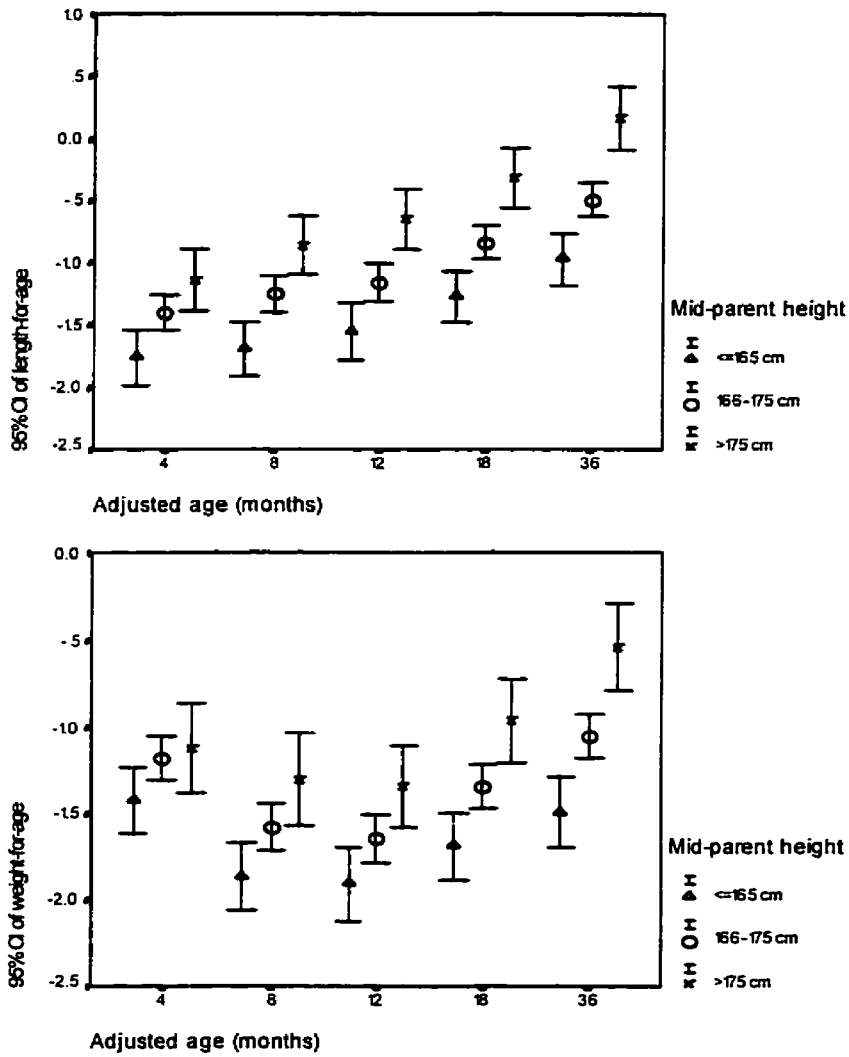


Figure 4-14 Mid-parental height and Z-scores for length and weight in VLBW infants

4.3.4 Some clinical conditions

Figure 4-15 to Figure 4-22 present the bivariate associations between some clinical conditions and the postneonatal growth in VLBW infants. Infants with BPD were shorter and lighter than those without BPD during infancy. The infants who had cerebral palsy were shorter and lighter than those without cerebral palsy, but there was a large overlap for weight. Obvious lower Z-scores were found for infants with necrotizing enterocolitis (NEC) than those without NEC in early months (4 and 8 months of age), but the differences were not so obvious in later months of age. Infants with RDS were slightly shorter at 4 months and lighter at 4 and 8 months of age than those without RDS, and there were no differences between them at other ages. At 4 and 8 months of age, infants with Apgar score at 5 minutes less than 6 were shorter and lighter than those with 6 or more Apgar score. No obvious differences were found in the mean Z-scores for both length and weight between infants with or without the presence of sepsis, apnea or PDA.

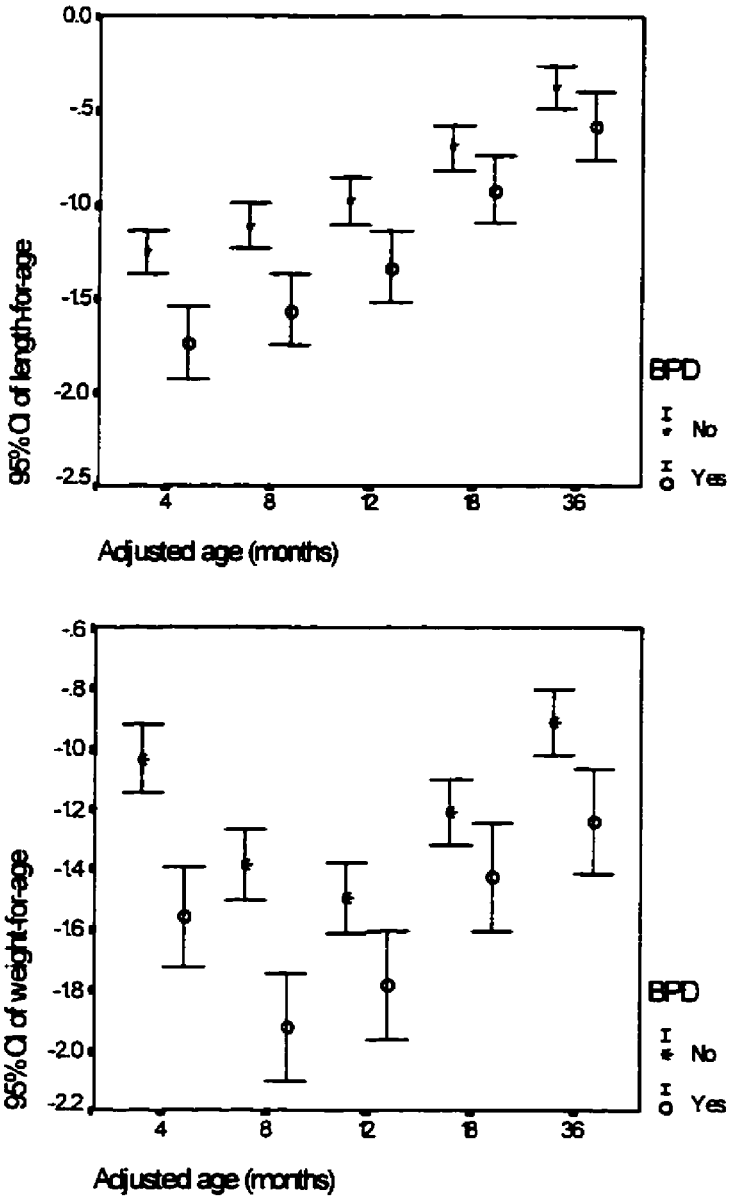


Figure 4-15 Bronchopulmonary dysplasia and mean Z-scores of length and weight in VLBW infants

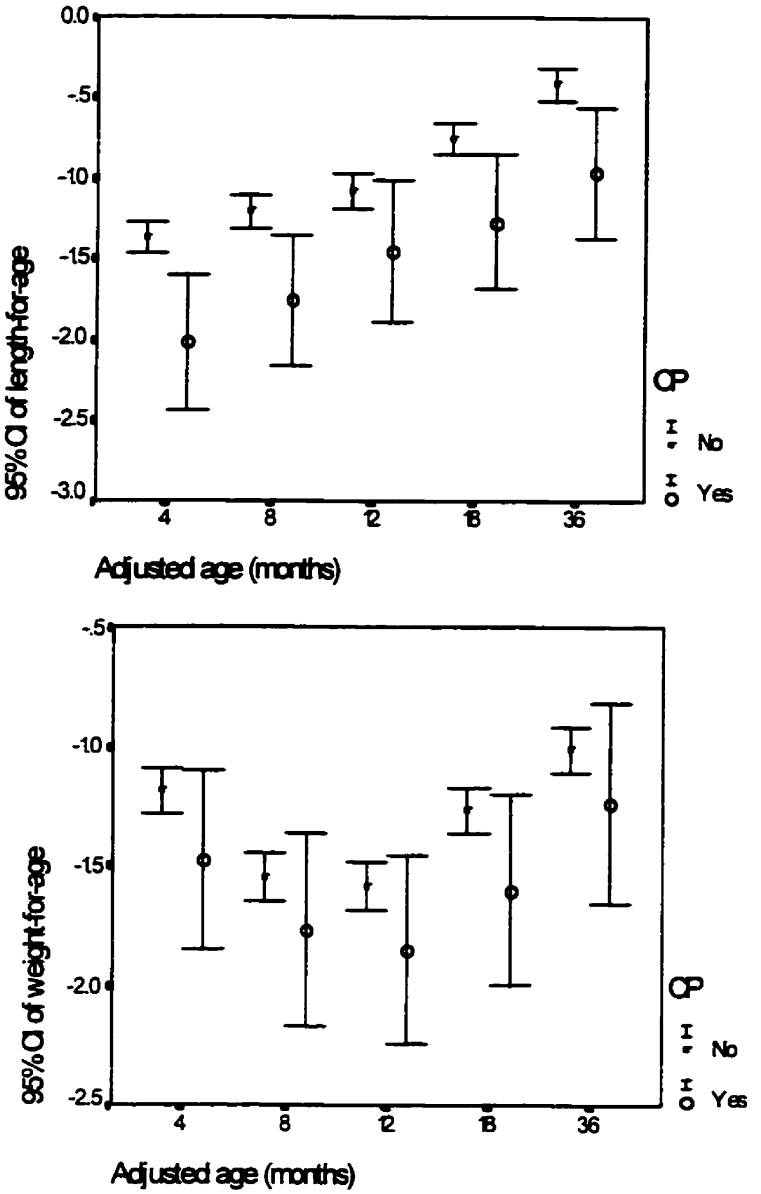


Figure 4-16 Cerebral palsy and mean Z-scores of length and weight in VLBW infants

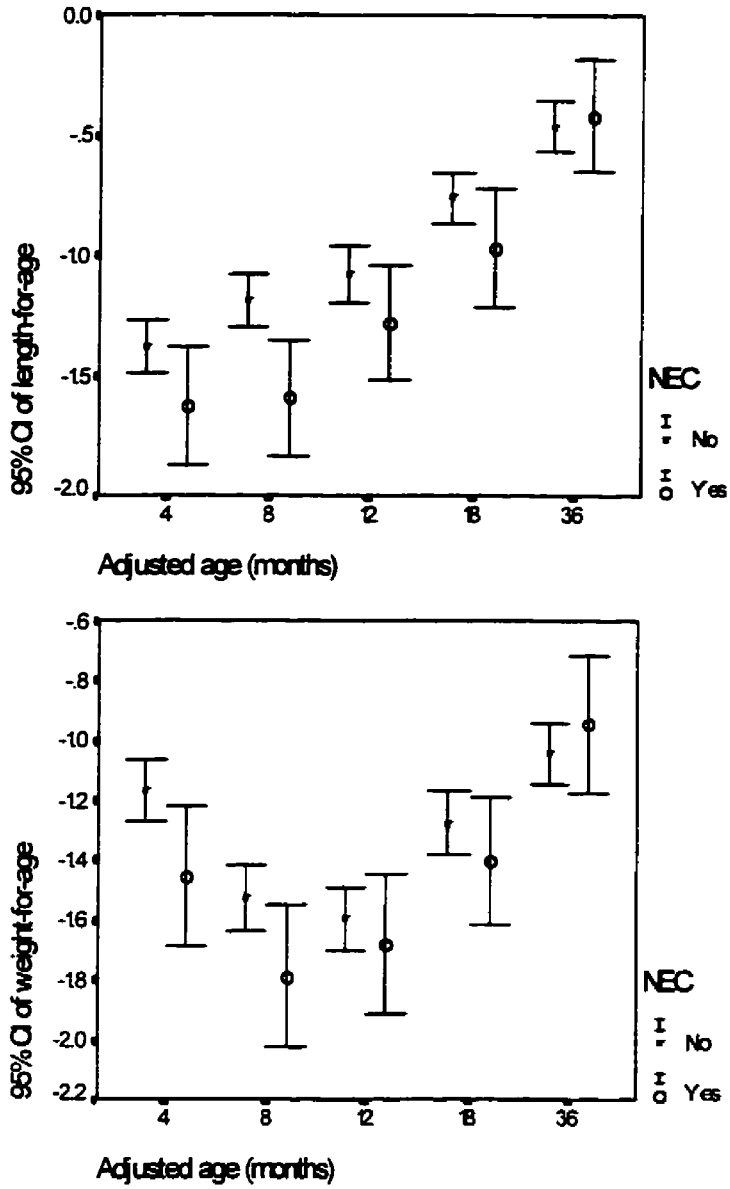


Figure 4-17 Necrotizing enterocolitis and mean Z-scores of length and weight in VLBW infants

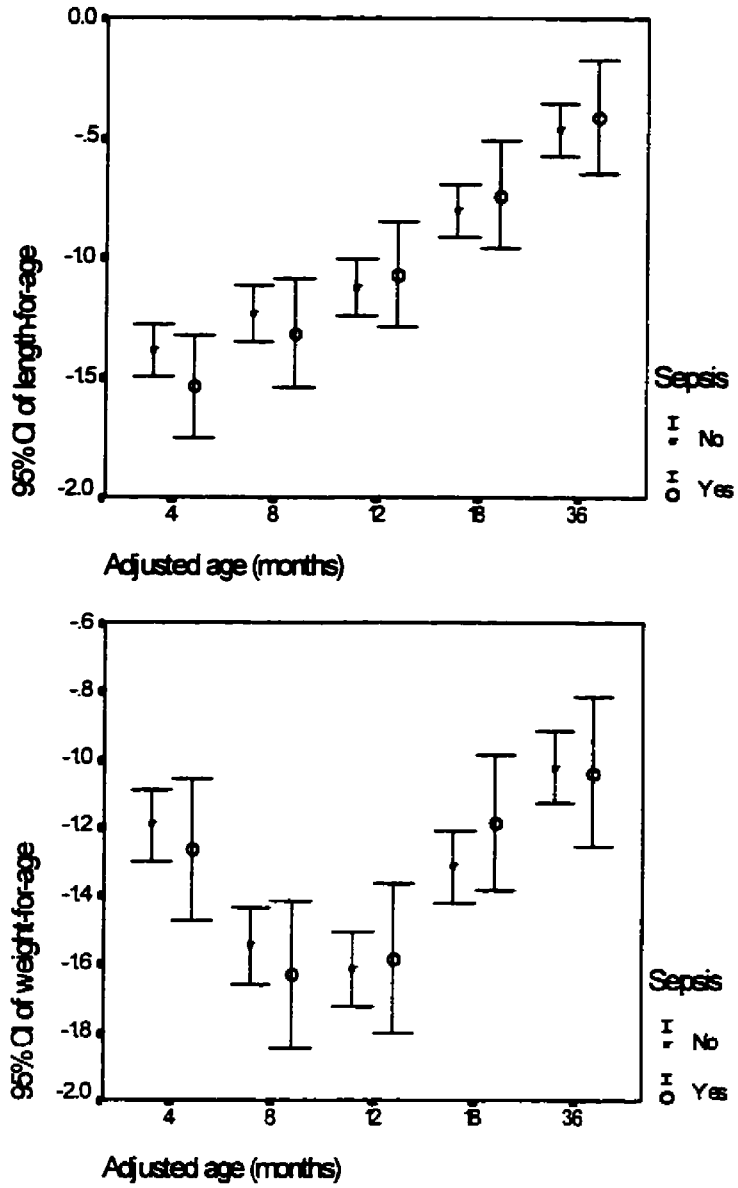


Figure 4-18 Neonatal sepsis and mean Z-scores of length and weight in VLBW infants

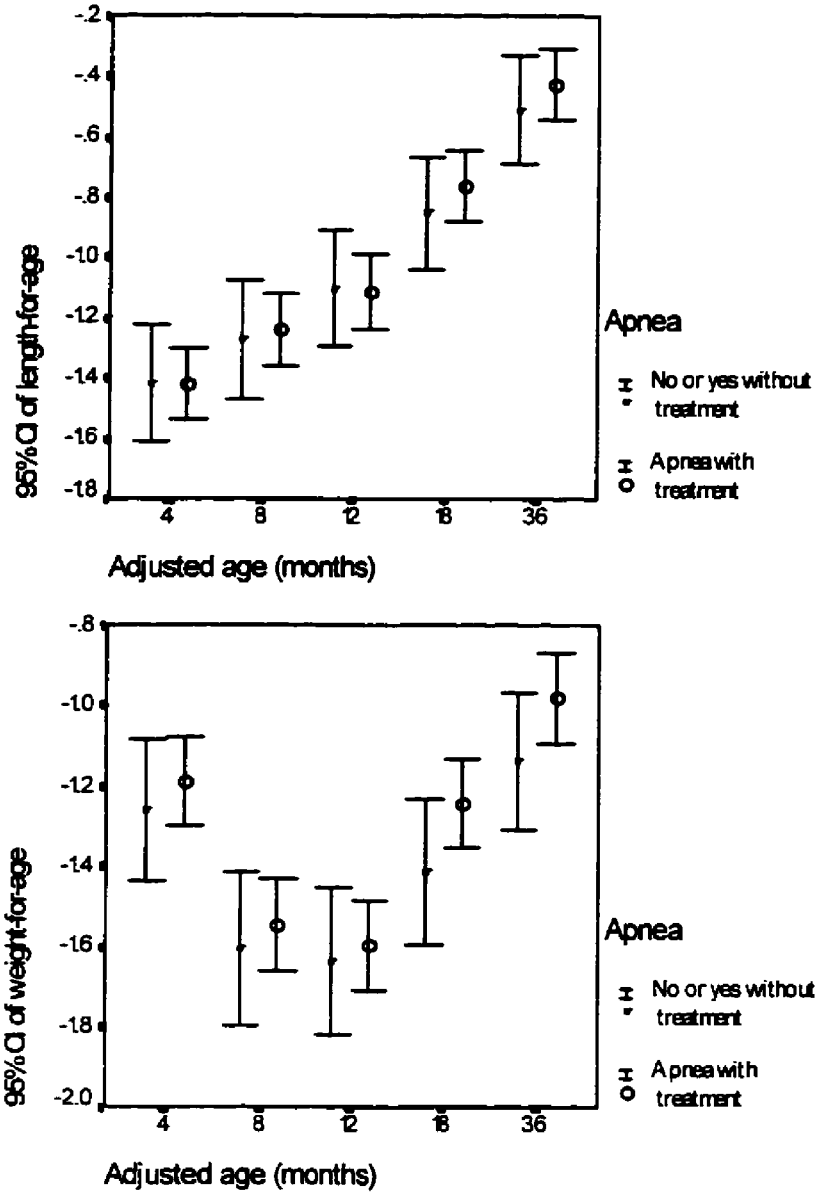


Figure 4-19 Apnea and mean Z-scores of length and weight in VLBW infants

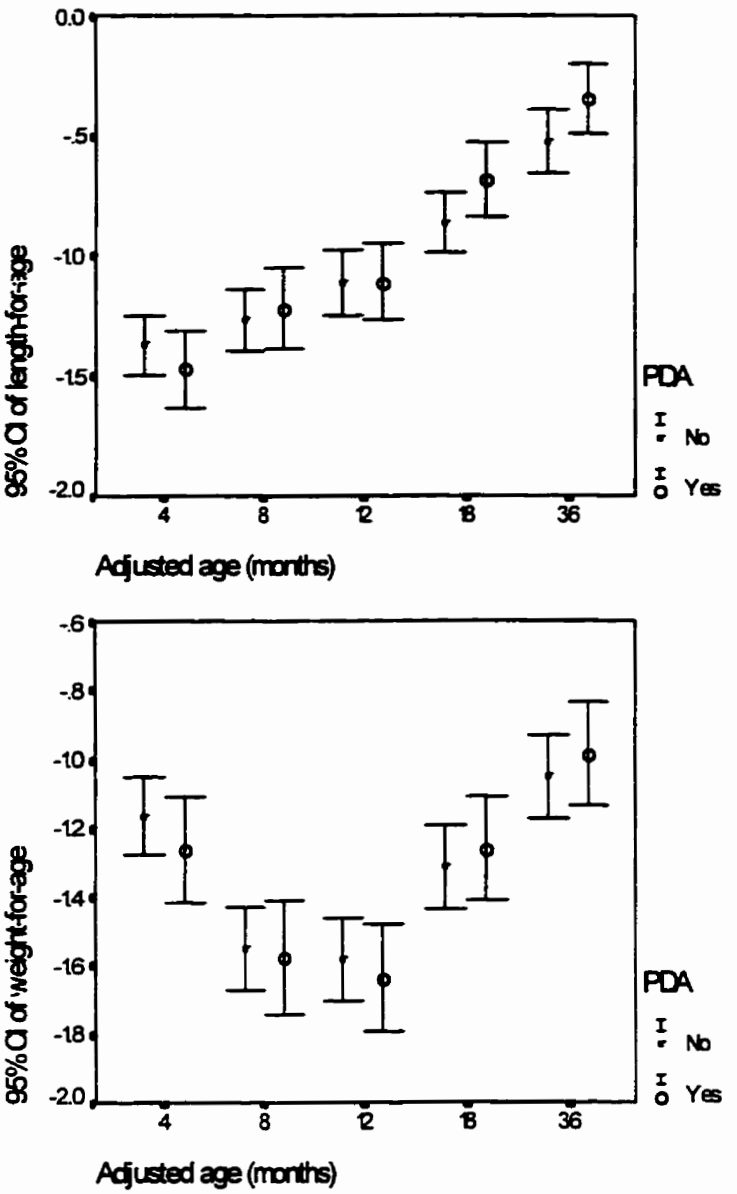


Figure 4-20 Patent ductus arteriosus (PDA) and mean Z-scores of length and weight in VLBW infants

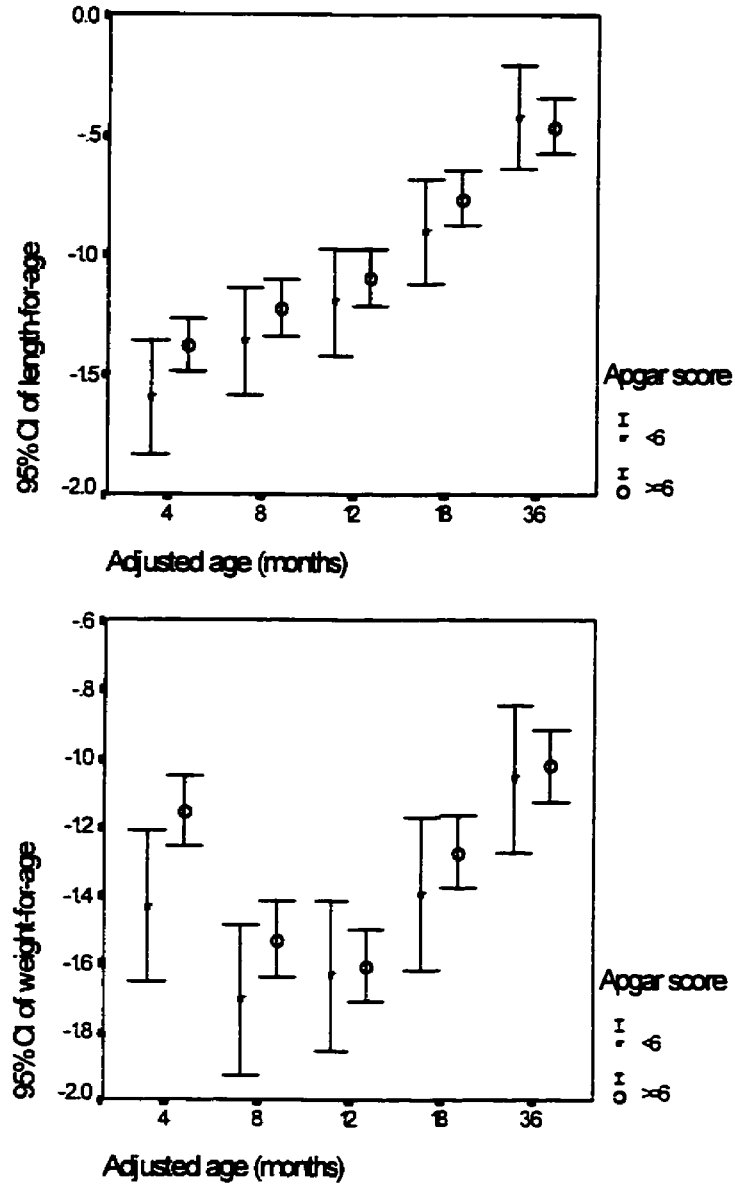


Figure 4-21 Apgar score at five minutes and mean Z-scores of length and weight in VLBW infants

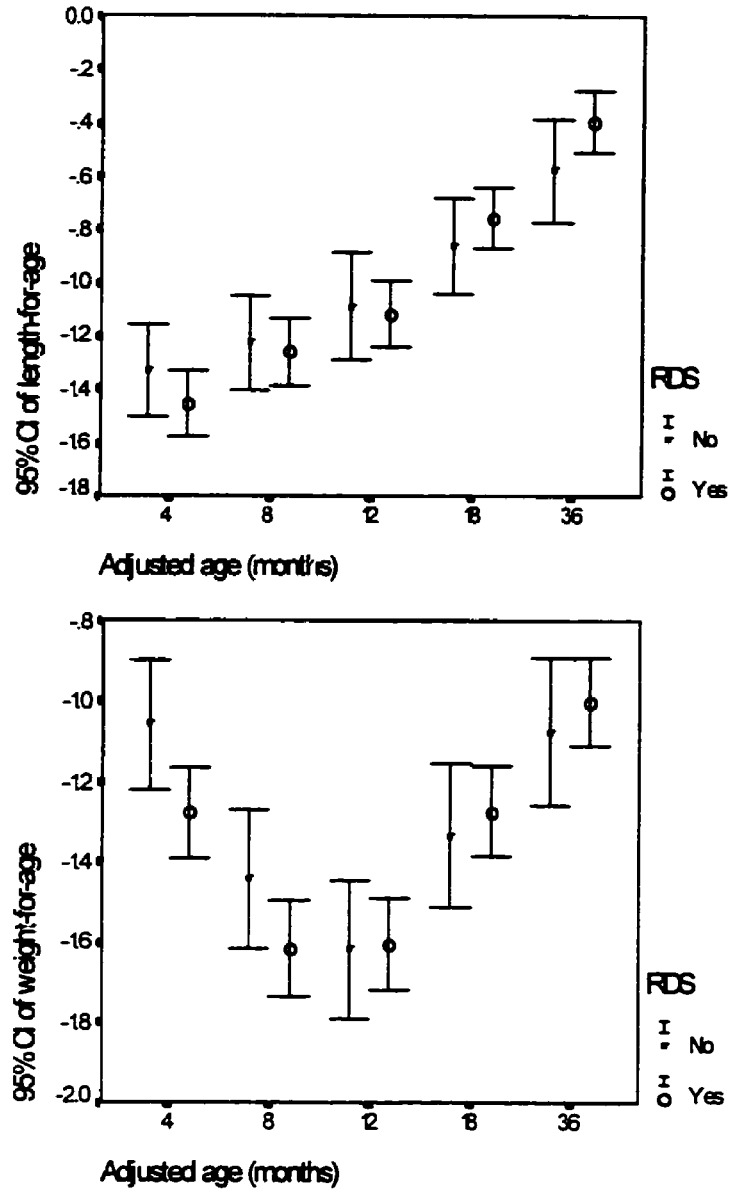


Figure 4-22 Respiratory distress syndrome and mean Z-scores of length and weight in VLBW infants

4.3.5 Sociodemographic factors

The infants of mothers who were 20 years old or younger were found to have lower mean Z-scores than those of mothers who were older than 20 years of age, see Figure 4-23. Although the confidence intervals for these two groups are wide because of small numbers of infants in oldest and youngest age groups, substantial differences were found between the group 20 or younger and the group of 21-35 years of maternal age. Because only a small number of infants were born to non-Caucasian mothers, it was not ideal to explore the association between maternal race and postneonatal growth based on growth data in the present study. The mean Z-scores of infants from Caucasian and non-Caucasian mothers were compared in Figure 4-24. The mean Z-scores were slightly higher for infants of non-Caucasian mothers than those of Causation mothers. However, the 95% confidence for infants of non-Caucasian mothers were very wide.

Infants were also classified into two groups according to their mother's education: less than 12 years and 12 years or more. Infants of mothers with less than 12 years of education were slightly higher in the mean Z-scores at 4, 8, 12 months adjusted ages in length and at 4, 8, 12 and 18 months adjusted ages in weight, but the confidence intervals were very wide, see Figure 4-25. To explore the family social-economical status (SES) and postneonatal growth in VLBW infants, infants were divided into two groups according to the value of Blishen index which measures the family SES: Blishen index <30 and ≥ 30. Higher Blishen index indicates higher family social economical status.

Infants from higher SES families were slightly longer and heavier during infancy, see Figure 4-26.

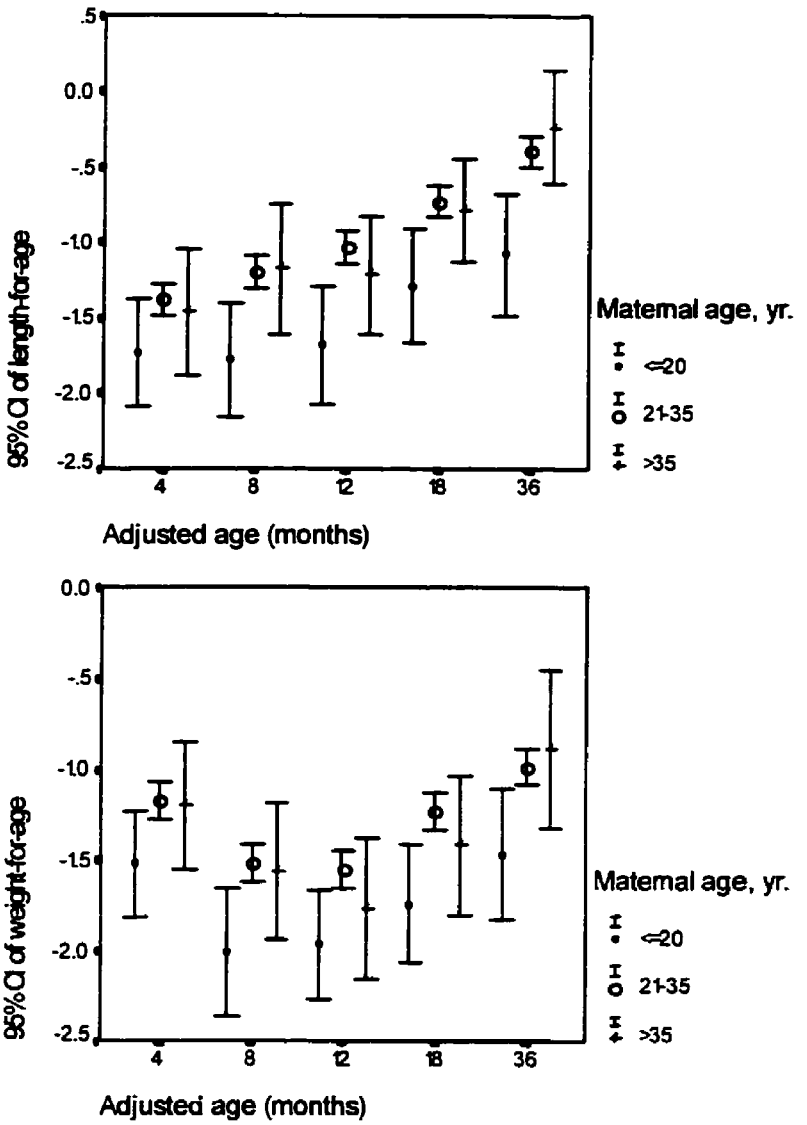


Figure 4-23 Maternal age and mean Z-scores of length and weight in VLBW infants

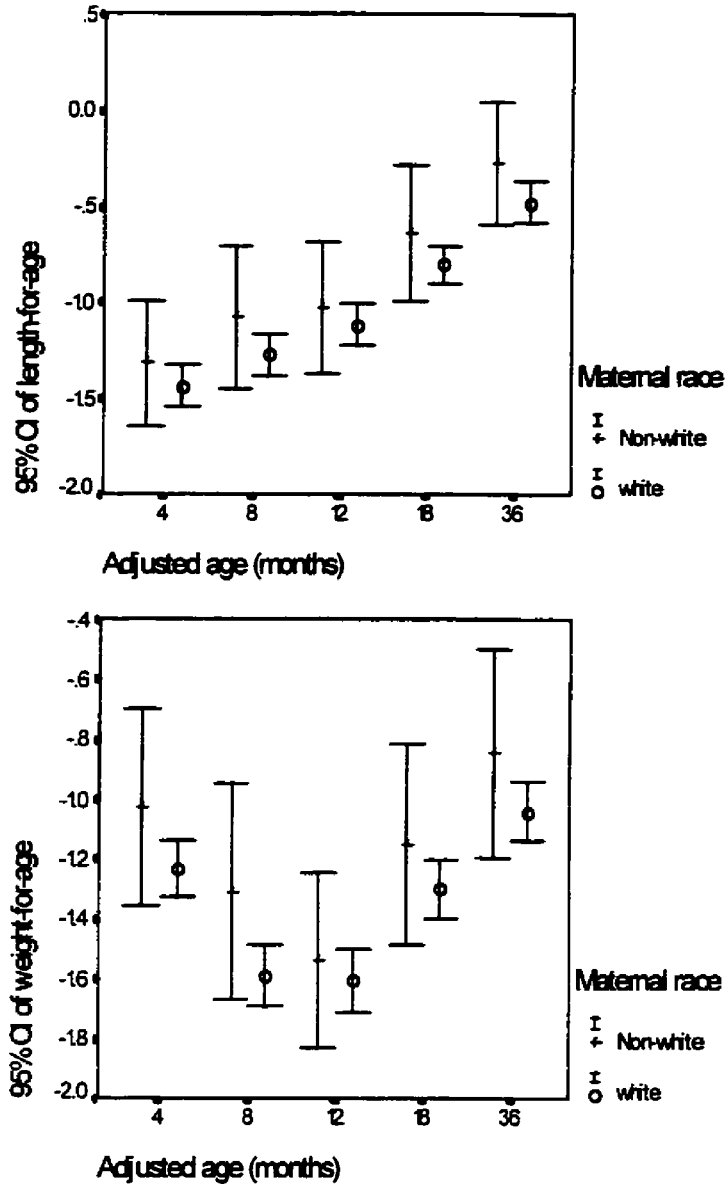


Figure 4-24 Maternal race and mean Z-scores of length and weight in VLBW infants

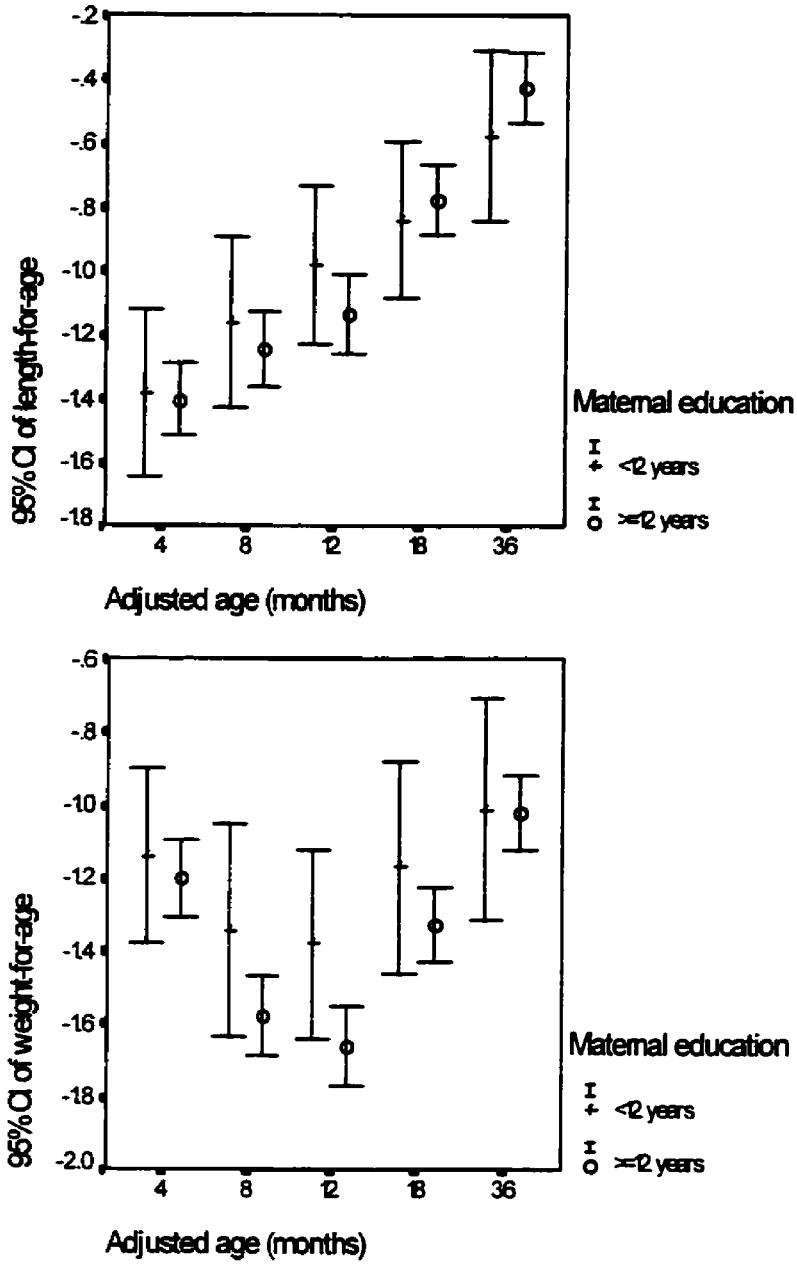


Figure 4-25 Maternal education and mean Z-scores of length and weight in VLBW infants

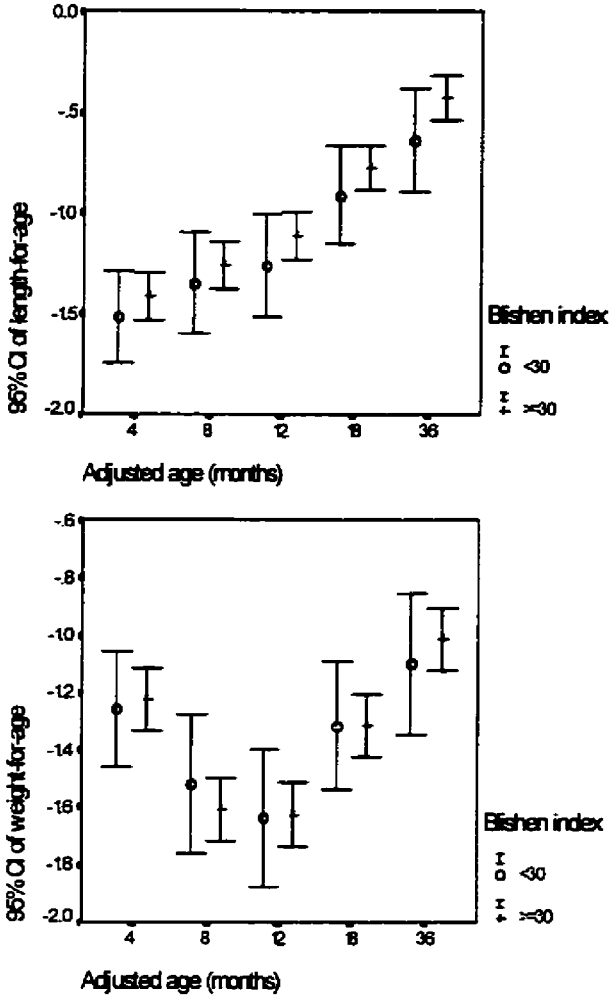


Figure 4-26 Socioeconomic status and mean Z-scores of length and weight in VLBW infants

4.3.6 Duration of hospital stay

Infants were grouped into four groups according to their duration of acute NICU stay. Duration of acute NICU stay was taken as an indicator of severity of clinical conditions. The longer the infants stayed in the acute NICU, the poorer they grew in

length and weight, see Figure 4-27. A trend of convergence in mean Z-scores among different groups was found as infants grew. The differences in mean Z-scores among different groups were smaller for older infants than for younger ones.

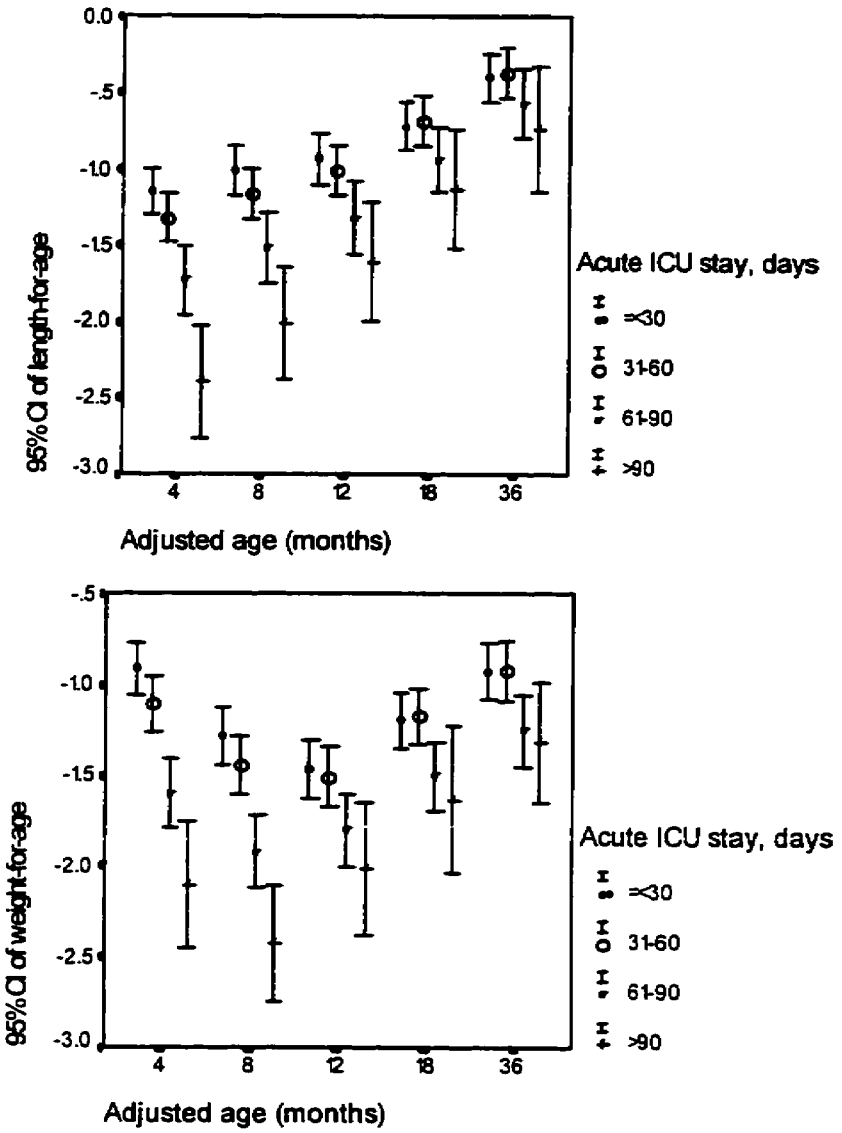


Figure 4-27 Duration in acute ICU and mean Z-scores of length and weight in VLBW infants

4.3.7 Antenatal steroids used

Infants in whom antenatal steroids were used were longer and heavier than infants born without the use of antenatal steroids. The differences were obvious in the first few months of life for weight, see Figure 4-28.

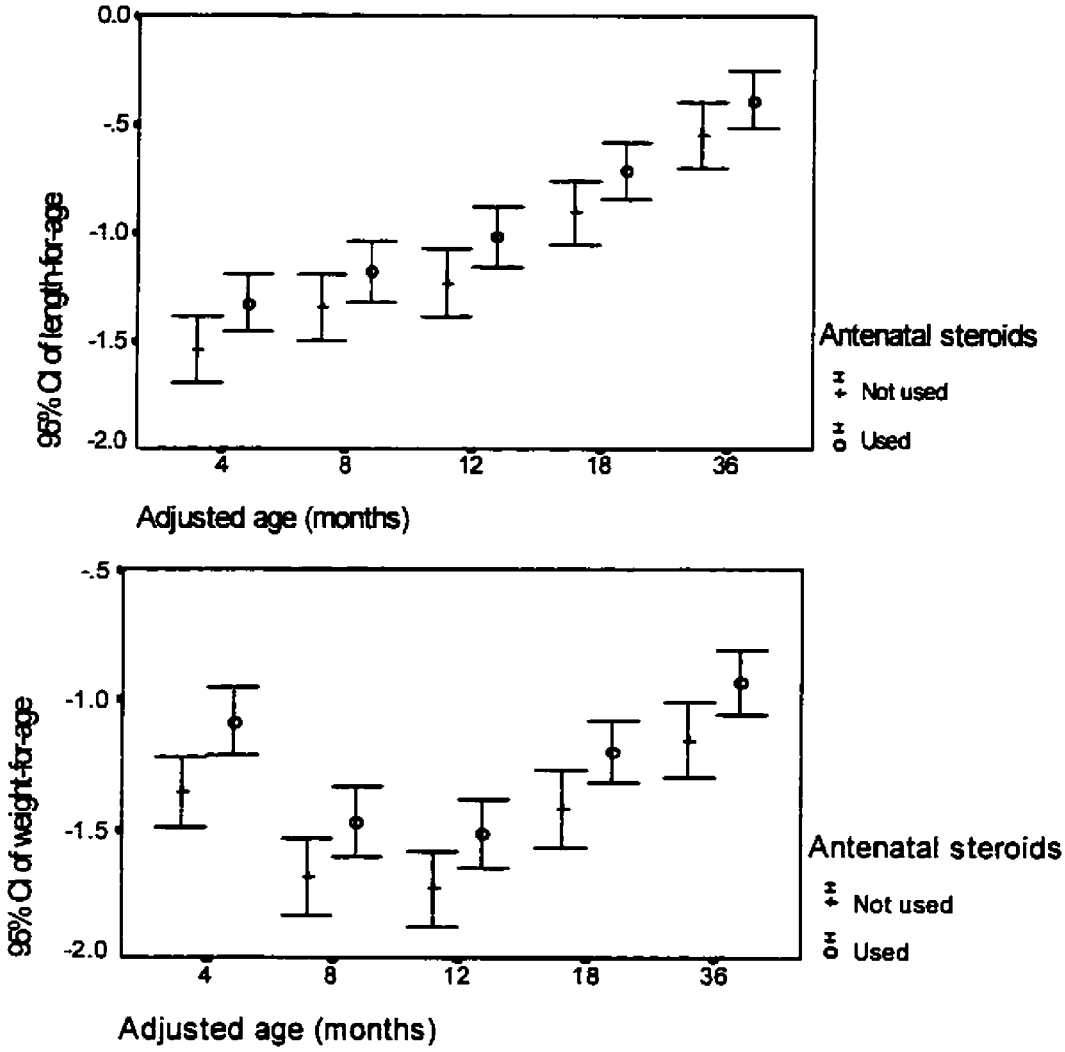


Figure 4-28 Antenatal steroids used during NICU and mean Z-scores of length and weight in VLBW infants

4.3.8 Breastfed during the NICU stay

There was no noticeable difference between infants who were primarily breastfed and infants who were primarily formula fed, see Figure 4-29.

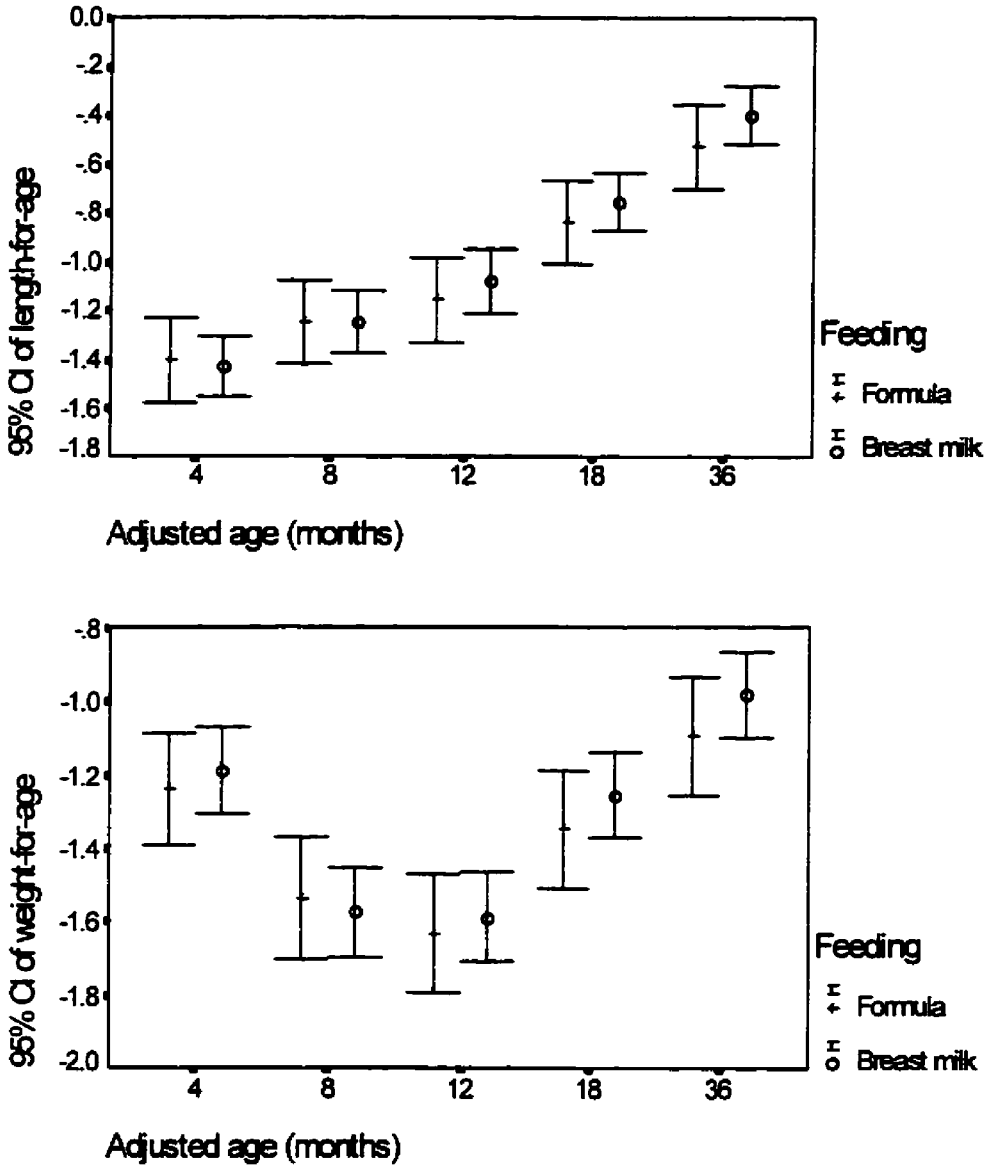


Figure 4-29 Breast feeding and mean Z-scores of length and weight in VLBW infants

4.3.9 Year of birth

Infants were arbitrarily divided into different groups according to the year of birth. Infants born during 1977 and 1980 appeared to be longer and heavier than infants of other groups. For infants born after 1980, there was a general trend that infants who were born in the recent years grew better than those born in early years, especially for younger infants, see Figure 4-30. Because of advances of prenatal and neonatal intensive care, many more tiny newborns survived in recent years. The distributions of birth weight for infants born in different years were calculated and compared in Figure 4-31. The distribution of birth weight changed with the year of birth. Number of infants at the extreme left tail of the birth weight distribution increases with the year of birth. Since the study sample only included infants who survived to discharge from NICU, the results are in keeping with the impression that more tiny neonates survived in the recent years.

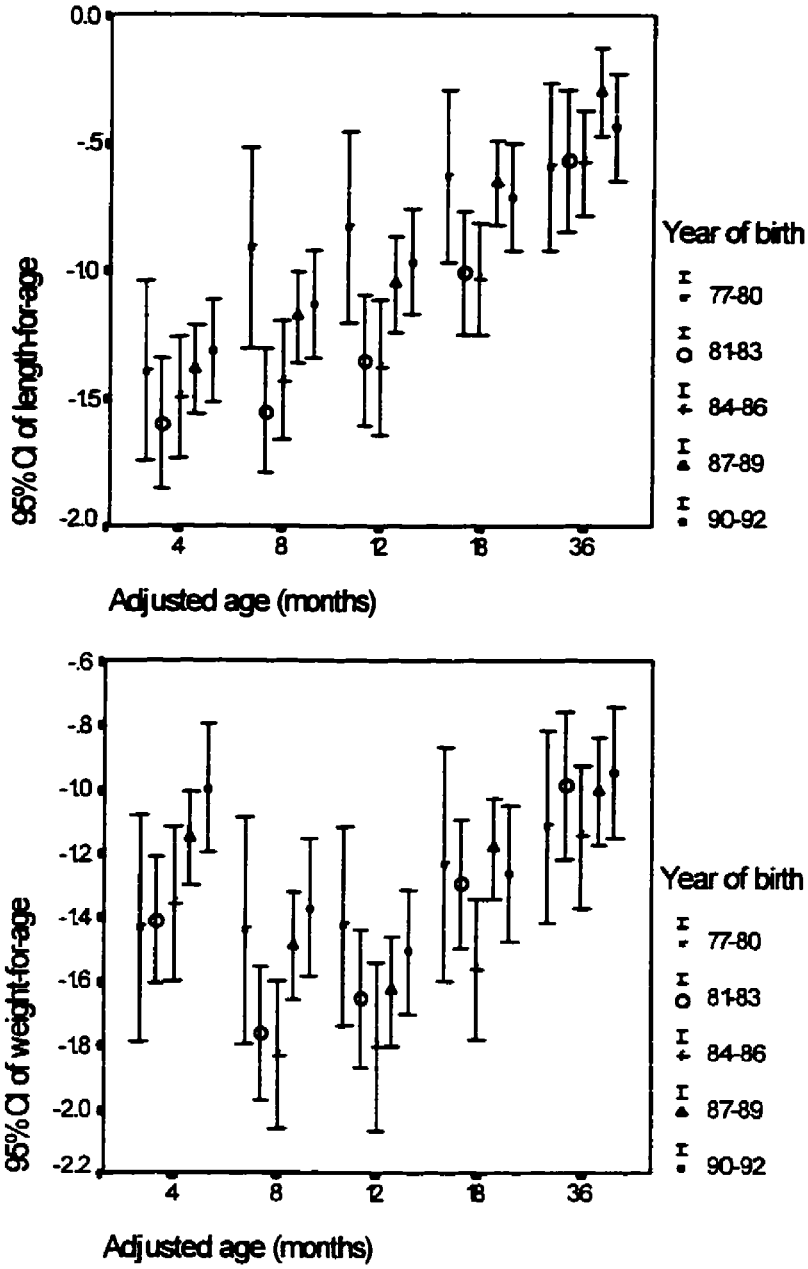


Figure 4-30 Year of birth and mean Z-scores of length and weight in VLBW infants

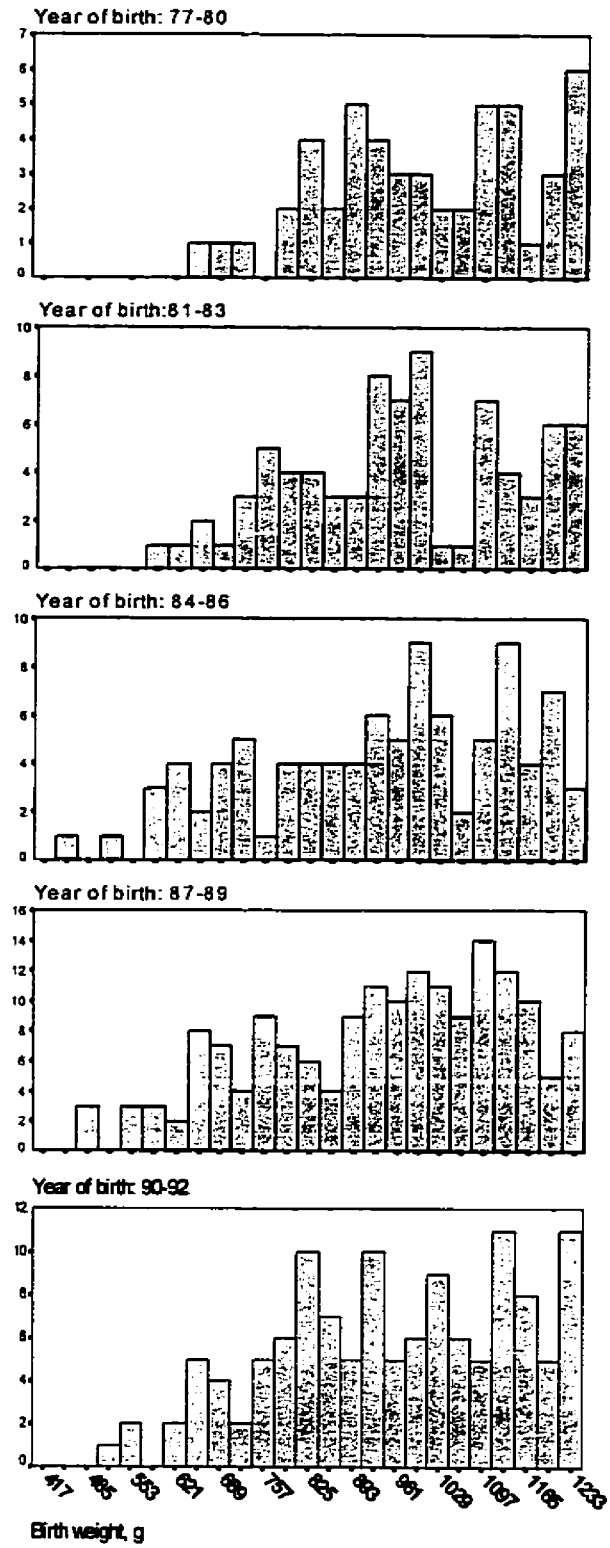


Figure 4-31 Year of birth and birth weight distribution in VLBW infants

4.4 MIXED EFFECTS MODELS OF POSTNEONATAL GROWTH IN VLBW INFANTS

4.4.1 Average growth patterns described by basic growth models

The main advantage of applying mathematical models to human growth is that multiple complicated data points can be distilled into a small number of parameters. These parameters can provide a means for direct comparison between individuals or groups. In this study, the basic models were fitted first to describe the general growth patterns of VLBW infants. The basic growth models represent the relations between age and the postneonatal growth in VLBW infants without considering any other covariates, and provide estimated average growth levels of the study sample.

To formulate a mathematical model that could appropriately describe the growth data of VLBW infants, several different mathematical components from growth models in the literature[132,137] were assessed based on the likelihood ratio test in the mixed effects models. The best basic models that could be found to describe growth of VLBW infants in this study are:

Length of an $\text{infant}_{it} = \beta_0 + b_{0i} + (\beta_1 + b_{1i})*\text{age}_t + \beta_2*\sqrt{\text{age}_t} + e_{it}$

and

Weight of an $\text{infant}_{it} = \beta_0 + b_{0i} + (\beta_1 + b_{1i})*\text{age}_t + \beta_2*\log(\text{age}_t) + e_{it}$.

The *i* represents an individual infant and *t* represents a certain point in age. The fixed effects β_0, β_1, and β_2 in Table 4-15 allow us to estimate the average growth levels and growth rates in VLBW infants, while the random effects b_{0i} and b_{1i} allow each individual

to have his /her own growth pattern. The β_0s are the estimates of intercepts of the population which are not important estimates because the observation began at 4 months of adjusted age in this study. The models show that the growth measurements do not linearly increase with age. The average growth rate at any age point during infancy can be estimated using two parameters, β_1 and β_2. Based on the parameters from basic growth models, the average growth patterns of VLBW infants were estimated, see Figure 4-32 (the solid line).

Table 4-15 The fixed effects in basic growth models

	Estimates	Approx. Std. Error	Z ratio
Length			
Intercept, β_0	39.286	0.306	123.6
Growth rate, β_1	-0.237	0.019	-12.7
Growth rate, β_2	10.313	0.153	67.2
Weight:			
Intercept, β_0	2.328	0.077	30.1
Growth rate, β_1	0.110	0.003	33.4
Growth rate, β_2	1.826	0.046	39.3

Because the time intervals between measurements are wide in the present study and growth rate changes rapidly during infancy, it is difficult to formulate a mathematical model that can accurately describe actual growth for ages at which the growth measurements were not taken. However, the growth models are appropriate for assessing

the change of growth status with age and identifying determinants of growth in VLBW infants since infants with different characteristics were measured at the same time intervals.

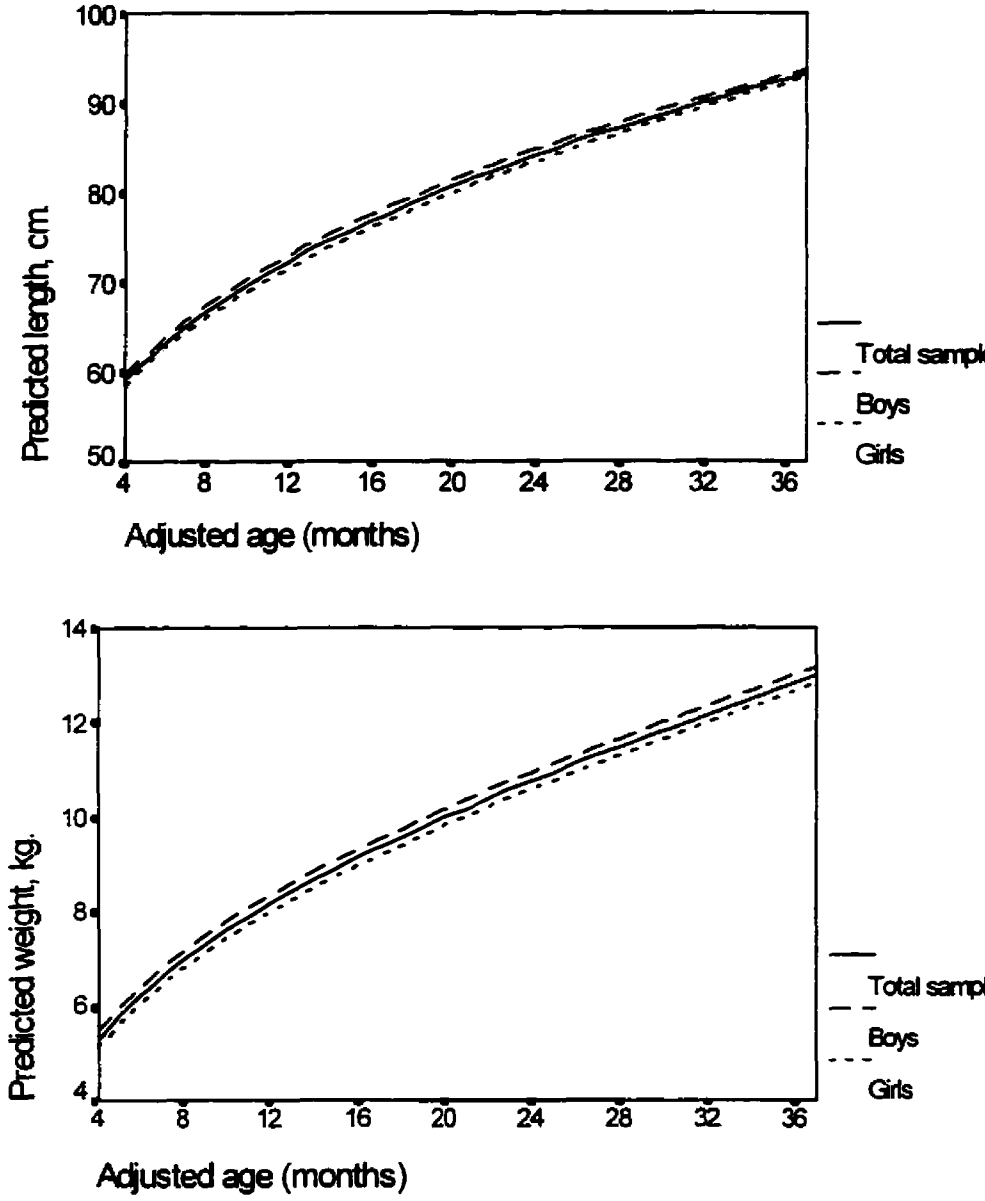


Figure 4-32 Predicted average level in VLBW infants

4.4.2 Gender specific growth patterns

To be able to compare the estimated average growth levels for VLBW infants from the study sample with the gender specific growth references; a covariate, gender, was added into the models. The inclusion of gender allows for separate models for subgroups or, equivalently, allows the parameters to depend upon the gender of infants. The mixed effects model for length is:

$Length_{it} = \beta_0 + b_{0i} + \beta_1 sex + (\beta_2 + b_{1i}) age_t + (\beta_3)\sqrt{age_t} + \beta_4 age_t * sex + \beta_5 \sqrt{age_t} * sex + e_{it}$.

For weight is:

$Weight_{it} = \beta_0 + b_{0i} + \beta_1 sex + (\beta_2 + b_{1i}) age_t + (\beta_3) \log(age_t) + \beta_4 age_t * sex + \beta_5 \log(age_t) * sex + e_{it}$.

The inclusion of β_1, β_4 and β_5 in the model allows infants with different genders to have different intercepts and growth rates. The likelihood ratio test showed that there was no statistically significant difference in intercepts (β_1) between boys and girls, while there were statistically significant differences for two parameters related to growth rate (β_4 and β_5). The estimated parameters of fixed effects are presented in Table 4-16.

The interpretations of these parameters are not straight forward. Both intercept parameters (β_0 and β_1) themselves have no direct interpretations since the observational range in this study did not cover the time of term (when adjusted age was zero) and growth measurement at birth cannot be estimated using these models. For both length and weight, the four parameters which are related to growth rates (β_2, β_3, β_4 and β_5) are found to be significantly different from zero using likelihood ratio tests. In other words, the

growth rates in VLBW infants depend on age and gender. The growth rates for either length or weight are not constant over ages. The difference between boys and girls in the growth measurements of length or weight also depends on age.

Table 4-16 The fixed effects in the mixed effects models included gender*

	Estimates	Approx. Std. Error	Z ratio
Length:			
Intercept			
β_0	39.60	0.42	93.19
β_1 (sex)	-0.46	0.61	-0.74
Growth rate			
β_2 (age*sex)	-0.174	0.025	-6.84
β_3 ($\sqrt{age}$)	9.836	0.211	46.68
β_4 (age*sex)	-0.132	0.037	-3.55
β_5($\sqrt{age}$*sex)	1.003	0.305	3.29
Weight:			
Intercept			
β_0	2.40	0.11	21.89
β_1 (sex)	-0.16	0.16	-1.02
Growth rate			
β_2 (age)	0.119	0.00045	26.14
β_3 (log(age))	1.661	0.0645	25.73
β_4 (age*sex)	-0.019	0.0066	-2.89
β_5 (log(age)*sex)	0.352	0.0934	3.76

* Length = $\beta_0+b_0+\beta_1$sex+(β_2+b_1)age+β_3*$\sqrt{age}$+$\beta_4$age*sex+ $\beta_5\sqrt{age}$*sex;

*Weight = $\beta_0+b_0+\beta_1$sex+(β_2+b_1)age+$\beta_3$log(age)+$\beta_4$age*sex+$\beta_5$log(age)*sex. Sex code: 0 for girl and 1 for boy

The difference in weight between boys and girls (estimated values for boys minus those for girls) is:

-0.16-0.019*age+0.352*log(age)

and in length is:

-0.46-0.132*age+1.003*sqrt(age).

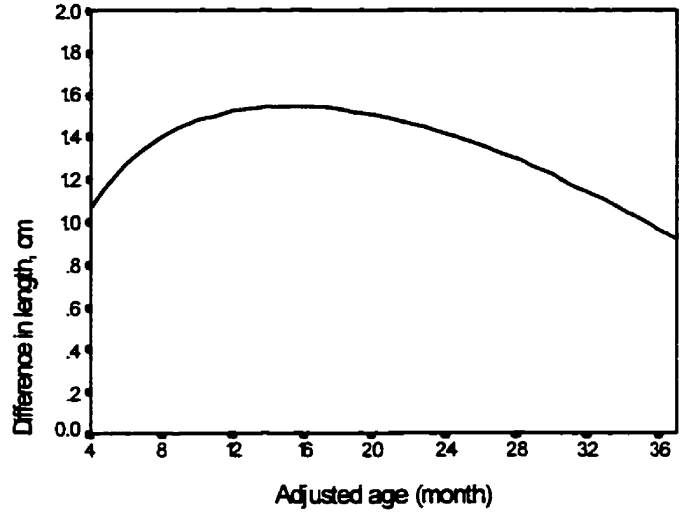
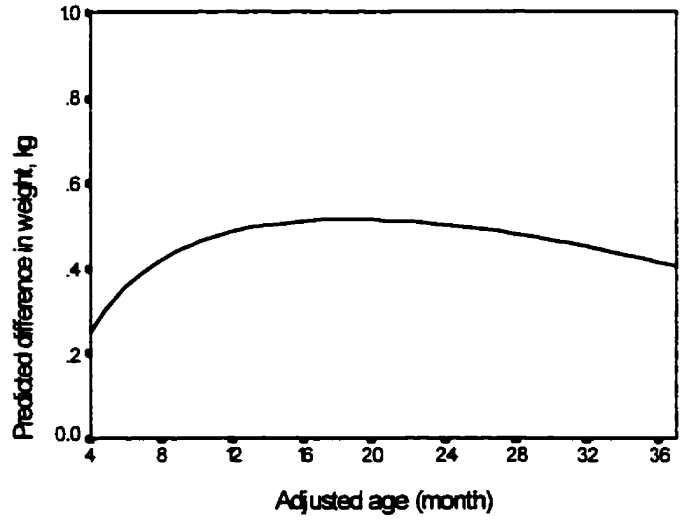


Figure 4.32 (a) boy minus girls in length



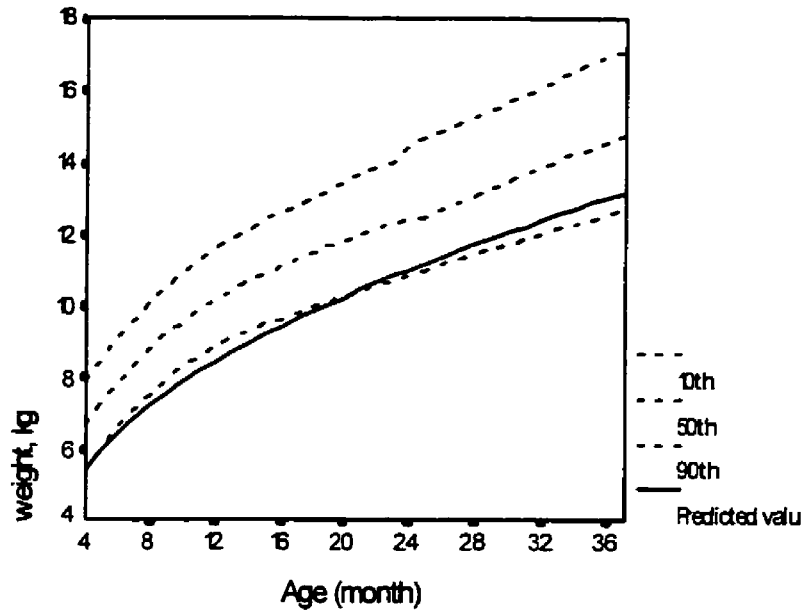
(b) Boys minus girls in weight

Figure 4-33 The difference between boys and girls in growth measurements

The growth levels for boys and girls are presented in Figure 4-32, the differences between boys and girls are presented in Figure 4-33. Through the observational period boys were longer and heavier than girls, but the differences were not constant over time. They were slightly higher during 12 and 18 months of age than the other ages.

Compared with the NCHS/WHO growth references, the estimated average weight for VLBW infants based on the growth models are close to the 10th percentile of the reference. From 8 to 18 months, the average weight of VLBW infants is lower than the 10th percentile while at 36 months of age it is higher than the 10th percentile of the reference, see Figure 4-34. The relative position for length in VLBW infants continuously rises as infants grow, see Figure 4-35. Compared with the Canadian growth references, the relative position for VLBW infants continuously rises as infants grow in both weight and length, see Figure 4-36 and Figure 4-37.

a) for boys



b) for girls

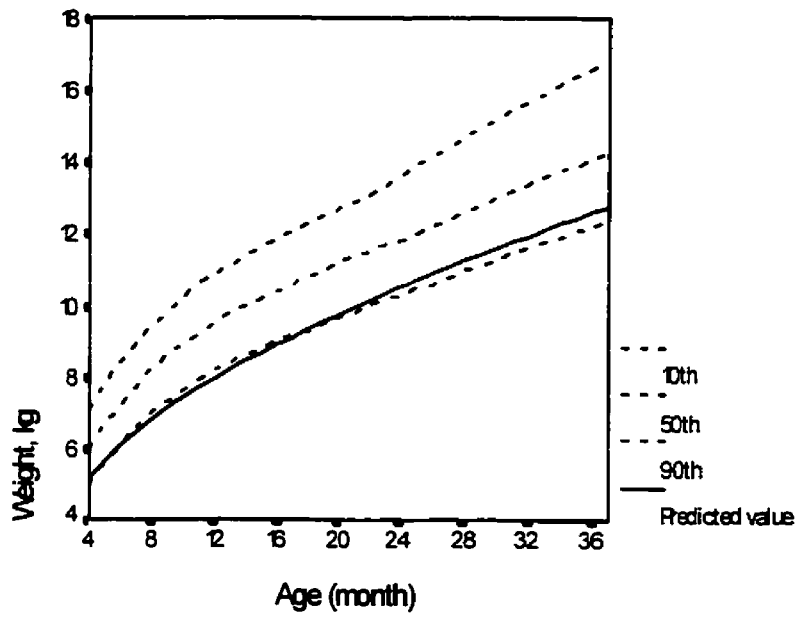
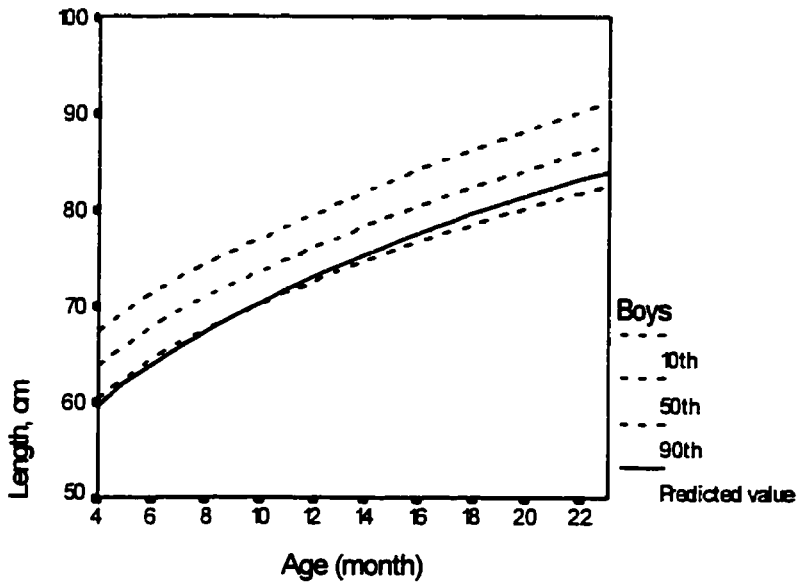


Figure 4-34 The average predicted value in weight for VLBW infants, compared with NCHS/WHO references

a) for boys



b) for girls

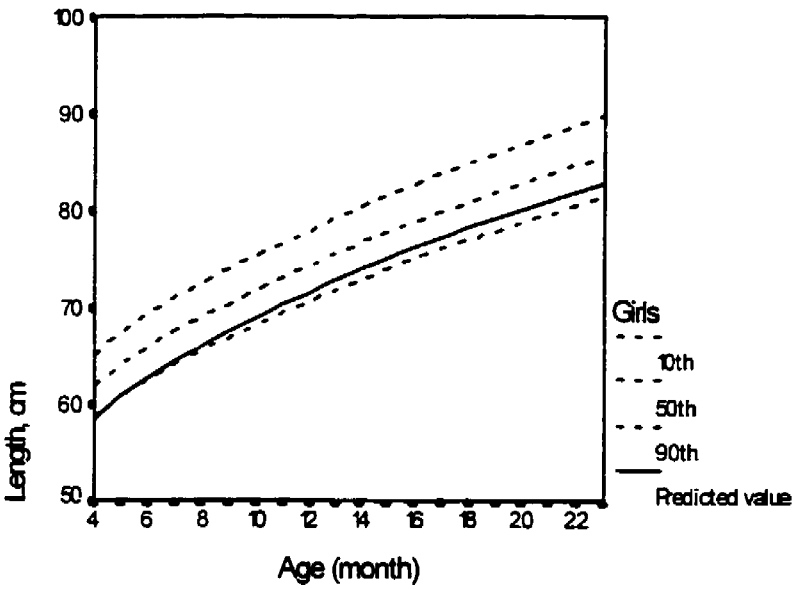
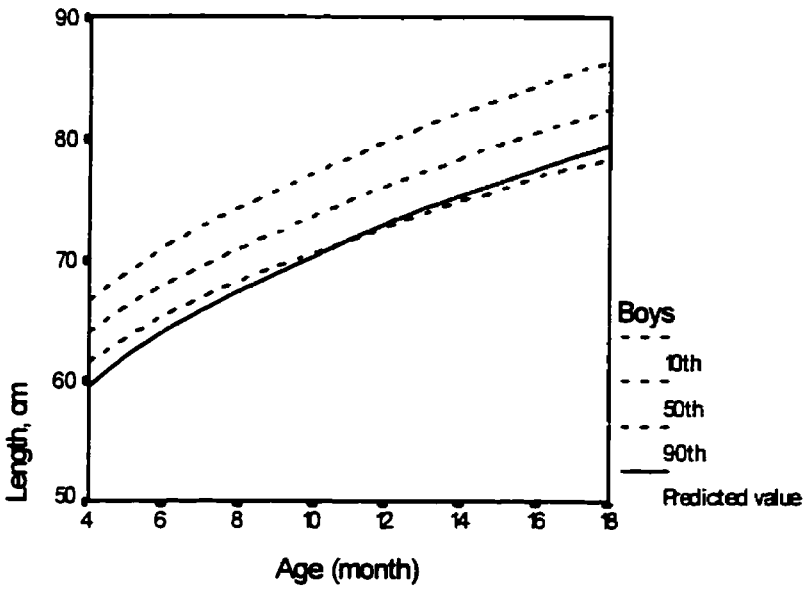


Figure 4-35 The average predicted value in length for VLBW infants, compared with NCHS/WHO references

a) for boys



b) for girls

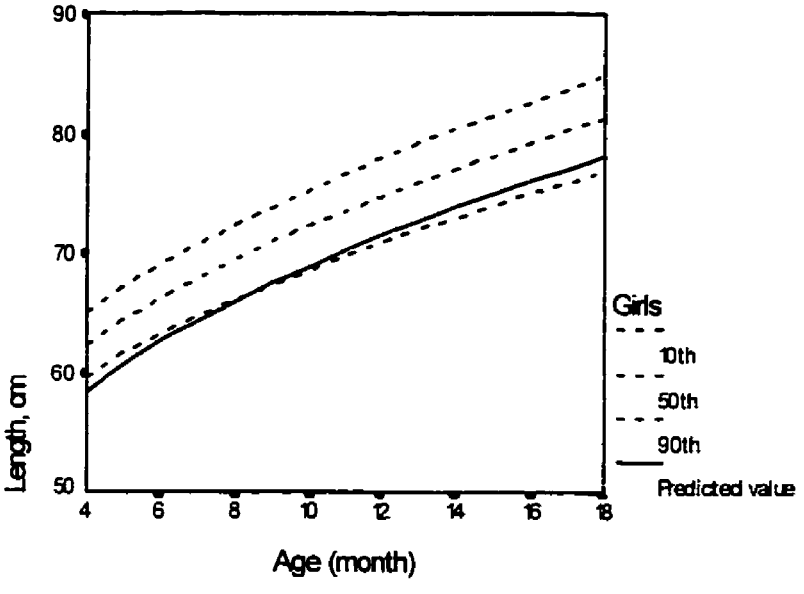
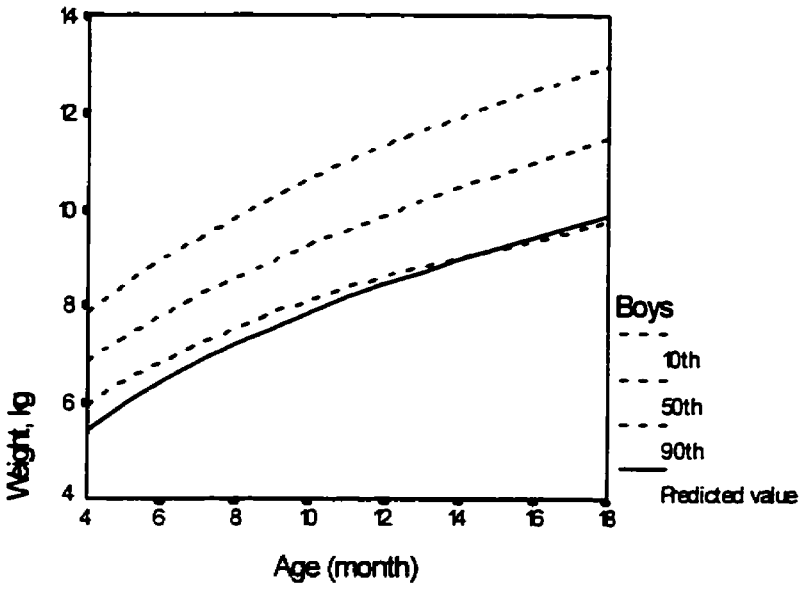


Figure 4-36 The average predicted value in length for VLBW infants, compared with Canadian references

a) for boys



b) for girls

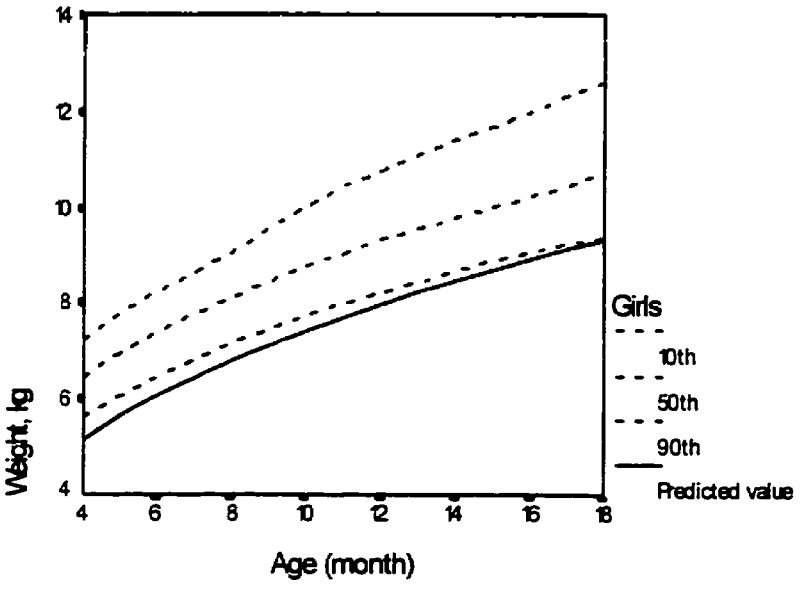


Figure 4-37 The average predicted value in weight for VLBW infants, compared with Canadian references

4.4.3 Determinants of postneonatal growth: Mixed effects models including covariates

4.4.3.1 Determinants of length

To assess the association between the potential influencing factors and postneonatal growth of VLBW infants, each variable was added individually into the models developed previously which included only gender and age. Two terms, the main effect term and the interaction term with age, were added into the model sequentially for each variable. The main effect term was added into the model first, followed by the interaction term. The interaction with age was used to test if the factor was associated with the growth rate. The main effect term was used to test whether the factor was associated with growth level assuming that it was not associated with the growth rate. For each variable, three models were fitted: i) a basic model including only sex and age, ii) a model with only the main effect term, and iii) a model with both the main effect and interaction terms. The association between a factor and postneonatal growth was tested using the likelihood ratio statistics.

Birth weight, mid-parental height, BPD, maternal age, NEC, PDA, sepsis and maternal education were associated with the growth rate in length, since their interaction terms with age were statistically significant, see Table 4-17. The lower birth weight infants grow faster than those with higher birth weights. The infants of taller parents grow faster than infants of shorter parents. The infants of mothers who are 20 years or younger grow slower than the infants of mothers who are older than 20 years of age. The infants

with BPD, NEC, PDA or sepsis grow faster than infants without each of these conditions, respectively. The infants of mothers with 12 or more years education grow faster than the infants of mothers with less than 12 years education. The presence of SGA and CP and the use of antenatal steroids are associated only with the growth level of length during the observed period. The SGA infants are shorter than AGA infants. Infants with CP are shorter than infants without CP. The infants whose mothers received antenatal steroid therapy are longer than those whose mothers did not receive the therapy. No associations with length were found for SES and breastfeeding during the NICU stay.

Since only age and gender were in the model in the above analysis, the observed association between a factor and length might be attributable to the confounding effects of other factors. To consider the confounding effects in the model, a model was fitted with the factors which have significant contributions to the growth in length in VLBW infants. The variables were added into the model sequentially in the order of the magnitude of the likelihood ratio from the previous analysis. The likelihood ratio statistics with the associated P-values were used to select the factors which have significant contributions to the postneonatal growth, see Table 4-18. The variables which could not be added into the model at early stages were still considered as candidates while more variables were added into the model. Besides age and gender, seven variables were found to have significant contributions to the prediction of postneonatal growth in length. They are birth weight, mid-parental height, maternal age, gestational age, CP,

NEC and BPD. The SGA was defined based on gestational age and birth weight, and the gestational age had a much higher likelihood ratio than SGA. Therefore, the gestational age was used in the model.

Table 4-17 Fixed effects for length: variables were added into the basic model individually

	Fixed effect	SE	z ratio	LR test*	P value
Birth weight				81.86 (df=2)[a]	<0.0001
BW, 100 g	0.61	0.065	9.36	70.10 (df=1)[b]	<0.0001
Age:BW	-0.0085	0.0025	-3.45	11.76 (df=1)[c]	0.0006
Mid-parental height				54.53 (df=2)	<0.0001
MPH, 10 cm	0.78	0.23	3.35	27.85 (df=1)	<0.0001
Age:MPH	0.042	0.0081	5.26	26.68 (df=1)	<0.0001
BPD				22.67 (df=2)	<0.0001
BPD	-1.32	0.28	-4.71	17.37 (df=1)	<0.0001
Age:BPD	0.023	0.010	2.31	5.30 (df=1)	0.021
Maternal age ≤ 20 yr.				19.47 (df=2)	<0.0001
Mage	-1.19	0.44	-2.71	6.14 (df=1)	0.013
Age:Mage	-0.039	0.016	-2.48	13.33 (df=1)	0.00026
SGA				12.14 (df=2)	0.0023
SGA	-0.98	0.28	-3.51	10.93 (df=1)	0.00095
Age:SGA	0.011	0.010	1.10	1.21 (df=1)	0.27
NEC				9.81 (df=2)	0.0074
NEC	-1.06	0.37	-2.88	5.57 (df=1)	0.018
Age:NEC	0.027	0.013	2.07	4.24 (df=1)	0.039
CP				9.58 (df=2)	0.0083
CP	-1.34	0.49	-2.75	9.29 (df=1)	0.0023
Age:CP	-0.0094	0.018	-0.54	0.29 (df=1)	0.59

(Table 4-17 continued)

	Fixed effect	Std.Error	z ratio	LR test	P value
PDA				7.90 (df=2)	0.019
PDA	-0.20	0.27	-0.75	0.01 (df=1)	0.93
Age:PDA	0.027	0.010	2.82	7.89 (df=1)	0.005
Antenatal steroids				5.97 (df=2)	0.051
Antenatal steroids	0.63	0.27	2.36	5.96 (df=1)	0.015
Age:steroids	-0.0010	0.010	-0.10	0.01 (df=1)	0.92
Maternal school				5.64 (df=2)	0.060
Mschool	-0.49	0.37	-1.32	0.44 (df=1)	0.51
Age:Mschool	0.030	0.013	2.29	5.20 (df=1)	0.023
Sepsis				4.65 (df=2)	0.097
Sepsis	-0.37	0.33	-1.09	0.24 (df=1)	0.62
Age:Sepsis	0.025	0.012	2.10	4.41 (df=1)	0.036
SES				4.21 (df=2)	0.12
SES	0.30	0.28	1.06	1.76 (df=1)	0.18
Age:SES	0.013	0.010	1.33	2.45 (df=1)	0.12
Breastfed				3.36 (df=2)	0.19
Breastfed	-0.031	0.27	-0.11	3.17 (df=1)	0.075
Age:Breastfed	0.017	0.010	1.78	0.19 (df=1)	0.66

* Three values are presented for each variable in likelihood ratio tests.

a: Drop of deviance when adding both main effect and interaction terms.

b: Drop of deviance when adding only main effect term.

c: Drop of deviance when adding only interaction term into the model with the main effect term.

Table 4-18 Likelihood ratio test for length: variables added into the model sequentially

	Likelihood ratio statisitc	P value
Birth weight	81.86(df=2)	<0.0001
BW,100 g	70.10(df=1)	<0.0001
Age:BW	11.76(df=1)	0.0006
Mid-parental height	52.20(df=2)	<0.0001
MPH, 10 cm	21.27(df=1)	<0.0001
Age:MPH	30.93(df=1)	<0.0001
Maternal age 20 ≤ yr.	29.62(df=2)	<0.0001
Mage	19.98(df=1)	<0.0001
Age:Mage	9.64(df=1)	0.0019
Gestational age	51.61 (df=2)	<0.0001
Gestational age	51.04 (df=1)	<0.0001
Age:gestational age	0.57 (df=1)	0.45
NEC	14.97 (df=2)	0.00056
NEC	12.23(df=1)	0.00047
Age:NEC	2.74(df=1)	0.098
CP	11.66(df=2)	0.0029
CP	11.23(df=1)	0.0080
Age:CP	0.41(df=1)	0.52
BPD	4.24(df=2)	0.12
BPD	4.08((df=1)	0.043
Age:BPD	0.16(df=1)	0.69

A final growth model was fitted by dropping the nonsignificant interaction terms from the model one by one and checking the likelihood ratio statistics. In this model, only significant interaction terms were included. If an interaction term was significant, both main effect terms would remain in the model. For variables without significant

interaction terms, only those with significant main effect terms remained in the model, see Table 4-19.

Table 4-19 Estimates of fixed effects in the final model for length

	Value	Std.Error	z ratio
(Intercept)	38.8010	3.9874	
sex	-0.5201	0.5644	-0.922
birth weight, 100 g	0.8743	0.0839	10.417
MPH, 10 cm	0.4233	0.2060	2.055
mage≤20 yr.	-1.4561	0.4838	-3.010
NEC	-0.9932	0.3249	-3.057
CP	-1.3554	0.4084	-3.319
BPD	-0.5342	0.2664	-2.005
Gestation, wk.	-0.5108	0.0633	-8.073
Slope:			
age	-0.8760	0.1364	-6.425
age:sex	-0.1310	0.0350	-3.739
age:BW	-0.0099	0.0026	-3.771
age:MPH	0.0472	0.0079	5.991
age:mage≤20 yr.	-0.0477	0.0185	-2.574
sqrt(age)	9.7916	0.1930	50.731
sqrt(age):sex	1.0160	0.2774	3.662

The factors which are associated with growth rate in length are birth weight, mid-parental height, maternal age and gender. The factors that are only associated with growth level are gestational age, NEC, CP and BPD. Examination of the residual plots and the

distribution of estimates of the random effects for this final model provided no evidence that any of the model assumptions were invalid. Further, the likelihood ratio tests suggested that no additional factors and interactions were necessary.

The fixed effects in Table 4-19 allow to assess the details of the association between a factor and postneonatal growth while the potential confounding effects of the other factors were considered. One way to express the association between a factor and postneonatal growth is to estimate the differences in length between infants with different exposure levels of a factor, assuming that they have the same other characteristics, Figure 4-38. For the factors which influence growth rates, such differences vary depending on age.

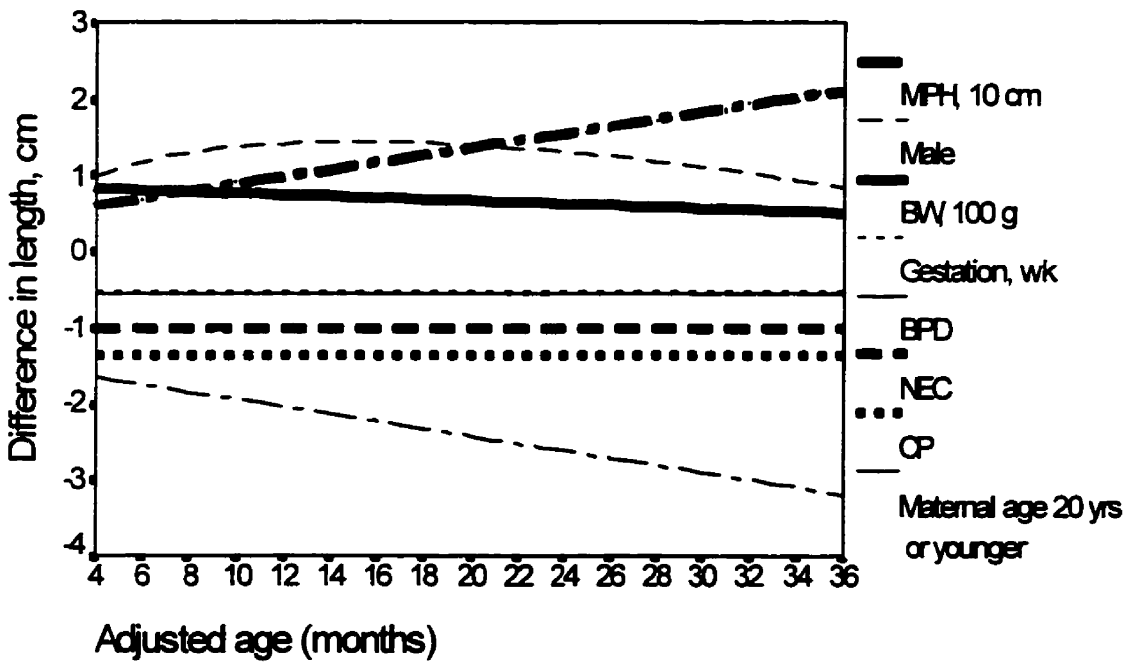


Figure 4-38 Relations between factors and length in VLBW infants

The line "MPH" in Figure 4-38 represents average differences in length between the infants of parents with 10 cm difference in height, assuming they have the same other characteristics which are known to be associated with the postneonatal growth. The differences between them represent the effects of the parents' height on length:

The difference = infants with 10 cm taller MPH - comparison infants

The line "male" represents average differences between boys and girls. The line "BW" represents the differences in length of the infants who were 100 grams heavier. The line "Gestation" represents the change in length if the infants were one week longer in their gestational age. Each of lines of BPD, NEC and CP represents the differences between infants with the presence of the condition and infants without it. The line of maternal age shows the difference between infants of mothers who were 20 years or younger in age and those of mothers who were older than 20 years.

The infants of taller parents were longer and grew faster than those of shorter parents; consequently, the difference between them increased with age. The infants with higher birth weight were longer and grew slightly slower than those with lower birth weight. The infants with longer gestational ages were shorter than those with shorter gestational ages. No differences were found in growth rate in length among infants with different gestational ages. Infants with CP, NEC or BPD were shorter than those without these conditions, and the differences remained constant during the observational period. The infants of mothers who were 20 years or younger grew slower than those of mothers who were older than 20 years of age.

Several factors were found to be associated with the postneonatal growth in length by bivariate analyses and the models without considering the confounding effects of other factors, but the associations of these factors and length no longer had statistical significance after adding other variables into the models. They are the presence of SGA, PDA and Sepsis, the use of antenatal steroids, and maternal education.

4.4.3.2 Determinants of weight

Without considering the confounding effects of other factors, seven factors were found to be associated with postneonatal growth in weight with statistical significance, see Table 4-20. They were birth weight, mid-parental height, the presence of BPD, SGA and NEC, maternal age, and the use of antenatal steroids. Among them, the birth weight, mid-parental height, the presence of SGA or NEC were associated with growth rate.

To explore the association of a factor while considering the confounding effects of other factors, the variables were sequentially added into the model according to their contributions to the prediction of weight. The significance of the contribution of each variable was assessed by the likelihood ratio test. Variables which contributed to the prediction of weight were birth weight, mid-parental height, gestational age, maternal age, NEC and BPD see Table 4-21.

The fixed effects in the final model for weight are presented in Table 4-22. After taking the confounding effects of other factors into consideration, birth weight, gender, mid-parental height, gestational age, maternal age, NEC and BPD were found to be

associated with the postneonatal growth in weight. Besides gender, four variables were found to be associated with the growth rate of weight. They are birth weight, gestational age, mid-parental height and maternal age. NEC and BPD were found to be associated only with the growth level of body weight.

The examination of the residual plots and the distribution of estimates of the random effects for the growth model for weight provided no evidence that any of the model assumptions were invalid. Further, the likelihood ratio tests suggested that no additional factors and interactions were necessary.

Table 4-20 Fixed effects for weight: variables were added into the basic model individually

	Value	Std.Error	z ratio	LR test*	P value
Birthweight				69.88(df=2)[a]	0.0001
BW	0.166	0.0211	7.85	65.34(df=1)[b]	<0.0001
Age:BW	0.0022	0.0010	2.14	4.54 (df=1)[c]	0.033
Mid-parental height				43.79(df=2)	<0.0001
MPH	0.078	0.074	1.05	3.72 (df=1)	0.054
Age:MPH	0.021	0.0032	6.49	40.07(df=1)	<0.0001
BPD				24.95(df=2)	<0.0001
BPD	-0.45	0.088	-5.05	23.84(df=1)	<0.0001
Age:BPD	0.0043	0.0041	1.06	1.11(df=1)	0.29
SGA				17.43(df=2)	0.0016
SGA	-0.18	0.089	-2.08	6.83(df=1)	0.0090
Age:SGA	-0.013	0.0040	-3.28	10.60(df=1)	0.0011
NEC				12.41(df=2)	0.0020
NEC	-0.34	0.12	-2.93	6.75(df=1)	0.0094
Age:NEC	0.013	0.0053	2.39	5.66(df=1)	0.017

(Table 4-20 continued)

	Value	Std.Error	z ratio	Likelihood ratio test	P value
Maternal age ≤ 20 yr.				11.56(df=2)	0.0031
Mage	-0.39	0.14	-2.79	9.29(df=1)	0.0023
Age:Mage	-0.0096	0.0063	-1.51	2.27(df=1)	0.13
Antenatal steroids				8.44(df=2)	0.015
Antenatal steroids	0.23	0.084	2.69	7.97(df=1)	0.0048
Age:steroids	0.0026	0.0038	0.69	0.47(df=1)	0.49
SES				3.73(df=2)	0.15
SES	0.12	0.087	1.37	2.44(df=1)	0.11
Age:SES	0.0047	0.0041	1.14	1.29(df=1)	0.26
Breastfed				3.18(df=2)	0.20
Breastfed	-0.035	0.085	-0.41	0.023 (df=1)	0.88
Age:Breastfed	0.0069	0.0039	1.78	3.16 (df=1)	0.075
CP				2.70(df=2)	0.26
CP	-0.25	0.25	-1.59	2.67(df=1)	0.10
Age:CP	-0.0012	0.0071	-0.17	0.039(df=1)	0.87
Sepsis				2.17(df=2)	0.34
Sepsis	-0.063	0.11	-0.60	0.15(df=1)	0.69
Age:Sepsis	0.0069	0.0049	1.42	2.02(df=1)	0.16
Maternal school				2.14(df=2)	0.34
Mschool	-0.17	0.12	-1.46	2.08(df=1)	0.15
Age:Mschool	0.0012	0.0054	0.23	0.05(df=1)	0.82
PDA				0.94(df=2)	0.62
PDA	-0.055	0.084	-0.65	0.29(df=1)	0.58
Age:PDA	0.0031	0.0039	0.81	0.65(df=1)	0.42

* Three values are presented for each variable in likelihood ratio tests.

a: Drop of deviance when adding both main effect and interaction terms.

b: Drop of deviance when adding only main effect term.

c: Drop of deviance when adding only interaction term into the model with the main effect term.

Table 4-21 Likelihood ratio tests for determinants of weight: variables added into the model sequentially

	Likelihood ratio statisitc	P value
Birthweight	69.88(df=2)	<0.0001
BW	65.34(df=1)	<0.0001
Age:BW	4.54(df=1)	0.033
Mid-parental height	40.81(df=2)	<0.0001
MPH, 10 cm	2.31(df=1)	0.13
Age:MPH	38.50(df=1)	<0.0001
Gestational age	33.19 (df=2)	<0.0001
Gestational age	22.86 (df=1)	<0.0001
Age:gestational age	10.33 (df=1)	0.0013
Maternal age ≤ 20 yr.	21.46 (df=2)	<0.0001
Mage	12.11 (df=1)	0.0005
Age:Mage	9.35 (df=1)	0.0022
NEC	8.24 (df=2)	0.016
NEC	12.23(df=1)	0.0069
Age:NEC	2.74(df=1)	0.33
BPD	7.30(df=2)	0.026
BPD	7.20(df=1)	0.0073
Age:BPD	0.11(df=1)	0.75

Table 4-22 Estimates of fixed effects in the final model for weight

	Value	Approx. SE	z ratio
(Intercept)	3.3445	1.3696	
sex	-0.0629	0.1497	-0.420
BW, 100 g	0.2157	0.0291	7.420
GA, week	-0.1059	0.0230	-4.602
MPH, 10 cm	0.0061	0.0696	0.088
Maternal age	-0.4137	0.1628	-2.541
NEC	-0.3237	0.1140	-2.840
BPD	-0.2519	0.0944	-2.669
Slope:			
age	-0.1357	0.0629	-2.155
log(age)	1.6436	0.0574	28.651
age:sex	-0.0174	0.0066	-2.650
log(age):sex	0.2918	0.0825	3.535
age:bw	0.0033	0.0013	2.540
age:GA	-0.0033	0.0011	-3.127
age:mph10	0.0187	0.0032	5.774
age:Mage	-0.0210	0.0075	-2.790

A detailed description of the association between each factor and the postneonatal growth in weight was presented in Figure 4-39. Infants of taller parents were heavier and grew faster than those of shorter parents. Infants with higher birth weights were heavier and grew slightly faster than those with lower birth weights. Infants with longer

gestational ages were lighter and grew slightly slower than those with shorter gestational ages. Infants who had NEC were lighter than those without NEC, but there was no difference in the growth rate of weight between them. The infants with BPD were lighter than those without BPD. The Infants of mothers who were 20 years old or younger were lighter and grew slower than the infants of mothers who were older than 20 years.

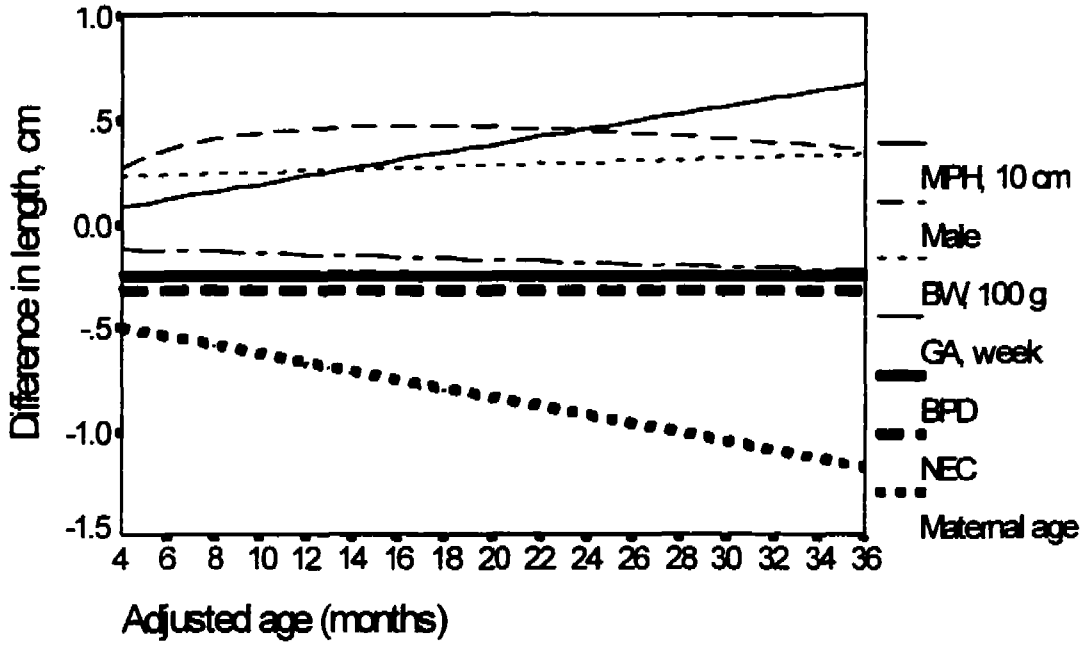


Figure 4-39 Relations between factors and weight in VLBW infants

4.5 Applying growth models to infants who were not included in the study sample

To assess the generalizability of the growth models developed in this study, the growth level for each infant who was not included in the study sample was estimated using the growth models. Only limited growth information was available for infants who

were not included in the present study sample. The predicted values in weight were plotted against the observed values in Figure 4-40.

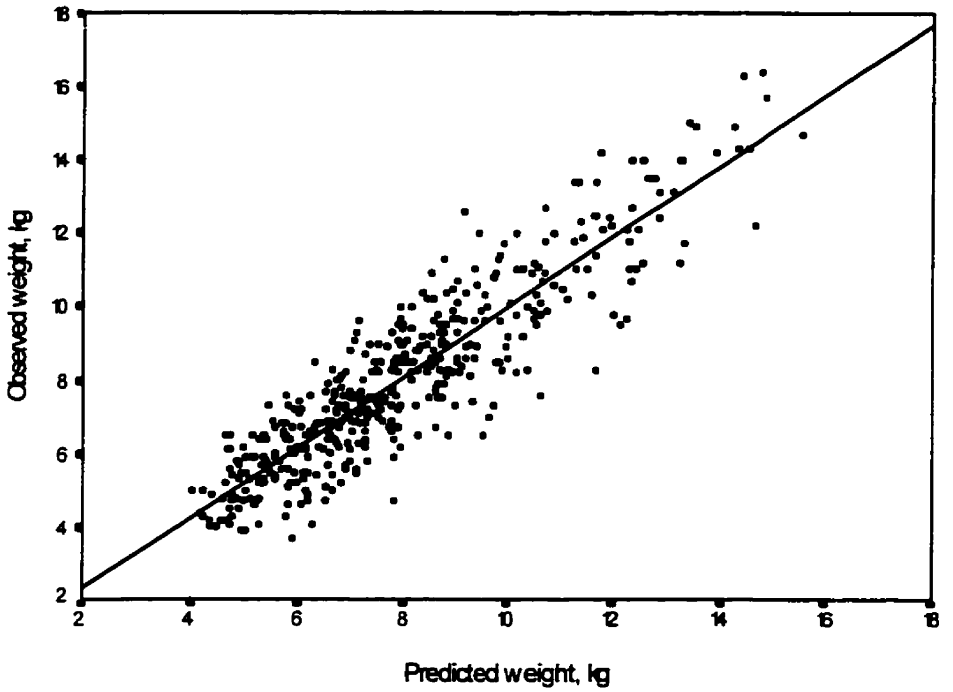


Figure 4-40 Predicted and observed weights for infants who were not included in the present study

The observed values distribute around the predicted values. The mean residuals for those infants were slightly higher than zero. The residuals are differences between observed weight and predicted values based on the characteristics of infants. The average residual is 0.10 kg. Therefore, the infants who were not selected for the present study were slightly (0.10 kg) heavier than infants with similar characteristics in the study sample, but the clinical significance of this is unclear.

4.6 PREDICTORS OF SUBNORMAL GROWTH AT THREE YEARS OF AGE

4.6.1 For length

To determine the factors which could predict subnormal growth at three years adjusted age, the infants were divided into two groups: subnormal and normal growth groups. Infants with a growth measurement equal to or less than the median minus 2 SD of the NCHS/WHO reference at 36 months adjusted age were taken as subnormal in growth. The mean values of continuous variables of potential factors for subnormal and normal groups are presented in Table 4-23.

Table 4-23 Characteristics of infants with subnormal and normal growth in length at age three years: means

	Subnormal (Z score≤ -2)			Normal (Z-score>-2)			
	Mean	SD	No.	Mean	SD	No.	95% CI of Difference
Birthweight, (g)	861.4	188.0	33	960.3	187.4	414	-165.5, -32.3
Gestational age (wk.)	28.2	2.6	33	27.7	2.3	414	-0.33, 1.3
Ponderal index	2.27	0.26	33	2.13	0.26	402	0.06, 0.24
Maternal age (yr.)	25.5	5.5	33	27.8	5.2	414	-4.1, -0.36
Acute NICU (days)	61.2	38.5	33	43.7	31.4	414	6.2, 28.9
Mid-parental height, cm	166.8	6.1	30	170.9	6.0	340	-6.3, -1.9

The bivariate analysis showed that subnormal growth infants had lower birth weight, higher ponderal index, younger maternal age, lower mid-parental height and longer

hospital stay than normal infants. Infants with subnormal growth in length at 3 years adjusted age were more likely to be infants with IUGR, CP, BPD, and subnormal growth at 4 months adjusted age than the normal growth infants, see Table 4-24.

Table 4-24 Characteristics of infants with subnormal and normal growth in length at age three years: Proportions

	Subnormal	No.	Normal	No.	P value[a]
Male	51.1	33	46.1	414	0.55
Apgar score less than 6:					
at 5 minutes	21.2	33	20.0	409	0.87
Race, Non-Caucasian	12.1	33	11.6	405	0.93
SGA	48.5	33	22.1	412	<0.001
Asymmetric at birth	3.0	33	14.9	402	0.07
CP	18.2	33	6.8	414	0.02
BPD	54.8	31	30.9	404	0.006
Necrotizing enterocolitis	9.1	33	15.3	412	0.33
PDA	30.3	33	41.8	414	0.20
RDS	66.7	33	68.6	414	0.81
Sepsis	21.2	33	18.6	414	0.71
Apnea	75.8	33	70.8	414	0.54
Low SES	32.3	31	22.0	369	0.18
Maternal education (< 12 yr.)	19.4	31	15.9	383	0.62
Subnormal growth at 4 months adjusted age	67.9	28	21.7	382	<0.0001

a: P values of Chi square test.

To determine the predictors of subnormal growth in length at three years of age, logistic regression models were fitted. First, a model was fitted without the growth status at four months adjusted age. Five variables were found to be associated with subnormal growth for length at three years of age. Birth weight and mid-parental height were negatively associated with the occurrence of subnormal growth. Gestational age, CP and BPD were positively associated with subnormal growth in length, see Table 4-25.

To assess the predictive importance of the previous growth status on growth outcome at three years of age, an indicator of subnormal growth at 4 months adjusted age was postulated. The growth status at 4 months adjusted age was associated with subnormal growth at 36 months adjusted age with statistical significance, see Table 4-26. After taking the predictive contribution of growth status at 4 months adjusted age into consideration, CP and BPD were no longer associated with subnormal growth at 3 years adjusted age with statistical significance. The point estimates of odds ratios for birth weight, mid-parental height, gestational age, CP and BPD decreased (close to 1) when growth status at 4 months adjusted age was included in the model.

In this analysis, the variables such as birth weight, gestational age and mid-parental height were taken as continuous variables assuming that the changes in the log odds of subnormal growth were the same per unit change of each of these variables within the observed age range. This assumption was examined by adding a quadratic term or logarithmic term in the model and testing the change of the residual deviance between

two models. No evidence was found against the linear relationships between these continuous variables and the log odds of subnormal growth at 3 years adjusted age.

No interactions among the potential factors could be added into the model with statistical significance. There was no evidence against the assumption that the association between a factor and subnormal growth at 3 years adjusted age depended on the level of other factors.

Table 4-25 Odds ratios for subnormal growth in length at 3 years of age computed from logistic regression analyses: model 1

Variable	Parameter	S.E.	P value	OR	95% CI
BW, 100 g	-0.4043	0.1439	0.0050	0.67	0.50, 0.88
MPH, 10 cm	-1.5101	0.4335	0.0005	0.22	0.09, 0.52
GA, week	0.2960	0.1126	0.0086	1.34	1.08, 1.68
Maternal age ≤20 yr.	1.5500	0.5847	0.0080	4.71	1.50, 14.8
BPD	1.0415	0.5067	0.0398	2.83	1.05, 3.17
CP	1.2172	0.6017	0.0431	3.38	1.04, 2.40
Constant	17.4905	8.0381			

Table 4-26 Odds ratios for subnormal growth in length at 3 years of age computed from logistic regression analyses: model 2

Variable	Parameter	S.E.	P value	OR	95% CI
BW, 100 g	-0.3394	0.1636	0.0380	0.71	0.52, 0.98
MPH, 10 cm	-1.3267	0.4572	0.0037	0.27	0.11, 0.65
GA, week	0.2652	0.1186	0.0254	1.30	1.03, 1.64
Maternal age≤20 yr.	0.8788	0.6736	0.1921	2.41	0.64, 9.01
BPD	0.9643	0.5618	0.0861	2.62	0.87, 7.89
CP	0.8569	0.6606	0.1946	2.36	0.65, 8.60
Subnormal at 4 mo.	1.0714	0.5328	0.0443	2.92	1.03, 8.30
Constant	14.3143	8.3504			

4.6.2 For weight

Infants who were subnormal in weight were found to have significantly lower birth weight, longer gestational age, higher ponderal index, older maternal age and higher mid-parental height than infants who were normal at 3 years adjusted age. Those subnormal infants had longer acute NICU stay than did the normal infants, but there was no statistical significance, see Table 4-27.

Table 4-27 The Characteristics of infants with subnormal and normal growth in weight at age three years: means

	Subnormal (≤Median -2SD)			Normal (>Median-2SD)			
	Mean	SD	No.	Mean	SD	No.	95% CI of Difference
Birthweight, (g)	873.0	207.8	71	968.0	181.6	376	-142.3, -47.7
Gestational age (wk.)	28.5	2.9	71	27.7	2.2	376	0.2, 1.4
Ponderal index	2.20	0.27	71	2.13	0.26	357	0.01, 0.14
Maternal age (yr.)	26.0	5.6	71	27.9	5.2	376	-3.2, -0.59
Acute NICU (days)	49.2	35.3	71	44.2	31.6	376	-3.2, 13.2
Total hospital stay (days)	90.9	36.9	65	87.5	34.5	344	-5.8, 12.7
Mid-parental height, cm	168.2	5.6	57	171.0	6.0	313	-4.4, -1.1

Intrauterine growth status (SGA), BPD, NEC, SES and subnormal growth at 4 months adjusted age were also found to be associated with subnormal growth in weight at 36 months adjusted age, see Table 4-28. A higher percentage of subnormal infants were SGA and subnormal at 4 months adjusted age. Also, a higher percentage of them had BPD while a lower percentage had NEC.

Table 4-28 Characteristics of infants with subnormal and normal growth in weight at age three years: Proportions %

	Subnormal	No.	Normal	No.	P value[a]
Male	42.3	71	47.3	376	0.43
Apgar score less than 6:					
at 5 minutes	21.1	71	19.9	371	0.82
Race, Non-Caucasian	9.0	67	12.1	371	0.46
SGA	49.3	71	19.3	374	<0.0001
Asymmetric at birth	11.4	70	14.5	365	0.49
CP	8.5	71	7.4	376	0.77
BPD	43.5	69	30.6	366	0.036
Necrotizing enterocolitis	7.0	71	16.3	374	0.044
PDA	43.7	71	40.4	376	0.61
RDS	59.2	71	70.2	376	0.066
Sepsis	23.9	71	17.8	376	0.23
Apnea	71.8	71	71.0	376	0.89
Low SES	30.8	65	21.2	335	0.092
Maternal education (< 12 yr.)	23.1	65	14.5	349	0.10
Subnormal growth at 4 months adj. age	55.2	67	14.6	343	<0.0001

a: P values of Chi square test.

The Odds ratios estimated from the logistic regression analysis are presented in Table 4-29. Only variables which significantly contributed to the prediction of log odds of subnormal growth were included in the model. Higher birth weight and mid-parental

height are negatively associated with subnormal growth in weight while longer gestational age and younger maternal age are positively associated with subnormal growth at three years adjusted age in VLBW infants. The presence of BPD is positively associated with subnormal growth, but the association does not have statistical significance. Since BPD is the only non-significant variable with P value <0.10, it remains in the final model.

Table 4-29 Odds ratios for subnormal growth in weight at 3 years adjusted age computed from logistic regression analyses: Model 1

Variables	Parameter	S.E.	P value	OR	95% CI
BW, 100 g	-0.4189	0.1130	0.0002	0.66	0.53, 0.82
MPH, 10 cm	-0.8871	0.3039	0.0035	0.41	0.22, 0.75
GA, week	0.3427	0.0842	<0.0001	1.41	1.19, 1.66
Maternal age≤20	1.9591	0.5030	0.0001	7.09	2.65, 19.01
BPD	0.6491	0.3840	0.0909	1.91	0.90, 4.06
Constant	7.1679	5.7171			

Adding the growth status at 4 months adjusted age in the model, the variables such as birth weight, gestational age, maternal age and mid-parental height still remained associated with subnormal growth with statistical significance, see Table 4-30.

Subnormal growth at 4 months adjusted age is strongly associated with subnormal growth that 3 years adjusted age. Infants with subnormal growth at 4 months adjusted age were more likely to be subnormal at three years adjusted age.

There was no evidence against the assumption of linearity between continuous variables and the log odds of subnormal growth. No interactions could be added into the model with statistical significance by examining the change of the residual deviance between the models with and without the interaction term.

Table 4-30 Odds ratios for subnormal growth in weight at age three years computed from logistic regression analyses: Model 2

Variables	Parameter	S.E.	P value	OR	95% CI
BW, 100 g	-0.3467	0.1195	0.0037	0.71	0.56, 0.89
MPH, 10 cm	-0.8926	0.3123	0.0043	0.41	0.22, 0.76
GA, week	0.2692	0.0857	0.0017	1.31	1.11, 1.54
Maternal age≤20 yr.	1.2112	0.5388	0.0246	3.36	1.17, 9.65
BPD	0.1955	0.4153	0.6379	1.22	0.54, 2.74
Subnormal at 4 mo.	1.6064	0.3713	<0.0001	4.99	2.41, 10.32
Constant	8.3917	5.8544			

4.7 PREDICTORS OF SUBNORMAL GROWTH DURING INFANCY

Generalized linear models for clustered data[25,30] via "generalized estimating equations (GEE)" in the computer program of S statistical package were used to assess the associations between potential factors and subnormal growth during the observational period. In the GEE approach analysis, different correlation structures were used. However, the similar regression coefficients were obtained using different correlation structures. The findings reported in Table 4-31 to Table 4-34 were computed using the "exchangeable" correlation structure in the model.

The infants of taller parents or with higher birth weight were less likely to have subnormal growth during infancy in both length and weight. The association between mid-parental height and subnormal growth in weight increased with age in terms of odd ratio of subnormal weight. The odds ratio of subnormal weight of infants whose parents were 10 cm taller deviates further from 1 as infants grew, see Figure 4-41. The 95% confidence intervals were calculated based on the standard errors and covariances of two variables: mid-parental height and infant's age. Infants with NEC, longer gestational age (given birth weight) , and maternal age $\leq$ 20 years were more likely to have subnormal length. However, the association between NEC and subnormal length decreased with age. The odds ratio of subnormal length for NEC infants relative to non-NEC infants approaches one as infants grew, see Figure 4-42. Infants with BPD, longer gestational age and maternal age $\leq$ 20 years were more likely to have subnormal growth in weight.

Table 4-31 Predictors of log odds of subnormal growth in length

	Estimate	S.E.	Z value	P value
Intercept	8.4046	3.4639	2.426	
age	-0.0435	0.0072	-6.067	<0.0001
mph, 10 cm	-0.7828	0.1809	-4.326	<0.0001
BW, 100 g	-0.5650	0.0712	-7.935	<0.0001
GA, week	0.3211	0.0589	5.454	<0.0001
Maternal age≤ 20 yr.	1.1588	0.3630	3.192	0.0014
NEC	1.0521	0.3082	3.414	0.0006
age*NEC (interaction)	-0.0311	0.0160	-1.942	0.052

Table 4-32 Odds ratios for subnormal growth in length computed from the GEE model

Variables	OR (95% CI)
MPH, 10 cm	0.46 (0.32, 0.65)
BW, 100 g	0.57 (0.49, 0.65)
GA, week	1.38 (1.23, 1.55)
Maternal age ≤ 20	3.19 (1.56, 6.49)
NEC, at 4 mo.	2.53 (1.45, 4.40)
NEC, at 36 mo.	0.94 (0.35, 2.50)

Table 4-33 Predictors of log odds of subnormal growth in weight

	Estimate	S.E.	Z value	P value
(Intercept)	-2.1062	3.6749	-0.5731	
age	0.4694	0.1634	2.8728	0.0041
age^2	-0.0025	0.0004	-6.2023	<0.0001
BW, 100 g	-0.3677	0.0619	-5.9359	<0.0001
GA, week	0.2226	0.0506	4.4007	<0.0001
MPH, 10 cm	-0.1294	0.1968	-0.6576	0.51
Maternal age≤20 yr.	1.3753	0.3634	3.7845	0.00015
BPD	0.6556	0.1983	3.3054	0.00095
age*MPH (interaction)	-0.0234	0.0095	-2.4715	0.013

Table 4-34 Odds ratios for subnormal growth of weight computed from the GEE model

Variables	OR (95% CI)
MPH, 10 cm at 4 mo.	0.80 (0.60, 1.08)
MPH, 10 cm at 36 mo.	0.38 (0.23, 0.63)
BW, 100 g	0.69 (0.61, 0.78)
GA, week	1.25 (1.13,1.38)
Maternal age ≤20 yr.	3.96 (1.94,8.07)
BPD	1.93 (1.31,2.84)

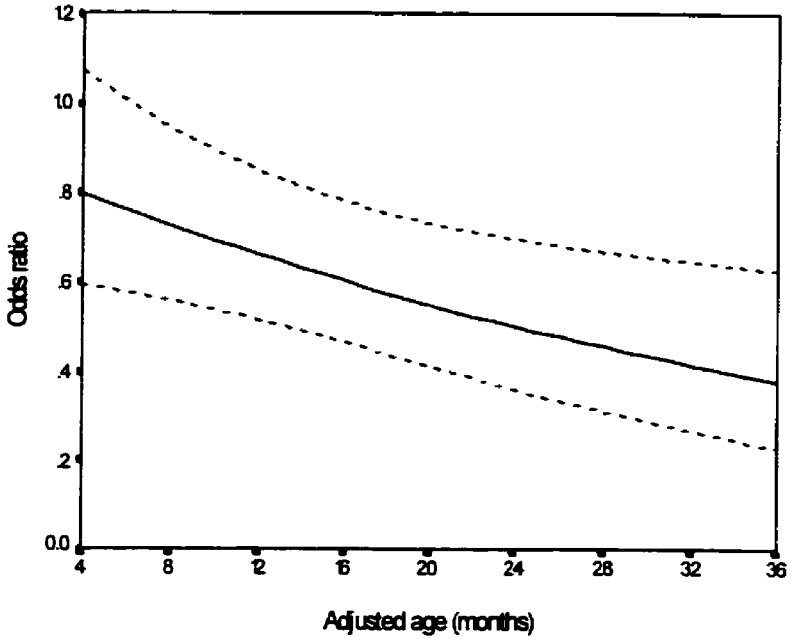


Figure 4-41 Odds ratio of subnormal growth in weight for infants of taller (10 cm) parents

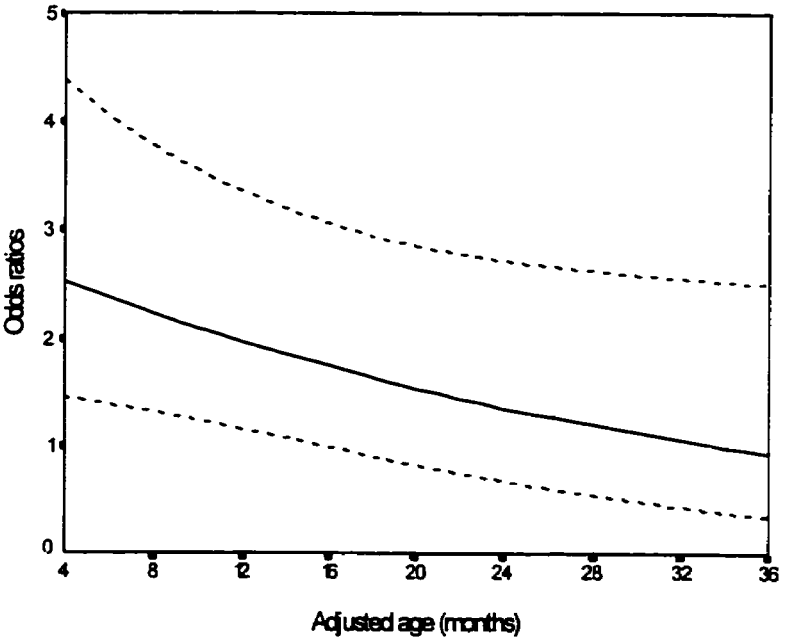


Figure 4-42 Odds ratio of subnormal growth in length for infants with NEC

CHAPTER FIVE: DISCUSSION

5.1 INTRODUCTION

There were two major goals in this study: to describe the growth patterns and to identify the determinants of postneonatal growth in VLBW infants. Both classical methods and mixed effects models were used to describe the growth patterns. VLBW infants were found to follow different growth patterns from the normal term reference population. Selecting growth references has important impacts on the outcomes of catch-up growth in VLBW infants. Different growth outcomes were obtained using different growth references. Infants with different perinatal and demographic characteristics have different growth patterns. Findings in this study show that age adjustment for the premature is an important concept for describing growth of VLBW preterm infants.

Three modelling approaches were implemented to identify the determinants of postneonatal growth in VLBW infants. Mixed effects models were used to identify factors associated with growth level and growth rate. Logistic regression models were used to identify predictors of subnormal growth at 3 years adjusted age. The GEE approach was used to identify predictors of subnormal growth during infancy. Higher birth weight and higher mid-parental height were positively associated with postneonatal growth while younger maternal age and longer gestational age were negatively associated with postneonatal growth. Infants with BPD, NEC and CP were found to have poorer

growth during infancy. The detailed associations between each factor and postneonatal growth in length and weight were described in this study. The most important finding in this study is that the associations between potential factors and postneonatal growth have been quantified. Such quantification is important for assessing and predicting growth in VLBW infants. The intent of this chapter is to discuss potential biases such as the representativeness of the study sample and issues related to growth assessment (such as selection of growth references and adjusting for prematurity), to review the findings within the context of contemporaneous studies, and to outline the weaknesses and implications of the study.

5.2 Representativeness of the Study Sample

The infants of the study sample had lower birth weight, shorter gestational age, older maternal age, higher maternal education and social economic status, and higher prevalence of some adverse clinical conditions than infants who weighed 1250 grams or less at birth but were not included in the present study. The average growth levels in this study describe the growth status of infants with the characteristics of the present study sample. Therefore, the average growth levels of VLBW infants may be underestimated in this study. However, the final goal of the present study was to describe the growth patterns of VLBW infants based on their perinatal and parental characteristics. The growth models developed in this study could be representative of the general population of VLBW infants only under the assumption that the infants who were not included in the

study due to incomplete follow-up grew similarly to those in the study sample if they had had the same perinatal and social demographic characteristics. Although the characteristics of the study sample were found to be different from those who were not included in the study, the difference in weight between predicted values using models developed in this study and observed values for infants who were not included in the present study was not substantial. Based on limited information available, infants who were not included in the study sample were found to be slightly heavier (0.10 kg) than the study sample assuming they had similar perinatal and parental characteristics. The causes of such differences are unknown. It might be due to the following: (a) infants with similar characteristics who were not included in the study were those with better growth outcomes than the study sample (selection bias); or (b) there might be some other factors, such as the severity of illness, which affected the growth of VLBW infants and were distributed differently in the study sample than in other infants. Those factors were not taken into consideration in the present study (confounding effects). The change of growth status during infancy in this study was a reasonable description of the change of growth status in VLBW infants since the comparisons of growth status at different ages were based on the repeated measurements of almost the same group of infants. Caution should be emphasized in any effort to apply the growth models developed in this study to a population with higher birth weight or to infants who are older than 3 years adjusted age.

5.3 Average Growth patterns of VLBW infants

The growth patterns were described in two levels: the average growth patterns of the study sample as a group and the growth patterns of infants with particular characteristics. The growth patterns of infants with particular characteristics will be discussed in section 5.4.2 "Factors associated with postneonatal growth" in page 159.

Different approaches were used to describe the growth patterns of VLBW infants. The mean values of Z-scores represent the differences in growth measurements between the observed mean of the study sample and the median of reference growth data in standard deviation units. The mean Z-scores were lower than zero during the observational period for both weight and length, which suggests that the average growth levels of VLBW infants were lower than those of the reference populations. The average growth levels of the study sample estimated by mixed effects models were also lower than the median of the growth references at all age groups for both weight and length. Like normal term infants,[193] a deceleration of growth rate was found in the study sample. However, as discussed above, these average growth levels may not represent the average growth levels of the population of VLBW infants since the study sample is different from infants who were not selected for the present study in some perinatal and social demographic characteristics.

Although the average growth levels are lower than those of the reference data, it is shown by both calculating the mean Z-scores and estimating the mean growth levels with the mixed effects models that the growth status of VLBW infants in the study sample

improved with age for both length and weight relative to the Canadian reference, and for length relative to the NCHS/WHO reference. The prevalence of subnormal growth decreases during infancy for both length and weight when using the Canadian reference and for length when using the NCHS/WHO reference. The prevalence of subnormal growth for weight relative to the NCHS/WHO reference increases before 12 months adjusted age and decreases afterward. Catch-up growth was found for length regardless of which references were used. Different results on catch-up growth in weight were obtained by using different references. Relative to the NCHS/WHO reference, no catch-up growth in the first 12 months adjusted age was observed while catch-up growth was observed relative to the Canadian reference.

A recent large sample study on the growth of low birth weight (≤2500 g) infants by Casey et al[7] reported that little catch-up was found in three low birth weight groups including a group with the same birth weight category as the present study sample. However, by comparing growth rates of length among three groups of low birth weight infants, they did find that the lowest birth weight (≤1250 g) infants grew faster than the other two groups at 12 months of age, which suggested some catch-up growth. No catch-up growth after 12 months of age for length and for whole observational period (up to 36 months of adjusted age) for weight was reported in their study. The differences between Casey et al's and the present study in terms of catch-up growth may be due to some methodological differences. Although the growth levels of low birth weight infants were compared with the NCHS growth reference in their study, no direct numerical

comparisons have been made by means of Z-scores or prevalence of subnormal growth. The growth rates were only compared among three low birth weight groups but not with growth references. The differences in the characteristics of the study samples might also be attributable to the discrepancies in the growth outcomes. Compared to Casey's study, the present study did not exclude infants who received more than 90 days of oxygen or were hospitalized more than 60 days after 40 weeks corrected for gestational age.[7] The mean growth levels of the study sample are slightly lower than the mean growth levels of the growth references developed by Casey et al.

Some studies in the literature reported no catch-up growth in VLBW infants. Kimble et al. reported that average growth levels of length in AGA VLBW infants (<1501 grams of birth weight) were between the 10th and 25th percentiles of the NCHS growth reference for weight, between the 10th and 15th percentiles for length for boys, and 25th and 30th percentiles for girls during the first three years of life. No catch-up growth in VLBW infants was found in their study.[4] Karniski et al. reported the mean Z-scores of weight and length in VLBW infants and no catch-up growth was found.[10] Both of the above studies were based on growth data of small sample sizes. The characteristics of their study samples were different from those of the present study. On the contrary, Brandt reported that growth and development of very small AGA preterm infants was similar to that of full-term control infants, provided that the nutrition was adequate, the environmental conditions were favorable, and the age was corrected[11]. However, the characteristics of the study sample are different from those of the present study. Some

higher birth weight infants were included in Brandt's study and the lowest birth weight limit was higher than that of the present study. Hirata et al. reported the growth levels of infants with 501 to 750 grams of birth weight up to 6 years of age and showed that catch-up growth did not occur before three years of age but occurred after 3 years of age.[194] Obviously their study only included very small infants.

Some studies showed the existence of an incomplete catch-up growth in VLBW infants. Both studies by Hack et al[8] and Qvigstad et al[1] showed that the proportion of subnormal growth decreased as infants grew. Their findings are comparable to the findings of the present study. Although the VLBW infants showed some degree of catch-up growth, their growth levels are still substantially lower than the median of the reference population and a substantially larger proportion of infants than expected remain "subnormal".

5.3.1 Growth references in describing growth patterns

The differences in growth references from different populations have been realized in the literature.[12,61,88,89,91] However, a WHO working group[92] pointed out that "for practical purposes they (the differences) are not considered large enough to invalidate the general use of the NCHS population both as a reference and a standard." In this study, substantially different growth outcomes for the same group of VLBW infants were obtained using different references: the Canadian (local) reference and the NCHS/WHO (international) reference, especially for younger infants. At 4 months adjusted age, over

twenty percent of infants were classified as "subnormal" growth in either length or weight using the Canadian reference but as "normal" using the NCHS/WHO reference. As the infants grew older, more of them were classified as underweight using the NCHS/WHO reference than using the Canadian reference, 37% vs. 27% at 12 months, and 25% vs. 18% at 18 months adjusted age.

The practical impact of using the NCHS/WHO reference and the reference data for breast-fed infants was discussed by examples of the growth data from developing countries and the growth data of American and European formula-fed infants; and the different results in growth outcomes were obtained by using different growth references.[61] In the present study, no differences in growth outcomes of VLBW infants using the Canadian reference and the breast-fed data were found; but both were different from using the NCHS/WHO reference.

The discrepancies in the growth outcomes using different growth references make us suspect the validity of the current growth references. Determining the most valid growth references is beyond the scope of the present study. However, the comparisons of the characteristics of the current growth references show that the Canadian growth reference seems to be more appropriate than the NCHS/WHO reference for the present study population. The original National Center for Health Statistics (NCHS) growth curves were formulated in 1975.[61] The reference data for ages 0-23 months was based on the growth data of a group of children in the Fels Research Institute Longitudinal Study, collected from 1929 to 1975. The Canadian growth reference data were collected in more

recent years than the NCHS/WHO growth data. The Canadian growth reference was based on the longitudinal data collected in two cities, Montreal and Toronto, during 1977 and 1978.[12,98] Canadian growth data are longitudinal while the NCHS/WHO growth data are cross-sectional. Also, the Canadian growth reference data were collected from populations with similar social contexts as the present study population. It may represent the current expected growth of normal term infants in the same social environmental context of population and with current high breast feeding rates.[195] The differences among growth references might also be attributable to the inconsistent findings on the growth outcomes in the previous studies since various growth references have been used in the literature.[3,4,11] It should be cautioned that even the same infant might be labeled as "subnormal" growth using one growth reference but as "normal" using another reference.

As mentioned previously, a growth reference for low birth weight infants was established by Casey et al.[7,100] Low birth weight infants were divided into three different groups according to their birth weights. The average growth levels for each group were calculated. These average growth levels estimated from the study sample can only provide the information of the general growth status for a particular group of infants. One should be skeptical of efforts to apply any average growth levels of a study sample to other groups of infants with different characteristics. The present study indicates that the postneonatal growth patterns of VLBW infants depend on the characteristics of infants. Even for infants free from adverse clinical conditions, the growth patterns are still

strongly associated with birth weight, gestational age, mid-parental height and gender. The difference in the growth outcomes among different studies may be attributable to the differences in the characteristics among study samples. No average growth patterns from a single study sample are adequately representative of the growth of all VLBW infants. Therefore, the characteristic specific growth patterns are more informative than the average growth patterns for predicting and assessing the growth of VLBW infants. The growth models developed in this study allow health professionals and researchers to obtain the expected growth patterns of an infant or a group of infants with a specific combination of the studied characteristics. These expected growth patterns can be used as the references for growth monitoring.

It should be pointed out that expected growth from the growth models is the average growth levels of infants with the same characteristics in the contemporary clinical and social environments rather than the "ideal" growth levels of the infants. The predicted average growth levels for infants with BPD, NEC or CP or infants of teenage mothers are low due to those adverse conditions. Even though the observed growth of an infant follows the predicted pattern by the models, this does not mean that the infant's growth is normal. However, the predicted growth patterns from the models can be obtained based on birth weight, gestational age, mid-parental height and gender assuming that the infant is free from other adverse clinical conditions such as BPD, NEC and CP and is not the infant of a teenage mother. It is reasonable to believe that these predicted growth patterns may be taken as current acceptable growth patterns.

It may be questioned whether it is necessary to have a growth reference developed from VLBW infants to assess the growth of VLBW infants. The reason against the use of this reference is that VLBW infants were not healthy newborns and the reference developed from this population did not represent the expected "standard" growth for VLBW infants. Hack and Fanaroff stated that "it is perhaps less cumbersome to use standardized growth charts (based on normal term infants) with the knowledge that deviations are normal." However, VLBW infants were found to follow different growth patterns from normal term infants in this study as well as in previous studies.[4,7] The growth reference for VLBW infants provides a useful tool to monitor the growth progress for VLBW infants. The growth levels in the majority of VLBW infants were found to be lower than the median of growth reference for normal term infants and a substantial proportion of them were lower than the mean or median minus 2 SD. Therefore, the growth progress of VLBW infants cannot be easily observed using references for normal term infants. The reference for VLBW infants allows health professionals to compare the growth progress of an infant with those infants who have similar characteristics.

5.3.2 Age adjustment for prematurity in describing growth patterns

Although adjusting of age for prematurity seems intuitively correct and has been recommended for the growth assessment of preterm infants,[11,36] few studies have explored the necessary period for the adjustment in VLBW infants discharged from

contemporary Neonatal Intensive Care Units (NICU). Brandt[11] studied appropriate for gestational age (AGA) infants, most with birthweights <1500 grams, in Germany; and concluded that the age adjustment for prematurity became unnecessary after 24 months of age for weight and about 3.5 years for length. However, the sample characteristics were different from those of the present study. The target population of the present study was VLBW infants discharged from the NICU in current clinical and social context. A recent study by Elliman et al.[15] suggests that adjusting for prematurity is necessary even up to 7 years of age for assessing growth in height in preterm infants with 2000 grams or less birth weight.

The adjusting of age for prematurity is based on the belief that the expected postneonatal growth before term for preterm infants is similar to intrauterine growth of fetus with the same "post-conception" age. If the postneonatal environment were more favorable to infants' growth than intrauterine environment is to the fetus, it might not be appropriate to adjust age by calculating age starting from 40 weeks of gestation. The term "partial correction" for prematurity appeared in the literature,[196] in which the adjusted age is calculated from sometime before 40 weeks of conception. However, Brandt compared the postneonatal growth of infants without intrauterine growth retardation with the six intrauterine growth standards developed by different investigators and found that the postneonatal growth of preterm infants was lower than all six intrauterine growth standards.[11] No reports have shown that the postneonatal growth of preterm infants is better than the intrauterine growth of fetus with the same conception age before term.

Therefore, the partial correction for prematurity may have little implication in assessing growth of preterm infants, although it may be useful in assessing other developmental aspects.[196]

Empirical evidence is provided on the differences in assessing growth status of VLBW infants using adjusted and unadjusted ages. The average growth level estimated by using adjusted age was higher than that estimated by using chronological age at each age group. However, the difference became smaller as the infants grew. This finding suggests that the adjustment for prematurity is more important for younger infants than for older ones. The differences between adjusted and unadjusted Z-scores remained statistically significant at the end of the observational period in the present study for both length and weight, which suggests that the necessary period of age adjustment for prematurity is beyond 3 years of adjusted age, which is different from Brandt's 24 months of age for weight,[11] but consistent with Elliman's findings for height.[15]

The differences in estimated prevalence of subnormal growth provide evidence of clinical and public health importance of adjusting age for prematurity. A substantially larger proportion of infants were labeled as having subnormal growth if age was not adjusted, which may cause unnecessary referrals, investigations or misplacement of resources, especially in early ages. Under the assumption that adjusted age for prematurity is appropriate for assessing growth in VLBW infants, this adjustment should be done up to at least three years adjusted age.

Age adjustment for prematurity may also influence our understanding of growth patterns of VLBW infants. Catch-up growth, which was measured by an increase in average growth level[7,10] relative to the growth reference data, or by a decrease in the prevalence of subnormal growth,[1-3,6,8,46] was obvious in VLBW infants using chronological age but not so obvious using adjusted age. Such findings are comparable to Karniski et al's results for premature infants with higher birthweight than the present study sample.[10]

5.4 Determinants of postneonatal growth in VLBW infants

5.4.1 Relations among potential factors

Infants growth is the result of a complex set of interrelated factors. Although the comprehensive possible relations among the perinatal and social demographic factors have not been explored, this study clearly indicates that some of the factors are associated with each other.

Extensive literature suggests that investigators differentiate infants into SGA and AGA groups when assessing growth and developmental outcomes.[8,11,132,149,151,197-202] The present study sample only included infants with birthweight 1250 grams or less, and all infants with gestation age 32 weeks or more were SGA. The intrauterine growth status described as SGA or AGA is associated with both gestational age and birth weight. The SGA infants have longer gestational ages and lower birth weights than AGA infants.

Some researchers studied the association of intrauterine growth status and postneonatal growth by comparing the growth of SGA with birth weight or gestational age matched AGA infants.[23] Since the identification of SGA is based on a cut-off point of birth weight given gestational age, there is still a wide range of birth weight within the group of SGA or AGA infants. The intrauterine growth rates may be different among infants within an SGA or AGA group. The distribution of fetal growth ratio (FGR) shows that there are not two distinct groups of infants with different intrauterine growth status. Based on the fetal growth ratio, the severity of intrauterine growth retardation was measured. Infants with more severe intrauterine growth retardation tend to have longer gestational ages and lower birth weights. Whatever methods are used to assess the intrauterine growth status, the necessary information for intrauterinc growth status is provided by two variables: birth weight and gestational age.

Miller and Hassanein[203] described different patterns of body proportions in newborn infants and interpreted these as different patterns of fetal growth. The finding of symmetrically small for gestational age infants was interpreted as the result of long lasting fetal growth retardation. Asymmetric growth retardation was considered a result of faltered fetal growth rate during the third trimester. The findings in the present study indicate that the body proportionality is associated with the severity of IUGR. Contrary to the general belief in the literature, more severely growth-retarded newborns tend to be more disproportionate than less severely affected neonates or those with normal fetal growth. These findings concur with the results from Kramer et al.[32,41,53,78] In the present

study the body proportionality was also found to be associated with birth weight, birth length and gestational age. Asymmetric infants appeared to be larger and more mature at birth than symmetric infants.

The presence of BPD, a common clinical condition in VLBW infants, was found to be associated with various perinatal factors. Infants with BPD are smaller at birth with shorter gestation and have more severe clinical conditions than those without BPD, which agrees with previous studies[20,110,125,158,159] Although the details of the associations among potential factors were not presented in this study, there is sufficient evidence from this example to believe that it is necessary to control the confounding effects when studying the association between a factor and the postneonatal growth.

5.4.2 Factors associated with postneonatal growth

Three different modelling approaches were used to identify the factors associated with postneonatal growth. The factors associated with growth patterns were determined using mixed effects models. Eight factors besides age were found to be associated with the postneonatal growth of body length in VLBW infants when confounding factors were taken into consideration. These factors are gender, birth weight, gestational age, mid-parental height, maternal age, and the presence of BPD, NEC and CP. Some factors, such as the use of antenatal steroids, IUGR, maternal education and the presence of PDA and neonatal sepsis, were found to be associated with postneonatal growth in length if

confounding factors were not taken into account in the analysis. These associations were no longer statistically significant when the confounding effects of other factors were accounted for.

Determinants of subnormal growth were assessed using logistical regression models and generalized linear models for dependent data (GEE). The findings are consistent for four variables: birth weight, mid-parental height, gestational age and maternal age. Higher birth weight and higher mid-parental height are positively associated with postneonatal growth outcomes. Longer gestational age and maternal age 20 years or younger are negatively associated with postneonatal growth.

5.4.2.1 Birth weight

Even among VLBW infants, birth weight was found to be associated with postneonatal growth for both length and weight. Findings from both bivariate and mixed effects modelling analyses indicate that the infants with higher birth weight remain at a higher level but grow slightly slower in length and slightly faster in weight than infants with lower birth weights. Therefore, the difference between infants with different birth weights decreases with age in length and increases with age in weight. The findings concerning the relationship of birth weight to growth confirm those of others.[112,145] Since the confounding effects of some other factors are taken into account in the mixed effects

models, the associations between birth weight and postneonatal growth are not attributable to the confounding effects of other factors included in this study.

The results of logistic regression analysis and GEE approaches suggest that the infants with higher birth weight are less likely to be subnormal in both length and weight. These findings are consistent to those in previous studies.[2,204] In Kitchen's study, lower birth weight predicted poor growth in weight.[2] Kelleher reported that infants with lower birth weight were more likely to have growth deficiency (failure to thrive).[204] A recent study by Hack et al.[205] shows that birth weight has a positive predictive value for the eight year height among low birth weight infants with a multiple regression analysis and that the higher birth weight infants are less likely to have subnormal growth in height at eight years of age with a logistic regression analysis. The present study extended the previous studies by examining the detail associations between birth weight and the process of postneonatal growth.

Figure 5-1 reflects the association between birth weight and postneonatal growth in VLBW infants with particular characteristics. For example, if a hypothetical infant girl is born at 28 weeks gestation with mid-parental height 170 cm and no evidence of BPD, NEC or CP, her growth levels will depend to a large extent on birth weight. The estimated growth levels of length and weight for infants with assumed birthweights of 500, 750, 1000, and 1250 grams are presented in Figure 5-1. If the birth weight was 500 grams, the estimated average growth levels are lower than 10th percentile of the reference data. If an infant has the same other characteristics with a birth weight 1250 grams, the

growth levels are expected to be close to the median of the reference data. Compared with the reference, the expected growth levels for the infant are improving during the infancy for length.

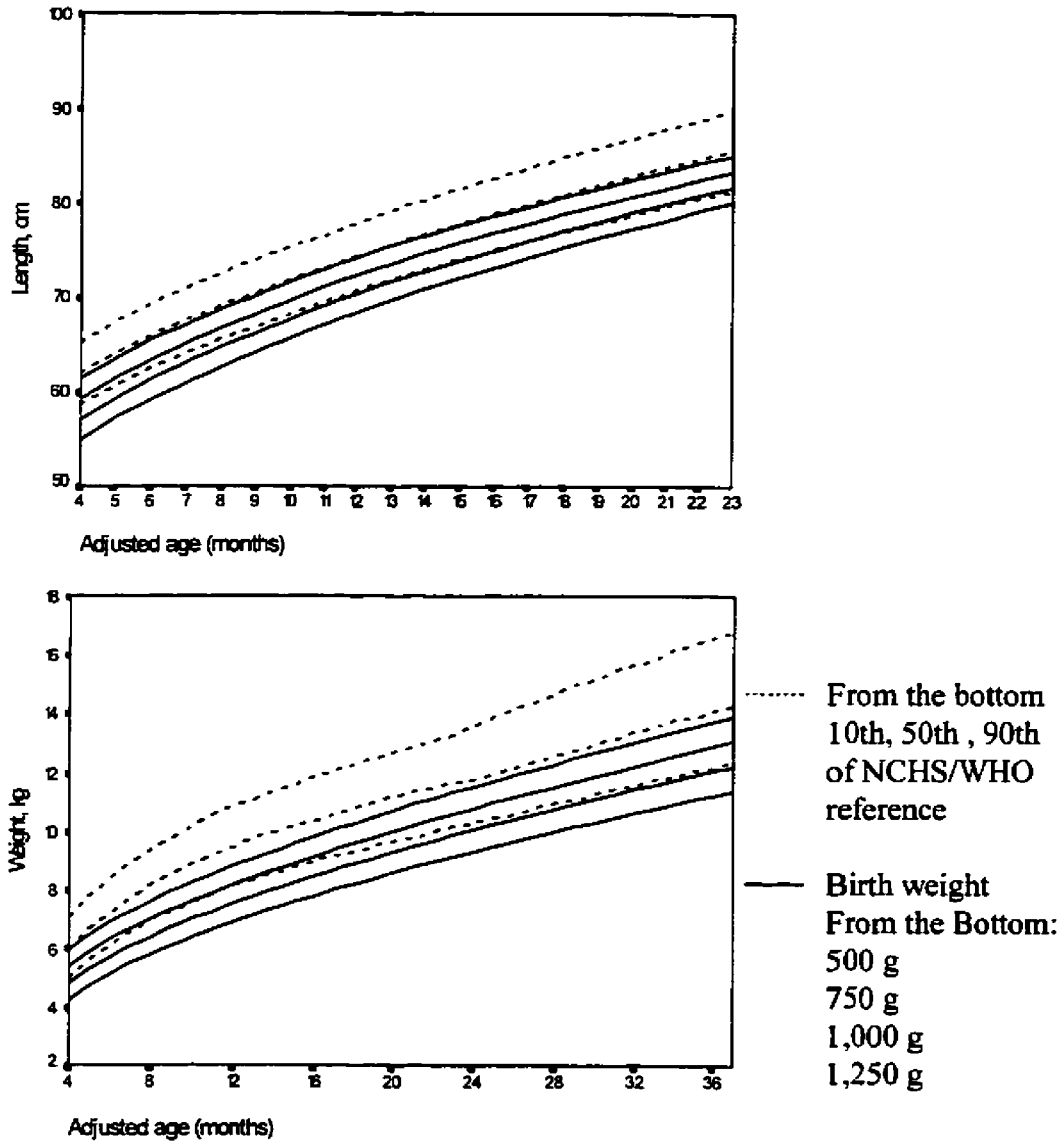


Figure 5-1 Birth weight and predicted length and weight for a hypothetical infant

5.4.2.2 Gestational age, intrauterine growth status and body proportionality

Since the subjects in this study were infants with birth weight less than 1251 grams, the infants born at longer than 27 weeks of gestation in the study sample did not represent infants with the same gestational age in the population. Infants born at over 27 weeks gestational age may have birth weight higher than 1,250 grams. These infants were not included in the present study. Therefore, it is not appropriate to explore the association between gestational age and postneonatal growth through a bivariate analysis. However, since birth weight and other factors were taken into account in the mixed effects models, gestational age was an indicator of intrauterine growth status rather than maturation of newborns. For infants with the same birth weight, those with longer gestational age have poorer intrauterine growth status. After birth weight and other factors were taken into account, gestational age was negatively associated with growth levels of length and weight. Findings from GEE approach indicate that infants with longer gestational age are more likely to have subnormal growth in weight and length. The results from logistic regression analysis suggest that the infants with longer gestational ages are at a higher risk of being subnormal growth at 3 years age in both weight and length.

As found by others,[8,23,202] intrauterine growth status and body proportionality were found to be associated with postneonatal growth in bivariate analyses. They did not contribute further to postneonatal growth after birth weight and gestational age were included in the mixed effects models. This may be due to the fact that the information on

intrauterine growth status was provided by including gestational age and birth weight in the models. The indicator of intrauterine growth status (SGA or AGA) had no further predictive value when birth weight and gestational age were in the model. This finding suggests that including birth weight and gestational age in the model can provide more information for predicting postneonatal growth than including an indicator of SGA or AGA.

Classifying infants as symmetrically or asymmetrically growth retarded by using ponderal index showed no additional predictive value for postneonatal growth given birth weights and gestational ages. This is consistent with the statement by Kramer et al.[78] who suggest that disproportionality is a proxy for severe IUGR and carries little or no additional risk. It is also consistent with the statement of Chart et al.[76] who believe that there is a continuum of birth weight and body proportionality rather than a distinct subgroup of asymmetrically growth-retarded infants. Peterson et al.[206] also report that given birth weight and gestational age of a newborn, body proportionality does not contribute further to judgment about fetal growth rate.

To express the association of gestational age and postneonatal growth, the predicted growth patterns of the above hypothetical infant with 1000 grams birth weight and different gestational ages were estimated and presented in Figure 5-2. If she had shorter gestational age, she would have had higher growth levels.

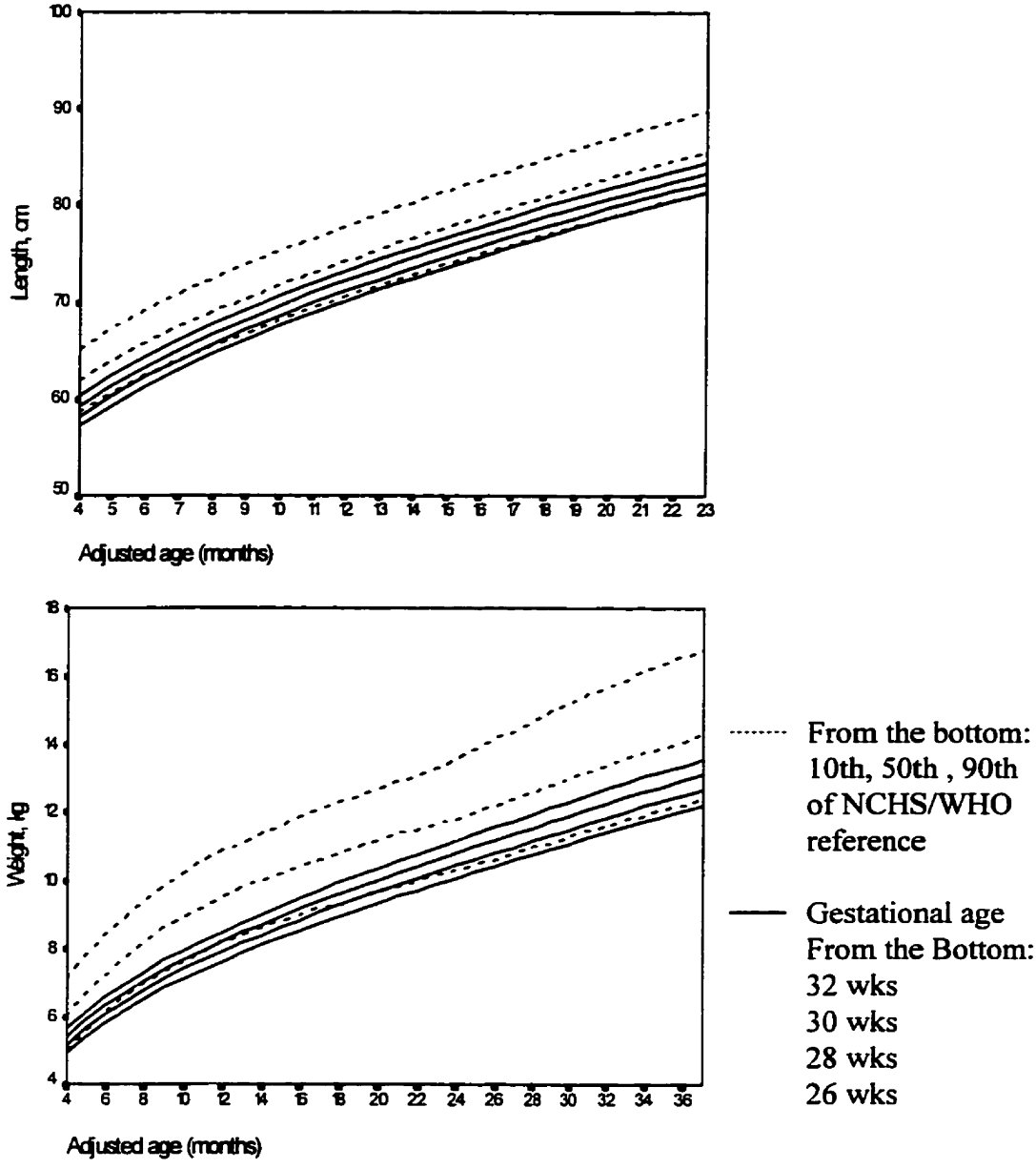


Figure 5-2 Gestational age and predicted length and weight for a hypothetical infant

5.4.2.3 Mid-parental height

Mid-parental height was found to be positively associated with postneonatal growth rate in VLBW infants in the present study. The infants of taller parents grow faster than

those of shorter parents so the difference between infants of taller and shorter parents increases with age. The same patterns of relationship exists after adjusting the potential confounding effects of birth weight, gestational age and other factors. The results of logistic regression suggest that shorter parental height predicted subnormal growth in both weight and length at three 3 years adjusted age. The findings from the generalized linear model for dependent data (GEE approach) suggest that the association between mid-parental height and subnormal weight becomes stronger as infants grow.

Although several parent-height-specific growth references have been developed for children in the general population in the literature,[80,101] no studies have been found to describe the detailed association between mid-parental height and growth in VLBW infants like the present study. However, a positive association between mid-parental height and growth levels at a certain point in age was found in previous studies,[1,2,47] which supports the findings of the present study. Kitchen et al.[2] reported that lower maternal height predicted poor growth in VLBW children at eight years of age. Albertsson-Wikland and Karlberg found that the mid-parental height of SGA infants who did not show catch-up growth (less than -2 SD of the reference means) at two years of age was 0.9 SDS (standard deviation score) shorter than the parents of the children in the catch-up group.[46] In these previous studies in the literature, the association of parental height and postneonatal growth was analyzed cross-sectionally. Therefore, the detailed relationships between parental height and postneonatal growth cannot be obtained in those previous studies.

Detailed relationships between mid-parental height and postneonatal growth were explored using statistical techniques for longitudinal data in the present study. To express how mid-parental height is associated with postneonatal growth, the predicted growth patterns of the above hypothetical infant with different mid-parental heights are presented in Figure 5-3. If her parents were taller, she would have a higher growth level and would grow faster in both length and weight.

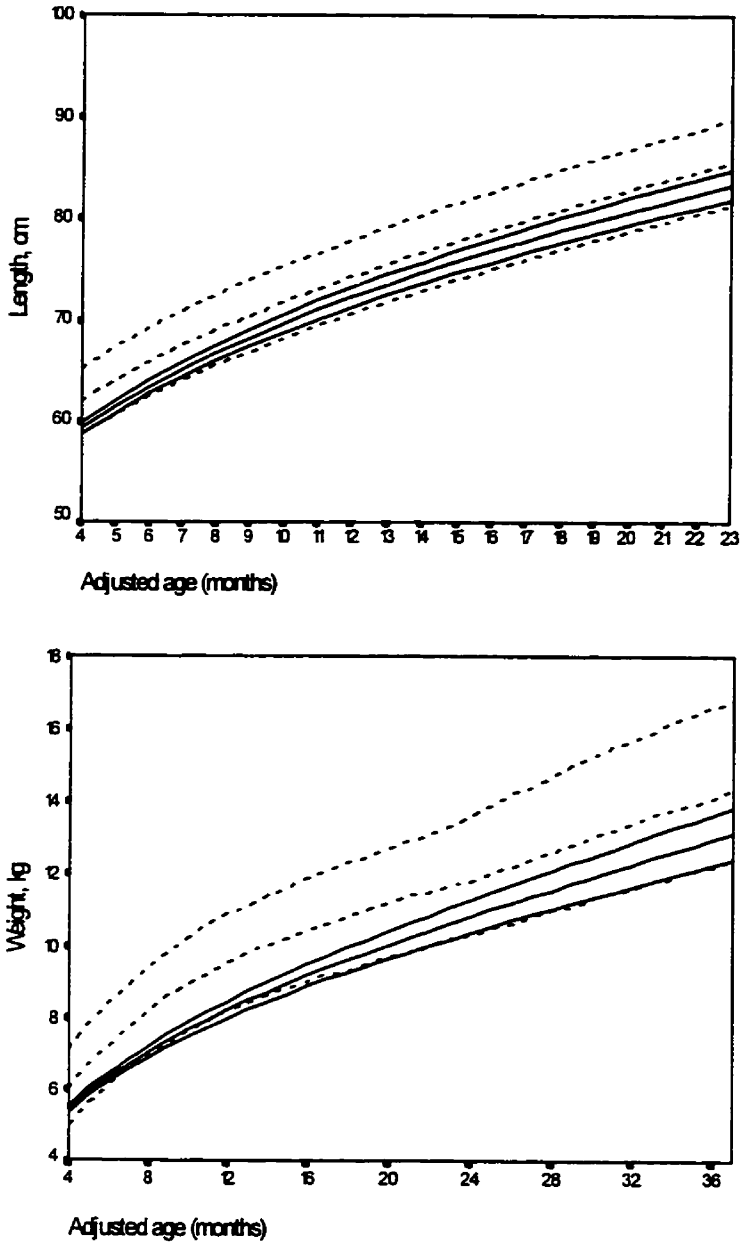


Figure 5-3 Predicted length and mid-parental height for a hypothetical infant

5.4.2.4 Clinical conditions

Several clinical conditions were found to be associated with postneonatal growth in VLBW infants in the present study. Before considering confounding effects in the analysis, BPD, NEC, CP, PDA and neonatal sepsis were associated with postneonatal growth. Three conditions, BPD, NEC and CP, were associated with length; while two conditions, BPD and NEC, were associated with weight after considering confounding effects in the mixed effects models.

The present study suggests that VLBW infants with histories of BPD have lower growth levels in both weight and length than their peers without BPD. This is consistent with most of the previous studies in the literature.[20,110,160] Sauve et al.[110] examined the growth of infants with BPD as compared to controls, and found evidence of poorer growth in the infants with BPD. Meisel et al.[20] found poorer growth in infants with BPD in the second year of life as compared to infants with respiratory distress syndrome but without BPD.

The debate in the literature is whether or not BPD has an independent negative effect on postneonatal growth in very low birth weight infants. It was found in this study that the presence of BPD was associated with birth weight, gestational age and the presence of CP. All of these factors were found to be associated with the postneonatal growth. It was also found in this study that when confounding effects of known correlates of postneonatal growth were taken into consideration in the models, the differences between

BPD and non-BPD groups were still statistically significant. Before considering other factors in the analysis, a stronger association was found between BPD and postneonatal growth. Infants with BPD were 0.43 kg lighter and 1.13 cm shorter than infants without BPD when only BPD, age and gender were in the mixed effects models. After considering confounding effects of other factors, infants with BPD are 0.30 kg lighter and 0.53 cm shorter than infants without BPD. The findings are contrary to the findings of three previous recent studies[157,159,207] in which the differences in growth outcome between infants with BPD and infants without BPD were not significant when confounders were taken into consideration. These previous studies were limited by small sample sizes. They did not find a statistically significant difference between infants with and without BPD but this may be due to the low statistical power in their studies. No reports have been found suggesting that the infants with BPD have higher growth levels than infants without BPD with or without statistical significance. Also, in the previous studies the duration of hospital stay was taken as a confounding variable, which is a proxy of severity of BPD. The true association between BPD and postneonatal growth could be masked by taking duration of hospital stay as a confounder in multiple regression analysis.

The explanation for the fact that infants with BPD have poorer growth may largely relate to reduced energy supply and increased energy expenditure.[156] The poorer growth in infants with BPD can not be explained by the associations between the presence of

BPD and lower birth weight, poor intrauterine growth status or the presence of CP which were taken into account in the present analysis.

The presence of NEC was found to be associated with growth in both length and weight while the presence of CP was found to be only associated with poor growth in length with statistical significance. The inability to find the statistically significant association between CP and poor growth in weight in this study may be attributable to the infrequency of CP in the study sample. The presence of NEC requires that nutrition management be restricted to parenteral nutrition for bowel rest.[156] NEC and CP may limit the ability of VLBW infants to intake and absorb nutrients. From the generalized linear model for dependent data, NEC was significantly associated with subnormal length in early months but not in later months of life.

Figure 5-4 shows the predicted growth patterns of the above hypothetical infant with and without BPD. She is expected to have a slightly lower level in both length and weight if she had BPD.

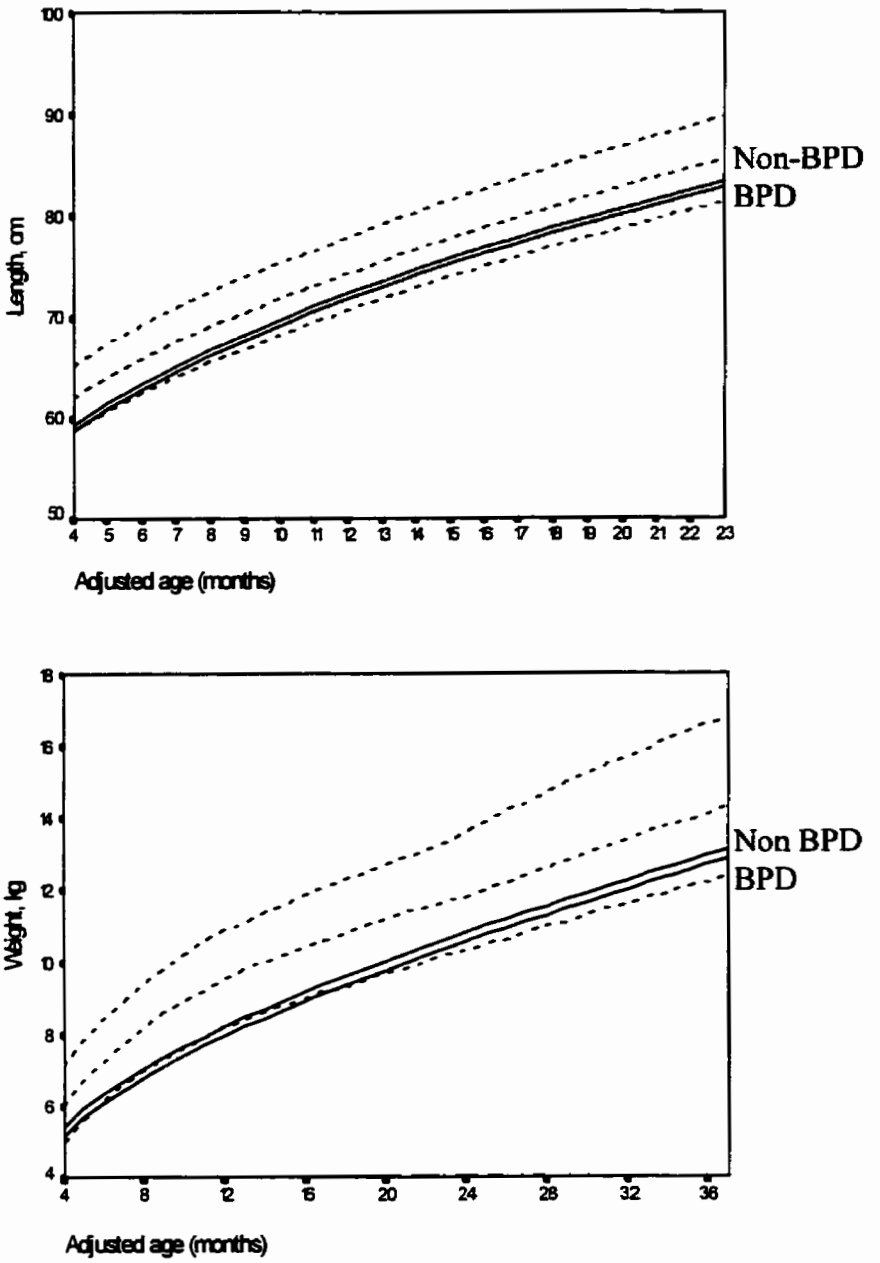


Figure 5-4 BPD and predicted length and weight for a hypothetical infant

5.4.2.5 Sociodemographic factors

Among the sociodemographic variables in this study, only maternal age was found to be associated with postneonatal growth. Infants of mothers 20 years old or younger grow poorer than infants of mothers older than 20 years of age. Maternal education was found to be associated with the postneonatal growth in length without considering confounding effects of other factors, but no independent association was found between maternal education and postneonatal growth after considering the confounding effects of other factors. The socioeconomic status was not found to be associated with postneonatal growth in VLBW infants. A few studies were found to investigate the relationships between social demographic factors and postneonatal growth in VLBW infants. Contrary to the present study, Qvigstad et al.[1] reported that parental level of education was associated with growth outcomes, and Hack et al.[8] found an association between socioeconomic status and growth. No association between SES and growth was found in Fitzhardinge and Inwood's study[49]and Bozynski et al.'s study.[159] It is possible that the sociodemographic factors have different impacts on the growth of VLBW infants in different social environments. For this study population, SES and maternal education may not be important for predicting postneonatal growth.

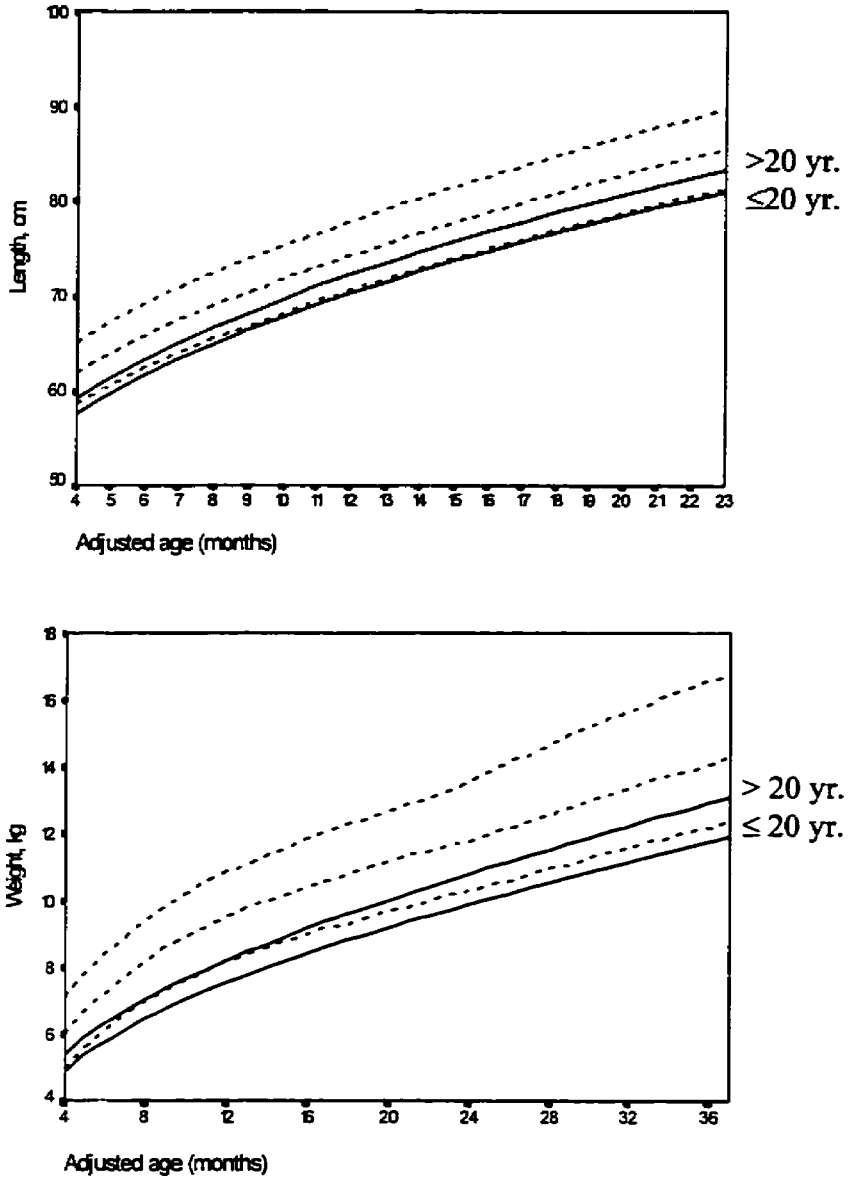


Figure 5-5 Maternal age and predicted length and weight for a hypothetical infant

Figure 5-5 shows the predicted growth patterns of the above hypothetical infant with different maternal ages. The infant would be shorter and grow slower if her mother were

younger than 21 years old. Maternal age here may capture the information of other biological and social demographic variables. The young mothers may have lower education, lower SES or poorer prenatal care than the mothers who are older than 20 years of age. Biologically, mothers of different ages are at different intrinsic maturity stages. Mothers of different ages may also have different previous exposures to environmental factors.

5.4.2.6 Gender

The findings in this study on gender and growth are consistent with the those of previous studies. The preterm VLBW boys tend to be heavier and taller than girls during infancy.[4,7,11] Although the differences in length and weight between boys and girls are not constant, boys remain longer and heavier than girls throughout infancy. Therefore, when assessing the growth status of VLBW infants, the growth of boys and girls should be assessed separately using different references.

5.4.2.7 Antenatal steroid therapy

Infants in whom antenatal steroids were administered were longer and heavier than infants without the use of antenatal steroids. The findings of the present study are consistent with those of previous reports.[161,162,173] However, the use of antenatal steroids did not contribute significantly to the postneonatal growth in VLBW infants while

considering the confounding effects of other factors in the models. It suggests that the improvement effect of antenatal steroids on growth may be indirect.

It has been found that antenatal steroid treatment significantly reduces neonatal mortality and morbidity.[166,167] It is reasonable to suspect that the antenatal steroid therapy improves postneonatal growth through the reduction of the occurrence of clinical conditions which are associated with the postneonatal growth in the study sample.

In the present study, infants with antenatal steroid therapy were found to have significantly higher birth weight than infants without antenatal therapy. The use of antenatal steroids was found to be associated with maternal age. The mothers who were younger than 21 year old are less likely to receive antenatal steroids than the mothers who were older than 20 years. Infants who received antenatal steroid therapy had a significantly lower prevalence of BPD than those without the use of antenatal steroids.

It may suggest that the positive effects of antenatal steroid therapy on postneonatal growth is indirect. The use of antenatal steroids improves birth weight of newborns and reduces the occurrence of BPD among the VLBW infants. Consequently, the growth status of VLBW infants is improved.

5.4.3 Summary of determinants

Birth weight, gestational age, mid-parental height, gender, maternal age and the presence of BPD, CP and NEC were significantly associated with the postneonatal growth in length. Birth weight, gestational, age, mid-parental height, gender, maternal

age and the presence of BPD and NEC were significantly associated with the postneonatal growth in weight. Birth weight, mid-parental height, gender and maternal age were related to the growth rate in length while gestational age, BPD, CP and NEC were only related with growth levels. Socioeconomic factors are not important in predicting postneonatal growth in our population of VLBW infants.

Birth weight, gestational age, mid-parental height, maternal age and BPD predict subnormal growth in length while birth weight, gestational age, mid-parental height, maternal age, and NEC predict subnormal growth in weight. The growth status at 4 months adjusted age is a predictor of subnormal growth at 3 years adjusted age.

5.4.4 Analytic methods used in the present study

Different statistical approaches were used in the present study. The classic approach of calculating Z-scores provide the general information on the growth patterns and associations between factors and postneonatal growth. The modelling procedures provide detailed information on the associations. Three modelling procedures were used in this study. Findings from different approaches are consistent though each has its own emphasis on a specific aspect of growth. Logistic regression was used to identify factors influencing subnormal growth at 3 years of age. Only longitudinal growth data obtained at one point in time were used in this model. Loss of information is a disadvantage of using conventional logistic regression to analyze longitudinal data. This may decrease the statistical power. Another disadvantage is that the detailed association between factors

and growth cannot be obtained. The detailed association between each factor and growth were obtained using two modelling approaches for longitudinal data.

In the GEE approach, the factors associated with subnormal growth during infancy were determined. The changes of the associations were explored in this analysis. The information on the changes of the associations cannot be obtained using logistic regressions.

In mixed effects models, the growth measurements are taken as continuous variables. The detailed association between factors and growth level can be obtained. Since the continuous variable of growth measurements are not categorized to two groups, mixed effects models utilized all the information that longitudinal growth data can provide. More variables were found to be associated with postneonatal growth using mixed effects models than using other two models. The approach of mixed effects models is more efficient than the other two modelling approaches in analyzing longitudinal growth data.

5.5 Limitations of the study and improvement in future studies

5.5.1 Representativeness of the study sample

The study sample was generated from a neonatal follow-up program which includes only infants from Southern Alberta and Southeast British Columbia. The findings may not be generalizable to infants in other geographic areas. This could be improved by selecting a random sample from newborns or at best all the newborns with birth weight

1250 grams or less from a variety of geographic areas, and maintaining a high follow-up rate in future studies.

5.5.2 Wide intervals between measurements

Since the growth rate decelarates during infancy, especially in the early months of age, detailed growth patterns cannot be obtained with measurements taken in wide intervals. Infants were measured at four month intervals in the first year of life in this study. Ideally, growth data should be obtained by serial examinations at 1-month intervals in the first year.[12] However, this may be impractical in large sample studies like the present one.

5.5.3 Uncontrolled confounding effects

The growth of an infant is the result of complicated related factors. It is possible that some factors, not studied in this paper, were associated with postneonatal growth in VLBW infants. These possible factors include maternal prenatal care, severity of illness, pregnancy exposure to tobacco, alcohol and drugs, and feeding problems during infancy. It is necessary to explore the predictive values of these variables in future studies.

5.5.4 Short duration of follow-up

It was found in this study that VLBW infants showed some catch-up growth but their growth levels remained substantially lower than the reference data by the end of

observation. Infants were only observed up to 3 years adjusted age in the present study. Whether VLBW infants will catch up to normal term infants and when this catch up will occur need to be answered in future studies with longer duration of follow-up.

5.5.5 Inability to derive confidence intervals for predicted values

Mixed effects models are still in the developmental stage. The confidence intervals of predicted values cannot be obtained using mixed effects models at this time. The relative position of an observed measurement to the distribution of predicted values could not be assessed directly. The Z-score and percentile of an individual's measurement can not be calculated. Only the percent of predicted value can be obtained since only one point estimate of predicted value is available.

Percent of predicted value = (Observed value/predicted value)×100%

However, the distribution of population residuals is helpful to assess the relative position of an observed measurement to the predicted values.

5.5.6 Lack of normal term control group

In this study, the growth patterns of VLBW infants were only compared with normal term growth references. Therefore, the present study does not provide information on how the growth patterns of VLBW infants are different from those of normal term infants from the same geographic area.

5.5.7 Other dimensions of growth

In the present study, only growth data of body length and weight were analyzed. Other dimensions of growth, such as head circumference, chest circumference and body fat are also important. Each represents a specific aspect of growth in VLBW infants. Those measurements were collected in all infants in the follow-up program but were not included in this study. Further studies should be conducted to describe the patterns and determinants of growth for different dimensions in VLBW infants.

CHAPTER SIX: IMPLICATIONS

Findings in the present study have implications in several areas: 1) growth assessments and growth predictions at clinical or community settings; 2) prevention of poor long term growth in VLBW infants; 3)recommendations for future studies; and 4) analysis of longitudinal growth data. Each will be discussed below.

6.1 GROWTH ASSESSMENT AND PREDICTIONS

The growth patterns described in this study are helpful to health professionals in understanding the growth process of VLBW infants. Findings on the differences in growth outcomes when different references are applied to the same population warns health professionals that the growth references that they are using may influence the observed growth outcomes of VLBW infants.

The growth status estimated from the growth models established in this study can be used as a reference for growth monitoring. The major difference of this reference from other references in the literature is that it depends on the multiple characteristics of individual infants. The growth models developed in this study have potential to be a useful tool for health professionals to assess and predict the growth of an individual or a group of VLBW infants.

6.1.1 Individual growth assessment

The predicted growth levels of an infant with particular characteristics can be estimated using the growth models. Such growth levels may serve as reference data to monitor the growth progress of a particular infant. Also, the expected growth levels of an infant can be estimated based on birth weight, gestational age and mid-parental height assuming that he or she is free from BPD, NEC and CP and that the mother is older than 20 years. The predicted values can be taken as the "reasonable" expected mean growth levels, based on which the infants at higher risk of poor growth can be identified.

Since there are numerous combinations of infants' characteristics, it is impractical to make a growth chart for infants with each combination of characteristics with a traditional approach. An efficient way to assess and predict growth based on the infant's characteristics is to develop a computer program based on the growth models described in this study. This program is easy for dietitians and other health professionals to use in the clinical settings. If we know an infant's perinatal and parental characteristics, we can predict the growth levels of weight and length at any time between 4 and 36 months adjusted age. The predicted value at a specific time point is the average level of infants with similar characteristics. By comparing the observed value with the predicted value, we can obtain the relative position in growth measurements of a particular infant among those with similar "characteristics." This information is important for counseling parents regarding the growth status of the infant.

When we have multiple growth measurements for an individual infant, we are able to observe how the relative positions of growth levels of the infant among those with the similar characteristics change over time. Therefore, the growth progress of this infant over a certain period of time can be accurately assessed, which is important for assessing the effects of an intervention on an infant's growth. This is an advantage of using the growth models over using growth reference data from normal term infants. Since infants with different characteristics follow different growth patterns, the characteristic specific growth curves provide appropriate references for comparison.

An example of comparing observed and predicted growth using the computer program: An infant is selected from our data base. This infant has following characteristics: 1) Gender: female; 2) birth weight = 1200 grams; 3) gestational age = 29 weeks; 4) Mid-parental height = 163 cm; 5) Maternal age = 33 years; 6) BPD=yes; 7) CP=no; and 8) NEC=no. After entering the values of these predictive variables into the program, we can obtain the predicted growth levels of weight and length at any time between 4 and 36 months adjusted age. Table 6-1 shows the predicted and observed growth measurements at several ages when the observations are available. In this computer program, the relative position of an observed value to the predicted value was expressed in three ways: 1) the absolute difference between observed and predicted values; 2) the ratio of observed over predicted values; and 3) the difference between observed and predicted values in standard deviations (Z-score).

Table 6-1 Growth assessment: an example of predicted growth levels

Adj. Age(mo.)	Observed (O)	Predicted(P)	O - P	(O/P)%	Z-score
Weight, kg					
5	5.9	5.92	-0.02	99.67	-0.02
8	7.1	7.03	0.07	100.98	0.08
13	8.2	8.39	-0.19	97.69	-0.20
18	9.3	9.49	-0.19	97.96	-0.18
Length, cm					
5	60.5	61.61	-1.11	98.19	-0.45
8	65.5	66.74	-1.24	98.15	-0.49
13	71.0	73.22	-2.22	96.97	-0.85
18	75.5	78.33	-2.83	96.36	-1.03

The weight growth for this infant is very close to the average growth level of infants with similar characteristics. However, it seems the length lags behind the peers as the infant grows. Whether these differences are clinically significant enough to bring health professionals' attention to the secondary health or nutritional problems depends on the context in which the growth assessment is made.

Since this infant suffered from BPD which has negative impacts on growth, the above predicted values are not the "target" growth levels for this infant. Efforts should be made to treat infants with BPD in order to improve their growth status. Therefore, our "target" growth levels for this infant should be the growth levels assuming she is free from BPD. In the computer program, these predicted growth values are labeled as

"expected" values. Table 6-2 shows comparisons between observed and expected growth levels for this infant. Obviously, the observed values lag further behind the "expected" than the "predicted" values.

Table 6-2 Growth assessment: an example of expected growth levels

Adj. Age(mo.)	Observed (O)	Expected(E)	O - E	(O/E)%	Z-score
Weight, kg					
5	5.9	6.17	-0.27	95.60	-0.33
8	7.1	7.28	-0.18	97.49	-0.21
13	8.2	8.65	-0.45	94.84	-0.45
18	9.3	9.75	-0.45	95.42	-0.41
Length, cm					
5	60.5	62.15	-1.65	97.35	-0.67
8	65.5	67.27	-1.77	97.37	-0.70
13	71.0	73.75	-2.75	96.27	-1.05
18	75.5	78.86	-3.36	95.74	-1.23

6.1.2 Assessment of a nutritional intervention at a population level

When assessing the impact of a nutritional intervention on the postneonatal growth at a population level, the randomization of treatment assignment is usually impractical for the population study. The results could be distorted by the confounding effects. Sometimes, it is difficult to find an appropriate control group. Using the growth models developed in this study is helpful for controlling confounding effects. When there are no control groups, the predicted values from the models can be used for comparisons.

6.2 Prevention of poor growth

Some factors influencing growth which were identified in this study are preventable before infants are born. Efforts to prevent low birth weight births, teenage pregnancies, and adverse clinical conditions such as BPD, NEC and CP have important implications in preventing poor growth in VLBW infants. Infants with these conditions should be considered a priority group for special nutritional support and other interventions. For infants whose growth levels are lower than the predicted values, efforts should be made to identify the "secondary" growth and health problems for consideration of early interventions when appropriate.

6.3 Recommendations for further studies

- Growth models described in this study are recommended for future studies in assessing the effects of nutritional and clinical interventions on postneonatal growth in VLBW infants. The development of a user friendly computer program which can generate the predicted and expected growth curves graphically is worthwhile for both clinical and research purposes.
- The growth models developed in this study have been used to predict weights and lengths of 158 VLBW infants from another geographic area, Northern Alberta (the data were provided by Dr. C. Robertson). The preliminary analysis shows that the predictions are satisfactory (results are not presented in this study). The growth models are recommended for growth prediction and assessment in the province of

Alberta, Canada. Whether these models are appropriate for VLBW infants from other provinces in Canada or other countries needs to be verified in the future studies.

- In this study, intrauterine growth retardation was not found to be associated with postneonatal growth in VLBW infants. It has been commonly believed to be an influencing factor of growth.[61] Findings in this study challenge the common practice of dividing infants into two distinct groups: SGA and AGA. Further studies are required to determine an optimal way to measure intrauterine growth status.
- Maternal age was found to be associated with postneonatal growth in the present study. Maternal age is a marker of biological, socioeconomic and environmental factors. Further studies are required to identify the true factors creating differences in postneonatal growth between infants of younger and older mothers.
- The findings in this study suggested that age adjustment for prematurity makes substantial differences in identifying subnormal growth in VLBW infants. It is recommended that the adjustment should be carried out throughout the first three years of life in assessing growth in VLBW infants.
- The interpretations of growth in VLBW infants vary substantially depending on which reference is used. When comparing growth status of two populations from different studies, there should be a common reference for both populations.

6.4 ANALYSIS OF LONGITUDINAL DATA

6.4.1 Longitudinal data from perinatal follow-up programs

This study also showed the importance of the longitudinal data from Alberta Children's Hospital Perinatal Follow Up Program in assessing the outcomes of VLBW infants. Since the extensive information has been collected on perinatal and social environmental factors, and the multiple outcomes of VLBW infants over decades, the associations between various factors and different outcomes can be explored quickly based on a large sample size, which would otherwise take over 10 years to collect data.

6.4.2 Modelling procedures for longitudinal data

This is the first study to describe the associations between influencing factors and growth in VLBW infants with the use of mixed effects models and GEE approaches. It has been shown that mixed effects models and GEE approaches are very powerful statistical techniques that can be used to analyze longitudinal data for the associations between influencing factors and growth. A distinct advantage of these modelling procedures for longitudinal data over traditional methods is the ability to describe the details of the associations during the process of growth. They will be useful tools for studying other developmental processes.

CHAPTER SEVEN: CONCLUSIONS

- The general growth patterns for VLBW infants are different from the current growth references for normal term infants. VLBW infants are heterogeneous. Infants with different characteristics follow different growth patterns.
- The observed growth outcomes are influenced by the growth references currently in use. For weight, VLBW infants show a trend of catch-up growth during infancy using the Canadian growth reference, but do not show such a trend in the first year of life using the NCHS/WHO. For length, a trend of catch-up growth was found using either reference.
- Age adjustment for prematurity makes substantial difference in assessing growth in VLBW infants. Such adjustment should be carried out throughout infancy.
- Various factors are associated with postneonatal growth in VLBW infants. For length, the factors that are positively associated with growth levels are: higher birth weight, higher mid-parental height, and male gender. The factors that are negatively associated with postneonatal growth levels are the presence of BPD, CP and NEC, young maternal age, and longer gestational age given birth weight. Except for the presence of CP that is not significantly associated with body weight, all other variables have the same directions of associations with body weight as they do with body length.

- The detailed association between factors and postneonatal growth described in this study allow accurate predictions and assessments of postneonatal growth in VLBW infants.
- The modelling procedures, the mixed effects models and the generalized estimating equation approach, provide more information than conventional methods in analyzing longitudinal growth data.

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APPENDIX A: STUDY APPROVAL LETTERS

Alberta CHILDREN'S Hospital
The child health centre and teaching hospital affiliated with The University of Calgary

1820 Richmond Rd SW
Calgary, Alberta, Canada
T2T 5C7
Tel (403) 229-7211
Fax 229-7221

February 1, 1996

Dr. Reg Sauve
Department of Paediatrics
Alberta Children's Hospital

Dear Dr.Sauve:

Re: Project 96-02 - Analysis of Patterns of Growth and Determinants of Postneonatal Growth in Very Low Birth Weight Infants, Using Modelling Procedures

The above named protocol has now been reviewed by representatives of the ACH Research Committee. This protocol has now been approved and will be forwarded to the Conjoint Medical Research Ethics Board, Faculty of Medicine, The University of Calgary for ethical review.

Our approval of this proposal is contingent upon:

1) Approval from the Conjoint Medical Research Ethics Board, The University of Calgary.

2) ACH personnel being involved for the duration of this project.

3) Alberta Children's Hospital be acknowledged in any publications arising from this work.

Please find attached, for your information, a few comments made by one of the reviewers. Should you wish to provide a corrected manuscript, please submit it directly to the Conjoint Medical Research Ethics Board.

I wish you a successful and informative study.

Sincerely,

R. Brent Scott, MD, FRCP(C)
Chair
ACH Research Committee

RBS/mee

cc Conjoint Medical Research Ethics Board, U of C

THE UNIVERSITY OF
CALGARY

Faculty of Medicine
Office of Medical Bioethics

22 February 1996

Dr. R.S. Sauve
Department of Community Health Sciences
The University of Calgary
Calgary, Alberta.

Dear Dr. Sauve:

Re: **Analysis of Patterns of Growth and Determinants of Postneonatal Growth in VLBW Infants. Using Modelling Procedures**
Student: Dr. Zhiqiang Wang **Degree: PhD**

The above-noted thesis proposal has been submitted for Committee review and found to be ethically acceptable. Please note that this approval is subject to the following conditions:

(1) a copy of the informed consent form must have been given to each research subject, if required for this study;

(2) a Progress Report must be submitted in one year, 1997-02-22, containing the following information:
  (i) the number of subjects recruited;
  (ii) a description of any protocol modification;
  (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
  (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
  (v) a copy of the current informed consent form;
  (vi) the expected date of termination of this project;

(3) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Committee's best wishes for success in your research.

Yours sincerely,

E.D. Burgess, MD, FRCPC, FACP
Chair, Conjoint Medical Research Ethics Board

c.c. Research Committee, ACH
Dr. L.R. Sutherland (information)
Dr. Zhiqiang Wang

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APPENDIX B: THE FORM OF FOLLOW UP DATA: OUTCOME I/II

PERINATAL FOLLOW-UP
OUTCOME I/II

Name: _____
Date of Birth: _____
Date of Assmt: _____
Date of Collection: _____

ID# _ _ _ _ _ _ _
Birthweight _ _ _ _
C.A. _ _
A.A. _ _
Date Seen _ _ _ _
Source of Info _
Cause of Death _
Autopsy _
Residence _

PHYSICAL EXAM _
PULMONARY _

NEURODEVELOPMENTAL _
Tone: upper * _
lower* _
truncal* _
DTR's _
Primitive Reflexes _

HEALTH HISTORY STATUS _
Blood Pressure _ _ _
_ _
Hemoglobin _ _ _
#LRI's _
#Otitis _
Hosp. (resp) _____ _
_____
Hosp. (other) _____ _
_____
Day Surg/Monitoring _____ _
_____
Visits Physician Office _
Visits Emerg _
Current Meds _
_
_
_

HEALTH HISTORY STATUS (Cont.)

Non-PNFU Involvement
ACH Clinics _
ACH Tx. Prog. _
Non-ACH Prog. _
ACH ind Cons/Tx _
Non ACH Cons/Tx _

Non-PNFU Referral
ACH Clinics _
ACH Tx Prog _
Non-ACH Prog _
ACH ind. Cons/Tx _
Non-ACH Cons/Tx _
Community School Involve _

PHYSIOTHERAPY _
Test Used _
Gross Motor _
Primitive Reflexes _
Intervention _
Fine Motor _

NUTRITION _
Energy Intake _ _ _
Protein Intake _ _
BF/24 hrs. _ _
Micronutrient Intake _
Feeding Probs _
Oral/Enteral Intake _
Feeding abil/skills _
Special Diet _
Energy Suppl* _
Standard Suppl * _
Intervention _

GROWTH RECORD _
GROWTH VELOCITY _
FAILURE TO THRIVE _
Arm Circ _ _ . _ _
Triceps _ _ . _ _
Subscapular _ _ . _ _
AM Area _ _ . _ _
Weight _ _ . _ _
Length _ _ _ . _ _
Head Circ _ _ . _ _
Chest Circ _ _ . _

OPHTHALMOLOGY/ORTHOPTICS _
Visual Acuity _
Refraction _
Ocular Structure _
Ocular Motility _
ROP - Rt. _
- Lt. _
RLF - Rt. _
- Lt. _
Treatment _

SPEECH: COMMUNICATION _
R.L. _
E.L. _
Phonological Skills _
Fluency _
Voice _
Intervention _

HEARING	_
ABR	_
Distorion Product Emission	_
Audiometry (Sound Field)	_
Audiometry (Head Phones)	_
TM Mobility	_
PE Tube Status	_
Hearing Aids	_
Repeat	_
PSYCHOLOGY	_
Test Used	_
Cognitive Index	_ _ _
Attention Span	_
Intervention	_
SOCIAL WORK	_
Characteristics Parent	_
Pregnancy Birth	_
Attachment Caretaking	_
Discipline Temperament	_
Support	_
Agency Utilization	_
Intervention	_
Family Status *	_
Blishen: Father	_ _
Blishen: Mother	_ _
OCCUPATIONAL THERAPY	_
Primary Test Used	_
Score	_
Secondary Test Used	_
Score	_
Feeding Outcome	_
Test Used	_
Intervention	_

SCREENING TESTS			_
TEST USED			_
CDI/IDI		**DISC**	
S	_	FM	_ _
SH	_	RL	_ _
GM	_	EL	_ _
FM	_	GM	_ _
EL	_	A-A&M	_ _
LC	_	V-A&M	_ _
L	_	SH	_ _
N	_	Soc	_ _
GD	_		

DISABILITY	_
Cerebral Palsy	_
Seizure Disorder	_
Mental Retardation	_
Blindness	_
Deafness	_
DIAGNOSTIC CODES	
Social Work	_ _ _ _
Nursing	_ _ _ _
Nutrition	_ _ _ _
Physical	_ _ _ _
Neuro	_ _ _ _
Physio	_ _ _ _
O.T.	_ _ _ _
Psychology	_ _ _ _
Speech	_ _ _ _
Audiology	_ _ _ _
Ophthalmology	_ _ _ _
	_ _ _ _
	_ _ _ _
	_ _ _ _
	_ _ _ _

* More than one source of data

Rev. 96/02/01

APPENDIX C: THE FORM OF N.I.C.U. DISCHARGE SUMMARY

N.I.C.U. DISCHARGE SUMMARY

Name: _____
I.D.#: _____
B.D.: _____
B.W.: _____

Baby's Name: _____
Last First Middle

GENERAL DATA

F.H. Hosp. # or assigned # [ ][ ][ ][ ][ ][ ] (1-6)
Card [ ][ ] 0 1 (7-8)
Birthdate (Yr-month) [ ][ ][ ][ ] (9-12)
*Follow-Up Criteria [ ][ ][ ][ ][ ] (13-17)

*0 = none
1 = low birth weight
2 = compl. ventilator course
3 = congenital infection
5 = neuro disorders
6 = other _____ specify
7 = ROP
8 = special study
9 = unknown

*Birthplace [ ] (18)
*Where Hospitalized [ ] (19)
Age at admission (hrs) [ ][ ][ ] (20-22)
Transported [ ] (23)
*Days hospitalized: Acute [ ][ ][ ] (24-26)
: Other ICN [ ][ ][ ] (27-29)
: Other hospital [ ][ ][ ] (30-32)

*000 = none
001 = ≤ 24 hrs.
002 = 2 days, etc.
999 = unknown

*Disposition [ ] (33)

*1 = home
4 = other hospital _____ specify
5 = died
8 = other
9 = unknown

Autopsy? [ ] (34)

Basic Codes

0 = no 4 = suspect
1 = yes 9 = unknown
(Code changes denoted by *)

*Place Codes

*1 = Foothills Hospital
2 = Other Calgary Hospital
3 = Other Alberta Hospital
4 = Out of Province Hospital
5 = Non-Hospital (eg. home, ambulance)
6 = Other _____

BASIC METHOD FOR DETERMINING # OF DAYS

The number of days are determined by subtracting the date of commencement of treatment (or date of admission) from the date of termination of treatment (or date of discharge) or, in other words, by counting calendar days and subtracting one day. If treatment begins and ends on the same day, count as 1 day. Otherwise the above method applies.

e.g. Ventilation begins on July 7 and stops July 9: number of days = 2

Admitted to Acute care July 7 and died July 7: Days hospitalized = 1

Admitted to Acute care July 7, transferred to Prem II on July 10, discharged home on August 3: Days in Acute = 3; days in Prem II = 24

Phototherapy begins July 7, stops July 10, recommences July 12, stops July 14: Total days on phototherapy = 5

Date Completed: _____

Rev: 1984-[illegible]

*Cause of Death (35-38)

*0000=not applicable (39-42)
9999 = unknown
Use H - ICDA codes for causes

_____ specify
_____ specify

*Sex (43)
*1 = Male
2 = Female

*Multiple Birth (44)
*0 = singleton
1 = twins
2 = triplets or greater

DEMOGRAPHIC DATA

Maternal:

Name: _____

Age at delivery (Yrs): (45-46)

*Marital Status (47)
*1 = two parent family
2 = single parent family
9 = unknown

*Race (48)
*1 = Caucasian
2 = Black
3 = Canadian Indian/Metis
4 = Other _____ specify
9 = unknown

Transported PTD? (49)

*If so, hospital of origin: (50)
*0 = N/A
Use place codes

*Total years in school (51-52)
*99 = unknown

Paternal:

Name: _____

Age at delivery (yrs) (53-54)

Occupation: _____

*Blishen Index (55-56)
*(see manual)

*Total years in school (57-58)
*99 = unknown

*Midparent height (cm) (59-61)
*999 = unknown

2.

*Mother's Obstetrical History (Biological)

(T) # of previous term births (62)

(P) # of previous pre-term births (63)

(A) # of spontaneous abortions (64)

(A) # of therapeutic abortions (65)

(L) # of living children (66)
(not counting this one)
* 8 = ⩾ 8
9 = unknown

LABOUR AND DELIVERY

Drugs in Labor & Delivery

Antibiotics (67)

Steroids (68)

Analgesics (69)

Drugs to arrest labor (70)

Antihypertensives (71)

Sedatives (72)

Prostaglandins (73)

Other _____ (74)
(specify)

*Anaesthesia for Delivery (75)
*0 = none
1 = pudendal, local, paracervical
2 = caudal
3 = epidural
4 = spinal
5 = general
9 = unknown

Meconium staining? (76)

*Rupture of Membranes (77)
*1 = < 24 hrs PTD
2 = ⩾ 24 hrs PTD
9 = unknown

Monitor? (78)

*Presentation at Delivery (79)
*0 = vertex
1 = breech
8 = other
9 = unknown

CARD 2
Duplicate columns (1-6)
Card [0][2] (7-8)

C - Section (9)

*If so, indications (10-12)
*0 = n/a
1 = fetal distress
2 = breech presentation
3 = abnormal lie
4 = failure to progress
5 = APH
8 = Other _____ (specify)
9 = Unknown

PERINATAL INFECTION
Foul smelling liquor (13)

Maternal fever (14)

Other evidence of maternal infection _____ (specify) (15)

*Risk Score (Coopland's) (16)
*0 = average
1 = increased
9 = unknown

*Resuscitation Required (17)
*0 = none
1 = O_2 ± bag and mask
2 = intubation
3 = cardiac massage
4 = yes, type unknown
9 = unknown

*Apgars: 1 minute (18-19)

5 minutes (20-21)
*99 = unknown

*Admission temp. (22-24)
(rectal °C)
*34.9 = too low to record
99.9 = unknown

*B.P. on admission (mmHg) (25-26)
*99 = unknown

Gestational Age (wks) (27-28)

*Intrauterine Growth Status (29)
*1 = SGA
2 = AGA
3 = LGA
9 = unknown

3.

*MEASUREMENTS *Percentiles

Birthweight (gms) (30-35)
Birthlength (cm) (36-40)
Head Circ. (cm) (41-45)
Chest Circ. (cm) (46-48)

*9's = unknown
04 = < 5th percentile
96 = > 95th percentile

*Ponderal Index (49-50)
*9.9 = unknown

NUTRITION

Minimum Wt. (gms) (51-54)

Total Wt. lost (gms) (55-57)

% b.w. lost (58-59)

*Age b.w. regained (days) (60-61)
*01 = birthdate or Day 1
97 = ≥ 97 days
98 = not regained prior to discharge
99 = unknown

Discharge Wt. (gms) (62-65)

Parenteral (days) (66-67)

*Age all feeds taken p.o. (68-70)
*001 = birthdate or Day 1
998 = not prior to discharge
999 = unknown

*Formula Used (71-74)
*0 = none
1 = EBM
2 = BBM
3 = 20 cal. formula
4 = 24 cal. formula
5 = Prosobee
6 = Pregestimil
7 = Nutramigen
8 = Other _____ (specify)
9 = unknown
(List in order of frequency of use - i.e. in box 71 enter most frequent; in box 74 least frequent)

*Formula at Discharge (75) ☐
*Codes as above
(2 = breast feeding)

CARD 3
Duplicate columns (1-6)
CARD 0 3 (7-8)

Feeding Problems
Blood in Stools (9) ☐
Frequent Regurgitation (10) ☐
Amino Aciduria (tyrosinemia) (11) ☐
NEC (12) ☐
Late Edema (13) ☐
Rec. Abd. Distention (14) ☐
Other _____ (specify) (15) ☐

*DRUG UTILIZATION
*0 = not used
1 = used once
2 = used > once
9 = unknown if used

Penicillin (16) ☐
Ampicillin (17) ☐
Cloxacillin (18) ☐
Gentamycin (19) ☐
Kanamycin (20) ☐
Other antibiotic or antifungal _____ (specify) (21) ☐
Mycostatin (22) ☐
Steroids (23) ☐
Digoxin (24) ☐
Lasix (25) ☐
Other diuretic _____ (specify) (26) ☐
Indocid (27) ☐
Atropine (28) ☐
Pavulon (Pancuronium) (29) ☐
Dopamine (30) ☐

4.

Priscoline (31) ☐
Morphine (32) ☐
Codeine (33) ☐
Phenobarbital (34) ☐
Dilantin (35) ☐
Theophylline (Aminophylline) (36) ☐
$NaHCO_3$ (37) ☐
Iron (38) ☐
Multivitamins (39) ☐
Vitamin E (40) ☐
Calcium (p.o) (41) ☐
NaCl (p.o.) (42) ☐
MCT (43) ☐
Polycose (44) ☐
*Other (45-46) ☐☐
*Specify number used
00 = none
01 = one, etc.
99 = unknown

Total Drugs Used (47-48) ☐☐

*Adverse drug reactions (49) ☐
*0 = none
1 = yes, BPD +/or ROP, RLF only
2 = other than BPD, ROP, RLF
3 = combination of 1 & 2 above
9 = unknown

HEMATOLOGY
*Blood Products (times given)
Packed rbc &/or whole blood (50-51) ☐☐
Plasma (52-53) ☐☐
Platelets/WBC (54-55) ☐☐
*00 = not given
99 = unknown
Hematocrit: max. (SI) (56-58) ☐☐☐
: min. (SI) (59-61) ☐☐☐

Partial Exchange (62)

*Clotting Disorder (63)
*0 = none
1 = thrombocytopenia only
2 = DIC (Incl. Thrombocytopenia)
8 = Other _____ (specify)
9 = unknown

JAUNDICE (64)

Days on phototherapy (65-66)

Exchange Transfusion (67)

*Etiology (68)
*0 = n/a
1 = blood group incompatibility
2 = other
9 = unknown

Max. bili: total(SI Units) (69-71)

: conj.(SI Units) (72-74)

CARD 4
Duplicate columns (1-6)
CARD 0 4 (7-8)

SEPSIS? (9)

Sepsis Work-ups
More than 2? (10)

*Work-ups on Day of Delivery
Blood (11-12)
CSF (13-14)
Stool (15-16)
Urine (17-18)
Auger/Trachea (19-20)
Skin (21-22)
Other _____ (specify) (23-24)

*First Postnatal Work-up
Blood (25-26)
CSF (27-28)
Stool (29-30)

5.

Urine (31-32)
Auger/Trachea (33-34)
Skin (35-36)
Other _____ (specify) (37-38)

*Work-up codes
00 = not done
01 = no growth
02 = staph. albus/epidermidis/coagulase neg
03 = staph. aureus/coagulase pos
04 = E. Coli 05 = Klebsiella
06 = pseudomonas
07 = Bacteriodes
08 = Proteus
09 = Group A Strep
10 = Group B Strep
11 = Strep fecalis/gamma strep
12 = Other _____ (specify)
13 = Other _____ (specify)
99 = no report

NEUROLOGIC
*Seizures (39)
*0 = no
1 = yes, one only
2 = yes, more than one
9 = unknown

*Onset (40)
*0 = N/A
1 = ≤ 4 days
3 = > 4 days
9 = unknown

*EEG (41)
_____ (Interpretation)

*CT Scan (42)
_____ (Interpretation)

*CUS (43)
_____ (Interpretation)

*0 = not done
1 = normal
2 = abnormal
4 = suspect
9 = unknown if done

*APNEA (44)
- *0 = no apnea
- 1 = apnea, no treatment
- 2 = apnea, drug treatment
- 3 = apnea, vent. treatment
- 4 = apnea, drug, & vent. treatment
- 6 = apnea, unknown if treated
- 9 = unknown

*Age of onset (days) (45-47)

*Age resolved (days) (48-50)
- *000 = n/a
- 001 = birthdate or Day 1
- 998 = not prior to discharge
- 999 = unknown

VENTILATORY ASSISTANCE (51)

*Age of Onset (52)
- *0 = N/A
- 1 = < 1 hour
- 2 = 1 to 24 hours
- 3 = > 24 hours
- 9 = unknown

Type and Duration

Pos. press. vent.? (53)

*Number of days (54-55)
- *00 = N/A
- 01 = ≤ 24 hrs
- 02 = 2 days, etc.
- 98 = ≥ 98 days
- 99 = unknown

Other (CPAP-ET, CPAP-prongs,CNP)? (56)

*Number of days (57-58)
- *00 = N/A
- 01 = ≤ 24 hrs.
- 02 = 2 days etc.
- 98 = ≥ 98 days
- 99 = unknown

Tracheostomy (59)

Orotracheal Tube (60)

Nasotracheal Tube (61)

*Max. insp. pressure (cm) (62-63)
- *00 = N/A

*Max. end exp. pressure (cm) (64-65)
- *00 = N/A

art. pO_2's > 100 (66-67)

cap. pO_2's > 50 (68-69)

Complications During Vent. Asst.

Atelectasis (70)

Prolonged Hypoxia (pO_2 art < 50) (71)

Prolonged acidosis (pH < 7.2) (72)

Nasal narrowing (73)

Post-extubation airway obstruction (74)

Pneumopericardium (75)

Emphysema (76)

Other extrapleural air (77)

Other _____ (specify) (78)

CARD 5

Duplicate Columns (1-6)
Card 0 5 (7-8)

Vessel Catheterization and Duration

Umbilical artery cath. (9)

*Days Catheterized (10-11)
- *00 = N/A
- 01 = ≤ 24 hrs.
- 02 = 2 days, etc.
- 98 = ≥ 98 days
- 99 = unknown

Other artery Cath. (12)

*#Days catheterized (13-14)
- *00 = N/A
- 01 = ≤ 24 hrs.
- 02 = 2 days, etc.
- 98 = ≥ 98 days
- 99 = unknown

*Complications of Catheterization (15)
- *0 = none
- 1 = vasc. trans.
- 2 = vasc. perm.
- 8 = other
- 9 = unknown

Total days in O_2 (16-18)

Days in O_2 & art. line (19-21)

>1 episode vent. support (22)

DIAGNOSES

7.

Cardiovascular

*PDA (23)
*0 = no
1 = yes, treated surgically
2 = yes, not treated surgically
4 = suspect
9 = unknown

VSD (24)

Persistent Fetal Circulation (25)

*Other (26)
*0 = none
1 = ASD
2 = pulmonic stenosis
3 = transposition
4 = coarctation
8 = other _____ (specify)
9 = unknown

Pulmonary

RDS (27)

Meconium aspiration (28)

Atelectasis (29)

*Pneumothorax - right (30)

- left (31)
*0 = no
1 = yes, spont. with tube
2 = yes, post-op. with tube
3 = yes, spont. no tube
4 = yes, post-op. no tube
9 = unknown

Transient Tachypnea (32)

Pulmonary insufficiency of prematurity (33)

BPD (34)

Emphysema (35)

*Other (36-37)
*0 = none
1 = aspiration, not meconium
2 = hypoplastic lung
3 = pulm. hemorrhage
4 = pneumonia, pneumonitis
5 = bronchial stenosis
8 = other _____ (specify)
9 = unknown

*Gastrointestinal (Congenital) (38-39)
*0 = none
1 = Inguinal hernia
2 = diaphragmatic hernia
3 = TE fistula
4 = gastroschisis or omphalocele
5 = small bowel obst.
6 = large bowel obst.
7 = mec. plug
8 = other _____ (specify)
9 = unknown

*Gastrointestinal (Acquired) (40-41)
*0 = none
1 = obstruction
2 = perforation
8 = other _____ (specify)
9 = unknown

*Genitourinary (Congenital) (42)
*0 = none
1 = cryptorchidism
2 = ambiguous genitalia
3 = neurogenic bladder
4 = hydronephrosis
5 = hypoplastic kidney
6 = polycystic kidney
7 = hypospadias
8 = other _____ (specify)
9 = unknown

*Genitourinary (Acquired) (43-44)
*0 = none
1 = UTI
2 = hematuria
3 = renal failure
8 = other _____ (specify)
9 = unknown

Neurology

Peripheral Nerve Injuries (45)

*Malformations of CNS (46)
*0 = none
1 = anencephaly
2 = hydrocephalus with ICH
3 = hydrocephalus without ICH
4 = microcephaly
5 = hydranencephaly
6 = meningomyelocele
7 = encephalocele
8 = other _____ (specify)
9 = unknown

Hemorrhages

Subarachnoid [ ] (47)

Cerebral [ ] (48)

*Intraventricular [ ] (49)
- *0 = no
- 1 = grade 1 (mild)
- 2 = grade 2 (moderate)
- 3 = grade 3 (moderate)
- 4 = grade 4 (large)
- 8 = yes, grade unknown
- 9 = unknown

Hypoxic Ischemic Encephalopathy [ ] (50)

*Musculoskeletal Abnormalities [ ] (51)
- *0 = none
- 1 = CDH/hip click
- 2 = club foot
- 3 = supernumary digits
- 4 = cong. amputation
- 8 = other _____ (specify)
- 9 = unknown

*Mouth, Larynx, Trachea Abnormalities [ ] (52)
- *0 = none
- 1 = cong. stridor
- 2 = subglottic stenosis
- 3 = cleft palate &/or lip
- 4 = supraglottic/glottic acquired abnormalities
- 8 = other _____ (specify)
- 9 = unknown

Miscellaneous

Dysmorphic Features not listed elsewhere [ ] (53)

Choanal atresia [ ] (54)

*Trisomy [ ] (55)
- *0 = no
- 1 = yes, 21
- 2 = yes, other
- 3 = yes, type unknown
- 4 = suspect
- 9 = unknown

Other syndrome _____ (specify) [ ] (56)

ASSESSMENTS IN N.I.C.U.

EYE

Ophthalmologic consult [ ] (57)

Vascularization Complete? [ ] (58)

*Cong. Abnormality [ ] (59)
- *0 = none
- 1 = cataract, unilateral
- 2 = cataracts, bilateral
- 8 = other
- 9 = unknown

8.

Chorioretinitis [ ] (60)

Conjunctival hemorrhage [ ] (61)

Retinal hemorrhage [ ] (62)

Vitreous hemorrhage [ ] (63)

*Retinopathy of prematurity [ ] (64)
- *0 = no
- 1 = yes, grade 1
- 2 = yes, grade 2, etc.
- 3 = yes, grade 3
- 4 = yes, grade 4
- 6 = yes, grade 3+
- 8 = yes, grade unknown
- 9 = unknown

*Retrolental fibroplasia [ ] (65)
- *0 = no
- 1 = yes, grade 1
- 2 = yes, grade 2
- 3 = yes, grade 3
- 4 = yes, grade 4
- 8 = yes, grade unknown
- 9 = unknown

Cryopexy? [ ] (66)

PHYSIO

*Gest. age at assess. (wks) [ ][ ] (67-68)
- *41 = > 40
- 99 = unknown

*Outcome [ ] (69)
- *0 = normal
- 1 = profoundly abnormal
- 2 = abnormal
- 4 = suspect
- 9 = unknown

*GM Reflex (months) [ ][ ] (70-71)
- *99 = unknown

*Tone - upper [ ] (72)

- lower [ ] (73)

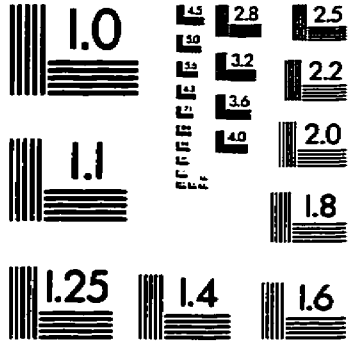
- trunk [ ] (74)
- *0 = normal
- 1 = increased
- 2 = decreased
- 9 = unknown

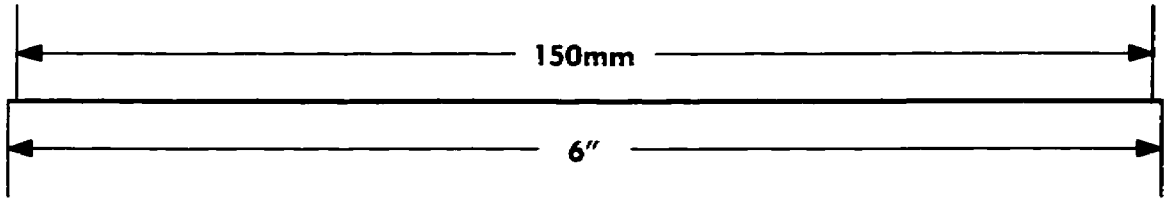
*Primitive Reflexes [ ] (75)
- *0 = normal
- 1 = abnormal
- 4 = suspect
- 9 = unknown

*N.I.C.U. HEARING [ ] (76)
- *0 = normal
- 1 = abnormal
- 4 = suspect
- 9 = unknown

DISCHARGE SUMMARY FORM # [2] (77)

TEST TARGET (QA-3)





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