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GROWTH AND MORBIDITY IN EXTREME PRETERM BORN INFANTS

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To Milan, Michal and Zuzana

ABSTRACT

Background: Rapid development in neonatal care during the past years has significantly improved long-term survival of extreme preterm born (EPB) infants creating a population of children with a high frequency of disabilities. Being lighter and shorter, as compared to full-term (FT) born child, predisposes the EPB infants to intensive nutritional interventions aiming for growth-promoting effect. The existing cross-sectional preterm growth charts reflect an intrauterine growth but are used for monitoring of extra uterine growth. Long-term data on postnatal growth are sparse. The **aim** of this thesis was to describe the growth pattern and morbidity from birth to 10 years in hospital-based cohort of EPB infants born 1990-2002 in Sweden and treated at Karolinska University Hospital (KS), Neonatal Intensive Care Unit (NICU) and/or Sahlgrenska hospital (SH). **Paper I** covers retrospective longitudinal cohort of 162 infants born before 26 + 0 weeks of gestation. We studied body weight (Wt), height (Ht) and head circumference (HC) from birth to FT age and compared it to the new Swedish birth size reference. We showed that the majority of the infants showed a pronounced postnatal growth restriction (PGR) and at discharge from NICU, 75 % of initially appropriate for gestational age infants were below –2 SDS for at least one of the body size variables. **Paper II** is a retrospective review of 114 children born before 25 + 0 weeks of gestation; we studied the frequency of ROP and visual acuity (VA). We found that 75% of the children developed severe ROP (stage ≥3), often in combination with additional functional deficits as a consequence of brain dysfunction. Normal VA (≥0.8) in at least one eye was found in 50% of all infants, more common in girls, while visual impairment (VA <0.33) was more common in boys. **Paper III** is a retrospective longitudinal study of 123 children born before 26 + 0 weeks of gestation; morbidity and body Wt, Ht, HC from FT to 10 years were studied comparing with the Swedish growth reference. We showed that a significant catch up (CU) in Ht and Wt occured; by age 10 years the attained mean Ht was in accordance with the genetic potential. Significant cognitive, motor disorder and/ or developmental comorbidity were found in 48% boys and 34% girls and severe ROP in 79 % and 66% respectively. In **Paper IV**, we studied the magnitude of catch-up (CU) growth 10 years after FT age and its impact for attained Ht and Wt during childhood in the cohort from Paper III. We showed that the most pronounced CU growth in both Wt and Ht occurred during the first year after FT age; followed by a plateau between 1 and 2 years but with more pronounced Wt than Ht development, a trend that continued until 10 years. Children with rapid CU in Wt three months after FT age were significantly heavier and taller at 1 and 2 years but not taller at 10 years compared to children with slower growth tempo. In **summary**, this thesis demonstrates that EPB infants show a continuous PGR in Wt, Ht and HC as compared to birth size references. Neither the birth-size derived growth curves nor the presented charts are supposed to be used as a single prescriptive standard for extra uterine growth of this population. By 10 years of age the majority of children had reached normal or near-normal Ht close to their genetic potential but Wt development was higher than Ht development, possibly leading to a disadvantageous metabolic situation. EPB infants, especially boys are at high risk for visual impairment and therefore rehabilitation of these children with a combination of disabilities is a challenge. The most challenging period is between birth and FT, which may be a critical window for development of the central nervous system.

LIST OF PUBLICATIONS

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals:

I. **Horemuzova Eva**, Söder Olle, Hagenäs Lars.
Growth charts for monitoring postnatal growth at NICU of extreme preterm-born infants.
Acta Paediatrica 2012: 101(3): 292-299

II. Jacobson Lena, Hård Anna-Lena, **Horemuzova Eva**, Hammarén Hannah, Hellström Ann.
Visual impairment is common in children born before 25 gestational weeks – boys are more vulnerable than girls.
Acta Paediatrica 2009; 98: 261-265

III. **Horemuzova Eva**, Åmark Per, Jacobson Lena, Söder Olle, Hagenäs Lars.
Growth charts for height, weight and head circumference for extreme preterm infants from birth to 10 years and long-term sequelae.
Manuscript

IV. **Horemuzova Eva**, Söder Olle, Hagenäs Lars.
Catch-up growth in preterm infants born before 26 weeks of gestation.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY

AC	Abdominal Circumference measured by ultrasound from an axial image of the abdomen at the level of the portal vein. The circumference of the head is typically larger than the abdominal circumference up to 34 weeks of gestation, and the abdomen becomes larger thereafter. In the presence of intrauterine growth retardation (IUGR), the abdominal circumference is affected early in the process whereas the head size tends to be affected only in more severe cases with progressive disease.
ADHD	Attention Deficit Hyperactivity Disorder; a developmental disorder characterized by inattention, motor restlessness and impulsivity.
AGA	Appropriate for Gestational Age; describes a fetus or newborn infant whose weight, length and head circumference is within the normal range (within ± 2SDS or from 3^{rd} to 97^{th} percentile) for his or her gestational age which is dependent on the used reference.
Autism-Spectrum Disorders	Represent a group of developmental disorders, milder or more severe, sometimes combined with intellectual disabilities and characterized by severe and pervasive deficits in social communication and interaction, restricted and repetitive pattern of behaviour, interests and activities. It is usually not diagnosed until after 3 years of life. In this work milder forms such as Asperger's syndrome and atypical autism are more often encountered.
Auxology	The study of all aspects of human physical growth; from Greek, auxo, or, auxano, "grow"; and, -logia. It is a highly multi-disciplinary science involving health sciences/ medicine including nutrition and genetics among others.
Birth length	The length of an infant at birth
BMI	Body Mass Index or Quetelet index; weight in kilograms divided by the square of height in meters. This index was originally devised by the Belgian statistician Adolphe Quetelet (1796-1874) who applied it to adults, not to children. For adults, the index describes the relation of weight to height, in effect adjusting weight for height. For adults, BMI provides a way to translate weights at different heights into a common metric.
Box-Cox transformation	Transformation that makes non-normally distributed data normal-like distributed.
BPD	Biparietal diameter; a measure correlated to fetus age and weight in the second and third trimesters. BPD measures the transverse diameter of the upper midbrain at the level of the thalamic nuclei and cavum septum pellucidum from the external surface of one proximal parietal bone to the inner surface of the contralateral parietal bone. The earlier the gestational age, the greater the

	predictive accuracy of the measurement. In the second trimester, a BPD measurement carries a predictive accuracy of ±7 days, whereas in the late third trimester it carries a predictive accuracy of ±3 weeks. The cephalic index, which measures the relationship between the short and long axes of the fetal head, should be measured, if the head shape appears abnormal. If this index is below 70 or above 86, the BPD should not be used in the fetal age and weight estimates.
BW	Birth weight; the weight of an infant at birth
CDC	Center for Disease Control
CU	Catch-Up growth, growth velocity above the statistical limits of normality for height during a defined period of time
CEDD	Corrected Expected Date of Delivery; adjustment of the EDD following an ultrasound examination at 18-22 weeks of gestation as an alternative to using LMP to determine gestational age.
Cerebral Palsy	CP is an umbrella term including a number of disorders with impaired development of movement and posture by a non-progressive injury to, or abnormal development of, the immature brain during pre-, peri-, postnatal life or early childhood. The functional consequences vary greatly between individuals and type of cerebral palsy. CP is often associated with other comorbidities, such as intellectual disabilities, vision and hearing problems, epilepsy and other problems with cognition and communication. Signs and symptoms appear during infancy or preschool years.
CGS	Child Growth Standards
Chorioamnionitis	An acute inflammation of the amniotic membranes and chorion of the placenta caused by infection, diagnosed by the presence of maternal fever, uterine fundal tenderness, maternal tachycardia (>100/min), fetal tachycardia (>160/min) and purulent or foul amniotic fluid.
Chronological age	The time elapsed from birth, usually described in days, weeks, months and/ or years.
CLD	Chronic lung disease with a need of supplemental oxygen at 36 weeks gestational age following bronchopulmonary dysplasia. It is inflammation and scarring of the lungs resulting in abnormal respiratory function and oxygen-dependency longer than 28 days of age, most common among preterm born children with a low birth weight who received prolonged mechanical ventilation to treat respiratory distress syndrome.
Conceptional age	The time elapsed between the day of conception and the day of delivery. Because assisted reproductive technologies accurately define the date of fertilization or implantation, a precise conceptional age can be determined in pregnancies resulting from such technologies. This term should not be used in routine clinical paediatrics (Committee on Fetus and Newborn 2004).
Corrected age (adjusted age)	Chronological age reduced by the number of weeks born before 40 weeks of gestation. The term is most appropriately used to

	describe children up to 3 years of age who were born preterm.
Comorbidity	The presence of one or more disorders (or diseases) in addition to a primary disease or disorder, often describing the effect of such additional disorders or diseases.
CPAP	Continuous-Positive-Airway-Pressure
CRIB score	The Clinical Risk Index for Babies used for evaluation of neonatal illness severity based on birth weight, gestational age, the presence of congenital malformations, worst base excess, maximum and minimum appropriate fraction of inspired oxygen during the first 12 h of life; a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units.
CRL	fetal crown-rump length
Cross-sectional reference	A reference constructed from measurements of individuals of different ages who are measured once at the same point of time. This design does not provide adequate information for following growth of an individual child over time and thus do not allow for judgment of the child's tempo of growth. In contrast, repeated cross-sectional studies provide very sensitive information about changes in the health status of the population thus allowing for monitoring of secular changes of growth.
CV	Coefficient of variation; the ratio of the standard deviation to the mean; it is a measure of variation of data in relation to the arithmetical mean
Cubic spline	Used to smooth noisy measurements. It is a function consisting of a sequence of third-order polynomials. Each polynomial is fitted to a limited number of consecutive data points and all polynomials together form a smooth line.
Cuf-off	A designated limit beyond which a subject or observation is classified according to a pre-set condition.
Developmental	A progression from a simpler or lower to a more advanced, mature, or complex form or stage
ELBW	Extremely Low Birth Weight; an infant with birth weight less than 1000 g
EPB	Extreme preterm born infant; infant born alive before completed 28+0 gestational weeks according to WHO; in this work defined as infant born before completed 26+0 weeks of gestation
EPIBEL	Extremely preterm infants in Belgium
EXPRESS	Extremely preterm infants study in Sweden
Fetal growth	The entire process of growth, maturation, differentiation, and development that occurs between conception and birth within the womb and is the result of adaptation to intrauterine environment.
FL	Fetal Femur Length (FL) measured by ultrasound involves measuring the diaphysis and metaphysis excluding the epiphysis. Gestational age prediction from femur length is subject to error either from measurement difficulties caused by difficulty in visualizing the ends of the bone or from biological variation.
Fovea	Central fovea or fovea centralis. A tiny pit located in the macula of the retina that provides the clearest vision of all. Only in the

	fovea are the layers of the retina spread aside to let light fall directly on the cones, the cells that give the sharpest image.
Fetal weight estimates	Ultrasound estimates of fetal weight have been derived from single measurements utilizing BPD or abdominal circumference as well as by combining both. These estimates contain inherent error which decreases as BW decreases. The use of multiple parameters, especially head, abdomen, and femur measurements, provides the most accurate measurements of fetal weight. However, it is still not accurate in extremely low- or high-birth-weight fetuses. Because fetal weight estimates remain imprecise, estimation of fetal age based solely on estimates of fetal weight should not be used.
GA	Gestational Age (completed weeks); time elapsed between the first day of the last menstrual period and the day of delivery. If pregnancy was achieved using assisted reproductive technology, gestational age is calculated by adding 2 weeks to the conceptional age.
GAMLSS	Generalized Additive Models for Location, Scale and Shape
GA prediction	Estimation of gestational age can be done using data from the LMP (last menstrual period) or through ultrasound examination. The latter is considered to be the most accurate but most predictions are based on the 50th percentile of a reference population.
Genotype	The inherited instructions that individual carries within its genetic code.
Growth	A dynamic process characterized by an increase in the size usually as a result of an increase in the number of cells. The principle parameters of somatic growth are length or height (measuring the skeleton), weight (measuring all tissues), and head circumference (reflecting brain growth).
Growth Chart	Series of smoothed curves representing the distribution of weight, length and head circumference within a population. Different smoothing techniques give different curves from the same measurements.
Growth Standard	Delineates the variation that is considered to be normal, optimal, or healthy. It represents the notion of a norm or desirable target, and thus involves a value of judgement (WHO. Report of WHO expert Committee: Physical status – The Use and Interpretation of Anthropometry. WHO Technical report no. 854. Geneva, Switzerland: WHO, 1995). Standard can also be described as prescriptive or normative.
Growth reference	Describes the variation of some measure within a reference population, often conditioned on age and sex. Reference is explicitly descriptive and represents population´s actual growth, irrespective of its health status.
Growth retardation	Failure of an individual to develop at a normal rate of height and weight for his or her age
HC	Head circumference, maximal fronto-occipital circumference

HFOV	High-Frequency-Oscillatory-Ventilation
IHDP	Infant Health and Development Program
Imprinted gene	A gene whose expression has been affected by genomic imprinting so that only a single allele functions, the other being turned off by epigenetic mechanisms during embryonic development.
Imputation	Is the process of replacing missing data with substituted values. Imputation preserves all cases by replacing missing data with a probable value based on other available information. There are several imputation techniques and one of them is regression imputation. Fitted values from the regression model are used to impute the missing values. A drawback of this method is that the imputed data do not have an error term included in their estimation, thus the estimates fit perfectly along the regression line without any residual variance. This suggests a greater precision in the imputed values than is warranted. The regression model predicts the most likely value of missing data nut does not supply uncertainty about that value.
INTERGROWTH	International Fetal and Newborn Growth Consortium
IUGR	IntraUterine Growth Restriction; refers to a condition in which a fetus is unable to achieve its genetically determined potential size.
IVF	In-Vitro-Fertilisation; a procedure where an egg is fertilized by sperm outside the body: in vitro. This treatment involves monitoring of woman's ovarian follicle growth, inducing ovulation and aspirating oocytes from the ovaries and fertilizing them in a laboratory setting. The fertilized egg (zygote) is then replaced in the uterus and implanted if the treatment is successful.
IVH	Intraventricular hemorrhage; a condition with bleeding into the hollow chambers (ventricles) normally reserved for cerebrospinal fluid and into the tissue surrounding them. Due to the degree and severity of bleeding various neurodevelopmental impairments may follow including post-hemorrhagic hydrocephalus.
Kurtosis	The degree of "peakedness" of a distribution. For example a high kurtosis distribution has a sharper peak and fatter tails compared to the normal distribution. By definition normal distribution has kurtosis equal to three but some definitions of kurtosis subtract 3 from the computed value so that the normal distribution has kurtosis of zero.
Learning disorder	A clinical diagnosis indicating difficulties in different learning processes such as reading, writing and mathematical skills. It is included reading disability (dyslexia), mathematics disability (dyscalculia) and writing disability (dysgraphia) within this concept.
Length	Distance between the top of the head and the sole of the foot when the individual is lying down.
Live-birth	In human reproduction, a live birth occurs when a fetus,

	whatever its gestational age, exits the maternal body and subsequently shows any sign of life, such as voluntary movement, heartbeat, or pulsation of the umbilical cord, for however brief a time and regardless of whether the umbilical cord or placenta are intact (World Health Organization. International statistical classification of diseases and related health problems. Tenth Revision. Vol 2. Geneva, Switzerland: World Health Organization, 1993:129).
LMS	Method for computing centiles and SD scores for skewed distributions. It is based on the Box-Cox power transformation, which normalizes the distributions. The parameters of this transformation are L (skewness), M (median) and S (coefficient of variation).
Longitudinal growth reference	A reference constructed from measurements of the same individual or group of individuals of similar ages who are measured at two or more occasions. The growth rate between the occasions is directly observed for each child, thus this reference can be used to estimate the variability in growth between children over time.
Maximum likelihood estimation	A method of estimating the parameters of a chosen statistical model. For example if we assume normal distribution for given data, the parameters to be estimated are mean and standard deviation.
Mean	The sum of the values divided by the number of values. The sample mean may differ from the population mean, especially for small samples, but the law of large numbers dictates that the larger the size of the sample, the more likely it is that the sample mean will be close to the population mean.
Median	The numerical value separating the higher half of a sample, a population, or a probability distribution, from the lower half. At most, half the population has values less than the median, and, at most, half have values greater than the median. The median can be used as a measure of location when a distribution is skewed, when end-values are not known, or when one requires reduced importance to be attached to outliers, e.g., because they may be measurement errors.
MGRS	Multicenter Growth Reference Study
Mode	The value that occurs most frequently in a data set or a probability distribution. In symmetric unimodal distributions, such as the Gaussian distribution, when graphed, gives the famous "bell curve", the mean (if defined), median and mode all coincide.
MBR	Medical Birth Registry that since 1973 includes birth data for all newborns in Sweden
MPH	Mid-parental height; using the parental heights for calculation of children´s genetic potential: Formula for boys (mother's height + 13 + father's height) / 2; for girls (father's height– 13 + mother's height) / 2 with height expressed in cm.

Mixed-longitudinal reference	A reference that is a compromise between a cross-sectional and a longitudinal reference, thus individuals are measured more than once, but not through the entire age range. This design may have less precision with respect to the measured parameter than an exclusively cross-sectional or longitudinal study.
NCHS	National Center for Health Statistics
NEC	Necrotising EnteroColitis is a condition predominantly seen in premature infants and is characterized by a combination of partial- or total intestinal wall ischemia and reperfusion injury, usually involving the terminal ileum. Initial symptoms include feeding intolerance, increased gastric residuals, abdominal distension and bloody stools. Symptoms may progress rapidly to abdominal discoloration with intestinal perforation and peritonitis and systemic hypotension requiring intensive medical care. Known risk factors are: prematurity, neonatal stress, formula feedings, surgery in the neonatal period, umbilical artery catheterization, bacterial infection and hypoalbuminemia. NEC prevents oral feeding for at least 2 to 3 weeks after the onset of NEC and it frequently takes more than 1 month for the successfully treated patient to attain adequate oral caloric intake.
Neonatal period	A period of less than 28 days after birth; can be divided to early (before 7 days of age) and late period (from completion of 7 days up to 28 days of life).
NHANES	National Health Examination Survey
NHES	National Health Examination Survey
NICU	Neonatal Intensive Care Unit
Normal visual acuity	The clearness of vision depends on sharpness of the retinal focus within the eye, function in the fovea, anterior and posterior visual pathways and cognitive visual function. Normal visual acuity in this work is ≥ 0.8.
PDA	Patent ductus arteriosus; a symptomatic ductus arteriosus necessitating pharmacological treatment, surgical ligation or both.
P50	The 50th percentile which corresponds to mean value in the distribution.
Prenatal development	Prenatal development is the entire process of growth, maturation, differentiation, and development that occurs between conception and birth. After the conception, several stages of cell division occur before the dividing ovum- blastocyst, with about 100 cells enter the uterus for implantation and thereafter form the placenta and the amniotic membranes. By the end of the seventh week all essential systems are present. Prenatal development may be adversely affected by several factors.
Postmenstrual age	The time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (chronological age), usually described in weeks.
Phenotype	Expression of the observable specific physical or biochemical characteristics or traits of the individual, based on genetic and

	environmental influences.
Preeclampsia	A medical condition characterized by high blood pressure and significant amounts of protein in the urine. Preeclampsia may progress into eclampsia, occurrence of life-threatening generalized seizures with risk of intracerebral hemorrhage. The disorder can develop from 20 weeks gestation.
Pregnancy	The period from conception to birth with one or multiple gestations, known as an embryo (during the first 8 weeks following conception) or fetus (from 8th weeks until birth), in a woman's uterus. The normal pregnancy duration is generally assumed to be 280 days (or 40 weeks of gestational age). However, an average duration of pregnancy is 38 weeks (266 days) from conception and is also called as fetal age (Guerrero 1969). Predicting the pregnancy due date based on conception, is the most accurate way to calculate one's due date, but usually the date of conception is not known.There is a standard deviation of 2 days if prenatal ultrasound measurements are used for calculation of due date in week 12-14 and 3 days in weeks 15-22.
PPROM	Preterm premature rapture of membranes is a spontaneous rupture of the membranes ≥1 h before the onset of contractions.
P-value	The probability of falsely rejecting the hypothesis being tested. In this work all p-values were compared to a level of significance set to 0.05.
PVL	Periventricular leucomalacia. A brain injury acquired during prenatal period of development affecting mainly cerebral white matter but also grey matter structures. It can lead to motor impairments (cerebral palsy), cognitive, visual or auditory impairments. Thus, constellations of white and gray matter abnormality are the principal determinants of variable degrees of brain injury and adverse neurodevelopmental outcomes.
ROP	Retinopathy of prematurity; an eye disorder which can occur in not fully developed retina of preterm born infants and that interrupt the normal blood vessel development. “Plus disease” is a complication and sign that ROP is worsening and may require treatment. It portrays abnormal blood flow in the retina causing the blood vessels to enlarge and become twisted. Visual function in preterm infants is threatened by ROP.
SD	Standard deviation; measure of variability or diversity used in statistics and probability. It shows how much variation or "dispersion" exists from the mean, or expected value. A low standard deviation indicates that the data points tend to be very close to the mean, whereas high standard deviation indicates that the data points are spread out over a large range of values.
Septicemia in newborn	The presence of pathogenic organisms in the bloodstream, leading to sepsis with atypical clinical symptoms as temperature instability, lethargy and hypotonia, apnea/ need of increased respiratory support and feeding intolerance, abdominal distension combined with abnormal white blood cell count, unexplained

	metabolic acidosis and hyperglycemia. Late manifestations are hepatosplenomegaly, jaundice and petechiae.
Severe brain injury	The presence of intraventricular hemorrhage ≥grade 3, based on findings by cranial ultrasonography according to Papile grading system: Grade I: isolated subependymal hemorrhage (SEH), Grade II: SEH with IVH, no ventricular enlargement, Grade III: IVH with enlarged ventricles, Grade IV: IVH and SEH with extension into brain beyond the ganglionic eminence.
SGA	Small for Gestational Age; Birth length or weight or both are below -2SDS for gestational age and sex. The classification of SGA is dependent on the used reference. SGA is NOT a synonym of low-birth-weight (LBW), very-low-birth-weight (VLBW) or extremely-low-birth-weight (ELBW). Not all fetuses that are SGA are pathologically growth restricted and, in fact, may be constitutionally small.
Skewness	A measure of asymmetry of a distribution. Zero value indicates even distribution of values on both sides of the mode. Negatively skewed distribution has more values on the left side of the mode and positively skewed distribution on the right side of the mode. A few much skewed values can dramatically affect the mean but will have less effect on the median.
SMBR	Swedish Medical Birth Register
Smoothing	"Final polish"; having a curve line free from irregularities, roughness, or projections; even.
Standards for birth size	Should be used for evaluation of birth size but not for following postnatal growth
Standard for fetal growth	Should be used for evaluation of intrauterine growth but NOT for postnatal growth
Transformation of data	Data transformation involves performing a mathematical operation on the original data, and thereby transforming it. This is usually done so that the transformed data appears closer to a pre-chosen probability distribution; usually a normal distribution.
Trimmed mean	A mean computed from a predefined interval of the data. The interval could be defined by ±SD or percentile range.
TPN	Total Parenteral Nutrition provides all of the carbohydrates, proteins, fats, water, electrolytes, vitamins, and minerals needed for the building of tissue, expenditure of energy, and other physiologic activities through the veins of the circulatory system, rather than through the digestive system.
Visual impairment	Unilateral or bilateral blindness or visual acuity <0.33 without glasses in at least one eye or significantly reduced visual fields. In a preterm born child visual impairment can have retinal and/ or cerebral origin.
Weight velocity	The rate of weight gain or loss over a period of time representing the slope of weight curve. Immediately after birth the normal weight loss is maximal by the third day and normally equals 7% of birth weight. Greater than 10 % is considered excessive in

	term infants.
WHO	World Health Organization
Z-score/ SDS	The number of SD units above or below the mean; often presents as a deviation of an individual's value from the mean values of a reference population and is calculated by subtraction of individual value from the mean values, divided by the standard deviation of the reference population. Z-score cut- offs or percentiles are statistically based, and are not based on health risk.

1 INTRODUCTION

Human growth is a complex process regulated by genes, nutrition and the social and economic environment. When the environmental conditions are optimal an individual reaches the genetically determined growth potential. Human growth is also a dynamic process because even under similar social and economic circumstances it can result in variable individual growth patterns (Hermanussen 2010). Rapid development in neonatal care during the past years has significantly improved long-term survival of extreme preterm infants. At the same time this development has created a population of children with a high frequency of disabilities due to premature birth and its complications. As survival has become an expected outcome, the focus has shifted towards means to improve postnatal health, including growth and neurodevelopmental outcome.

Growth monitoring in infancy and childhood is a widely-used tool for defining health and nutritional status of children (de Onis M and Habicht 1996) and can be considered as a screening program with intention to identify growth disorders early and by intervention reduce the risk of growth disorder or its complications. At the individual level, growth monitoring usually includes measuring of infant's height, weight, head circumference and parental height. These measures are then plotted on a growth chart of a reference population and interpreted in order to decide whether the infant's growth is normal or not.

Although the literature contains many growth references in the form of figures and tables to describe normal growth, it is important to select charts which best describe the population for which they are to be utilized. The most reliable growth charts are usually those formulated from within the population that is to be investigated assuming correct mathematical modelling and thus giving confident results. At first sight it appears reasonable to assume that an "expert approved" recent national growth chart does appropriately represent growth of the population of interest and is a relevant tool to depict individual growth patterns (Hermanussen 2012). However, it is important to recognise that things are easily believed if they are comforting, and that many clinical notions are accepted because they are comforting rather than because there is any evidence to support them (Asher, Lancet 1959). Any observations can be interpreted in entirely different ways. Our path is cumbered with guesses, presumptions and conjectures (Sir Clifford Allbutt) but "the words used in clinical medicine have a tremendous influence on the subject they describe or purport to describe. They perpetuate illnesses, syndromes and signs whose existence is beyond question and moreover, they distort text-book descriptions to conform to the chosen word" (Asher 1972).

The aim of this thesis is to describe the complexity of growth and its interpretation in the most immature population- in children born before 26 weeks of gestation- from birth to 10 years of age. The studies evaluate several different aspects of growth: epidemiology, fetal growth physiology, nutrition, morbidity, methodology behind creating a growth reference and a clinical interpretation of body measurements by pediatric endocrinologist.

2 BACKGROUND

2.1 GROWTH MONITORING AS A SCREENING PROGRAM

Evidence-based referral criteria are needed if growth monitoring is used as a screening program (van Dommelen 2008). According to the United Kingdom national screening committee (NSC), screening is defined as "a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications"(Gray 2004).
Growth monitoring can be considered as a screening program but growth monitoring is usually more complex than other screening programs: 1. A growth referral to pediatrician is often based on a combination of abnormal growth and other clinical symptoms, while the result of a conventional screening program usually only depends on the result of a test. 2. Growth monitoring is aimed at identifying multiple diseases simultaneously, while a screening program is often aimed at identifying one disease. 3. Growth monitoring is usually performed over a long-time periods, while a screening program offers a test to the population at one moment in time or several tests at a given age (van Dommelen and van Buuren 2013).

The 22 NSC screening quality criteria can be subdivided into four groups (van Dommelen and van Buuren 2013):

a) Epidemiology of the condition, defining the condition as an important health problem
b) Properties of the test, implying that the referral criteria should be acceptable to the population, safe, precise, simple and validated. The simplest criterion consists of comparing a single anthropometric measurement to some norm, but more advanced criteria may involve multiple measurements over time. Validated or evidence-based referral criteria are then able to detect, at an early stage, as many children with growth-related conditions as possible (high sensitivity) at the account of only a limited number of children with a false-positive result (high specificity).
c) Any treatment options, indicating that there should be an effective treatment or intervention for the children with conditions identified through early detection, with evidence leading to better outcomes than late treatment.
d) The acceptability of the screening program, implying that the screening program should be cost-effective but from a societal perspective, a high specificity for the referral criteria is desirable to minimize unwanted health costs, to free clinical practitioners from being overloaded by work, to evade unnecessary interventions and treatments for healthy children and to reduce parental and child's anxiety.

In summary, many steps have to be taken into account for growth monitoring to fulfil the quality criteria of a screening program (van Dommelen and van Buuren 2013).

2.2 EPIDEMIOLOGY OF PRETERM BIRTH

2.2.1 Definition of preterm birth

Preterm birth is defined by World Health Organisation (WHO) as birth at 37 weeks of completed gestation or less. Preterm infants are defined in 3 categories: 1. late preterm - born between 32 and 37 weeks, accounting for 84% of total preterm births, most of them surviving with supportive care. 2. very preterm - born between 28 and 32 weeks, requiring extra supportive care leading to survival of most of them and finally 3. extremely preterm - born before 28 weeks. Survival of these infants require the most intensive and expensive care. Thus in developed countries, extremely preterm born infants have more than 90% chance of survival in the neonatal intensive care units, though they may suffer lifelong physical, neurological, and learning disabilities. In contrast, in low-income countries the survival rate of these extremely preterm born infants is less than 10% (WHO report).

2.2.2 Incidence and causes of preterm birth

The problem of preterm births is not confined to low-income countries; in the low-income countries, on average, 12% of babies are born too early, compared to 9% in higher-income countries. The United States and Brazil both rank among the top 10 countries with the highest number of preterm births. In the United States, for example, about 12%, or more than one in nine of all births, are preterm. However, of the 11 countries with preterm birth rates over 15%, all but 2 are in sub-Saharan Africa. Those contrast with the 11 countries (Belarus, Ecuador, Latvia, Finland, Croatia, Samoa, Lithuania, Estonia, Antiqua/Barbuda, Japan and Sweden) with the lowest rates of preterm birth ranging from 4 to 6 % (WHO report).

In high-income countries, increases in the number of preterm births are linked to increases in the mean age of birth-giving women, increased use of fertility drugs resulting in multiple pregnancies and medically unnecessary inductions and Caesarean deliveries before full-term. In many low-income countries, the main causes of preterm births include infections, malaria, HIV, and high adolescent pregnancy rates. However, both in high- and low income countries, many preterm births remain unexplained. A number of risk factors has been identified including a prior history of preterm birth, the mother’s underweight or obesity, diabetes, hypertension, smoking, infection, low (under 17 years) or high (over 40 years) maternal age, genetic factors, multi-fetal pregnancy (twins, triplets, and higher), and short inter-pregnancy interval. However, little is known about the interplay of these and other environmental and social factors.

In general, preterm births can further be divided into two categories: spontaneous, i.e. preterm births resulting from early onset of labour or premature rupture of the membranes, and health-care provider-induced. Provider-induced early deliveries may occur when the health of the mother or fetus is in jeopardy, such as in pre-eclampsia (high blood pressure in pregnancy), for convenience of the doctor, midwife or mother, or by an error in due dates.

2.2.3 Survival

Improvements in neonatal care have increased the survival rates of a new population of extremely preterm born infants, born before 26 weeks of gestation. Reported short-term survival of the infants until discharge from the hospital during 1986-1997 is based on 37 international studies (0-21% at gestational age (GA) of 22 weeks, 0-46% at GA of 23 weeks, 17-59% at GA of 24 weeks and 35-85% at GA of 25 weeks) (Social Ministry of Health and Welfare 2004). Ranges are wide due to a small number of study participants from hospital-based compared to population-based studies, uncertainty of reported GA assessment and inclusion of stillbirths in some studies. Data from EPICure study (Costeloe 2000) in 1995 showed that around 50 % of live-born infants at 23 weeks, 82% born at 24 weeks and 92 % at 25 weeks were admitted to NICU. Overall survival to discharge was 39%, rising from 20 % at 23 completed weeks to 52 % at 25 completed weeks. Of the 314 survivors, 6 are known to have died during the first year resulting in 78% survival rate (241 children) at 6 years. Another example is Extremely Preterm Infants study from Belgium (EPIBEL) study with 45% survival rate at discharge based on 19 centers in Belgium with inter-center variation 32-93%, median 52% (Vanhaesebrouck 2004).

2.2.4 Situation in Sweden (SMBR 2004)

Swedish medical birth registry (SMBR) reported, between 1985 and 2001, a constant prevalence of 0.2% of single live-births at GAs below 28 weeks in contrast to multiple pregnancies in 1985 of 1.7% and in 2011 of 2.8% of the same GAs. There are 1591 extremely preterm live-born infants, born before 26 weeks of gestation, registered in SMBR between1985-2001, (270 infants at GA of 23 weeks, 504 infants at GA of 24 weeks and 817 infants at GA of 25 weeks). According to SMBR for 1999-2000, the survival of live-born children was 42% at 23 weeks, 62% at 24 weeks and more than 85% at 25 weeks. Single children surviving at 22 weeks have been reported.

Recent reports of one-year survival rates of 70 % (Fellman 2009) and 78% (The EXPRESS group 2010) in extremely preterm live-born Swedish cohorts (GA<26 weeks + 6 days) at 2004-2007 contrast to 48% of cohort born in 1990-1992 with birth weight (BW) ≤ 1000 g (Farooqi 2006) indicating an increased survival of most immature infants since 1990s. However, this increase in survival rates was accompanied by an increase in neonatal morbidity, with the exception of severe intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL) where the rates remained unchanged.

2.2.5 Morbidity and interventions in extreme preterm born survivors

Although many extremely preterm infants even among those with major neonatal morbidities develop normally, neonatal morbidities are important antecedents of later neurodevelopmental disability. Similar to short-term morbidity, incidence of significant sequelae increases with decreasing pregnancy duration and BW. In general, the majority of surviving extreme preterm born (EPB) infants has at least one severe complication during the neonatal period, which increases risk for later sequelae. Therefore, it is very difficult to give prognosis on survival and/or risk for serious and

long-term sequelae in the perinatal and neonatal period (Social Ministry of Health and Welfare 2004).

Conditions associated with poor long-term outcome include IVH ≥grade 3 (Luu 2009), PVL (De Vries 2004; CLD (Majnemer 2000); retinopathy of prematurity (ROP) (Msall 2000); NEC (Hintz 2005); neonatal infection (Stoll 2004); and poor growth from birth to discharge (Ehrenkranz 2006). The presence of three particular neonatal morbidities (CLD, severe ROP (≥stage 3), brain injury) strongly predicted the risk of late death or neurosensory impairment in extremely low birth weight (ELBW) infants at 18 months (Schmidt 2003).

Neonatal morbidity in survivors of extreme preterm birth in relation to pregnancy duration is described in a Table 1, modified from the Social Ministry of Health and Welfare report in 2004 (Marsal 2004); the data are based on 11 international studies from USA, Canada, United Kingdom and Finland. Study populations were born in 1988-1999.

Table 1. Neonatal morbidity in survivors of extreme preterm birth in relation to pregnancy duration; chronic lung disease; severe brain injury; severe visual impairment. This table is modified from Table III (supplement 3). Data are based on 11 studies from populations born from 1988 to 1999 from USA, Canada, UK and Finland. Perinatalt omhändertagande vid extrem underburenhet. Socialstyrelsen. Item number: 2004-123-15, published www.socialstyrelsen.se, april 2004, s.132. CLD chronic lung disease (oxygen-dependency at 36 weeks postconceptional age); Severe brain injury (IVH grade III and IV); Severe visual impairment (ROP stage ≥ III).

GA	CLD (%)	Severe brain injury (%)	Severe visual impairment (%)
23	50-100	7-83	25-55
24	32-89	9-64	13-37
25	16-71	7-22	10-27

2.2.6 Situation at NICU

The most comprehensive report from the situation in Sweden comes from Extremely Preterm infants study in Sweden (The EXPRESS group 2010), which provides information on morbidities and associated factors in surviving EPB infants, born 2002-2004 before 27 weeks of gestation. Altogether 60 % of these infants were intubated at birth and given surfactant within 2 h after birth. Of 497 infants, 85% needed mechanical ventilation (MV) at some time during the hospitalization with the median (range) duration of 11 (1-34) days for the whole group and varied from 42 days at 22 weeks, 24 days at 23 weeks, 19 days at 24 weeks, 10 days at 25 weeks to 6 days at 26 weeks. The proportion of infants who needed MV was 100 % at 22 and 23 weeks, 95% at 24 weeks, 89% at 25 weeks and 72% at 26 weeks. Moreover, 41% of survivors in EXPRESS developed septicemia, 61% had a symptomatic PDA and 5.8% NEC

diagnosis. 73% had any form of CLD and 25% had severe CLD compared to 45% in the EPIBEL study. The rates of any form of CLD and severe ROP increased with decreasing GA (The EXPRESS group 2010). However, of the 497 infants, 23% survived without any CLD, severe ROP and severe brain injury.

Advancing GA, higher BW and maternal antibiotics increased whereas male gender, obstetric complications, iatrogenic birth, small-for-gestational age (SGA) status, PDA and increased duration of MV decreased the odds of neonatal complications (EXPRESS 2010).

2.2.7 Periventricular leukomalacia

PVL is a brain injury acquired during 24-34 weeks of gestation which means that in full-term infants it has prenatal and in preterm born infants' pre- and postnatal origin (Volpe 2010). PVL affects cerebral white and gray matter which can lead to motor impairments (cerebral palsy), cognitive, visual or auditory impairments (Staudt 2000).

The constellations of white and gray matter abnormality are the principal determinants of variable degrees of brain injury and adverse neurodevelopmental outcomes. These abnormalities of the neuronal-axonal unit are in large part a combination of disturbances of normal development and compensatory reparations resulting in cells that seem not to have the capacity for full differentiation to myelin-producing cells. The rapidity and complexity of these developmental events makes the brain vulnerable to injuries by exogenous and endogenous insults, such as ischemia, inflammation, excitotoxicity and free-radical attack (Volpe 2010).

Neuroimaging studies indicate that PVL in its various forms is by far the most common, occurring in 50% or more of VLBW infants (El-Dib 2010). De Vries in 1992 classified PVL by ultrasound into four grades, ranging from increased periventricular echogenicity persisting more than 7 days to occurrence of deep subcortical cysts in deep white matter (De Vries 1992).

When the pathology of PVL was first described in 1962 by Banker and Larroche, interruption of axons was noted within the optic radiation adjacent to the occipital horns suggesting that visual field defects would be a possible consequence of this damage (Banker and Larroche 1962). Later it has been documented that preterm born infants with white matter damage can exhibit a wide spectrum of visual symptoms, from early-onset isolated esotropia to severe cerebral visual impairment (Jacobson 2006). Visual dysfunction due to PVL is characterized by subnormal visual acuity, eye motility disorders, restriction of visual field and cognitive visual impairment including difficulties in visuospatial analysis, recognition, simultaneous perception and visual memory (Jacobson 2006).

2.2.8 Retinopathy of prematurity

The first recognized case of ROP, previously called retrolental fibroplasia dates back to 1940 and was published by Dr. Terry in 1942. ROP continues to be a worldwide problem in preterm born infants (Tasman 2011). Initially ROP was connected to prematurity, later to uncontrolled oxygen supplementation in low-birth weight (LBW)/

preterm born infants and thereafter to increased survival of extremely preterm born infants. High percentage of oxygen given to a preterm born or LBW child has for a long time been recognized as the cause of high incidence of ROP. When setting 40% limit for oxygen supply the incidence of ROP-related blindness decreased (Tasman 2011). However this was accompanied by lower survival of preterm born infants and increased incidence of cerebral palsy (Crosse, Evans 1952).

In preterm born infants, the retina is not yet fully vascularized and has a peripheral avascular zone which is largest in the most immature infants. This avascular retina is a subject to periods of relative hyperoxia even while preterm infants should be in room air since in utero the arterial oxygen pressure of the fetus is low (22 to 24 mmHg) (Chow 2003). ROP develops in two phases (Smith 2003). In phase one, occurring from birth to corrected age of 30-32 weeks of gestation, a vessel growth restriction occurs as a reaction to the relative hyperoxia due to oxygen supplementation during longer periods of assisted ventilation. In phase two, starting at corrected age of 32-34 weeks gestation, a vessel proliferation occurs instead, as a result of increasing metabolic demands in the immature non-perfused hypoxic areas of the retina. In the first phase, low levels of vascular growth factors restrict vessel growth while high levels, in the second phase, stimulate neovascularisation of the retina, which in severe cases may result in retinal fibrosis and retinal detachment (Chow 2003). A study carried out in a single tertiary neonatal center in Los Angeles showed that meticulous control of oxygen therapy decreased the incidence of severe ROP from 12.5% to 2.5% for all infants with BW below 1500 g between 1997 and 2001 (Chow in 2003). This article provides details of the applied policy for management of fraction of inspired oxygen and oxygen saturation monitors in VLBW infants. However, although oxygen use and low GA and low BW are major risk factor for ROP development, other factors as sepsis, anemia, CLD (Chen 2011), poor postnatal weight gain (Hellström 2003) and genetic predisposition (Shastry 2010) may be some of the important predictors of this disease.

Screening for ROP in EPB infants is usually performed weekly from postnatal week 5. The most immature infants seemed to develop ROP at an earlier postnatal age than more mature infants (Austeng 2010). Altogether 20% of infants in the EXPRESS study (The EXPRESS study group 2010) were treated for ROP, mostly by laser photocoagulation, cryotherapy, cerclage and vitrectomy (in a few cases). Although the treatment for ROP has long been in a focus, all these treatment options are in fact destructing the avascular retina (Jacobson 2009) and are a balance between preserving the visual acuity on the expense of visual field defects.

In 2002, in highly developed countries as Sweden and USA, the population of EPB infants with BW below 1000 g was at higher risk for development of severe ROP than in former Eastern European countries Bulgaria and Lithuania (Gilbert 2005). In highly developed countries, infants who developed ROP were born at 25 weeks of gestation with the mean BW of 750 g whereas in the developing countries BW ranged from 900 to 1500 g with corresponding GA of 26.3-33.5 weeks (Gilbert 2005).
In 2010, the incidence of severe ROP was reported to be higher in the Swedish EXPRESS study (The EXPRESS study group 2010) than in any other comparable national studies undertaken during the last decade in Norway (Markestad 2005), Finland (Tommiska 2007) and Belgium (Allegaert 2004); 34% of the EXPRESS

infants developed severe ROP as compared to 20% in the EPIBEL study. High survival rate, poor postnatal weight gain and high levels of oxygen supplementation in the EXPRESS cohort had been discussed as a possible reason (The EXPRESS study group 2010).

ROP is a lifetime disease (Tasman 2006) and whether treated or untreated in infancy, the retinas in adults who were preterm born may have a different appearance than in those born at full-term age. Myopia is prevalent among adults with ROP and adults with cicatricial ROP may also develop retinal detachment (Tasman 2011).

2.2.9 Intraventricular hemorrhage

IVH is another complication of extreme prematurity and associated with increased morbidity and mortality. The classic grading system of germinal matrix (grade I-IV) was initially described by Papile, based on observations from CT scan performed on 46 VLBW infants (Papile 1978). However this grading system has some limitations. In grade I there is no intraventricular element to justify calling it IVH and with increasing knowledge of the pathophysiology of IVH grade IV, it is now more widely accepted as periventricular hemorrhagic infarction (El-Dib 2010).

Acquired severe brain injury, defined as the presence of either IVH of grade 3 or 4 or the presence of cystic PVL (cPVL), was present in 14% of the EXPRESS survivors. In a Norwegian cohort born at 22-26 weeks in 1999-2000 (Markestad 2005), 8% of the infants suffered from severe IVH and 7% of infants from PVL as compared to a Belgian cohort (Vanhaesebrouck 2004) of 12% and 10%, respectively. In the EXPRESS cohort moderate to severe white matter damage, documented on MRI at corrected term age, was associated with severe IVH and post-hemorrhagic ventricular dilatation (Horsch 2007).

2.2.10 Poor postnatal growth

Poor postnatal growth was previously described as a universal finding in studies involving ELBW infants (Lemons 2001, Hintz 2005). Moreover, poor postnatal growth is believed to be an independent risk factor for a poor neurodevelopmental outcome (Ehrenkranz 2006). At 36 weeks GA, 44% of the EXPRESS infants were classified as having postnatal growth failure, using reference of estimated fetal weights (Marsal 1996), and proportion of these infants increased with decreasing GA. All neonatal morbidities except severe brain damage were associated with poor growth at 36 weeks.

2.2.11 High risk for sequelae after extreme preterm birth

The messages emerging from reported long-term studies suggest that many children overcome their early problems (Hack 2006). However most of these reports are based on short-term follow-up studies from 18-36 month of age and the results vary due to variable definitions, limited number of participants and different timing of follow up (Coyen 2002, Salocorpi 2001). Historical cohorts are usually stratified according to BW (Whitaker 2006) rather than GA, and therefore it is possible that comparisons are made between growth-restricted but biologically older children and EPB children.

The most comprehensive overview presently available about outcomes of EPB infants in 1995 comes from the EPICure study (Costeloe 2006). The cohort consisted of 283 infants, born before 26 weeks of gestation, and showed the presence of cerebral palsy and severe motor disability at 30 months corrected age after parenchymal hemorrhage, cystic changes or ventricular dilatation.
All surviving children from EPICure study have been offered standardized medical and neurodevelopmental assessment at 2.5 and 6 years and many of these children are reportedly doing well. However, at the age of 6 years, depending on the interpretation (particularly of cognitive measures), between 54% and 75% of the population were functioning within the normal range or had a mild disability that should not prevent them from being independent. Of the children assessed at 6 years, 13% had neuromotor problems with associated disability, 7% had moderate or severe visual impairment and 6% had moderate or severe hearing loss (Costeloe 2006).

The observation in the EPICure study that the proportion of children with moderate to severe cognitive problem varies from 21% to 41%, depending on whether one uses the test norm or refers to the comparator group from the same class the child attends, highlights the difficulty in understanding the significance of the findings in these children. At the time of their last assessment, the EPICure children were only 6.5 years old, and considerable caution is needed in predicting what those observations mean in terms of their journey through adolescence and out into the adult world (Hack 2006).

2.3 DEFINING NORMAL AND ABNORMAL FETAL GROWTH

An ideal definition of normal fetal growth should include the growth potential of the fetus, current fetal size, fetal and placental health and fetal growth velocity. None of these factors alone seems to be able to discriminate between normal and abnormal growth indicating that discrimination between constitutionally and pathologically small fetuses is a matter of judgment.

What is still unclear is whether fetuses of different race/ ethnic groups have a similar growth pattern, how fast a normal fetus is supposed to grow at different stages of gestation, and how to improve fetal weight estimations (Zhang 2009). Fetal anthropometry measured longitudinally throughout gestation would allow us to develop interval velocity curves for GA, customized for genetic and physiological factors and thus individualized standard for fetal growth potential (Zhang 2012). An integrated definition that incorporates these findings could be potentially a useful tool in various countries, races and ethnicities to improve classification of whether a fetus is growth restricted or not.

We cannot determine what is abnormal until we have agreed what is normal. Thus we cannot describe disease without first describing normal physiology.
Normal fetal growth depends on the genetic potential of the fetus modulated by environmental, hormonal, nutritional, fetal, maternal and placental factors. Fetal growth is a critical component of a pregnancy and the long-term health of the offspring. Changes in the pattern of intrauterine growth have phenotypic consequences for specific tissues and organ systems long after birth. Therefore, the factors regulating growth in utero have an important role in determining adult health and susceptibility to

diseases such as hypertension, coronary heart disease and type 2 diabetes (Barker 1994).

Conception is the beginning for growth and maturation of the offspring. Initially, after a robust cell division, implantation of the blastocyst takes place. Period from conception to implantation with its micronutrients is particularly important for fetal growth and development (Cetin 2010). In fact, initial development of the placenta and fetal membranes occurs far more rapidly than development of the almost microscopic fetus itself (Guyton and Hall, 2006). In the pre-embryonic period, from weeks 1-3 after conception, the ectoderm, mesoderm, and endoderm are formed within the embryonic disk. From week 4 to 8, there is rapid growth and differentiation to form all the major organ systems in the body and fetal blood is supplied from the mother to the placenta by two umbilical arteries and drained by one umbilical vein. In general, growth of the fetus depends on its transplacental supply of glucose, amino acids, lipids, various essential minerals, vitamins and availability of oxygen for oxidative phosphorylation. The nutrients provide the carbon and nitrogen required for tissue accretion. During the first trimester, the fetus establishes tissue patterns and organ systems; in the second trimester, the fetus undergoes major cellular hyperplasia and, in the third trimester, organ systems mature in preparation for extra uterine life.
The orchestration of combination of rapid cell division and differentiation as well as organ development is dependent in part on a class of developmental homeobox genes which are involved in patterning embryonic structures such as axial skeleton, the limbs, digestive and genital tracts, and in craniofacial and nervous system development. Thus abnormalities in human homeobox genes usually give rise to specific organ malformations but even on whole body growth, as an example SHOX-gene mutations causing short stature in Turner syndrome or Leri-Weill dyschondrosteosis.

2.3.1 Size at birth correlates to mothers' size

There is a competing interest between paternal and maternal genes on the fetal growth on the offspring's fetal growth. It is in the interest of the father's genes to produce larger offspring who will be able to survive and compete with mother's resources, while the better outcome for the mother's genes would be for all her offspring to survive to adulthood and reproduce. Mother has to be able to divide her resources among several offspring in some cases, without compromising her own needs. Thus, throughout gestation, fetal growth is constrained by maternal factors and placental function and coordinated by growth factors. Usually infants of small parents tend to be small, with maternal size having the greatest influence indicating that the infant's size at birth has to be considered in relation to the mother's size. There is a linear relationship between maternal height and the child's BW. For each 1 cm increase in maternal height, BW increases by 16.7 g. These calculations are based on data from 2.2 million singleton pregnancies in the German Perinatal Survey involving boys and girls born after 23-43 completed weeks of gestation in 1995-2000 (Voigt 2012). Thereby "genetically" small and "genetically" large healthy neonates can be classified more adequately. Several maternal polymorphisms have been associated with intrauterine growth retardation (IUGR), depending on the ethnic group, and partially giving rise to a genetic predisposition of the disease (Cetin 2013).

2.3.2 Nutrition, insulin and IGF-I are important factors for fetal growth

The nutrients provide the carbon and nitrogen required for tissue accretion, whereas the fetal hormones regulate their distribution between oxidative metabolism and mass accumulation. Hormones have an essential role in feto-placental growth as they match the fetal growth rate to the fetal nutrient supply (Fowden 2009). Generally, the growth stimulatory hormones (insulin, IGFs, thyroid and pituitary hormones) are anabolic, thus acting as signals of nutrient stores, rising in fetal circulation with increases in the availability of glucose, amino acids and oxygen. Close to full-term age rising growth inhibitory hormones (glucocorticoids), documented by increased cortisol concentrations in cord blood at term age (Seckl 2004), switch fetal tissues from accretion to differentiation and, hence, slow fetal growth whilst maturing organs essential for neonatal survival, such as lungs, liver, gut and kidneys (Vaughan 2011).

The first trimester of gestation is the most sensitive to nutritional insults leading to impaired fetal survival and growth. Maternal nutritional status, diet and exposure to environmental factors leading to hypoxemia are increasingly acknowledged as potential factors affecting fetal growth. Mechanisms leading to the impaired fetal growth and/ or survival are altered nutrient availability to the fetus, modulation of placental gene expression and thereby modification of placental function resulting in changes of placental weight, surface and nutrient transfer capacity which depends on the severity of the nutritional challenge and on the time of deprivation (Cetin 2010). Placental epigenetic modifications, including DNA methylation, histone modifications and microRNAs expression, seem to represent one of the major mechanisms by which nutritional and environmental factors affect fetal growth (Cetin 2013).
Maternal undernutrition in the first part of gestation leads to a compensatory increase in placental mass, surface and transport and thereby not leading to decrease in BW (Dutch famine 1944-45). However, if maternal undernutrition occurs during the last part of gestation, a compensatory decrease in growth and BW is seen (Vaughan 2012).
Maternal overnutrition in obese and overweight women can also lead to compromised fetal growth, probably through altered nutrient quality with low maternal S-folate (Kim 2012) and 25-OH-D-vitamin (Josefson 2013), impaired uteroplacental blood flow and metabolic derangements related to obesity. Interestingly, obese mothers who lose weight during pregnancy have an increased risk of compromised fetal growth as well. Several explanations have been discussed: ketosis, deficiencies of nutrients in the fetus because of increased utilization by maternal tissues and elevations of cortisol that inhibit fetal protein synthesis (Wu 2012).

In a diverse intrauterine environment, fetal hormones act to optimize growth of the fetus with respect to its genetic potential in the prevailing nutritional conditions, and can advance maturation of fetal tissues. Preterm elevations of fetal cortisol levels will decrease growth and although increasing the chances of perinatal survival, disruption of the normal balance between tissue accretion and differentiation in utero can lead to permanent changes in tissue structure and function with consequences for infants' health status before and directly after birth, and later in life (Sfferuzzi-Perri 2013).

Insulin is an important growth hormone during intrauterine life, mostly during the third trimester when it stimulates a rapid accumulation of adipose tissue. The primary

growth-promoting action of insulin is on tissue accretion rather than tissue differentiation as tissue differentiation during late gestation appears to precede normally in both hypo- and hyperinsulinemic fetuses (Fowden 1998). In humans, genetic variation in the length of insulin gene variable number of tandem repeats (VNTR) on chromosome 11, which is thought to control transcription of the insulin gene and is associated with higher BWs and lengths when the class III INS/VNTR genotype is inherited from both parents (Dunger 2007).

IGF-I and IGF-II act as fetal growth and cell maturation factors in preparation for extra uterine life in late gestation and have a major influence on pancreatic beta-cell mass and the capacity for insulin secretion in the fetus (Fowden 1998). While IGF-I may act as a nutrient sensor that ensures fetal growth, IGF-II provides the constitutive drive to fetal mass accumulation by regulation of placental morphology. The profound biological activity of IGF-I during fetal life is due to its presence with binding protein in a binary complex. IGF-II is the predominant growth factor in early (from week 6) and mid-gestation with a gradual switch to IGF-I, which is first found in the circulation around week 9, in the late gestation (Baker 1993). BW is positively correlated to plasma IGF-I but not IGF-II concentrations (Fowden 2003). Genetic variations, especially in genes coding for IGF-I and IGF-II, and their receptors might be associated with fetal growth (Dunger 2006, Kaku 2007).

Growth hormone (GH) levels are higher than adult levels in mid-gestation and fall towards term with only a minor effect on fetal growth. Infants with congenital GH or GH receptor deficiency are born around 1 standard deviation (SD) shorter than population mean but there is hardly any effect on BW (Gluckman 1992, Woods 1997).

Glucocorticoids play an important role in tissue maturation and thereby survival advantage in preterm-born infants (Roberts 2006). They act as signals of nutrient insufficiency and rise in concentration in response to fetal hypoxemia and hypoglycemia having catabolic effect on protein accretion and thereby size of the fetus (Fowden 2000).

2.3.3 Fetal period - the most intensive growth period

Intrauterine growth with birth at term represents in humans the most intensive growth period. At full-term age the newborn infant has reached about 25 % of its adult height in contrast to about 5 % of its adult weight. Based on data from live-born EPB infants from SMBR 1990-2002, born at GA 22-25 weeks of gestation and BW below 1000 g (n=1344), the median weight 700 g and length 31 cm (Horemuzova, unpublished) represents 20% of the body weight and about 60 % of body length of infant born at full-term age.
The growth velocity in length of the fetus accelerates almost in proportion to age reaching its maximum at about 20 weeks of gestation; thereafter a rapid deceleration occurs. Thus, between weeks 4 to 12, crown-rump growth velocity is 33 cm/year, between 12 to 24 weeks 62 cm/year, and between 24 weeks to term 48 cm/year. Weight gain over the same intervals, extrapolated to kg/year, shows a different pattern with modest gains initially 0.1 kg/year followed by 2.7 kg/year and 8.7 kg/year corresponding to weight gain of 5 g/day in 14-15 week of gestation, 10 g/day in 20

weeks and 30-35 g/day in 32-34 weeks of gestation with nadir of 230 g/week at 33-36 weeks of gestation (Hagenäs 1995). Growth velocity is therefore maximal in the second trimester. In contrast, maximal weight gain is achieved in the third trimester when the weight doubles, from 1500 g to 3000 g by fat and protein accumulation, with a declining weight velocity in the last weeks of pregnancy. Fat accumulation during the third trimester corresponds to about 500 g compared to only 50 g during the first and the second trimester together. The magnitude of this fat accumulation is a combination of the mother´s nutritional composition and the fetus' insulin response to it.

2.3.4 Factors associated with poor fetal growth

Fetal factors associated with poor fetal growth include multiple gestation (Klebanoff 1989), intrauterine infection (Goldenberg 2000; Dammann 2005), Rhesus disease, radiation injury, chromosomal abnormalities (Down syndrome, trisomy 13, 18, Turner syndrome and other major congenital malformations). Placental factors include infection, infarction, reduced surface area (Maulik 2008) or tumor (hydatidiform mole, chorioangioma). Maternal factors include chronic disease (hypertension, renal failure, cardiac failure, SLE), pregnancy associated disease: pre-eclampsia (proteinuric hypertension), anemia, infection, hypoxemia (high altitude, cyanotic cardiac or pulmonary disease, sickle cell disease), malnutrition, maternal short stature, early menarche, short interpregnancy interval, high maternal parity, cigarette smoking, alcohol consumption, drug abuse (cocaine, heroin) and caffeine. Heavy alcohol even in the periconceptional period (Patra 2011) and tobacco (Krstev 2012) exposure during pregnancy increases risk for preterm birth and reduced BW, birth length and head circumference (HC).

2.3.5 Genetic imprinting

In general, the fetus inherits two working copies of genes, one from the mother and one from the father. Some genes are imprinted, and for these imprinted genes, the fetus inherits only one functioning copy. Depending on the gene, either the copy from the mother or the copy from the father is epigenetically silenced. Silencing usually happens through the addition of methyl groups during egg or sperm formation. The epigenetic tags on imprinted genes usually remain for the life of the organism but they are reset during egg and sperm formation. Regardless of the parental origin, certain genes are always silenced in the egg, and others are always silenced in the sperm.

The role of gene imprinting on fetal growth and its modifying environmental factors has recently been evaluated in several studies. Maternal diet and metabolism of amino acids (glycine, histidine, methionine and serine) and vitamins (B6, B12 and folate) plays a key role in providing metyl donors for DNA and protein methylation (Serbert 2011). Maternal malnutrition can thus affect placental development and function leading to growth impairment of the fetus (Wu 2012, Wang 2012) or alter the epigenetic state of the genes that regulate fetal hypothalamic-pituitary-cortisol axis (Jiang 2012). The global DNA methylation in cord blood is decreased by tobacco smoke exposure (Joubert 2012) and the methylation of repetitive elements in human term placentas was recently found to be positively associated with BW percentile and to differ significantly among infants exposed to tobacco smoke and alcohol (Wilhelm-Benartzi 2012).

2.4 ASSESSMENT OF GESTATIONAL AGE

An accurate assessment of GA is vital for surveillance of maternal and child health as well as for research. However, one of the puzzles of modern obstetrics is how to accurately date the pregnancy. Surprisingly, there is no consensus concerning the duration of a normal pregnancy. The WHO defines term as being between 259 and 293 days from the last menstrual period (LMP). In Sweden, 280 days duration of pregnancy is used to estimate the day of delivery. Information about GA assessment from SMBR during 1990-2002 indicates that dating of pregnancies of infants born after completed 22-25 weeks of gestation was based in 80% of cases on ultrasound examination and in 20% of cases on the information about LMP.
Correct assessment of GA at birth is crucial in distinguishing for example the very immature infant with appropriate weight for age from that undernourished but biologically older one because these two infants have a different postnatal growth pattern. Misclassification of GA can be mostly observed on birth certificates of infants with lower GAs by showing bimodal distribution of BW, with the second (right-sided) mode having a mean BW consistent with that of term infants (Tentoni 2004).

2.4.1 LMP- estimate as a proxy for expected date of delivery

In the past, the most often used method for dating of pregnancy in clinical obstetrics was calculation from the first day of the last menstrual period (LMP). LMP-estimate is based on formula developed by a German obstetrician Dr. Franz Naegele (1833); it adds 7 days to the first day of LMP, and then subtracts 3 months from this result to get the due date. Naegele's rule is based on the assumption that ovulation/conception occurs on cycle day 14 in the "average" 28 day regular menstrual cycle. In this way of dating the pregnancy, the pregnancy is 40 weeks (280 days) in duration (on average) instead of the actual 38 weeks. Thus LMP dates the pregnancy, on average, two weeks longer than it is.
However, dating pregnancies based on methods using the LMP is subject to various errors since the time of ovulation varies among different women and from cycle to cycle. The occurrence of irregular menstrual periods, spotting during early pregnancy and unreliable dates of LMP (10-45% of pregnant women) are other factors. 18% of women with certain dates for their LMP have significant differences between menstrual and ultrasonographic dating according to ultrasound (Geirsson 1991). As only 4% of all babies are born precisely on the estimated date of delivery (EDD), it is more useful to give a range for the likely date of birth (eg, EDD ±2 weeks). Due date estimation based on early ultrasound usually underestimates GA by three days compared to due date based on LMP, a difference usually attributed to late ovulation (Yang 2002).

Clinicians have long recognized limitations of LMP- based GA assessment. The difference between estimated and the real date of delivery is smaller when GA is based on ultrasound dating compared to LMP (Tunon 1996). In the U.S. and Australia, a common practice is to combine the LMP with dating according to ultrasound in what is known as the 10-day rule or 7-day rule, although no advantage in using these rules has been shown (Mongelli 1996). For example, with the 10-day rule, if LMP dates and ultrasonographic dates are in agreement within 10 days, LMP dates are accepted. On the other hand, if the discrepancy exceeds 10 days, ultrasonographic dates are used. The

rationale for using these rules is to exclude large errors from incorrect menstrual dates but the assumption of this method is that menstrual dating is preferable to ultrasonographic dating.
A discrepancy more than 7 days between dating according to LMP and ultrasound is noted in 25% of pregnancies. It is more common in women with BMI >30, in whom the estimated due date is often postponed due to delayed ovulation (Simic 2010). A large trial in nulliparous women demonstrated that the risk of Caesarean section increased from 10% to 60% when EDD based on ultrasound exceeded the EDD based on LMP by 4 to 21 days, respectively (Grewl 2010). At the same time, for each day the ultrasound-based estimate exceeded the LMP-based estimate, BW increased by 10 g.

2.4.2 Ultrasound

The ultrasound-based GA estimates below 24 weeks of gestation are more accurate overall than menstrual estimates (Taipale 2001). However, this method is not without error either. Assessment of gestational length by ultrasound in the second trimester is based on an assumption that fetuses of the same GA have equal biparietal diameter (BPD), femoral length (FL) and abdominal circumference (AC). Thus, ethnic, gender or genetic variations in fetal growth, already evident by the time of the second trimester scan may bias estimates of GA. Prenatal ultrasound is known for its systemic under-estimation of true GA in cases of early intrauterine growth restriction (Yang 2002, Morin 2005). Another example of a systematic bias using this method is gender difference resulting in a smaller HC and AC in female fetuses, apparent already at 18 weeks of gestation (Goldenberg 1993, Marsal 1996, Henriksen 1995, Morin 2005, Skalkidou 2010). A systemic misclassification of GA by ultrasound should also lead to proportionally fewer boys than girls being considered to be born preterm (Skalkidou 2010). Interestingly, transabdominal ultrasound may underestimate GA by an average of 1.6 days compared with transvaginal ultrasound (Lohr 2010).

GA in the first trimester is usually calculated using the fetal crown-rump length (CRL). This is the longest demonstrable length of the embryo or fetus, excluding the limbs and the yolk sac. The correlation between CRL and GA is excellent up to approximately 12 weeks amenorrhea. Accuracy of determining GA decreases by the end of the first trimester (Robinson 1975). The 95% confidence interval of the GA estimate was ±4 days at 6 weeks and ±8 days at 14 weeks of gestation (McGregor 1987).
Algorithms used for dating pregnancies in the first trimester often use the CRL assuming fetal growth as a quadratic function: $GA = –0.0007 \times (CRL)^2 + 0.1584 \times (CRL) + 5.2876$ (Westerway in 2000). According to the National Institute for Health and Clinical Excellence (NICE) guidelines on antenatal care, if CRL is greater than 84 mm, the HC should be used to determine GA (NICE 2012).

In general, BPD, HC and FL in a combination during the second trimester can yield acceptably accurate estimates of GA from 12 to approximately 22 weeks of amenorrhea (Westerway 2000). The accuracy of ultrasonographic biometry at 12-14 weeks gestation is probably more accurate than examinations performed after 14 weeks (Sladkevicius 2005, Saltvedt 2004). The best parameters are the BPD and HC as racial differences are not present and they are virtually linearly related to GA. GA estimates based on BPD or HC have a 95% confidence interval of ± 8 days. The FL can also be

used and is nearly as accurate as HC measurements (Mongelli 2003, Johnsen 2006) but racial differences in FL are significant and accurate measurements are more difficult to achieve in the first trimester.

In Sweden since 1990, a routine ultrasound scanning has been offered to all pregnant women and 95% of them accept this offer (Cnatttingius 1990, The Swedish Council on Technological Assessment in Health Care 1998). Thus, ultrasound estimates of GA, usually based on a second-trimester ultrasound estimate, have been since then a basis for pregnancy dating and clinical decision-making. Ultrasound scans are usually performed between 16 and 20 weeks of gestation, at latest at 22 weeks, and GA assessment is based on a combination of BPD and FL measurements (Persson&Weldner 1986). Recently, in 2013 a new national policy has been adopted, using only the BPD measurement between 12 and 22 gestational weeks.

Fetal biometry in the third trimester is subject to much greater individual size variations than in the second trimester. Its accuracy for GA assignment is reduced considerably, and estimates have confidence intervals of ±2-3 weeks (Hadlock 1984, Mongelli 2005). Assessment of fetal weight using ultrasound is an indirect method of weight assessment of the fetus. Measurement errors may be derived from inter- and intraobserver variability, the use of 2-dimensional measurements to estimate a 3-dimensional fetal volume. Wide availability of 3-dimensional ultrasonography offers opportunities to search for new and improved methods to estimate fetal weight. Using fetal thigh and upper arm volumes seem to be better predictors of fetal weight than 2-dimensional measurements (Lee 2001) but these methods need validation (Zhang 2009). In Sweden, fetal weight estimates based on ultrasound (Marsal 1996) are not used prior to 24 gestational weeks.

2.4.3 Pregnancy following assisted reproduction techniques

The GA of pregnancies resulting from in vitro fertilization (IVF) can be precisely calculated from the time of embryo replacement; however, conception may be delayed a few days in pregnancies resulting from intrauterine insemination. In patients who have had ovulation induction, calculation of GA is recommended from the day of administration of human chorionic gonadotropin.

2.4.4 Clinical estimates include antenatal or newborn assessment

Antenatal clinical assessment of GA includes information on LMP, dating using ultrasound and, before ultrasound era, even assessing the size of the uterus by measuring the distance from pelvic symphysis to the uterus fundus. Measurement error of ±4-6 weeks was present as uterus size could be misleading in the presence of multiple pregnancy, uterine fibroids, or a full bladder.
In 1969 Dubowitz Neurological Assessment test was developed to assess maturation of the term newborn but was also frequently used for assessment of gestational age (Dubowitz 1970). In 1979 Ballard modified Dubowitz tool to estimate the GA of premature infants starting at GA 26 weeks and in 1991 expanded the scoring system to include ELBW infants with GA from 21 weeks, called New Ballard Score (Ballard 1991).

2.5 BIRTH WEIGHT VERSUS GESTATIONAL AGE AS A PROXY FOR INTRAUTERINE GROWTH?

The size at birth is affected by growth velocity early in gestation and growth restriction diagnosed at birth is preceded by slower first- and early second-trimester fetal growth (Milani 2005). The fetal growth restriction in stillbirths seems to be a cumulative process as the difference in birth size between live-births and stillbirth increases with advancing GA (Zhang 2012). However, as growth is a dynamic process it is not feasible to equate BW adjusted for GA as a proxy of growth tempo during intrauterine life. This is because it is not clear how variations in size at birth relate to GA and how the relationship between them can be used as a proxy for variations in intrauterine growth (Keirse 2000).

The general consensus that fetal weight depends on GA is not a fact but just a hypothesis while the alternative hypothesis could be that fetal size determines fetal age, instead of being dictated by it (Wilcox 1981). What we need to understand is how adverse prenatal influences affect both GA and size at birth, instead for assuming that size at birth is a proxy for intrauterine growth.
It is important to take into consideration that there is a gender aspect that relates to growth potential. Girls have lower weight-for-GA in addition to being shorter and having a smaller HC at birth, which implies that girls' GA at birth can be easily judged as a younger one compared to boys of the same age (Marsal 1996, Skalkidou 2010).

Most clinicians' and researchers use terms SGA and IUGR interchangeably which produces problems in a clinical judgment of the infant. The child born smaller than the reference population with a chosen cut-off is not necessarily pathological but may be constitutionally small healthy infant. The term IUGR requires that growth tempo had been evaluated at least 2 times during the pregnancy and the infant failed to follow the predestined growth tempo. Thus, all of these infants will have diagnosis SGA at birth, based on previous IUGR.
The most common cut-off used for the diagnosis of SGA at birth is set to below 10% or -2 SDS of the reference. This indicates that if BW should be used as a proxy for intrauterine growth, a number of constitutionally small infants will be over-diagnosed and thus exposed to unnecessary medical attention or treatments.

2.5.1 Variations in intrauterine growth: Are babies getting bigger?

Mean BW in full-term- and post-term age infants has increased substantially since seventies in many developed and developing countries, including USA (Institute of medicine 1990), Canada (Arbuckle 1989, Wen 2003), UK (Alberman 1991, Power 1994), Finland (Oja 1991) and India (Singhal 1991) but not in France (Blondel 1997). In the Canadian cohort, born between 1978 and 1996, the reported reason was an increase in maternal anthropometry (decrease in short stature and low prepregnancy BMI but increase in tall stature and proportion of overweight/obese women and thus increasing proportion of diagnosed gestational diabetes). The other factors were a significantly reduced proportion of heavy cigarette-smoking mothers, changes in socio-demographic factors such as increase in proportion of births to women 35 years or

older, and decrease in teenage pregnancies and increase in maternal education (Kramer 2002).
However, the mean BW in infants born before 28 weeks of gestation from the Canadian population-based study was reported to decrease from 786 g in 1981-83 to 734 g in 1995-1997, based on 2000 infants in each time period (Wen 2003). The coefficients of variation (CVs) were high (30%) indicating high variability of presented birth weights. One important limitation of the study was the absence of information on the validity of GA, which increases the unreliability of growth measures categorized by GA.

A hospital-based study from Israel (Davidson 2007) with altogether 350 EPB infants, born at GA of 24-28 weeks, reported mean BWs of 897 g, 914 g and 897 g in 1986-1987; 1994-1996 and 2003-2004 with CVs 21%, 26% and 38%, respectively. GA assessment was based mainly on the LMP. The magnitude of CV's suggests again probably wrongly assigned GAs in this cohort. Moreover, this study is not population-based and therefore no conclusions about secular trends can be made. Neither in this nor in the Canadian cohort, has data on maternal, environmental and other determinants of fetal growth been presented.

When comparing data between different generations, it is important to consider that population of childbearing women could become more heterogeneous regarding racial and ethnic background than the first data set collected (Keirse 2000), inducing more variability in birth size to expect.
As the fetal growth potential is essentially genetically determined and the genetic constitution differs too little to account for differences in intrauterine growth, it is obvious that variations in intrauterine growth among different human populations are determined predominantly by factors that restrict fetal growth. Thus these differences can be considered as a result of growth inequalities in the care and sustenance available to human fetuses and their mothers (de Onis 1998, Kramer 1998, Bakketteig 1998). This implicates that any constraint of intrauterine growth, known to affect optimal fetal and placental growth, does not deserve to be seen as a variation in fetal growth.

2.5.2 Ultrasonographically based fetal size vs. birth size

Already early in pregnancy, average BWs are known to be lower than intrauterine estimated fetal weights, i e infants born preterm are smaller compared to fetuses that remain in utero at the same age (Secher 1987, Hutcheon 2008, Zhang 2012) suggesting an impaired intrauterine growth as a cause for their preterm birth (Bukowski 2001). Theoretically, all infants born preterm, may be growth restricted and it is then not possible to estimate the weight of a normal infant born in that week (Källen 1995). It means that birth size references show the typical weight for each week. This mean weight is a result of the "normal" degree of growth restriction and not necessarily the weight of a subsequent full-term baby had it been born at that early gestational week (Källen 1995).

In contrast, the fetal weight estimate is based on indirect measurements of the fetus and assumes proportional fetal growth throughout pregnancy and models fetal growth "by dividing each daily value predicted by the formula by the 280-day value and fitting a third-degree polynomial of GA" (Scoscia 2008). A large number of ultrasound-based

fetal references have been published and the accuracy of 35 formulas was reviewed by Dr. Scoscia. Most formulas provided accurate estimates when the actual BW was between 2500-3500 g. They tended to overestimate fetal weights below 2500 g and underestimate those with weight over 3500 g. The most commonly used is Hadlock's formula which relates the intrauterine (ultrasound) estimated fetal weight (EFW) to GA in weeks: log (EFW) = 0.578 + 0.332 x GA – 0.00354 x GA^2 that predicts a mean BW of 3619 g at 280 days. This approach assumes that different fetuses follow a similar growth pattern to reach their respective BW at the end of the normal pregnancy. Most of ultrasound-based fetal references have retrospective, cross-sectional design which means that each pregnant woman contributed data with only one measurement. The quality of these references is questioned due to selection bias (why a woman received an ultrasound examination at a gestational week when routine ultrasound examination is not given) (Sauer 2007).

Prospective longitudinal references have improved the quality on this subject since 1980 but some of them (Marsal 1996) had a small sample size and most of them had been performed in Europe, predominantly in white women. Swedish intrauterine growth curves based on ultrasonically estimated fetal weights (Marsal 1996), described growth of in 86 singleton fetuses (53 boys and 33 girls) from uneventful pregnancies with delivery at full-term; 55% of women were nulliparous and 24% smokers with less than 10 cigarettes daily. GA was confirmed by ultrasound measurements of BPD in the early second trimester in 72 cases or of CRL in the first trimester in 14 cases. Fetal weight was calculated according to the formula developed by Persson and Weldner by using a stratified sample of 10 pregnancies in each 500 g weight classes (below 500, 501-1000, 1001-1500 up to 5000 g). BPD, AC and FL were measured within 48 hours of delivery or legal termination of pregnancy. The best fit of the data was found using a fourth degree polynomial equation and the curves were calculated for boys and girls separately. The weight were normally distributed and the SD was calculated cross-sectionally for each week of gestation with variation of 9-12% and finally an uniform SD value of 12% was adopted in all weeks for boys and girls. The authors discussed that due to difficulty in collecting sufficient number of comparisons between ultrasound-estimated and true BW in very preterm fetuses, some degree of uncertainty exists regarding the reliability of fetal weight estimation in the late second trimester (Marsal el al 1996).

Ziegler published in 1976 the normative fetus, known as reference fetus, which is actually based on measurement at a time when no attention was given to the GA of the infants that were included an no information was provided if intrauterine growth restriction could be the cause of death of the infants. However, despite these important uncertainties, the reference fetus is generally used not only to evaluate the size of the infant at birth but also to evaluate weight gain after birth (Sauer 2007).

In summary, the ideal monitoring of fetal growth should be able to distinguish accurately between normal and abnormal fetal growth leading to perinatal morbidity and death or even life-course morbidity. As preterm infants are more likely to be growth impaired compared to term babies, birth size curves are poor surrogates for expressing fetal growth.

2.6 WHAT IS A GROWTH REFERENCE AND WHY SHOULD WE HAVE IT?

2.6.1 Growth reference

A growth reference describes the genetic variation of height, weight, HC or any other anthropometric measurements within a group of individuals irrespective of their health status at a particular time and place. A growth reference is a tool for grouping and analyzing data, often conditioned on age and sex and provides a common basis for comparing populations (WHO Technical report 1995). As growth is a mirror of the condition of society (Tanner 1986) the differences between different populations can be explained by differences in genetic and non-genetic factors as nutrition, social and economic environment. However, it is important to mention that a growth reference reflects usually an extensive series of transformations and smoothing procedures of the original weight, height or HC-data.

2.6.2 Reference versus standard

A growth reference describes how a population actually grows in contrast to a growth standard that depicts the genetic variation of height, weight, HC or any other anthropometric measurements within a group of individuals but under ideal, health promoting circumstances. A variation in a growth standard prescribes what is considered to be normal, optimal or healthy and thus have a notion of norm or desirable target (van Buuren 2007). Growth standard can be any growth reference "designated by experts" which does not mean that the chosen reference actually have self-evident qualities for it. The WHO recommends choosing "the references that resemble, as far as possible true standards, so that the same deviation from the reference data has the same biological meaning (WHO Technical report 1995). However, although WHO charts can be considered as an important tool for cross-population comparisons, it is unclear whether this new standard is applicable to a given child or a specific population (van Buuren and van Wouve 2008).

2.6.3 Validity of reference versus standard

Both standards and references serve as a basis for comparison of growth on the population and not individual level since both standard and reference describes the distribution of measurement for each age category and do not provide information about individual´s own growth pattern during infancy, childhood or puberty. Despite the fact that both standards and references serve as a basis for the comparison of growth pattern, each enables a different interpretation. Since a standard prescribe how height, weight, HC or any other anthropometric measurement should be distributed for each age category, deviation from this pattern are assumed as evidence of abnormal growth. In contrast, a reference, describes how anthropometric data are distributed and that's why deviations from that growth pattern should not lead to judgment of abnormal growth (van Buuren 2007). However, in practice references often are mistakenly used as standards (WHO Technical report 1995).

Growth references are an essential component for the neonatologist's and pediatrician's clinical judgment to decide the degree to which physiological need for growth and development are met during initial postnatal period, infancy, childhood and adolescent

period and a tool for screening, diagnosis, monitoring and prognosis of growth-related diseases (WHO 1995). Growth references can also be used on a population level in evaluating the effects of interventions, monitoring trends and identifying groups at risk (van Buuren 2007).

2.6.4 National use of growth references or standards

Many European countries use a state-specific reference chart while countries in Asia, Africa, Latin America and Caribbean, Northern America and Oceania mainly adopt the WHO growth chart (WHO Multicenter Growth Reference Study Group. 2006). The United States uses the growth charts of the Centers for Disease Control and Prevention (CDC) (CDC Growth Charts for the Unites States 2000). Based on the comparison between the CDC growth reference and the WHO growth standards and input from the expert panel, CDC and American Academy of Pediatrics recommended that the WHO growth standard charts should be used for children younger than 2 years of age and the CDC 2000 growth reference charts should be used for children aged 2 to 19 years.

2.6.5 Preterm growth charts

Adequate growth charts for moderately and EPB infants are needed because their poor growth, compared to birth-size references, is an indication for interventions such as specific feeding strategies or improved caring technology but also for monitoring of excessive weight gain that might go otherwise unnoticed during the early perinatal period.

2.7 IS THERE A DIFFERENCE BETWEEN A CROSS- SECTIONAL AND LONGITUDINAL REFERENCE?

2.7.1 Cross-sectional versus longitudinal references

A cross-sectional growth reference is one in which children of different ages are measured once at the same point of time and this reference suits as a screening reference for evaluating the status of a child in a situation where only one measurement is made. A cross-sectional reference cannot be used to estimate growth variability between children over time (van Buuren 2007). Repeated cross-sectional studies provide information about changes in the health status of the population and depict secular changes of growth. However, they do not provide adequate information for longitudinal growth follow-up of population over time.

2.7.2 Birth size references versus extrauterine growth references for prematurely born children

The existing preterm growth charts are often based on distributions of cross-sectional data for BW, length and HC where percentile or standard deviation score (SDS) levels for each GA are connected to a series of curves. These curves are assumed to be representative for intrauterine growth but are used in the clinical practice for monitoring of extrauterine growth even for the EPB population. They reflect an ideal growth pattern that is rarely achieved within this population. Published longitudinal extrauterine growth references for premature children are often based on BW instead of GA (Wright 1993, Ehrenkranz 1999) or have a small sample size (Niklasson 2003).

Some examples of birth size references are from Sweden (Niklasson and Albertsson-Wikland 2008, Lawrence 1989/Niklasson 1991), USA (Riddle 2006), Norway (Skjaerven 2000), Israel (Davidson 2008), Germany (Voigt 2006), Canada (Kramer 2001) or more historical ones published by Dancis 1948, Lubchenco 1963, Hansman and Boyd 1966, Usher and Mc Lean 1969). Another example is the recently published reference by Fenton 2013, which is a meta-analysis of birth size data from Germany, Canada, Australia, Scotland, Italy and WHO 2006.

2.7.3 Growth references with cross-sectional design

The existing growth charts based on distribution of cross-sectional data of full-term children are German reference (Schaffrath Rosario 2011), WHO reference from 18 to 71 months of age (WHO 2006), CDC growth reference (CDC 2000), all five Dutch growth references (de Wijn and de Haas 1960, van Wieringen 1971, Roede, van Wieringen 1985, Fredriks 1999, Schönbeck 2013).

2.7.4 Longitudinal versus cross-sectional references

Longitudinal growth references depict children measured at two or more occasions and having multiple measurements per child increases the credibility (reliability) of the presented reference. This kind of reference enables calculation of growth velocity in an individual child and can serve for description of the variability in growth between children over time.

Examples of longitudinal studies in preterm-born/ VLBW population are: from USA (Cassey 1991, Guo 1997, Ehrenkranz 1999, Hack 2003, Saigal 2006), UK (Powls 1996, Wood 2003), Netherlands (Finken 2006), India (Mukhopadhyay 2012), Sweden (Niklasson 2003, Farooqi 2006), Czech republic (Kytnarova 2010), Norway (Westerberg 2010) and Netherlands (Bocca-Tjeertes 2012) or charts based on fetal ultrasound (Marsal 1996, Johnsen 2006).

A mixed longitudinal – cross sectional study design is a compromise between a cross-sectional and a longitudinal one. It means that individuals are measured more than once, but not throughout the entire age range. However, this kind of design has less credibility (reliability) than an exclusively cross-sectional or longitudinal design (van Buuren 2007). An example is WHO 2006 growth reference 0-60 months which consists of a longitudinal part between full-term age and 2 years and a cross sectional part thereafter. Another example is the Swedish growth reference (Albertsson-Wikland 2002) since study participants are not measured throughout the entire age range.

2.8 WHAT IS NORMAL OR OPTIMAL GROWTH?

2.8.1 Normality as a statistical extent in a population versus biological meaning of normality

The word normal has many, often conflicting, meanings. In a medical context it is closely associated with health or being healthy, not pathological but other meanings include common, frequent, occurring as a rule, not deviating, not disturbing and

conforming to norm or regulation (Gräsbeck 2004). Thus that what is normal does not need to be healthy.

Health and normal growth are thus relative concepts. The World Health Organisation (WHO) defined health in its broader sense in 1946 as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity (World Health Organization 1946, 2006). As such healthy persons are a minority or difficult to find in the population, we accept as healthy those persons who fit our purpose, but as purposes differ, so do the criteria of health (Gräsbeck 2004). Human growth is a complex process regulated by genes, nutrition and the social and economic environment. When the environmental conditions are optimal an individual may reach its genetically determined growth potential. Human growth is however a dynamic process because even under similar social and economic circumstances it can result in variable individual growth patterns (Hermanussen 2010).

2.8.2 Normality in prematurely born children

Our knowledge of the normal ranges of extrauterine growth across the entire range of preterm GAs is incomplete. What is normal growth in EPB infants depends on a clinical judgment, based on infants physiological or pathological limitations due to their functional immaturity, and used reference. As “healthy” EPB infants born below 26 weeks of gestation can hardly be defined or found, it should be considered that specific growth charts for these infants cannot be a prescriptive standard.

2.8.3 Difference between assessment of intrauterine size and birth size

Should birth size of an EPB infant be compared to the mean of a birth size reference or to a fetal weight estimate for judgment if the body size is normal? Is the mean of a population-based full-term growth reference a desirable target for follow-up of EPB infants’ growth? Should we consider -2 SDS of full-term reference as a normal cut-off for EPB infants or is it the relation of infants’ growth to parental height SDS that is the most important?

2.9 IS POSTNATAL GROWTH OF EXTREME PRETERM BORN CHILD A MIRROR OF A GOOD MATERNAL, NEONATAL AND CHILDREN’S HEALTH CARE SYSTEM?

Ideally, growth in preterm born infants should be comparable with that in full-term infants, if prenatal and postnatal nutrition is comparable and adequate, but then genetic factors as parental adult height, child’s health status and environmental/psychosocial factors are not taken into account.
What is normal feeding practice in a full-term born child may not be achievable in a preterm born child due to its immaturity limitations. Then should extrauterine growth approximate intrauterine growth? No, it should not as EPB infant is not comparable with an infant delivered at full-term age and not even with fetus that grows in a sterile and temperature-controlled environment with a continuous nutritional supply. Thus, they all have a completely different postnatal environment and are receiving completely different nutrition. Preterm birth is a nutritional emergency as it interrupts fetal

nutrition and thus body weight position on a growth chart shortly postnatally decreases in contrast to expected increase, assumed by continuation of the pregnancy and by using birth-size or fetal weight estimates as a reference for postnatal growth in this population. For comparison between birth size reference, fetal size reference and extra uterine growth of EPB infants, see Figure 1.

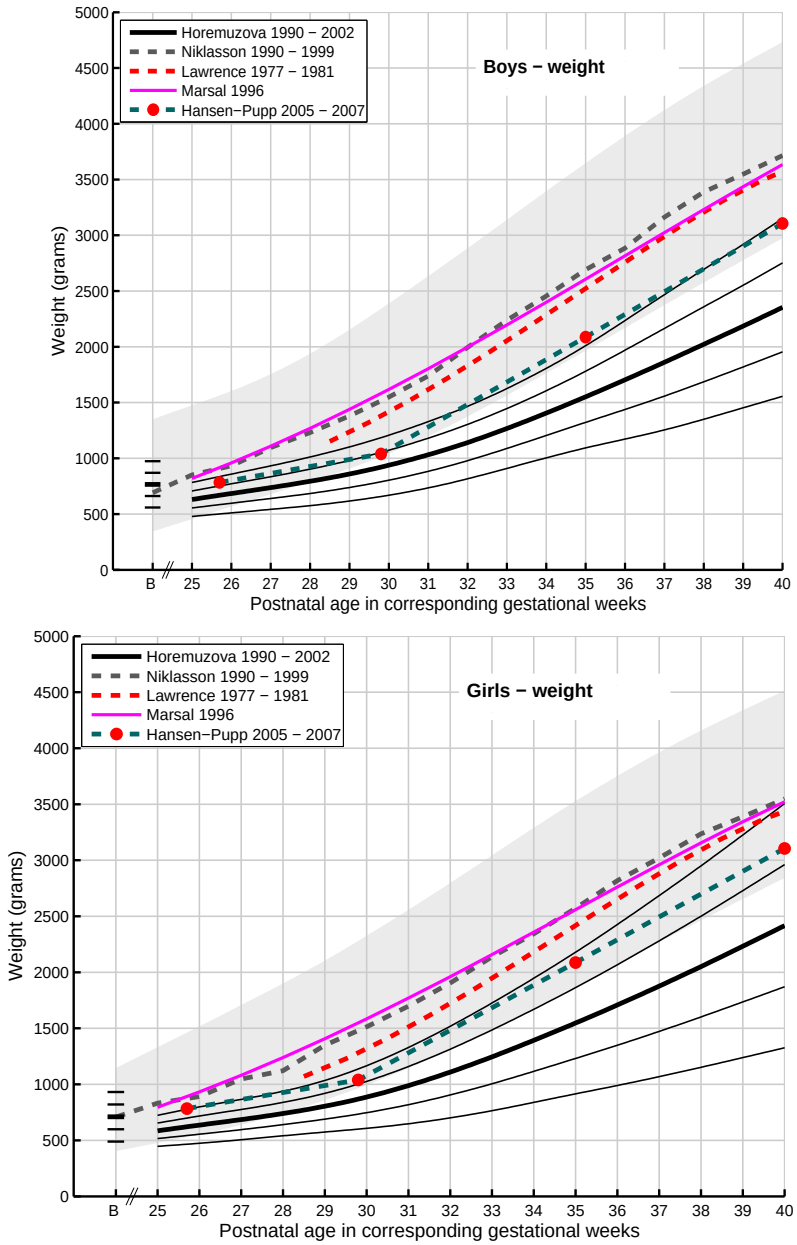


Figure 1 Comparison between extrauterine (Horemuzova 2012, Hansen-Pupp 2011) and intrauterine (Niklasson and Albertsson-Wikland 2008, Lawrence1989/Niklasson 1991, Marsal 1996) growth. Weight-for-age development (mean±2SD) until full-term age in a cohort of the EPB infants as compared to the Niklasson and Albertsson-Wikland birth size reference (grey area showing mean±2SD) and fetal growth reference. Boys up, girls down.

Postnatal growth of the EPB infants (Horemuzova 2011, Hansen-Pupp 2011) is completely different from the predicted intrauterine (Marsal) or birth size references (Lawrence 1989/Niklasson 1991 and Niklasson and Albertsson-Wikland 2008). Birth size reference (Lawrence 1989/Niklasson 1991 and Niklasson and Albertsson-Wikland 2008) and intrauterine reference (Marsal 1996) does not seem to be identical. Hansen-Pupp cohort was born in 2005-2007 when current nutritional guidelines were applied and represent 52 infants corresponding to 30 % of the total study population. Hansen-Pupps' weight curve is derived from published SDS values (using Marsal 1996 reference) at only four postmenstrual ages (25.7 wks; 29.8 wks; 35 and 40 wks). Weight development of the selected cohort is higher than Horemuzova 2012 EPB cohort.

2.9.1 Following growth of prematurely born children using birth size reference curves

In clinical practice, postnatal growth restriction of EPB infants, based on the use of birth-size or fetal weight estimate references, has been widely documented (Embleton 2001, Cooke 2004) but our knowledge of the normal ranges of growth across the entire range of preterm GAs is incomplete. The recommendation of the Committees on Nutrition of the European Society of Pediatric gastroenterology, Hepatology and Nutrition Committee on Nutrition and the American Society of Pediatric state that the goal of nutrient supply to the preterm infant is to achieve postnatal growth approximating that of a normal fetus of the same postmenstrual age but the nutritional requirements to reach this goal are not known (Agostoni 2010). Thus the clinical focus of pediatricians, nutritionists and dietician had been on optimization of preterm infants' nutritional supply with a goal to attain catch-up growth in these infants. In the neonatal medicine, the close association between poor growth and adverse neurodevelopmental outcome has given added impetus to this practice (Ehrenkranz 2006).

2.9.2 Is it possible or desirable to supply "normal nutrition" to the prematurely born child?

The term "programming" has been suggested to describe the relationship between the early exposures and disease at a much later stage in the life course (Lucas 1991); mediated by e.g. DNA-methylation or modulation of DNA-chromatin structure and accessibility. There is an increasing concern that accelerated growth in infancy following postnatal hypercaloric nutrition may amplify subsequent metabolic abnormalities induced by fetal or early postnatal undernutrition. Adverse long-term consequences (Corpeleijn 2013), particularly development of obesity, insulin resistance, cardiovascular disease and dyslipidemia, have previously been described by Barker as a metabolic syndrome. Barkers work was mostly focused on metabolic consequences of SGA infants born at full-term age that contrasted with later development of obesity; a thin individual at birth become obese in later life. If consequences of hypoalimentation during neonatal period followed by hyperalimentation during later postnatal life should be extrapolated to preterm infants born appropriate for gestational age (AGA) is not clear either; an individual with normal BW that becomes thin during initial postnatal life and develop relative obesity with increased amount of visceral fat in later life. However, it has been demonstrated

that ex-preterm infants have relatively more visceral fat than full-term born infants (Sauer 2007). High blood pressure has been documented already in early childhood (Estedt-Bonamy 2011) in EPB survivors. On contrary "beneficial undernutrition" as demonstrated in an animal model with long periods of low growth rate from relative undernutrition was followed by increased longevity (Hales 2003).

It is not obvious if promoting the goal of catch-up growth is desirable or even achievable (Martin 2009). Thus the use of birth size or ultrasonically estimated fetal size growth curves for evaluation of postnatal growth may not be appropriate (Sauer 2007, Bertino 2008).

2.10 CHOICE OF STUDY POPULATION AND WHAT IS A REPRESENTATIVE SAMPLE?

Although the literature contains many growth references in the form of figures and tables which describe normal growth, it is important to select charts which best describe the population for which they are to be utilized. Sample size is the most important factor affecting the reliability of the reference interval but other important determinants are study design, the timing of measurements and the method of curve fitting (van Buuren 2007).

The anthropometric measures can be described by medians, means, SD, coefficient of variations, confidence intervals, percentiles, Z-scores or LMS- values. For all presented data it is suitable to inform about number of observations. In normally distributed variables it is adequate to present mean and SD. In skewed distributions it is adequate to present median, mean and mode and variability for data distribution can be described by percentiles.

Inclusion and exclusion criteria portray the reference population and indicate if the reference population is coming from ideal and healthy environment or not. References describing infants who are raised in a healthy environment might not be suitable for the population not living under these ideal and healthy circumstances. Limitations of "healthy references" is a systematically selection bias missing the other infants from the population. In contrast, descriptive references should include all children in the population. Thus a major methodological issue in a population-based growth study is whether the procedure sufficiently ensures a representative sample, adequately stratified for the variables known to affect height. In general, the consequence of a "healthy reference" will be smaller variability with respect to the mean. This is due to the uniformity of included population in contrast to "descriptive reference" with a higher variability, due to mixture of healthy and "non-healthy" individuals. The magnitude of the difference in mean and SD would be affected by the variability and mean of the included sample of "unhealthy" infants.

2.10.1 Birth size surveys

The **UK90 reference** comes from five birth size surveys from 1983 to 1994 (Cole 1998) where three of them were based in Cambridge providing 85% of all BW measurements. The data for weight, height, BMI, and HC from 37 000 children were used for construction of the reference. However, the total number of BW measurements

in the surveys in GA 23, 24 and 25 weeks is 36, 72 and 115, for length at birth 0, 1 and 3 and for HC at birth 8, 31 and 50 respectively. The raw UK90 birth data for weight, length and HC has been reanalyzed (Cole 2011) using the LMS method and presented as LMS tables and centiles, between 23-42 weeks gestation but the data were undersampled for the youngest, at mid-gestation and after 42 weeks. Pooled data by sex for all full-term infants (born between 37-42 postmenstrual weeks of age) were analyzed separately. Based on the revised birth centiles, the authors proposed that for weight the skewness and variability values increase with gestation, while the median values rise, with median for weight 4-6% less in girls than in boys. Thus, weight distribution get more positively skewed with increasing gestation, being normally distributed at 30 weeks in both sexes, slightly negatively skewed at earlier gestations. Length and HC showed similar trends by gestation.

A **new version of the Swedish growth reference** was published 2008 (Niklasson and Albertsson-Wikland 2008) out of a compilation of a large cohort of birth size data (n=801 641 for weight, 808 312 for length and 775 399 for HC) from the Swedish Birth Data Registry between 1990-99, that was mathematically and graphically connected to the Swedish growth reference from 2002, between full-term age and 2 years. The birth-size part presents age- and gender-adjusted weight, length and HC from 24 weeks to 42 weeks of gestation. Unfortunately this reference does not state the number of included participants per age category but information is given about relatively low sample size in lower ages, GA 24-29. The population was defined by exclusion of deliveries with stillbirths, severe congenital malformations, multiple birth, maternal diseases (urinary tract infection, kidney disease, diabetes, epilepsy, asthma, ulcerative colitis, SLE), infants delivered by Caesarian section due to possible overrepresentation of growth restricted infants. Records with missing gender and GA were also excluded.

The **previous Swedish birth size reference** (Lawrence/ Niklasson 1989/1991) was based on data from Swedish Medical Birth Register and included a healthy population born from 1977 to 1981 at GA 28-43 weeks; presenting data from 28.5 to 42.5 weeks. Altogether 20 % of the original population was excluded due to factors that were thought to affect intrauterine growth (multiple births and still-births, maternal infection, diabetes, pregnancy disorders as anemia, UVI, infants with malformations).

Comparison between these two birth-size references is presented in a Figure 1. An interesting finding is a 132-193 gram difference between means of the previous (Lawrence 1989/Niklasson 1991) and the new birth-size references (Niklasson and Albertsson-Wikland 2008); see Table 2 for details.

Table 2. Difference in BW/GA between the new Swedish birth size reference (Niklasson and Albertsson-Wikland 2008) and the previous reference (Lawrence1989/Niklasson 1991). The new reference is age-interpolated to the corresponding gestational age (GA) as published in the previous reference. The previous birth-size reference presented anthropometric data corresponding to half completed weeks (GA=28 corresponds to 28 weeks and 3.5 days (28.5 weeks) in contrast to the new reference to completed weeks (GA=28 corresponds to 28 weeks+0 days).

GA (weeks)	Difference for Weight (g) between Niklasson and Albertsson-Wikland 2008 and Lawrence1989/Niklasson1991	
	Boys	**Girls**
28.5	+152	+173
29.5	+143	+193
30.5	+139	+197
31.5	+150	+192
32.5	+167	+186
33.5	+173	+175
34.5	+166	+163
35.5	+157	+156
36.5	+156	+148
37.5	+158	+132
39.5	+150	+114
39.5	+141	+105

The **US reference** (Riddle 2006), described a retrospective hospital-based cohort born 1986-1997 in Vanderbilt which included all infants of ≤37 weeks of completed gestation admitted to the NICU; 1234 infants born below 29 weeks of gestation were included, 89% singleton, 55% boys, 76% Caucasian, 18% African American. BW data at 23, 24 and 25 weeks of gestation were represented by only 46, 151 and 172 infants respectively with even lower numbers for length and HC at birth. Weight, length and HC at birth were reportedly normally distributed at each week of gestation.

A reference from Israel (Davidson 2008) included 85 320 singleton neonates (49% boys) delivered at 24-43 weeks gestation from 1991 to 2005 from Beilinson hospital. However, BW was documented for only 66 and 75 infants born at 24 and 25 weeks, respectively; no data on length was given but HC data were described for 32% of the sample. GA was determined mainly by LMP and infants with implausible anthropometric measurements for GA (outside ±5SDS) were excluded.

A new and improved population-based **Canadian reference** for BW for GA (Kramer 2001) included all births contained in the linked file of live births and infant deaths registries in the provinces and territories of Canada (with the exception of Ontario) born between 1994 and 1996. Ontario was excluded from the study because of documented problems with data quality (Kramer 2001). In most of the included cases no information was provided about the method used for GA assessment. No information on racial origin of mothers' was provided as this information is not included in

Canadian birth certificates. The reference is based on 676 605 singleton children (51% boys) born from 22 to 43 weeks of gestation. Boys/girls' at 23, 24, 25 weeks were represented only by 114/106, 156/148 and 202/184 infants respectively. The authors assumed that the true distribution of BW at each GA was normal but that the reported GAs was a mixture of correct and erroneous values which was consistent with the frequently observed curve "bump" at the upper centiles for EPB infants (Kramer 2001).

New Dutch reference curves for BW (Visser 2009) are based on the data from the Netherlands Perinatal Registry for 2001. This reference excluded multiple pregnancies, antepartum stillbirths but not intrapartum deaths and infants with congenital malformations. Mothers came from seven ethnic backgrounds and GA was calculated from LMP or from an early ultrasound dating scan. Due to the restricted number of births between 22 and 24 weeks of gestation curves could only be constructed from 25 weeks onwards. No information about number of participants in each gestational week is provided.

In Table 3 means of different birth-size references from Sweden, Germany, USA, Canada , Norway and Israel (Niklasson and Albertsson-Wikland 2008, Voigt 2006, Riddle 2006, Kramer 2001, Skjaerven 2000, Davidson 2008) are compared to preterm-born surveys from UK and Sweden (Costeloe 2000, Horemuzova 2012), according to study design and data collection.

Table 3. Birth weight in EPB infants presented as mean, standard deviation (SD), coefficient of variation (CV) in published international populations, adjusted for gender and gestational age.

Published studies	**Gender N**	**Mean BW gram**		**SD BW gram**		**CV-BW %**	
	Boys :Girls	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Costeloe 2000	**UK+Ireland, 1995, Population-based prospective study**						
GA 23	70:61	630	600	89	74	14	12
24	166:132	712	652	107	87	15	13
25	187:170	780	740	141	104	18	14
Horemuzova 2012	**Sweden, 1990-2002; Retrospective hospital-based cohort at Karolinska**						
GA 23	7:7	637	598	59	35	9	6
24	24:29	772	668	86	81	12	12
25	45:49	810	751	91	114	11	15
Niklasson 2008	**Sweden, 1990-1999, Retrospective population-based study**						
GA 24	?	692	708	263	183	38	26
25	?	851	832	315	265	37	32
Voigt 2006	**Germany, 1995-2000; Retrospective population-based study**						
GA 23	67:54	634	599	115	117	18	19
24	113:79	710	665	124	126	17	19
25	111:100	800	747	157	151	20	20

Riddle 2006	**USA 1986-1997, Retrospective hospital-based cohort in Vanderbilt**						
GA 23	46	597		67			11
24	151	660		86			13
25	172	727		118			16
Kramer 2001	**Canada, 1994-1996, Retrospective population-based study, without Ontario region**						
GA 23	114:106	598	564	114	95	19	17
24	156:148	697	656	125	121	18	18
25	202:184	800	754	147	152	18	20
Skjaerven 2000	**Norway, 1987-1998, Retrospective population-based study**						
GA 23	277	625	580	110	100	18	17
24	390	725	670	125	120	17	18
25	586	835	765	140	140	17	18
Davidson 2008	**Israel, 1991-2005, Retrospective hospital-based cohort from Beilinson**						
GA 24	66	650	634	130	136	20	21
25	75	785	730	143	153	18	21
Fenton 2007	**Kramer 2001 study, using LMS method for each weekly measurement**						
GA 23	220	575		98		17	
24	304	670		123		18	
25	386	770		152		20	
Cole 2011	**UK90, from five studies mainly from Cambridge 1983-1994 using LMS method**						
GA 23	36	610	560	97	97	16	17
24	72	710	660	115	117	16	18
25	115	820	760	136	138	17	18
Visser 2009	**Netherlands Perinatal Registry 2001**						
GA 25	?	749	102	705	117	14	17

2.10.2 Surveys monitoring growth after full-term age

Another major issue is what is meant by the term "population" of the country, in particular with respect to second- and third- generation immigrants. In Netherlands 40-60% of the children in the four largest cities have non-Dutch parents and 17% of the whole population is immigrants (Roelants 1993). Since the inclusion of individuals of non-Dutch origin would have a major impact on the growth references; height of children with Turkish and Maroccan decent is approximately 1.5 SD lower than of Dutch children; separate growth references were constructed for each of these populations (Fredriks 2000).

Consecutive **Dutch cross-sectional growth studies**: The 1965 study in Netherlands (van Wieringen 1986) demonstrated that mean height for age was related to geographical regions (Northern children were taller than southern), socioeconomic status (children from higher socioeconomic strata were taller), and educational levels (children attending special education and lower secondary education were shorter). In

1980, these differences had diminished, but still existed (Roede and van Wieringen 1985). In the 1997 study, mean height was related to geographical region, family size and educational level of the parents and the child (Fredriks 2000). Height difference between the north and south of the Netherlands has diminished since 1997 according to the latest Dutch growth study (Schönbeck 2013), possibly due to fewer health inequalities or change in national motility (more migration between geographical regions).

The common **Swedish growth reference** Albertsson-Wikland in 2002 has chosen a different approach for population selection. 5111 healthy full-term born pupils, born between 1973 and 1975 (55% born in 1974), in the final grade of school in 1992 in Gothenburg, were selected for a retrospective collection of growth data from birth to 18 years of age. Altogether 12% of 5111 originally selected refused participation or failed to attend investigation and 19% were excluded due to lack of birth data, pre- or postmaturity or due to chronic diseases or medical treatment. The final sample was 3650 children (1849 boys and 1801 girls) or 71% of the original population. Age- and gender-adjusted weight and height are presented from birth at full-term age (defined as interval between 37-43 weeks of gestation), 3, 6, 9, 12, 18, 24 months and thereafter yearly to 18 years of age. HC measurements are provided at birth, 3, 6, 9, 12, 18 months, 2, 3, 4 years. The number of participants in each age group varies from over 1100 at birth, 3, 6, 9 months, 4 years and 18 years of age to 276 - 866 at other ages.

The **German growth reference** (Schaffrath-Rosario 2011) originates from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) that is a population-wide, nationally representative survey based on 17 641 participants (n=8985 boys, 8656 girls) aged 0–17 years. KiGGS was conducted as a cross-sectional study from May 2003 to May 2006, with an overall response rate of 67%. A population-based sample was drawn, consisting of 167 communities and excluded infants younger than 3 months of age, all preterm-born infants during first year of life, infants with severe infections during first year of life or last 4 months prior to inclusion, infants with chronic renal, gastrointestinal diseases, infants with trisomy 21, cystic fibrosis, pubertas praecox, micro- or hydrocephalus, TBC, rheumatic diseases, cancer, congenital heart disease with impairment of physical fitness, infants with current intake of growth hormone or on medication for ADHD, participants with missing information or invalid values.

WHO released in 2006 the **new WHO Child Growth Standards 0-5 years** (WHO-CGS) which combines growth data from 1997 to 2003 from six large cities in the six counties (Davis-California, USA; Muscat-Oman; Oslo-Norway; Pelotas-Brazil; Accra-Ghana; South Delhi-India). The aim of constructing the WHO/CGS reference was to present an ideal growth pattern that should be applicable all over the world with the intention to serve as growth standard (WHO 2006, Technical report).

Thus a highly selected sample of children from aforementioned sites were included for the longitudinal part of the study (0-2 years): healthy term singleton births, who were fed according to the WHO prespecified feeding recommendations for breast and supplementary feeding (i.e exclusive or predominant breastfeeding for at least 4 months, introduction of complementary foods by the age of 6 months, and continued

partial breastfeeding up to at least 12 months), and whose mothers received intensive counseling and support and did not smoke before, during and after pregnancy and children were not subjected to socioeconomic constraints on growth. Thus children's growth was considered to represent optimal growth.
However, it is important to mention that 83% of mother-infant pairs were ineligible for this study. The main causes of ineligibility was low socioeconomic status based on parental education and/ or income levels (mainly Brazil, Ghana, India and Oman) and parental refusal (mainly Norway and USA), resulting in 882 infants included (48% boys). Eligibility criteria for the cross-sectional component (18-71 months of age) were the same as those for the longitudinal part with the exception of infant feeding practices; a minimum of three months of any breastfeeding was required. For the cross-sectional component, 69% of screened mothers-infant pairs were excluded for reasons similar to those observed in the longitudinal component (WHO 2006 Technical report).

Children were followed longitudinally; weight, height and HC was measured at birth, and (except length) at 1, 2, 4, 6 weeks, from 2 to 12 month monthly and from 12 to 24 months bimonthly. In the cross-sectional component, children aged 18-71 months, from the same sites as in the longitudinal component, were measured once, except in the two sites (Brazil and USA) that used a mixed-longitudinal design in which some children were measured two or three times at three-month intervals.

The limitation of the previous WHO standard 0-19 years from 1977, based on NCHS-data, was that data used for their construction, covering birth to three years of age, came from a longitudinal study of children of European ancestry in Ohio (1929-1975), performed by Fels Research Institute, thus from a single community of formula-fed infants. Another limitation was the frequency of measurements, every three months, which was considered to be inadequate to describe the rapid and changing growth rate in early infancy (WHO 2006, Technical report). Differences between recumbent length in the Fels data set and stature on the national data used for older children charts were large, leading to a disjunction between the infant and older child growth curves between 24 and 36 months of age (Dibley 1987). Moreover the percentiles for height from the normalized version (NCHS 1978) were not identical to the original 1977 NCHS percentiles and weight-for-stature charts ended at 10 or 11 years of age, making it impossible to evaluate weight adjusted for stature during adolescence. (Ogden 2002).

The subsequent combined **WHO growth reference 2006/2007 (0-19 years of age)** is a compilation of data from WHO-CGS (0-5 years) and the ages 5-19 years from the US NCHS 1977 (National Center for Health Statistics) growth reference as a growth reference also covering school-aged children and adolescents.

A multicenter study, similar to WHO-CGS, for construction of WHO child growth reference from 5 to 19 years would not be feasible as it would not be possible to control the dynamics of older children environment. Therefore, as an alternative, the experts suggested using existing historical data for construction of a growth reference for this age group (de Onis 2007). After re-reviewing 34 data sets from 22 countries that met the inclusion criteria by the expert group, even these most promising studies showed great heterogeneity in methods and data quality, sample size, age categories and socio-

economic status. Thus WHO proceeded to reconstruct the 1977 NCHS/WHO growth reference from 5 to 19 years, using the original (non-obese) sample.
The main objective for reconstructing the 1977 NCHS/WHO reference was to provide a smooth transition from the WHO-CGS standard curves to the reference curves for older children (de Onis 2007).

Thus WHO/NCHS 2006/2007 reference for school-aged children and adolescents is based on NCHS data from 1963-1974, from 40 different locations throughout the US, which is a compilation of three national health surveys of non-institutionalized healthy children; NHES Cycle II for 6-11 years (1963-1965), NHES Cycle III for 12-17 years (1966-1970) and NHANES I for 1-17 years (1971-1974). Given the similarity of the three data sets, the data were merged without adjustments.
The total sample size was 22 917 children (50% boys); for indicator Ht-for age 0.07% (n=8) boys and 0.12% (n=14) girls were considered as outliers, for indicator weight-for-age 2.8% (n=321) observations for boys and 3% (n=356) for girls were excluded for unhealthy weight-for-height situation.
Thus final sample used for construction of the growth curves from 18 months to 24 years included 30 907 observations (50% boys) for weight-for-age and 30 018 (50% boys) for height-for-age.
Weight-for-age, height-for-age and HC-for age are presented as LMS-values, Z-scores (±3) and smoothed percentiles (1^{st}, 3^{rd}, 5^{th}, 15^{th}, 25^{th}, 50^{th}, 75^{th}, 85^{th}, 95^{th}, 97^{th}, 99^{th}).

American **CDC 2000 growth reference** has its origin in NCHS 1977 growth reference that was normalized (presented in percentiles) in 1978 and adopted by WHO as CDC/WHO reference. Availability of data NHANES III and improved statistical smoothing procedures led to a revision of the charts and the release in May 2000 of the CDC growth standards for the United States (Ogden 2002). Data are collected cross-sectionally and represent all socioeconomic and racial groups in the US (Ogden 2002).

This reference is a compilation of five nationally representative health examination survey data sets NHANES I (1971-1974) for 1-19 years; NHANES II (1976-80) for 6 months to 19 years; NHANES III (1988-94) from 2 months to 19 years; NHES II (1963-1965) for 6-11 years; NHES III (1966-1970) for 12-17 years.

The reference populations represent the composite of feedings practices that infants received in the 1970s and 1980s; during this period 1/3 of US infants were breast-fed up to age 3 months, and the other 2/3 were predominantly formula-fed. Data for all VLBW (<1500 gr) were excluded primarily due to the fact that the growth of VLBW infants is known to be markedly different from that of higher birth-weight, full-term infants. Infants' ≥6 years from NHANES III (1988-1994) were excluded due to fear for overrepresentation of overweight individuals (CDC Technical report).

A source of supplemental data sources from birth to 36 months for weight-for-age data was national birth certificates from Unites States Vital Statistics; for length-for-age data birth certificates from Wisconsin and Missouri (1989-1994) and CDC Pediatric Nutrition Surveillance system data for 0.5, 1.5, 2.5, 3.5, and 4.5 months; for HC-for age data from Fels longitudinal study. Data from more than 82 million US birth certificates and the cross-sectional databases were used, which included a total of 4697 infants' age

2 to 24 months. However, the data were sparse in the first few months of life; in fact, there were no data between birth and age 2 months. Thus the curves for birth to age 2 months represent only the mathematical function used to smooth the data for the entire infant growth chart (Greer 2008).

CDC 2000 reference presents separate curves for age 0 to 36 months and for age 2 years 20 years and the data is available in mean, SD, LMS and smoothed percentiles (3^{rd}, 5^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97^{th}).

2.10.3 Should we use a common global growth reference or local references?

If we consider that a reference chart describes anthropometry of a given population, then we need as many references as the number of different populations but if we assume that all healthy infants under optimal environmental conditions reach the full genetically determined growth potential then a common global reference, based on the healthy population and growing under optimal environmental conditions, should be appropriate to use.

The assumption that physical growth under optimal conditions is independent of time and location implies that environmental factors are the principal determinants of observed secular and country-to country variation in growth (Garza 2004). However, this assumption does not rule out the possibility that some country-to-country variation is genetic (van Buuren and van Wouve 2008).

The WHO-CGS does not provide information about actual growth in a given country and will not eliminate the need for country-specific references (van Buuren and van Wouve 2008). Moreover, the limitation of selecting just one site per region (WHO-MGRS) is that it might exclude a healthy population that grows in a different way from those selected. As an example healthy breastfed children from India and China are smaller than those from Australia, Chile, Guatemala, Nigeria and Sweden (World Health Organisation Working group on the Growth reference protocol, task force on methods for the natural regulation of fertility 2000).
WHO-CGS growth charts can be used for cross-population comparisons from the global reference and the challenge is to interpret and explain such differences (van Buuren and van Wouve 2008).

EU- growth chart is another example of pooling data from different populations including 27 European countries with a data collection between 1998 and 2011 (van Buuren 2012). The overall coverage for height was 90% and for weight 87% of the EU-population. Pooling data from these heterogeneous populations increased the spread between centiles, thus giving higher SD as compared to country-specific curves. The SD of height at 18 years in the EU reference is equal to 7.1 cm and 6.7 cm for boys and girls respectively. For comparison, the averages of the Member States-specific SD are smaller: 6.5 cm and 6.3 cm, respectively.

The mean height at 18 years of the EU-population is equal to 177.6 cm (boys) and 164.7 cm (girls). The difference in mean height at 18 years between the tallest

(Netherlands) and the shortest (Bulgaria) population is large, for boys: 10.1 cm and for girls: 8.3 cm which corresponds to 1.4 SD and 1.2 SD respectively. The EU- growth chart might serve for monitoring of secular changes but is not suitable for longitudinal growth evaluation of populations. The common acceptance of EU- growth curve in the European States would diminish concern for children with short stature. Whether these children, not identified according to EU-growth curve but labeled as short stature on the population-specific charts, have any growth-related disorder is a challenge.

2.10.4 Inclusion of term low-BW (<2500 g) infants to growth studies

Term low-BW (<2500 g) infants (2.3%) were included to WHO/CGS 2006 reference, since it was likely that in well-off populations such infants represent small but normal children. Their exclusion would have artificially distorted (increased) the standards' lower percentiles (WHO 2006, Technical report). These infants were not either excluded from the Dutch 1997 study since their inclusion has only a slight effect on mean height by age (Fredriks 1997, Schönbeck 2013). However this population was excluded from comparisons of differences in height among five Dutch references because Dutch growth studies before 1997 did not included these infants. Unfortunately the Dutch references 1997 and 2013 do not state the number (proportion) of included infants with BW below 2500g. Theoretically, inclusion of these infants would lower the mean weight of the reference population and increase the SD but will not influence the median. The magnitude of the difference in mean and SD would be affected by weight variability and mean of the included sample with BW<2500 g. Assuming the proportion of individuals with BW<2500g to the total sample size is constant for different studies, the size of the reference sample would have only minor impact on the magnitude of the mean decrease and SD increase. The minor differences would depend on the distribution of weights in the BW<2500g sample.

2.11 SHOULD GROWTH IN INFANCY AND CHILDHOOD BE PRESCRIPTIVE; USE OF WHO GROWTH STANDARD IN SOCIOECONOMIC DEPRIVED POPULATION?

The WHO growth reference is based on an assumption that this reference fits to all children in the world since it describes human growth under optimal environmental conditions and thus can be used to assess children everywhere, regardless of ethnicity, socio-economic status and type of feeding (WHO Multicenter Growth Reference Study Group 2006). The issue is how this ideal and for most children in the world unrealistic model, documented by the extremely high study exclusion rate, can be applied to a population reference using different selection criteria than those depicted in the WHO reference.

Is it reasonable to compare growth of infants from low- or medium socioeconomic conditions from Oman, India, UK or China to the WHO standard? On the one hand, infants' growth will reflect its relative position to the WHO standard, and thus provide an impetus to further improve life conditions (Tanner 1986) inclusive nutrition. On the other hand, as the WHO standard might not be feasible for socioeconomic deprived

population, health care workers, doctors and parents may wish to settle for a reference group that is closer to the local population (van Buuren and van Wouve 2008).

2.12 STUDIES DESCRIBING GROWTH OF PRETERM BORN/ VLBW INFANTS

There are several published studies on postnatal growth in preterm born/ VLBW infants in the literature and study populations vary with respect to years of data collection, number of participants, inclusion/exclusion criteria and time interval for follow up as well as mode of data presentation of weight, height, HC; in absolute values and/or Z-scores in tables or in figures only.

2.12.1 National longitudinal studies

The Swedish study (Farooqi 2006) presented 83 survivors (93% of the original cohort), 47% boys, born after 23 to 25 weeks gestation, from April 1990 to March 1992, without severe motor disability and without growth hormone treatment. The infants were gender-matched with a healthy full-term born infants born at the same hospital and time (±7 days). 67% of the cohort was born at 25 weeks of gestation. The mean BW was 765 ±110 g. Altogether 11% of infants were classified SGA with cut-off -2 SDS according to Marsals' intrauterine reference. Incidence of severe ROP stage ≥III was 26 % (n=22), of severe brain damage IVH grade 3, 4 and periventricular leucomalacia was 11 % (n=9) and of CLD was 37% (n=31) of survivors. Infants with multiple births were included and represented 17% of the cohort. Height, weight and HC were followed at birth, 40 wks, 3, 6, 9, 12 months; height and weight thereafter yearly from 2 years to 7 years and at 9 and 11 years; HC one year after full-term age and at 2, 3 and 11 years. Height, weight and HC are presented as mean and SD. Weight at birth and at corrected age of 40 weeks was also presented in Z-scores using fetal reference of Marsal 1996 and after full-term age using Albertsson-Wikland 2002 reference. Z-score for length after full-term age (and HC until 4 years) was calculated using Albertsson-Wikland 2002 and for HC thereafter using UK90-reference. Neurosensory impairment, medical or psychiatric illness with duration ≥12 months at 11 years of age were reported in 45% of infants.

An Australian study (Roberts 2013) from state Victoria, from three level-III perinatal centers, describes all consecutive survivors born below completed 28 weeks of gestation in 1991-1992, n=225 (50% boys), who were gender-matched with full-term controls (n=253). Weight and height data are presented in Z-scores (using British growth reference 1990) at birth, discharge, 2, 5, 8 years of age in 94% of the total sample and at 18 years in 74%. Authors concluded that height at age 2 is a better predictor of final height than midparental height (MPH).

A US study (Ehrenkranz 1999) reported 1600 infants who were inborn or admitted at 24 hours of age or less to any of the 12 NICHD (National Institute of Child Health and Human Development) centres with 65-233 infants/center. The children were born between Aug 1994 and Aug 1995 with BW 501-1500 g (which correspond to average weight at about 23-32 weeks of gestation), survived >7 days (168 hours) and were free of major congenital anomalies. This study's primary aim was to define postnatal

longitudinal growth for VLBW hospitalized at NICU. Weight, height and HC were measured weekly (weight daily during the first 2 weeks until weight regain) from birth to 2000 g (n=898→ 54%), from birth until discharge at 35 weeks of gestation (n=482→30%)), from birth to transfer (n=173→ 10%), from birth to death (n=84→ 5%), or from birth to age 120 days (n=23→1%). GA assessment was based on best obstetric estimate, if one existed, otherwise on LMP, standard obstetric exam and ultrasonography but not by neonatologist´s assessment. Infants were stratified to 100-g BW intervals from 501g to 1500g with 695 infants born below 1000g. Growth curves were constructed for weight, length, HC within each interval from 1 to 98 days after birth. As weight varied nonlinearly with time, quadratic regression splines were used for modeling. Strength of this study is a big sample size of the well-defined cohort including information about nutritional practices with the frequency of measurements that captured postnatal growth pattern. This study has shown that most VLBW infants did not achieve catch-up growth during the NICU hospitalization when compared with the median BW of a reference fetus of the same postmenstrual age. Infants who experienced neonatal morbidities regained BW later and gained body weight more slowly than infants without neonatal morbidities.

A part of **US, IHDP** (Infant Health and Development Program)-National collaborative randomized clinical trial at 8 medical schools was the study (Casey in 1991) that described growth in weight, height and HC from full-term age and ages 4, 8, 12, 18, 24, 30, 36 months with 90% follow-up rate in infants with BW below 1250 g who reached 40 weeks gestation at 1985 (n=147; 50% boys). There was a small sample size within each site and GA was assessed by Ballard score to ensure that all participants were ≤37 weeks GA.

The total IHDP clinical trial (Guo 1997) had a primary inclusion criterion low BW infants born at GA ≤37 weeks (n=867) who reached 40 weeks gestation in 1985. Primary aim was to define a larger set of percentile values in addition to those published by Casey 1991 and provide comparison of weight, height and HC development between VLBW (<1500 g) and LBW (1501-2500 g). The children with BW below 1500 g represent 25% (n=219) of the original cohort with 50% boys. Black and white infants dominated in the study sample with a few Hispanics and Asians included. GA assessment using Ballard score was done within 48 hours after birth. Exclusion criteria were multiple gestations, oxygen supplementation more than 90 days, hospitalization longer than 60 days after full-term, neural tube defects, severe neurological abnormality, severe sensory defect, chromosomal- or multiple anomaly syndrome, mothers with poor fluency in English, maternal abuse of drug and alcohol, maternal report of psychiatric hospitalization and parental refusal. Growth data are provided in absolute values at birth and 40 weeks but in Figures only at 4, 8, 12, 18, 24, 30 and 36 months as 5th, 25th, 50th, 75th and 95th percentile lines. Most of the measurements (80%) were provided within ±4 weeks from the scheduled ages and interpolated to target ages.

UK and Irish EPICure study (Wood 2003) represent 92% (n=283) of all survivors discharged from 145 NICU, born between March and December 1995, at GA below 26 weeks. Weight, height, HC was followed at full-term age and 30 months of corrected

age and presented in Z-scores (using UK 1990 growth reference). Children with neuromotor disabilities were presented separately.

The Dutch POPS study (Project on Preterm and Small-for Gestational Age; Finken 2006) describes children of Caucasian origin, born in Netherlands in 1983, at a GA below 32 weeks and/ or VLBW (<1500g) with complete data on weight and height at birth and three months after birth, without any diagnosed syndrome. Size at 3 months after birth was used as a proxy for size at full-term age. The final cohort consisted of 380 infants (66% of the original cohort).The primary aim of this study was to compare growth from birth to adulthood of 3 groups of preterm children; SGA at birth (defined by cut-off value of -2SDS, using Niklasson 1991 reference); AGA children at birth (using Niklasson 1991 reference) who between birth and three months after birth exhibited extrauterine growth restriction (defined by cut-off value of -2SDS, using Fredriks 2000 reference), and AGA group who three months postnatally did not show a restrictive growth pattern (length above -2SDS, using Fredriks 2000 reference). Median GA in the groups was 30.9; 29.3 and 30.4 weeks, respectively. The biggest group, accounting for 72% of study participants, was represented by AGA without postnatal growth restriction followed by AGA with postnatal growth restriction (21%) and SGA group (7%).

Z-scores for weight, height are presented at birth and 3 months thereafter and Ht only at 1 year, 2 years, 5 years, 19 years, as a median and range. All auxological data were reported to be normally distributed. “To adjust for possible bias caused by the relatively greater availability of growth data of taller persons at the age of 19 years, missing data for adult height SDS was predicted from the available height SDS data at 5 years through imputation for each group separately by linear regression analysis” (Finken 2006). This has implications for calculated Z-score at 19 years since the mean height at this age is a result of mathematical data processing and not calculated from measured values. Imputed values at 19 years represent 30 % of data for SGA group, 33% for AGA growth restricted group and 41% for AGA non-growth restricted group. Should these heights be interpreted as truly final heights?

2.12.2 Hospital-based longitudinal studies

A Swedish study (Niklasson 2003) describes preterm infants, born before completed 29 weeks of gestation between 1988 and 1991 who were previously included in an ophtalmological study of visual function (n= 52). This cohort includes nine survivors, born before 26 weeks of gestation (GA of 24 weeks, n=4 and GA 25 weeks, n=5). Weight is presented in absolute values and Z-scores at 28 wks, 32 wks, 36 wks, 40 wks (using the intrauterine reference of Marsal 1996). At 1, 2, 3 and 6 months and from 1 to 7 years yearly Z-score is calculated as mean and 95% confidence interval for the whole study group using the reference of Albertsson-Wikland 2002. According to the authors of this study the data based on estimated fetal weight are in agreement with the reference data based on Swedish preterm-born infants (Niklasson and Karlberg 1999) which reference unfortunately is not available in PubMed databases.

A US study from central-West Ontario (Saigal 2006) presents 45% survivors until hospital discharge (n=167) with BW 501-1000g, born between 1977 and 1982; the

mean GA of 27.0±2.4 weeks in boys and 27.2±2.2 weeks in girls and the mean BW of 835g. Altogether 22% were born before 26 weeks of gestation and 25% were SGA. The majority of cases were singletons, with a need of assisted ventilation, about half had diagnosis CLD and 28% neurosensory impairment. Diagnosis SGA was defined as BW less than the 3rd centile using Usher Mc Lean reference 1969 and thus found in 22% of the original cohort. Length/height at birth is reported for 89% of the long-term survivors (n=147; 44% boys); at 1 year, 2 years, 3 years, 8 years, 11-16 years and at 21-26 years for 94%, 82%, 74%, 88%, 86% and 98% respectively. Data are presented in absolute values and Z-scores using Kramer 2001 reference for BW and using CDC 2000 reference from 1 year of age.

A US study from Cleveland, Ohio (Hack 2003) depicted a cohort of 195 infants (53% boys) born 1977-1979 who represented 68% of the survivors without neurosensory impairments or diagnosed syndromes. Altogether 54% of participants were black. Inclusion criteria were infants with BW below 1500g. The mean BW was 1192 g in boys and 1187g in girls with SD of 214g at a mean GA of 30±2 weeks suggesting a biologically older but growth restricted population. Weight and height were followed at birth, 40 weeks, 8 months and 20 months, 8 years and 20 years and presented in absolute values and Z-scores using CDC 2000 reference.

A Czech study (Kytnarova 2010) reported 72 infants (53% boys) from Charles University, Perinatal center in Prague, born 1999-2002 at GA 22-25+6 weeks who were provided with early TPN and compared to cohort born at GA 26-27+6 weeks at 2 and 5 years of chronological age. All measurements of height, weight and HC were done by one person and data are presented in absolute values and Z-scores, using the reference of Kobzová 2004, as mean ± SD and 95% confidence interval of absolute values.

A study from India (Mukhopadhyay 2013) presented 35% of all live-born infants and 79% those discharged from NICU. Infants were born from March 2001 to June 2002, before 34 weeks of gestation, BW below 1500 g and had no major congenital malformations or gastrointestinal abnormalities. Infants with BW below 1000 g represented 15% of the cohort. GA assessment was based on LMP or first trimester ultrasound and postnatally by New Ballard score. These infants were previously included in a randomized controlled trial on human milk fortification (Mukhopadhyay 2007). Weight, height and HC were followed at 40 wks, 3, 6, 9, 12 months with approximately 100 infants in each age category. The data are presented in Z-scores using WHO 2006 reference. SGA diagnosis was based on cut-off level of 10th percentile for gestation using Lubchenco 1966 reference.

2.12.3 Cross-sectional studies

The hospital-based **cohort from University of Alabama in Birmingham** (Peralta-Carcelen 2000) presented growth of 57% survivors (n=53; 42% boys), and 43% black, without neurodevelopmental disabilities (MR, CP, blindness, deafness) between 12-17.9 years of age. The population was born in 1978-1984 with BW below 1000 g (mean BW 849g) and the mean GA 28 weeks suggesting an impaired intrauterine growth. Mean height, weight and HC are presented with sexes combined in absolute values and in Z-scores (height, weight using CDC 2000 reference; HC using Roche

reference 1987). At mean age of 14.9 years, the mean ± SD for weight was 55.3 ± 15; for height 160.5 ± 9.3 and for HC 54.7 ± 2.1.

UK study (Powls 1996) presented two pooled cohorts of altogether 138 children (49% boys) born between January 1980 and November 1983, with a BW of the first cohort below 1251g and the second cohort below 1500g and both cohorts born before 31 week of gestation. Children were previously included in a separate neurodevelopmental follow-up studies. At age of 10.8-13.7 years they were compared with a normal BW controls, represented by classmates of the same sex and similar age. No EPB children had any major neurodevelopmental deficits. Height and weight is presented in absolute values as a difference in cm and kg from controls and in Z scores using UK 1990 growth reference. Details on maternal height were available for 89% of children and paternal height for 87% children.

2.13 DATA QUALITY:

2.13.1 Accuracy of measurements

Infants are difficult to measure accurately which causes variability in height measurements in the same child within one occasion. The recommendation is standardized measurements with regularly calibrated equipment provided by specially trained health caregivers. In case of multicenter studies, identical measuring equipment is necessary for comparison between sites and instruments needed to be highly accurate and precise, sturdy and portable (WHO, Technical report 2006).

In a cooperative child a height measurement variability of maximum 2 mm in a three consecutive measurements at one occasion is considered to be satisfactory (Lo Neumeyer, personal communication). CGS study observers were working in pairs when collected anthropometric data. Each observer independently measured and recorded a complete set of measurements, after which the two compared their readings. If any pair of readings exceeded the maximum allowable difference for a given variable (weight 100 g, length/ height 7 mm), both observers once again independently measured and recorded a second and if needed a third set of readings for the variable in question.

The accuracy of routinely collected height and weight measurements from child health records, that are widespread used in research and clinical care, has been discussed in children born 1991-1992 who represented 10% (n=123) of the original ALSPAC cohort from Bristol growth study (Howe 2009). The routine measurements slightly overestimated heights of tall children and underestimated those of short children but had a good accuracy of routine weight measurements, particularly from age 8 months onwards, supporting their use for both clinical practice and research.

2.13.2 Frequency of measurements

In order to capture growth pattern during first year of life, frequent measurements are needed. Swedish full-term reference (Albertsson-Wikland 2002) does not adequately represent early childhood growth as children were measured every three months during

the first year of life, which is inadequate to describe the rapid and changing rate of growth in early infancy (WHO 2006 Technical rapport).

2.13.3 Data distribution

Mathematicians believe that the normal distribution is an empirically established fact and to scientists it is a mathematical law (Poincare 1892). The meaning of SD analysis of normally distributed data around the mean is that mean ± 1 SD reflects 67% of sample data; mean ± 2 SD reflects 95% of sample data; mean ± 3 SD reflects 99% of all individuals of the same age in the reference sample.

The reason statistical analysis is necessary, is because we want to be able to describe a large dataset in as few parameters as possible. Theses parameters can include the mean, median or standard deviation, etc. A further characterization of the data includes skewness and kurtosis. Skewness is a measure of the degree of asymmetry of a distribution. If the data distribution is symmetric then the mean is equal median and skewness is equal to zero. Tapering sides of the data distribution are called tails, and they provide a visual means for determining which of the two kinds of skewness is present. The negative skew or left-skewed distribution has the left tail longer which means an excess of data which have a lower than expected value. In contrast the positive skew or right-skewed data have the right tail of distribution longer indicating an excess of data which have a higher than expected value. Applying this to growth measurements, the left-skewed weight distribution contains excess of infants with a lower weight than expected in the population in contrast to the right-skewed height distribution that contains excess of children that are taller than expected in the population. As a few much skewed scores can dramatically affect the mean but will have less effect on the median of this distribution, the median should be presented in the skewed data set. The median from the skewed population does not mean that 50% of values are on the right and 50% on the left of the presented data as in the normal or Gaussian distribution.

Weight has usually not normal (Gaussian) distribution in the population but is skewed (positively skewed in Lawrence 1989/ Niklasson 1991 reference but negatively skewed for boys in Niklasson and Albertsson Wikland 2002 reference). Negatively skewed BW (-6.14) in boys, at 24 weeks of gestation, indicate more growth restricted boys than expected. In contrast positively skewed BW (+4.2) in girls, at the same age, suggests more girls with a higher BW than expected.

Height and HC measurements are usually normally distributed. However, in Niklasson and Albertsson-Wikland 2008 reference both length and HC in girls at 24 and 25 weeks of gestation were positively skewed (+3.5) indicating that more girls were longer and have a bigger head size than expected. The published SD value of 2.74 cm for HC at GA 24 weeks or of 3.45 cm for length at the same age does not have any biological significance because SDs are calculated from not normal data distributions.
The skewed data distributions need to be mathematically “normalized” in order to calculate meaningful mean and SD. The usual way to normalize a skewed distribution is to perform a Box-Cox family power transformation (i.e. square root, logarithmic transformation) (Osborne 2010). After the transformation the data are approximately

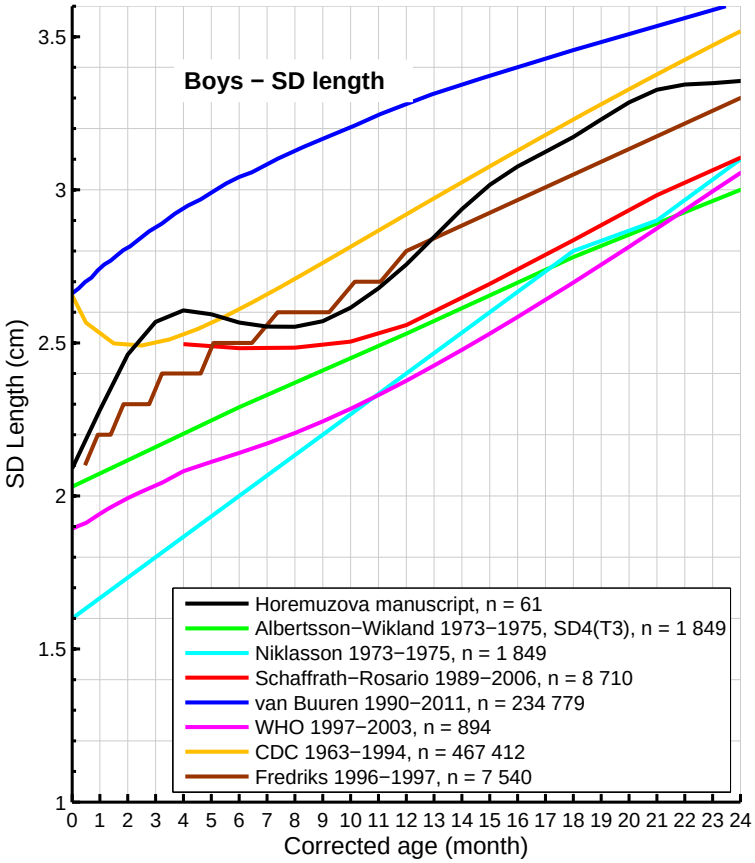
normally distributed so mean, ±1SD, ±2SD and ±3SD can be computed. After this computation all the values are back-transformed, i.e. data are expressed in kg. As a result of the transformation, the difference between mean + 1SD values is not equal to mean - 1SD values. Hence the back-transformed SD-curves represent centiles: +1SD curve corresponds to 84.1% centile, -1SD curve 15.9% etc. As an example, we can take boys' weight at 0.75 year from Table 5 in Albertsson-Wikland 2002; the difference between curves corresponding to +1SD and mean is 0.95 kg and between mean and -1SD is 0.86 kg.
As the normalization transformation is approximate, there is always risk that the centiles corresponding to ±1SD, ±2SD, ±3SD, ±4SD etc. do not match the original data. For example there should be 0.1% measurements below the back-transformed -3SD curve, but the actual percentage obtained from the raw measurements can be significantly different, e.g. 2%. This increases the risk that normal weight individual could be deemed as underweight.

Before using normalizing methods, it is important to answer the questions "Why is the data non-normally distributed?" Is the skewing caused by bias in how the data was collected or was there a special cause that occurred in the time period for the measured data which could bias the results? It would be adequate to normalize the data as long as any potential risks from that normalizing are accounted for when interpreting the results.

Kurtosis is a measure of the peak of a distribution, and indicates how high the distribution is around the mean. By definition normal distribution has kurtosis equal to three but some definitions of kurtosis subtract 3 from the computed value so that the normal distribution has kurtosis of zero. Higher kurtosis (for length +18 for girls born at GA 24 weeks in Niklasson and Albertsson-Wikland 2008 reference, for weight +47 in boys born at GA 24 weeks in the same reference) means that more of the variance is due to infrequent extreme deviations as opposed to frequent modestly-sized deviations. Lower kurtosis depicts a relatively flat data distribution due to more uniform data.

2.14 WHY IS SD OF THE REFERENCE POPULATION INTERESTING?

Age-conditional growth diagrams shows how an anthropometric measure as height, weight, HC varies both within and across age. A variation within the age delineates usually the variation of anthropometric measure from -2SD to +2SD.
The magnitude of SD depicts variability of the reference population and is dependent on the inclusion/ exclusion criteria, mathematical data processing and finally on curve-fitting (smoothing) procedure.
The knowledge about different magnitudes of SDs from the different references can help us to understand limitations of these references in our interpretation of children's growth. In the Figure 2 and Figure 3 see comparison between SD of international full-term references and EPB infants (Horemuzova, manuscript) 2 and 10 years after full-term age, corrected for preterm birth before 26 weeks of gestation.



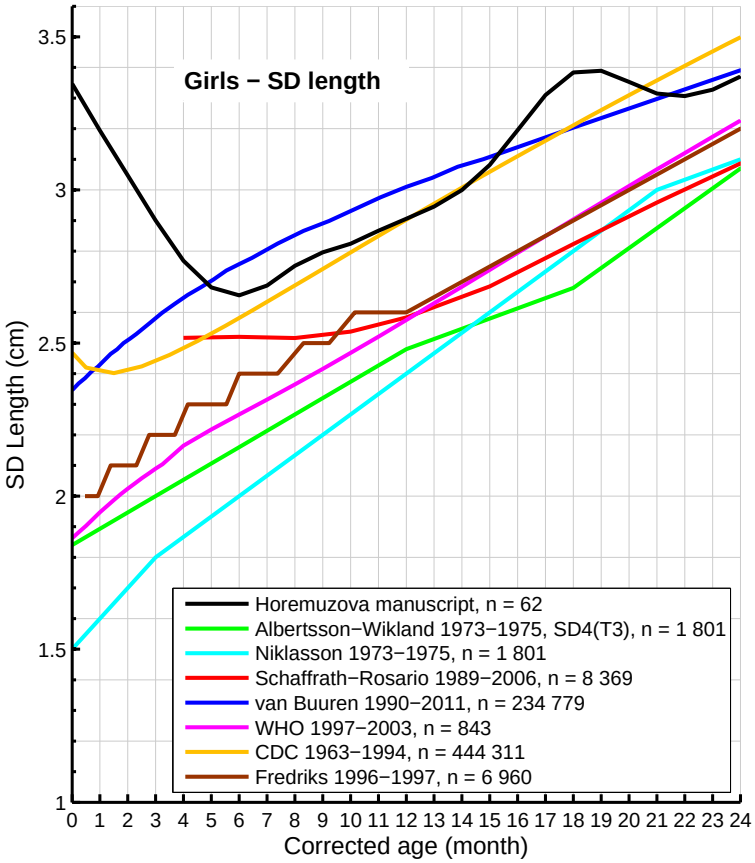
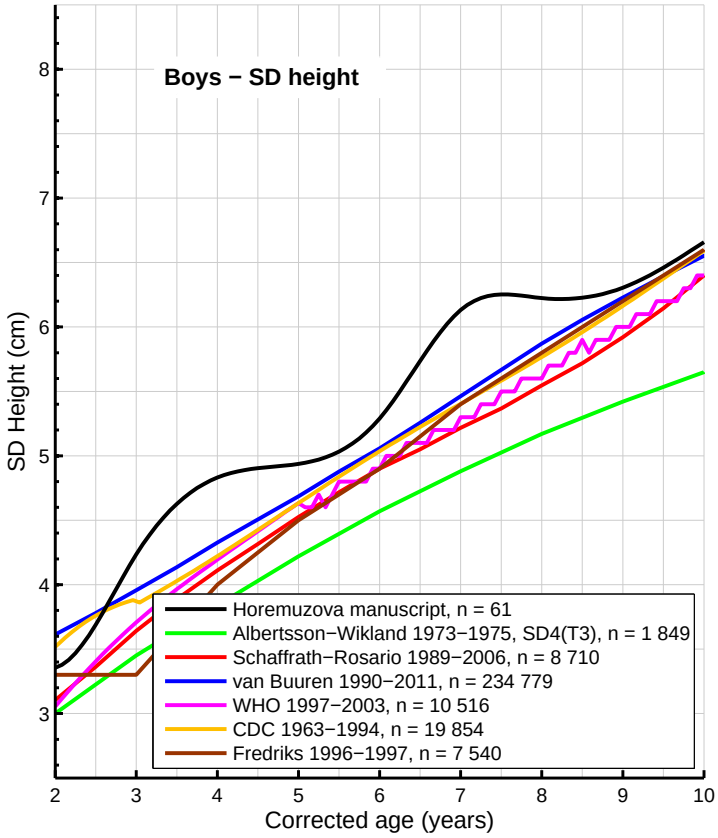


Figure 2. Comparison in SD length between EPB infants (Horemuzova manuscript, black line) and full-term international references (Albertsson-Wikland 2002,

Schaffrath-Rosario 2011, van Buuren 2012, WHO 2006, CDC 2000, Fredriks 2005) according to year of data collection, 2 years after full-term age. Boys up, girls down. All published references included only healthy full-term infants whose data were mathematically processed in different ways by lower degree polynomial function and smoothing and have thereby erased a biological variability of the presented populations. This contrasts with Horemuzovas' preterm cohort that included all survivors and with a smoothing by relatively low-degree of polynomial function thereby preserving realistic preterm born population variability. SD magnitude increases linearly with age except for decreasing trend in EPB girls until 5 months of age. In general, SD is small for both the references (at full-term age varying 1.6-2.7/ 1.5-2.5 cm in boys/ girls; at two years of age 3-3.6/ 3.1-3.5 cm) and for EPB children (at full-term age 2.1 / 2.4 cm; at 2 years 3.3/ 3.4 cm).
The smallest presented SD at birth is in Albertsson-Wikland 2002 and the largest SD in van Buuren EU 2012 and CDC 2000. The relatively high variability in length at birth in van Buuren reference can be explained by inclusion of the 27 different European populations of newborns with different genetic/ biological growth potential and for CDC 2000 which is based on Medical Birth registry data from Wisconsin and Misssouri, which may represent populations with different ethnic backgrounds. The zic-zac pattern of SD in Fredriks reference from birth to 1 year is caused by using only one decimal in the published SDs. A straight line between 1 and 2 years of age depicts no available data between these ages.



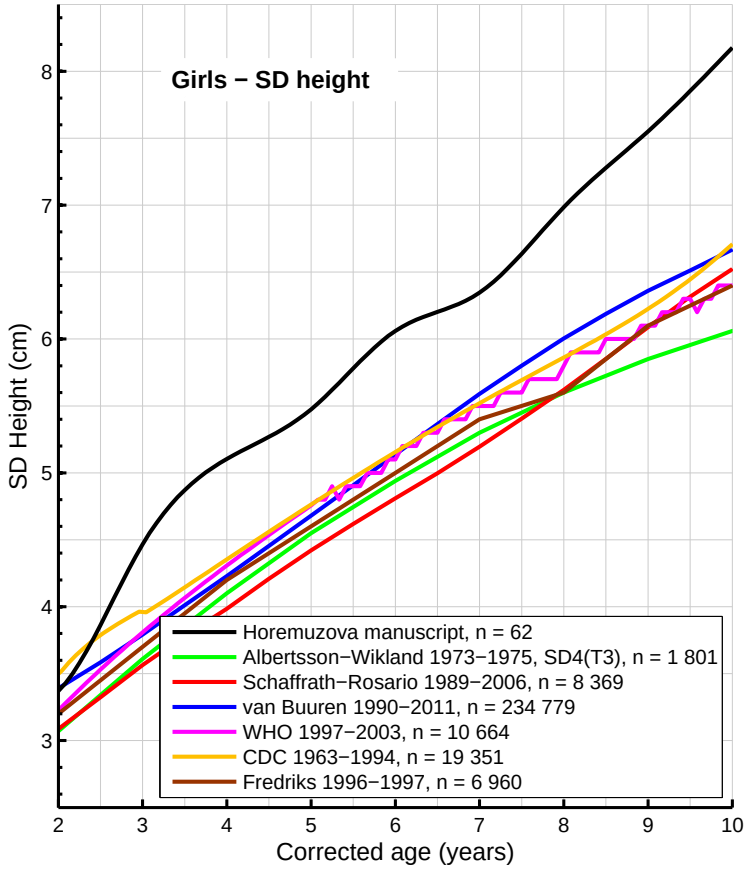


Figure 3. Comparison in SD length between EPB infants (Horemuzova manuscript, black line) and full-term international references (Albertsson-Wikland 2002, Schaffrath-Rosario 2011, van Buuren 2012, WHO 2006, CDC 2000, Fredriks 2005) according to year of data collection. SD in length from 2 years to 10 years after full-term age in a cohort of EPB infants as compared to the means of international references. Boys up, girls down.
This magnitude increases linearly with age and is general small for both the full-term references (at two years of age varying 3-3.6/ 3.1-3.5 cm in boys/ girls; at 10 years of age 5.6-6.5 cm/6.0-6.6 cm) and for EPBs (at 2 years 3.3/ 3.4 cm; at 10 years 6.6 cm/ 8.2 cm in boys/girls, respectively). Interestingly, the magnitude of SD in increasing in EPB girls after 7 years of age suggesting an earlier somatic maturation compared to boys. The smallest presented SD at 2 years and 10 years is in Albertsson-Wikland 2002 and the largest SD in van Buuren EU 2012, CDC 2000 and EPB cohort. Albertsson-Wikland's chosen SD (SD4), in the publication (Albertsson-Wikland 2002) presented without corresponding mean, represents an extrapolation of SD of height raw data (SD1) from birth to 18 years by omitting the SD´s during adolescence by using second-degree polynomial function. The zic-zac pattern of SD in WHO reference from 5 to 10 years is caused by using only one decimal in the published SDs in contrast to a straight line between 2 and 5 years of age depicts no SDs presented in 4 decimals.

Some countries present their growth charts in percentiles and others are calculating SD-scores (SDS) or Z-scores. Z-scores can be translated to percentiles and vice versa. They indicate a child's position within the distribution of the reference population; i.e if a child had a height-for-age at the 84th centile, then 84% of the reference population of

same age and sex are shorter that this child. 84th percentile corresponds to Z-score of +1. The limitations of centiles is that a measurement below the 3rd centile cannot be accurately defined on the growth chart and the distances between centiles are not equally distributed (the difference in cm between the 10th and the 20th percentile is larger than between the 20th and 30th percentile) (van Buuren 2007).

Coefficient of variation (CV) is another measure of data variability in relation to the arithmetical mean and can be calculated by the ratio of the standard deviation to the mean. Multiplication of this ratio by 100 is percentage. An example of CVs in different studies on EPB infants or birth-size references is presented in Table 3.

2.15 SDS IS A VERY SUBJECTIVE MEASURE AND THE MAGIC OF CUT-OFF VALUES

The SDS can be calculated by subtraction of individual value from the mean value of the reference population, divided by the SD of the reference population adjusted for age and sex. Thus, a Z-score or SD score represents the number of SD units above or below the mean, so that, e.g. a Z score of +1 refers to a value that is 1SD above the mean. Assuming a normal (Gaussian) distribution, the 0 SDS line represents the mean or 50th percentile which means that at every age, 50% of values in the reference population are above this line and 50% below it.

There is a plethora of different references of weight, length/ height, HC and other anthropometric measures that can be used for monitoring of children's growth. Different references have different population mean and can have vastly different SD which results in different calculated Z-scores for the same individual. For example infants' body weight is 1200 g at a certain age and the mean of one selected reference population is 1500 g and the other is 1700 g, at the same age. If both references have identical SD of 100, then the same individuals Z-score for weight is equal to either -3 (calculated from the population mean of 1500g) or -5 (based on population mean of 1700 g). Furthermore if we assume that the magnitude of SD in the reference population of 1500 g is smaller, as an example 80, and in the other reference population with a mean of 1700g is higher, for example 120, then the same child's calculated SDS (Z-score) value corresponds to -5 and -4.2 respectively.

Another example of different results of calculated Z-scores comes from two Swedish references, Albertsson-Wikland 2002 and Niklasson and Albertsson Wikland 2008 describing growth in height and weight from birth at full-term age, defined as a combination of 37 - 43 gestational weeks, to 18 years, and from birth at 24 weeks of gestation to 40 weeks of gestation, respectively. Using these two references for calculation of Z-scores at age corresponding to full-term gives different Z-scores for the same child. How is it possible? Each reference use different definition of full-term age and thereby present different mean and SD. The mean weight for boys at 40 weeks is 3715 g according to Niklasson and Albertsson Wikland 2008 reference but 3580 g according to Albertsson-Wikland 2002 reference with corresponding SDs of 453 g and 490 g. A similar situation is observed for girls with a mean weight of 3548 g and 3450 g and SD of 433 g and 480 g. This has implications for calculation of Z-score for EPB child at age corresponding to full-term age and can lead to different clinical judgments.

The body weight of 2349 g/2458 g (boy/girl) at corrected age of 40 weeks in a previously EPB children corresponds to Z score of -3.0/-2.45 using Niklasson and Albertsson-Wikland 2008 reference but -2.51/-2.06 using Albertsson-Wikland 2002 reference. Thus using Niklasson and Albertsson-Wikland 2008 at full-term age gives about 0.5 lower Z-scores for height, weight and HC.

Even after full-term age the calculations of Z-scores using Albertsson-Wikland 2002 reference might give different results for the same child. What is the reason for that? Weight-, length/height- and HC-for-age in this reference is summarized in seven different tables leading to difficulties which values to use for calculations of Z-scores for an individual child. In each of the tables the data are presented as three different means (mean1, mean2, mean3), four different SDs (SD1-4) together with skewness and kurtosis. As an example, length/height of the Swedish reference is presented in Table 2 and 3. In Table 2 height reference values are presented without relation to age for peak height velocity (PHV) and in Table 3 height reference mean and SD values are related to 3 months interval of the mean age at PHV. In this reference, mean3 and SD4 are used for the graphical presentation of Swedish height reference between full-term age and 18 years, but is it not clear from which Table the mean and SD values come. Figures for height-for-age and weight-for-age from birth to 7 years and from 5 to 18 years are presented as age-interpolated and smoothed values (mean3 ± SD4).
It is not clear which values of weights should be used for calculation of SDS, since they are presented in Table 5 as base 10 logarithms as well as in Table 4 in kg. The mean values from both tables should be equal, but it is not the case. For instance Mean3 boys' weight at 0.75 year from Table 4 is 9.43 kg, but from Table 5 it is 0.9772, which yields 9.49 kg.

What these different means and SD represent? SD1 is the calculated SD from the mean of measured values at each particular age; SD2 is the interpolated value to the exact ages; SD3 is the smoothed value to interpolated age. It is important to mention that SD3 value was not calculated from the mean3 but estimated by a polynomial function from the curve-fitting of all SD1 values from 0 to 18 years of age. SD4 represents an extrapolation of SD1 from birth to 18 years by omitting the SD´s during adolescence by using second-degree polynomial function which authors explain as an attempt to reduce the influence of the puberty timing. SD4 is similar to SD1, SD2 and SD3 until 8 years of age but thereafter the presented SD4 values are a result of extrapolation and thus have no clinical meaning or biological significance and should not be used in the clinical practice. In Figure 4, four different SD compilations from the Swedish growth reference are presented. Is it feasible to use a combination of mean3 and SD4 for the construction of the reference?

Figure 4. Comparison between four different standard deviations (SD) in height/year published in full-term reference by Albertsson-Wikland 2002 from the reference´s Table 2.

The calculated Z-score or SDS is often assumed to serve as a tool for screening, diagnosis and growth monitoring but it is important to recognize that the percentile or Z-score cut-offs have digit preference, they are statistically based, and are not based on health risk (Flegal and Ogden 2011). Thus the 2 SDS below the mean should not be intended as a clinical definition. However, chosen cut-off limits of minus 2 or minus 2.5 often leads to medical follow-ups, judgments and treatments of a child. The minus 2 SDS should rather provide a common set of definitions that can be used internationally for descriptive and comparative purposes. Nevertheless the fair comparison of growth between different populations would be possible if the published data were presented both in kg, cm and Z-scores.

The UK90 reference use an inter-centile bandwidth of 0.67 SDS instead of 0.5 or 1 SDS, so that the two lower centiles are the 0.4th and 2.3th centiles, equivalent to -2.67 and -2.0 SDS. If the 0.4th centile (-2.67 SDS) was used as a cut-off value instead of -2.5 SDS (0.6th centile), specificity of the height SDS would be slightly higher and sensitivity slightly lower than calculated for a height SDS of -2.5 (Grote 2008).

2.15.1 Different interpretations of underweight by using WHO 2006 and CDC 2000 growth charts

The WHO has recommended the use of cut-off values of -2 or +2 SDs (Z-scores corresponding to the 2.3rd and the 97.7th percentiles) from the mean which contrasts to CDC 2000 recommendations of cut-off of 5th percentile. The differences in the prevalence of underweight (<5th percentile of weight-for-height or of weight-for-age for CDC 2000 and <2.3rd percentile WHO 2006) were documented with the recommended cut-offs in NHANES 1999-2004 cohort of 3920 children, examined

from birth through age 5 years. The prevalence of underweight was notably lower when using the WHO 2006 curves with a cut-off of <2.3 percentile and higher using CDC 2000 <5th percentile. This difference probably reflects a problem in the generation of the CDC 2000 curves, which then overestimate underweight (Greer 2008). As the matter of fact, the percentage of infants with underweight increased by adoption of the 2000 CDC curves compared to the previous NCHS 1977 curves (Ogden 2002). Perhaps an upside of using the WHO 2006 reference, in which fewer children are considered as underweight, would be a decrease in the number of children referred to the pediatric endocrinologist/ gastroenterologist for medical check-up and a decrease in the number of mothers overfeeding their children who have been labeled as "underweight". Whether all of the children identified as underweight on the CDC 2000 curves but not on the WHO 2006 curves are truly at a healthy weight remains to be determined (Greer 2008). The global acceptance of WHO 2006 curves, based on exclusively breast-fed infants, would diminish concern for the exclusively formula-fed infants at age 5 months with a complementary food introduced by 4 months who is <5th percentile on the CDC 2000 curves but still in the normal range on the WHO 2006 curves (Greer 2008).

In summary, understanding of calculated Z-score strength and limitations can prevent from many unnecessary growth referrals of healthy infants with short stature.

2.15.2 SDS charts as a measure of childrens´growth instead of plotting absolute values

SDS growth charts have been since 1977 recommended as a better way to present growth data (Waterlow 1977). 0 SDS indicate an average growth velocity with respect to a used reference. Lower than average growth velocity results in decreasing height SDS and higher than average growth velocity results in increasing height SDS and thus serial SDS can depict growth dynamics of an individual child. The difference between two SDS measured at two different ages, divided by the time interval between the measurements reflects growth velocity of rate of change in SDS rather than the rate of change in the measurements themselves (Hermanussen 2012). An example of SDS chart is presented in Figure 5 which describes comparison in length-growths between preterm born/VLBW cohorts and full-term reference according to Horemuzovas' EPB reference (manuscript).

2.16 GROWTH-MODELLING PROCESS

The biometric measurements usually distribute themselves "as they like" or "as Nature feels it" and parametric (curve-constructing) statistics only imitate the distribution with a function that allows calculation of desired normative indices (Gräsbeck 2004). The term reference values imply that all values are presented but if parts of the observations are eliminated, due to e.g. statistical calculations, the term reference interval is more appropriate. Reference limits is only one way of presenting data and should not be confused with decision limits which definitely should be sought (Gräsbeck 2004).

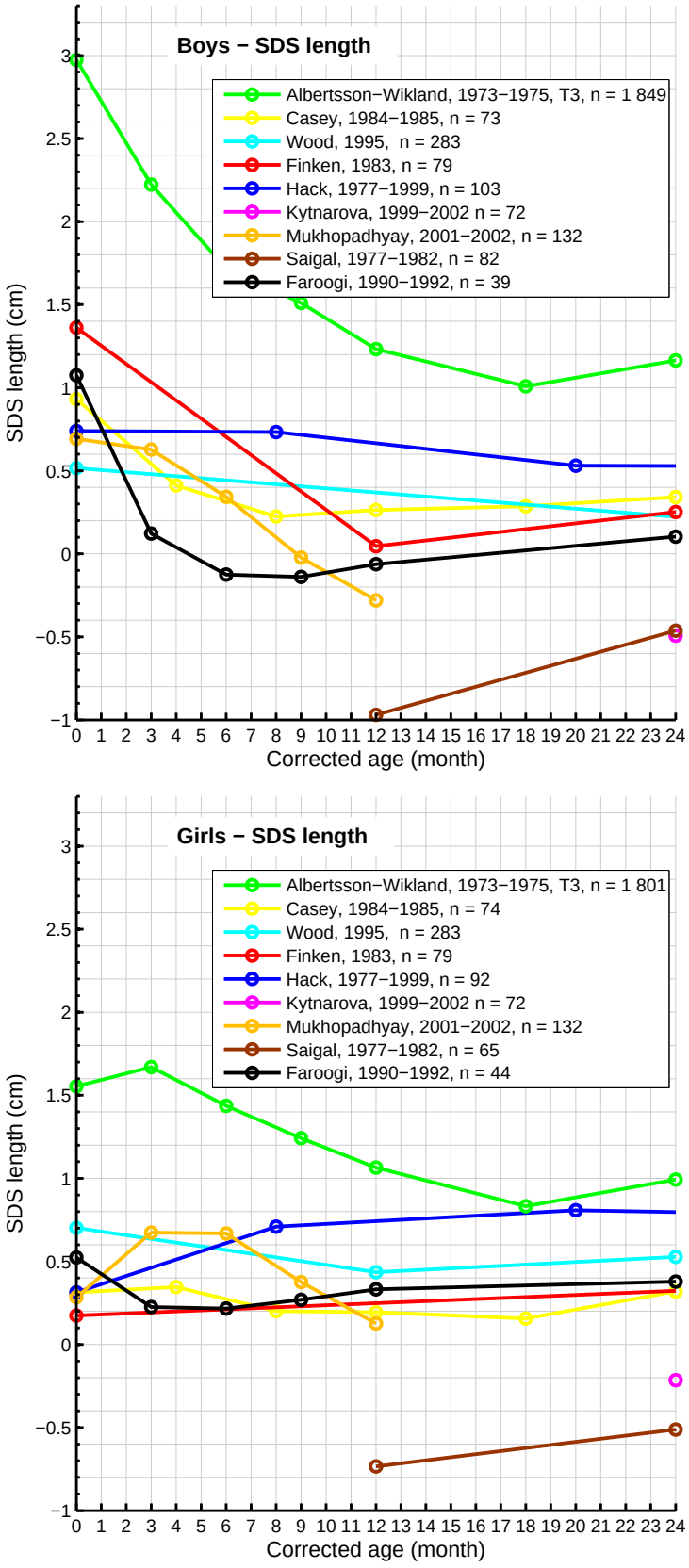


Figure 5. Comparison in SDS (Z-scores, in dots) for length, 2 years after full-term age, between preterm born (PB)/ VLBW cohorts (Cassey, Wood, Finken, Hack, Kytnarova, Mukhopadhyay, Saigal, Farooqi) and the full-term reference (Albertsson-Wikland 2002) according to EPB cohort (Horemuzova in manuscript). Boys up, girls down.

Mean and SD/age from Horemuzova's EPB cohort is applied to the different magnitude of means of the VLBW/preterm surveys which gives different calculated SDS (Z-scores) in length. The smaller the difference in mean is between EPB and the surveys, the lower SDS value will be calculated and vice versa. At full-term age, boys/girls from VLBW/preterm surveys are +0.5-1.4 SDS/ +0.2-0.7 SDS taller and at 2 years -0.5→+0.3 SDS/-0.5→+0.5 SDS taller, respectively, compared to EPBs. The relative big difference in SDS in Saigal's cohort is caused by significantly shorter study infants compared to Horemuzovas EPBs.

The basic method for construction of age-adjusted growth references consists of three main steps: Classification of measurements into age group; calculation of the data distribution and estimation of desired percentiles or SD-units per age group and finally smoothing of each desired percentile or SD-value across age to form an age-dependent curve. The major task in SD or percentile construction is to smooth the data distribution in two directions simultaneously, between age and within age. Estimated percentiles can be smoothed separately or together or based on predefined age groups (van Buuren 2007).

2.16.1 Data cleaning

A principle question is if all data are going to be used for the growth curve construction or not. An example can be BW range of 820-3200 g for GA 25 weeks that gives a positively skewed data distribution which is not clinically feasible. Should all these data be used for construction of the reference or is it more feasible to "clean" the data first? The basis for evaluation of data distribution can be provided by using descriptive statistics that includes frequency tables, contingency tables, scatter plots or histograms. For longitudinal studies, each anthropometric measurement can be plotted for every child from birth to the end of his/ her participation and examined individually for any questionable patterns with following investigation and correction or confirmation and thereby increasing data quality (WHO 2006).

Authors of Swedish growth references (Lawrence 1989/Niklasson 1991 and Niklasson, Albertsson Wikland 2008) used only "acceptable" observations by data "truncation" conditional on GA. Mean ± 6SD had been accepted as a biologically realistic length, weight and HC values suggesting that these data might not have been clinically realistic for given GA. Dutch reference accepted mean ± 5SD, after checked for data entry errors and corrected data wherever possible. If no correction was possible, these measurements were considered erroneous and defined as missing (Schönbeck 2013). To avoid influence of unhealthy weights for length/height, observations falling above +3 SD and below -3 SD of the sample median were excluded prior to constructing the WHO standards for 0-2 years. For the cross-sectional sample, from 2 years to 5 years of the WHO 2006 reference, the +2 SD cut-off (i.e. 97.7 percentile) was applied instead of +3 SD as the sample was exceedingly skewed to the right, indicating the need to identify and exclude high weights for height (WHO 2006 Technical report).

2.16.2 Age-interpolation and different methods for calculation of mean and SD

All growth references use age-interpolation for calculation of mean and SD for height, weight, HC or any other anthropometric variable. Full-term reference (Albertsson-Wikland 2002) used a linear regression model (Preece 1981) for computation of mean by fitting the curve to measured data for each individual child that estimated missing data from the measured values in any certain time point resulting in age-interpolation of the data. A mean value/age category was calculated from the sum of means, resulting in mean2 and SD2. The mean values/ age category were then smoothed with a high-degree polynomial (R^2>0.99, indicating that the chosen polynomial passed almost all measured points); best curve-fit was seen when time periods from 0 to 3 year and from 3 to 18 years were treated separately. Mean3 was derived from mean2 interpolated values by reapplying the same mathematical function and smoothed separately at three different age intervals, 0-2, 3-10 and 11-18 years in order to get the best curve-fit.

Mean values in the birth size reference (Niklasson and Albertsson Wikland 2008) were calculated from a "central part of age-adjusted data" per gestational week which means that only a central part of the data set was used, by using a trimming method. The size of the used interval was determined by testing different intervals (mean ± 0.5 SD, mean ± 1 SD, mean ± 1.5 SD, mean ± 2 SD). The interval, where acceptable skewness and kurtosis suggested normally distributed data was chosen to compute the mean. These values were then recomputed for whole sample. The trimming method assumes normally distributed data, which is not the case in the reference: only truncated (central part) data are normally distributed. Therefore the computed SD and CV in the reference are clinically unrealistic. As an example, in the new Swedish reference SD for length at birth in 24 weeks for boys/girls is 1.69 cm/3.45 cm with corresponding CV percentage of 5%/11%, respectively; the SD for HC at 24 weeks for boys/girls is 0.93 cm/3.43 cm with CV percentage of 4%/15%, respectively. The similar situation is present in the reference for birth at 25 weeks of gestation.

In a prescriptive approach, by the prespecified criteria for sample selection by WHO for construction of growth standards WHO 2006 (see section Surveys monitoring growth after full-term age), it was assumed that the resulting growth charts will define optimal growth of children (Mei 2008). However, after the data were examined, it was thought necessary to also exclude weight-for height data by trimming for some children whose achieved growth was considered unhealthy. As a result, before calculating smoothed percentiles of weight-for-height, WHO trimmed the weight-for-height data to eliminate the observations for those children and used the same trimmed weight and height data to calculate the smoothed percentiles of BMI-for-age. Thus, for weight-for-height and BMI-for-age, the sample of children used for the WHO growth charts was additionally selected on the outcome variable (Flegal 2012).

2.16.3 Statistical methods for constructing the growth curves or a story about normalization process

In non-normal (non-Gaussian) data distribution the data need to be "normalized" in order to calculate mean and SD that was previously discussed in the section Data

distribution. Although Box-Cox transformation can be found to yield an approximately normal distribution, the transformed data are not necessarily perfectly normally distributed. In particular, the tails of the distribution may not correspond to those of a normal distribution even after an approximate transformation to normality. Modeling the behavior in the tails is more difficult than modeling the central part of the distribution and would require strong assumptions (Flegal 2009). Moreover, the transformed data are not suitable for use in clinical practice. Therefore, after the calculation of transformed SD, data are transformed back to the original domain, i.e. data are expressed in kg. Birth size references published by Niklasson and Albertsson-Wikland 2008 are given in logarithms, since a power transformation was used to remove skewness in original data. Since no back transformed SD value are given in the reference it is not possible to compute SDS values uniquely.

Worm plots (van Buuren and Fredriks 2001) are method for visualization of the difference between the measured data and the assumed data model conditioned on the successive age groups. A linear plot corresponding to 0 value on y axis delineates perfect goodness of fit between the measured and the assumed value.

GAMLSS is a software package for statistical modeling of non-normally distributed data. It contains more than 60 different distributions that can be matched to data. Smoothing functions are included too. This software package was initially used for construction of WHO 2006 growth charts but had been further replaced by LMS method since it was not necessary to model the weight-for-age related to kurtosis (de Onis 2007). The strength of this software is that it can model data distributions with a high kurtosis.

The lambda-mu-sigma (LMS) method models the entire distribution into three smooth curves taking into account degree of skewness (L curve), central tendency or median (M curve) and dispersion or coefficient of variation (S curve). Accurate estimation of percentiles from the LMS method relies on the assumption that after transformation and smoothing, the variables of interest are normally distributed and this method permits then calculation of Z-scores as well as percentiles of any desired percentile. The limitation of this method is that the outer tails beyond ± 3SD of the distribution are highly affected by extreme data points even if very few (WHO 2006 Technical report). For height-for-age in WHO 2006/2007 reference, the data followed the standard normal distribution, so it was not necessary to model either the parameter related to skewness or to kurtosis (de Onis 2007).

The LMS method was used for compilation of EU growth charts (van Buuren 2012). Firstly, all Member States references were interpolated to a common age grid using linear interpolation of the LMS values. The common age grid used consisted of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18,20, 22, 24, 26, 28, 32, 36, 40, 44, 48, 52, 56, 60 and 64 weeks; followed by every half a year throughout the age interval 1.5-18 years. For a Member State with an incomplete age range, LMS-values from the matched Member State was taken, defined as the smallest sum of squared difference between their observed M-values. For entirely missing data, the authors used a donor Member State ("borrowed" the values from a similar State, similar defined as close in geography). For each Member State, they created a dataset by randomly drawing data from the local

LMS-distribution, where the number of drawn records was proportional to the Member States population size. Finally, the LMS values were estimated for the common EU growth reference by fitting a statistical model on the synthetic data for all 27 Member States.

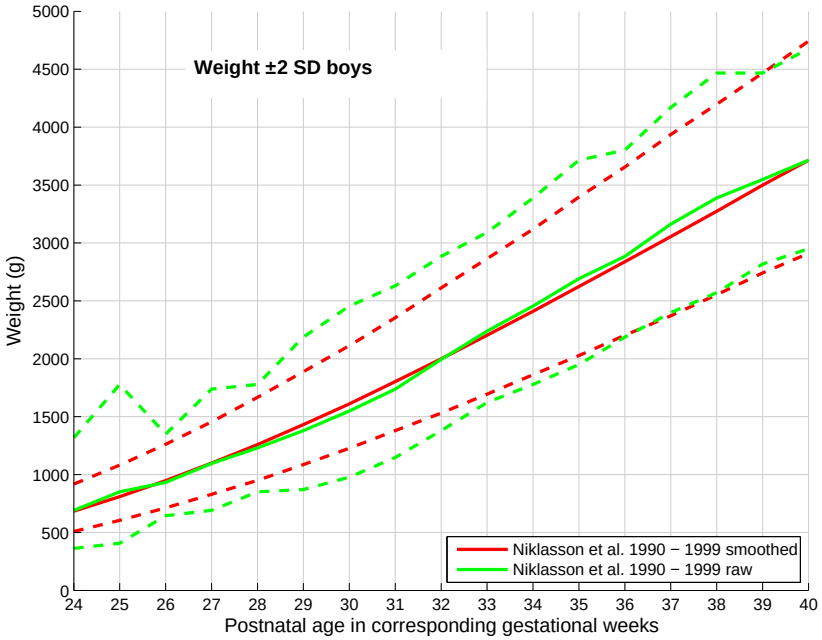
CDC 2000 used a transformed LMS method for calculation of their growth percentiles. After calculation, nine estimated percentiles (3rd, 5th, 10th, 25th, 50th, 75th, 90th, 97th were directly smoothed which means that the LMS parameters used in CDC 2000 were not derived directly from the underlying data but rather only from the previously smoothed percentiles and generated as a best solution to the equations rather than as likelihood-based estimates from empirical data. The LMS method was not used either to create those smoothed percentiles. Instead these percentiles were smoothed by other methods and the LMS parameters were selected to match the already smoothed percentiles (Flegal 2009).

In summary, although the normalized growth references allow users to better quantify growth at extremes, normalization does not refer to an improved instrument to qualify growth as “normal” or as a “standard” (CDC 2000).

2.16.4 Curve fitting procedure (smoothing)

Growth references are often presented as a set of smoothed percentile curves showing the distribution of different aspects of body size for infants, children and adolescents. Generally, some smoothing process is applied to an empirical data distribution to generate smooth curves by using different mathematical functions to fit the data with a purpose to get a cosmetically nice, smoothed layout. Moreover, the aim of smoothing is to reduce the effect of small random measurement errors, i.e. to remove small zic-zac pattern from the curves. However, curves should not be oversmoothed (losing too much variability) as the variations in the measurements can be biologically significant and thereby erased from the growth curves. An example of over-smoothing are new birth-size Swedish growth charts (Niklasson and Albertsson-Wikland 2008), illustrated on the Figure 6. Due to a slight over-smoothing, values for +2SD are systematically lower than the empirical +2SDs, for details see Table 4. The curves should not be either undersmoothed (preserving too much variability). Thus it is important to preserve a balance between mathematical processing and the information on biological variability of the reference population as the chosen smoothing technique may influence the layout of the presented curve and thereby the interpretation of childs’ growth pattern.

There is no objective criterion for choosing the smoothing parameter (Flegal 1999). One approach of generating smoothed percentiles is to first calculate empirical percentiles or SDs and to smooth those percentiles by cubic splines (Kramer 2001, WHO 2006 growth charts). Another approach is using the LMS method which had been used for the construction of the most of the presented references including birth size data (Cole 2011, Voigt 2010, Fenton 2007, Visser 2009).



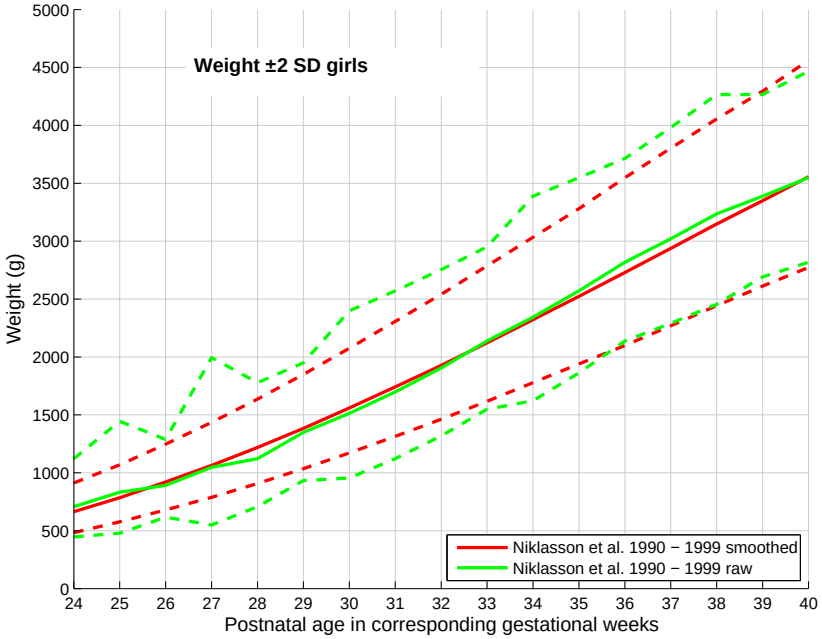


Figure 6. Comparison between smoothed and raw (measured) data for mean+2SD in weight in the new birth size reference by Niklasson and Albertsson-Wikland 2008. Boys up, girls down. Smoothed data are "a bit" under measured data. See Table 4 for details.

Table 4: Maximal difference between raw (measured) and smoothed data for +2SD in the new birth size reference by Niklasson and Albertsson-Wikland 2008. Smoothed data are "a bit" under measured data.

GA (weeks)	Weight (g)		Length (cm)		HC (cm)	
	Boys	Girls	Boys	Girls	Boys	Girls
24	+400	+210	+1.07	+4.85	-1.29	+3.90
25	+697	+376	+1.24	+5.66	-0.66	+4.39

26	+87	+41	+1.39	+2.31	-0.42	+4.96
27	+282	+560	+4.47	+5.52	+2.23	+2.45
28	+111	+141	+2.24	+2.20	+0.35	-0.35
29	+300	+101	+4.07	+2.47	+1.33	+0.72
30	+341	+324	+2.94	+2.86	+1.30	+1.05
31	+275	+264	+2.48	+2.97	+0.63	+0.64
32	+272	+213	+2.47	+2.28	+0.60	+0.56
33	+226	+165	+2.05	+1.95	+0.51	+0.47
34	+270	+355	+1.69	+2.18	+0.59	+0.69
35	+319	+267	+1.27	+1.60	+0.45	+0.81
36	+146	+167	+1.00	+1.11	+0.27	+0.49
37	+233	+179	+1.02	+0.97	+0.07	+0.26
38	+269	+211	+0.84	+0.71	-0.07	-0.02
39	0	-30	+0.38	+0.41	-0.27	-0.28
40	-65	-94	+0.16	+0.26	-0.44	-0.40

Imputation is the process of replacing missing data with substituted values. Imputation preserves all cases by replacing missing data with a probable value based on other available information. There are several imputation techniques and one of them is regression imputation. Fitted values from the regression model are used to impute the missing values. A drawback of this method is that the imputed data do not have an error term included in their estimation, thus the estimates fit perfectly along the regression line without any residual variance. This suggests a greater precision in the imputed values than is warranted. The regression model predicts the most likely value of missing data but does not supply uncertainty about that value. This method has been used for reducing or elimination of discontinuities as an adjustment for smooth transition from length to height measurements (WHO 2006, CDC 2000, Dutch 2009 study by Schönbeck 2013).

A smooth transition from the WHO Child growth standards (0-5 years) to the reference curves beyond 5 years was provided by merging data from the growth standards´ cross-sectional sample (18-71 months) with the NCHS final sample before fitting the new growth curves. The growth curves for ages 5 to 19 years were thus constructed using data from 18 months to 24 years (de Onis 2007).

In summary, a growth reference reflects usually an extensive series of transformations and smoothing procedures of the original weight, height or HC-data.

2.17 CLINICAL JUDGMENT

The clinical routine is to plot child´s weight and height to the graphical presentation of the reference while calculation of exact Z-scores is usually reserved for different mostly research protocols. For early detection of growth disorders adequate growth reference, frequent measurements of height and weight of children and evidence-based-referral criteria are required (von Dommelen 2012).

2.17.1 Age correction for prematurity is important

Calculating corrected age from chronological age is performed by subtraction of the number of weeks (months) the child was born preterm from his/her chronological age. In practice, preterms' calendar age is often adjusted for GA. For example, a preterm born child at a GA of 25 weeks and a calendar age of 15 weeks is treated as a newborn for anthropometric and neurodevelopmental data. This adjustment depends on untested assumptions (Bocca-Tjeertes 2012).
Plotting preterm born childs' growth measurements to a reference growth chart without correction for preterm birth might lead to incorrect judgment of child's growth. It is important to consider that the impact of changing from correcting to not correcting involves a shift across growth channels but it should not impact assessment of growth velocity. Recommendations for how long to correct measurements for prematurity vary from 1-3 years of age. Correction is no longer necessary when the weeks or months of prematurity become a small fraction of the total age (CDC 2000).

2.17.2 Target height and mid-parental height

The distance between the child's height Z-score and MPH Z-score is the best screening tool for the children with short stature (Witt and Oostdijk 2011) but this distance is dependent on the formula used (Grote 2008). The most common formula for calculation of TH is based on the mid-parental height, the average of the heights of the two parents, that is, MPH = (fathers' height+ mothers' height)/2 (Galton 1886) and corrected for sex (Tanner 1970), that is TH (boys) = (fathers' height + mothers' height + 13)/2 and TH (girls) = (mothers' height + fathers' height - 13)/2. An alternative form is Z score for TH which is the average of height Z-scores of the two parents proposed by Cole (Cole 2000), that is TH SDS (boys)=(TH-mean height for adult man of the reference)/SD of the reference and TH SDS (girls)= (TH-mean height for adult woman of the reference)/SD of the reference. Other formulas take into account secular trend or adjust for assertive mating and regression to the mean (von Dommelen 2011).
Moreover, when using reported parental height, one should notice that a discrepancy between measured and reported heights has been noticed; men tend to overestimate and women underestimate their height (Braziuniene 2007).

3 AIMS

3.1 GENERAL AIM

The general aim of this thesis was to describe extrauterine growth in a hospital-based retrospective and well-defined cohort of all surviving extremely preterm born infants. Longitudinal and frequent measurements during a long time period should be collected of individual child's weight, length/ height and HC after birth from available health records, to capture the growth pattern.

3.2 SPECIFIC AIMS

Paper I
To provide growth charts for clinical monitoring of extrauterine growth from birth to full-term age, in infants born before 26 weeks of gestation and hospitalized at neonatal intensive care unit in comparison to a commonly used Swedish preterm reference by Niklasson and Albertsson-Wikland 2008.

Paper II
To assess the frequency of retinopathy of prematurity and visual impairment defined by WHO as visual acuity below 0.33, in two hospital-based groups of children born before 25 weeks of gestation.

Paper III
To provide detailed information about growth pattern from full-term to 10 years, in infants born before 26 weeks of gestation, comparing with long-term sequelae and analyze how their growth differs from Swedish growth standards by Albertsson-Wikland 2002.

Paper IV
To describe the magnitude of catch-up growth, 10 years after full-term age and its impact for attained height and weight during childhood in infants born before 26 weeks of gestation.

4 POPULATION AND METHODS

4.1 POPULATION

4.1.1 Paper I

All live-born infants before 26 weeks of gestation, between January 1990 and December 2002, who were admitted to NICU Karolinska Hospital, Stockholm, Sweden and surviving to discharge for later care to associated level II nurseries (Table 5).

Table 5. The total number of live-born infants by gestational age at Karolinska hospital 1990-2002. The study population comprises boys=76 and girls= 86.

GA (week)	Total n	Survivors	Survival (%)	Participants
22	2	1	50	1
23	18	14	78	14
24	85	53	62	53
25	142	102	72	94
Sum	**247**	**170**	**69**	**162**

One girl was born at 22 weeks, fourteen infants (7M) were born at 23 weeks, fifty-three (24M) at 24 weeks and ninety-four (45M) at 25 weeks of gestation. Out of the 162 infants in the cohort, 156 were Caucasians.

Non-survivors are presented in Table 6 and Table 7. In the final publication of Paper I the information about 5 infants who died at NICU and 72 infants died before admission to NICU is not correct. The correct information is that 2 infants died before admission to NICU and 75 died at NICU, mostly during the first two weeks after admission.
All live-born infants, survivors and non-survivors together, are presented in Table 8.

Table 6. The total number of non-survivors from NICU born before 26 weeks of gestation. This cohort comprises 56 boys and 19 girls.

GA	Boys n (%)	Girls n (%)
22	1 (2)	-
23	3 (5)	2 (10)
24	20 (36)	8 (42)
25	32 (57)	9 (47)

Table 7. Non-survivors – birth weight, birth length and head circumference by gestational age. CV coefficient of variation.

	GA = 24 weeks		**GA = 25 weeks**	
Gender	**Boys**	**Girls**	**Boys**	**Girls**
Birth weight in gram (n)	20	8	32	9
Mean ± SD (CV)	683 ± 132 (19%)	670 ± 109 (16%)	744 ± 148 (20%)	687 ± 129 (19%)
median	698	637	749	691
range	486 - 1095	578 - 874	464 - 1020	427 - 845
Births length in cm (n)	19	7	29	8
Mean ± SD (CV)	31.1 ± 2.2 (7%)	31.4 ± 1.4 (4%)	32.5 ± 1.9 (6%)	31.4 ± 1.4 (4%)
median	31.5	32	33	32
range	25.5 - 31.5	29.5 - 33	29 - 36	26 - 35
Head circumference in cm (n)	18	5	20	7
Mean ± SD (CV)	22.1 ± 0.9 (4%)	21.9 ± 0.7 (3%)	23.3 ± 1.2 (5%)	22.7 ± 0.9 (4%)
median	22.9	21.8	23.1	23
range	20.5 - 23.5	21 – 22.7	21 – 25.1	21.6 - 24

Table 8. All live-born infants, **survivors and non-survivors together** – birth weight, birth length and head circumference by gestational age.

	GA = 23 weeks	
Gender	**M**	**F**
Birth weight in gram (n)	10	9
Mean ± SD (CV)	638 ± 61 (9%)	608 ± 32 (5%)
Median	661	595
Range	519 - 700	568 - 656
Births length in cm (n)	10	9
Mean ± SD (CV)	30.6 ± 1.8 (5%)	31.0 ± 1.3 (4%)
Median	30.2	31.0
Range	27 - 34	29 - 33
Head circumference in cm (n)	9	8
Mean ± SD (CV)	21.3 ± 0.8 (4%)	20.7 ± 0.5 (2%)
Median	21.5	20.9
Range	20.0 - 22.5	19.5 – 21

	GA = 24 weeks		GA = 25 weeks	
Gender	**M**	**F**	**M**	**F**
Birth weight in gram (n)	44	37	77	58
Mean± SD (CV)	705 ± 110 (16%)	669 ± 86 (13%)	782 ± 121 (15%)	741 ± 118 (16%)
Median	710.5	654	791	759
Range	486 - 1095	462 - 874	464 - 1020	426 - 950
Births length in cm (n)	43	36	74	56
Mean± SD (CV)	31.8 ± 1.5 (5%)	31.5 ± 1.5 (5%)	33.0 ± 1.6 (5%)	32.7 ± 2.1 (6%)
Median	31.8	31.7	33	32.8
Range	25.5 - 35.5	26.8 - 35	29 - 36	26 - 37
Head circumference in cm (n)	42	34	65	56
Mean± SD (CV)	22.1 ± 0.9 (4%)	21.6 ± 0.7 (3%)	23.3 ± 0.9 (4%)	22.8 ± 0.9 (4%)
Median	22.2	21.5	23.3	22.8
Range	20.5 - 23.5	20 – 23.3	21 – 25.5	20.5 – 24.5

Obstetric characteristics and interventions of mothers to NICU survivors:
Infants from our study were most common the second child in the family and for 44% of women the extremely preterm born infant was the product of their first pregnancy. 21% of mothers reported smoking during pregnancy. 59% of women were administered antenatal steroids (any dose) and 40% of them were given a complete course. 73% infants were born vaginally and 27% of infants were delivered by Caesarian section; the rate increased with advancing GA and ranged from 7% at 23 and 24 weeks to 32% at 25 weeks. 82 % of mothers had pregnancy complications (antepartum haemorrhage 40%, PROM 35%, preeclamptic toxaemia 5%, chorioamnionitis 2%). Two women were treated with anticoagulation agents because of trombosis, one for herpes infection type I in combination with group B streptococci infection. One mother had rapidly progressing HELLP syndrome with toxaemia. Two women were treated because of pyelonephritis due to hydronephrosis and cystitis during the pregnancy.
All except 9 mothers were previously healthy women, free from chronic diseases before the actual pregnancy. Two women had a history of sexually transmitted disease; three mothers had a history of hepatit B/C; one was treated with antiepileptic drugs because of the previous history of benign brain tumor operation; one was treated with L-thyroxin after the previous thyroidectomy due to thyreotoxicosis; one had diabetes type I and one mothers had Crohn`s disease operated during the pregnancy.

Infant characteristics of NICU survivors:
Of 162 survivors 47% were males. 17 % of the cohort were multiples (9% IVF/Clomifene) comprising 17 pairs of twins and one triplet. 11 complete twin pairs were included in the final analysis. One of the twins/triplet from the other 7 multiple

pregnancies died 1 week –1 month after the delivery due to the septicaemia. Surviving twins/triplets were born at week 23: three infants, at week 24: ten infants, at week 25: seventeen infants.
Of 162 infants, 91% needed mechanical ventilation at some time during the hospitalization; the proportion was 100 % at 23 weeks, 96% at 24 weeks, 87% at 25 weeks. The median (range) duration of mechanical ventilation in treated infants was 26 (1-95) days for the whole group and varied from 38 days at 23 weeks, 25 days at 24 weeks, 14 days at 25 weeks. Of 162 survivors, 14% acquired severe brain injury, 73% had any form of CLD and 55% developed ROP ≥ stage 3.The rates of any form of CLD and severe ROP increased with decreasing GA; for CLD and ROP at 23, 24 and 25 weeks of 86%, 74%, 70% and 79%, 72%, 44% respectively. 81% of survivors developed septicaemia, 77% had PDA and 14% had NEC/pre-NEC diagnosis

4.1.2 Paper II

Table 9. All live-born infants before 25 weeks of gestation, between January 1990 and December 2002 who were screened for ROP in Stockholm (Karolinska hospital, n=68) and Gothenburg areas (Sahlgrenska hospital, n=48) and surviving to 4 years of age.

ROP category (stage 1-5)	Boys (n=49) n (%)	Girls (n=65) n (%)	Total (n=114) n (%)
No ROP	2 (4)	1 (1)	3 (3)
1-2	6 (12)	20 (31)	26 (23)
3	32 (65)	39 (60)	71 (62)
4-5	9 (18)	5 (8)	14 (12)

4.1.3 Paper III and IV

Table 10. All infants born before 26 + 0 weeks of gestation, between January 1990 and December 2002, who were admitted to NICU Karolinska Hospital, Stockholm, Sweden, and surviving to age 10 years. The details about the study population have been described in Paper I.

GA week	Survivors N (%)	Participants n (%)	M n	F n
22	1 (50)	1 (100)	0	1
23	14 (78)	8 (57)	4	4
24	53 (62)	39 (74)	19	20
25	94 (66)	75 (80)	38	37
Sum	**162 (66)**	**123 (76)**	**61**	**62**

4.2 METHODS

4.2.1 Study design

Retrospective longitudinal one hospital-based cohort (Paper I, III, IV) and two hospital-based cohorts (Paper II). The studies were performed at the Pediatric Endocrinology Unit, Karolinska Hospital (Paper I, III, IV) and in collaboration with Sahlgrenska hospital (Paper II).

4.2.2 Data collection

All available neonatal health records including weight, length and HC were retrospectively scrutinized, from birth until full-term age, from hospital files (Paper I) and from full-term age until age 10 years, from well-baby clinic and school health care (Paper III, IV). All neonatal records were scrutinized regarding maximal ROP stage and treatment for ROP and visual outcome was obtained from records from ophthalmology departments, child health centres and school health services (Paper II).

4.2.3 Data quality

From birth to discharge from NICU (Paper I) body weight was measured daily, crown-heel length twice a month and HC weekly according to the routine clinical practice. Trained nurses at the NICU performed all the measurements.
From full-term age, defined as age of 40 weeks corrected for prematurity, to 10 years (Paper III, IV) weight, height (before age 2 years; measured in horizontal position) was measured monthly until age 1 year corrected for prematurity, every 3 months until 2 years and yearly until 10 years of age and according to routine practice. HC was measured monthly from full-term age until 1 year of age, at 15 months and at a study visit (attended by EH) at Pediatric Endocrinology Unit, Karolinska hospital, Stockholm at median age of 8.1years in boys and 9.7 years in girls (range 2-14), including height and weight measurement in both parents and children. If parents were not available for measurements, information on their heights was collected by telephone.
Information about children´s morbidity was collected from interviews with parent.
GA was assessed by hierarchic estimation for each infant. The neonatologist´s assessment (according to new Ballard score (Ballard 1991) had the highest priority compared to the corrected expected date of delivery (CEDD), based on gynaecologist's clinical examination corrected after early ultrasound examination.

4.2.4 Data exclusions

If children were growing 2 SDs above their MPH, earlier pubertal start could be assumed and corresponding weights and heights were excluded from the data processing.

4.2.5 Data processing

All available growth data for weight, length/height and HC, from birth until age 10 years, were retrospectively analysed. Coefficient of variation (CV) was defined as the ratio of the standard deviation (SD) to the mean. Median, skewness and kurtosis were calculated in order to validate distribution of the population as well as the quality of the data.
Individual SD scores (Z-scores) (Paper I, III, IV) were calculated using "mean" and "SD" values of gender-specific, not smoothed Swedish reference data for birth from GA 24 weeks until full-term age at 40 weeks gestation (Niklasson and Albertsson-Wikland 2008). After full-term age Z-scores were calculated using age-interpolated, gender-adjusted and smoothed reference data for weight (mean3, SD3 in Table 4 in reference (Albertsson-Wikland 2002)), height (mean3, SD3 in Table 3 in reference

(Albertsson-Wikland 2002)), and HC (mean3, SD3 in Table 7 in reference (Albertsson-Wikland 2002)).
Mean gain in body weight-, length- and HCSDS between birth and the discharge from NICU (ΔSDS) and from full-term age to 10 years was calculated from the individual changes.
Gender-adjusted mid-parental height (MPH) was calculated using the parental heights, using formula for boys [(height mother + 13 + height father) / 2]; for girls [(height father – 13 + height mother) / 2].
The gender comparison in body weight, length and HC was performed for means (student's t test), median (Mann-Whitney test) and standard deviation (Fisher´s F test) using two-sample test for independent samples (Paper I-IV).

4.2.6 Growth-modelling procedure

The Statgraphics Centurion Package version XV was used for the statistical analysis of the data and MatLab version R2007b for the graphical construction of postnatal growth curves. For each postnatal age at corresponding gestational week we calculated mean and SD of body weight, length and HC. These values were smoothed using cubic smoothing spline (by MatLab function csaps). In the csaps-function the user can choose a smoothing parameter. It determines the relative weight we would like to place on the contradictory demands of having our curves being smooth versus having them close to the data. The value of this parameter ranges from an interval 0-1 where zero means linear regression (least square fit of line) and 1 means natural cubic spline passing all data values. Our goal was to filter out the variations caused by the measurement errors and at the same time to preserve the biological variations. As a criterion for the choice of the smoothing parameter, we used a chosen maximal "clinically feasible" difference between measured and smoothed data. Then we searched for such a smoothing parameter which produced smaller differences than the chosen limit and at the same time a smooth curve. We considered the following difference between measured and smoothed 2SD curve as clinically feasible: weight 60 g, length 1.5 cm, HC 1 cm (paper I) and weight 100 g, height 0.5 cm, HC 0.5 cm (Paper III). Since the data for body weight, height and HC showed little variability, we chose the smoothing parameter 0.1 (Paper I, III). Body length measurements from birth to discharge were "noisier" with greater variability and therefore we chose smoothing parameter 0.02 (Paper I). In addition, each weekly mean value was assigned with a weight (importance factor) during the spline fitting. This weight was computed as square root of the number of measurements. It means that mean values computed from smaller number of measurements will have smaller influence on the spline´s form. All smoothed growth curves of mean values and SD are presented in Table S6 (Paper I) in Table 3 (Paper III).

4.2.7 Ethics

Ethical approval was granted from the research ethics committee at the Karolinska University Hospital (Paper I, III, IV). Ethical committee review was not required for the retrospective review of the routine clinical practice (Paper II). Data were analysed anonymously.

5 RESULTS

5.1 PAPER I

The postnatal growth of almost all the extremely preterm infants grossly deviated from the reference mean of Niklasson and Albertsson-Wikland 2008; the deviation from the reference was increasing with age. At discharge from NICU 75 % of originally appropriate-for-gestational age infants were below –2 SDS for at least one of the growth variables. The most common finding was growth restriction for the combination of weight, length and HC followed by weight and length only.

5.2 PAPER II

Almost all children developed ROP and 75% of them severe ROP (stage ≥3) with a majority treated with retinal ablation. Severe ROP was often diagnosed with additional functional deficits as a consequence of brain dysfunction. Normal visual acuity (VA >0.8) in at least one eye was found in 50% of all infants, more often in girls while visual impairment (VA <0.33) was more common in boys. The frequency of VA<0.33 was present in 15/46 boys and 6/65 girls.

5.3 PAPER III

After being born with length, weight and HC appropriate-for-gestational age, a pronounced deceleration in all these variables occurred until full-term age. Thereafter a significant catch-up occurred for weight and height. Both boys and girls had by 10 years reached average or near-average height and weight, close to their genetic potential for height. Significant cognitive, motor disorder and/ or developmental comorbidity were found in 48 % of the boys and 34 % of the girls. Severe ROP stage ≥III was present in 79 % of the boys and 66 % of the girls. In general, the non-sequelae and sequelae cohorts had similar mean weight, height and HC at birth, full-term, 1, 2 and 10 years. However, boys at 1 year with severe ROP had smaller head size than those with milder forms of ROP. At follow up clinic at a median age of 8.1 years (range 2-14) they also had smaller head size and at 10 years they were shorter, while in girls no significant growth difference was observed between these cohorts.

5.4 PAPER IV

A significant catch-up growth occurred in both weight and height during the first year after full-term age with the most intensive period in the first three months. This intensive growth period was followed by a plateau between one and two years of corrected age but with more pronounced weight than length development, a trend that continued until 10 years. Children with rapid catch-up growth in weight at three months after full-term age were significantly heavier and taller at 1 and 2 years but they were not taller at 10 years compared to children with slower growth tempo during the same period.

6 DISCUSSION

6.1 HOW DOES THIS THESIS CONTRIBUTE TO CURRENT KNOWLEDGE?

This thesis describes growth and morbidity from birth to 10 years in EPB infants, admitted to Karolinska University hospital between 1990 and 2002, and shows that being born before 26 weeks of gestation gives different growth pattern than that predicted by birth size (Paper I) or full-term reference (Paper III).
Length at birth is normal but followed by slow growth after birth, which calculated in SDS, results in a pronounced fall. The lowest level of Z-score for weight (-3.2 in boys and -2.8 in girls) was observed at age corresponding to 39 weeks, for length (-3.7) at 39 weeks and for HC (-2.2) at 35 weeks of gestation (Paper I). Thereafter catch-up growth starts with the most pronounced weight, length and head size gain during 3 months after full-term age (Paper IV).
The steady-state position for weight SDS is seen between 3 years and 8 years corrected age in boys and 3 years to 7 years in girls; for height SDS between 4 years and 7 years in girls but in boys between 4 years and 10 years corresponding to -0.6 SDS/ -0.5SDS below the MPH for girls/boys respectively. The steady state position for HC SDS starts after 3 months corrected age for both genders.
By 10 years the children had reached normal population average or near-average height and weight and were for height close to their MPH (Paper III). However, a continued catch-up activity in height in girls after 7 years of age may indicate an earlier somatic maturation, i.e. no real catch-up or gain in final height.
Comparison with other growth studies is difficult since the inclusion criteria of study populations differ and therefore the variability of the population differs. Moreover, published growth references reflect usually an extensive series of transformations and smoothing procedures of the original anthropometric measures, which have impact on the calculated SDS and consequently different judgments for children's attained weight, height or HC.

Ten years after birth, significant cognitive, motor disorder and/ or developmental comorbidity was present in 48% of the boys and 34% of the girls (Paper III). Severe ROP was documented in the majority of children (79 % boys, 66 % girls) and treated with ablation in 90 % and 73 % of those respectively (Paper II, III). EPB children, especially boys, are at high risk for visual impairment, often in combination with additional functional deficits as a consequence of brain dysfunction (Paper II).

6.2 STUDY POPULATION

The well-defined cohort, with a high follow-up rate, comes from a single neonatal unit for the study of growth (Paper I, III, IV) or from two units for the study of ROP complications (Paper II); both units with level III neonatal care. This population included both low-risk and high-risk pregnancies followed by EPB with perinatal complications related to the pronounced immaturity. The majority of mothers were healthy but with a high frequency of pregnancy complications. About 20% of women reported smoking. Boys represent 47% (Paper I), 43% (Paper II) and 50% (Paper III and IV) of the cohort and 17% of infants came from multiple pregnancies. The majority

(91%) of EPB infants (Paper I), similar to the EXPRESS study (85% of 497 individuals born before 27 weeks of gestation during 2004-2007) (The EXPRESS group 2010), needed mechanical ventilation (MV) sometime during the hospitalization but the median duration of MV was approximately twice longer in EPB cohort (Paper I) compared to the EXPRESS cohort. However, the 73% prevalence of chronic lung disease (bronchopulmonary dysplasia) was similar to that in EXPRESS but significantly higher than in the EPIBEL cohort born 1999-2000 (45%). Compared to the EXPRESS cohort our study subjects had more complications: twice as many infants in the present cohort had septicemia, three times as many infants suffered from NEC and more than half of them had symptomatic PDA resulting in intermittent interruption of enteral feedings.

6.2.1 Analysis of non-survivor's birth size and aspects on intrauterine growth

Paper I depicts birth size and postnatal growth only for live-born infants who survived until discharge from NICU and thus the presented weight, length and HC at birth do not represent all live-born infants. Subsequent analysis of non-survivors (n=75) birth size showed that at 24/25 weeks of gestation boys (75% of all the non-survivor cohort) were -89 g/-66 g lighter; -1.2 cm/- 0.7 cm shorter and had similar/-1.2 cm smaller head size; girls were -31 g and -64 g; similar/-1.5 cm; -0.3 cm/-0.9 cm, respectively. Non-survivor boys were heavier, longer and had a bigger head size compared to girls and the variability (CV) of BW was slightly higher (19-20%) compared to survivors (11-15%); the similar situation seen in girls non-survivors (16-19%) compared to survivors (12-15%).

Inclusion of all live-born infants admitted to NICU irrespective of subsequent survival seems to have implications for the published calculated birth size in boys but not in girls (Paper I). Mean BW would decrease in boys by -67 g and -28 g at 24 and 25 weeks, length at birth would be -0.5 cm smaller at 24 but not at 25 weeks and without any change in HC; resulting in not significant gender difference for weight (+26g at 24 weeks and +41g at 25 weeks) and still significantly larger HC for boys. Gender difference in BW at this early GAs, with boys heavier than girls, has been reported previously from SMBR (Källen 1995).
Furthermore, variability in BW in boys would increase from the published 11% (Paper I) to 15-16% that is similar to other birth size surveys (for details see Table 3 in section birth size surveys) but contrasts to the new Swedish reference of Niklasson and Albertsson-Wikland 2008.

Although the majority of infants born in early weeks is regarded to have "normal" body weight, this mean weight is a result of the "normal" degree of growth restriction and not necessarily the weight of a subsequent full-term baby had it been born at that early gestational week (Källen 1995). The mean BW of all live-born boys at 24/25 weeks of gestation, admitted to Karolinska NICU from 1990 to 2002 was 705g/782g and thus similar to published international references (Kramer 697g/800g, Skjaerven 725g/835g, Voigt 710g/800g) but higher compared to non-survivors (683g/744g). This suggests more pronounced intrauterine growth restriction in non-survivors and thereby probably increased vulnerability to perinatal insults. In contrast, mean BW of boy-survivors born

at 24 weeks of gestation was 772g (Paper I), which is 50-80g higher compared to the average BW of the published references and suggests inclusion of biologically older but growth restricted boys.

6.3 DATA QUALITY

The presented anthropometric data (Paper I, III, IV) are based on frequent measurements (Sherry 2003) and could thus capture growth patterns in infants from birth to 10 years corrected age. Although length in infants is difficult to measure accurately, which can result in implausible results between different measurement occasions, it is impressive how smooth the measured values were during the infants' period at NICU. The overall accuracy of routinely collected height and weight measurements from records of child health centers and school health care services 10 years after full-term age had been confirmed by the data smoothness with the measurements at follow up clinic at median age of 8 years (range 2-14 years) (Paper III) and/ or from hospital files for those children who attended specialist out-patient clinics. The further strength of the presented studies (Paper III, IV) is that we used measured and not reported height and HC for parents, as a measure of childrens' genetic growth potential (van Dommelen and van Buuren 2013).

6.4 EARLY POSTNATAL GROWTH AND NUTRITION

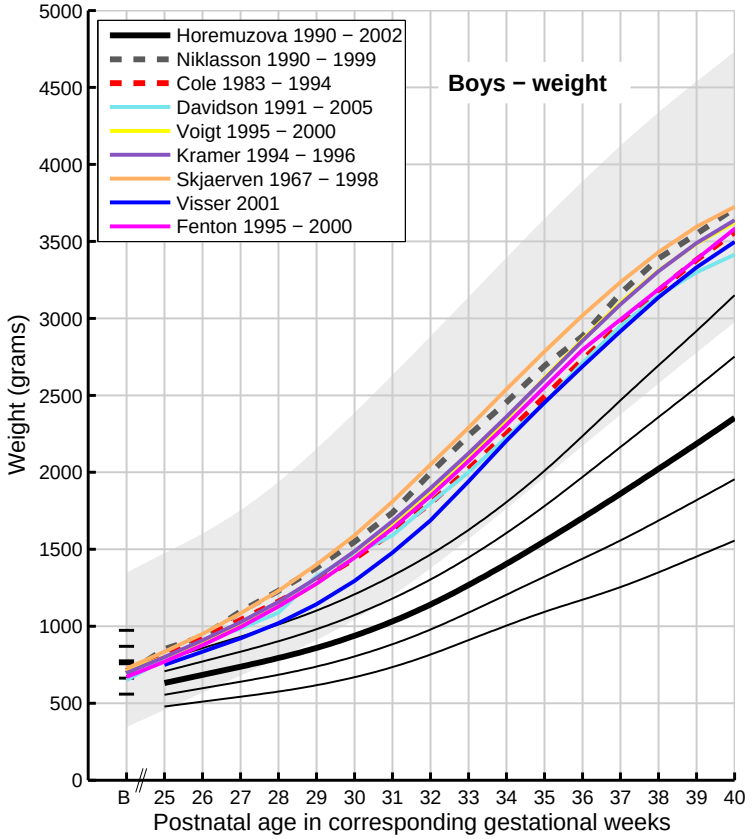
It is possible that in a child born extremely preterm a fetal-related growth physiology persists during the early postnatal period, which means that the regulation of postnatal growth from birth to full-term age might be partly regulated by fetal mechanisms. Thus nutritional, health and environmental factors during this period might program infants' growth and metabolism.

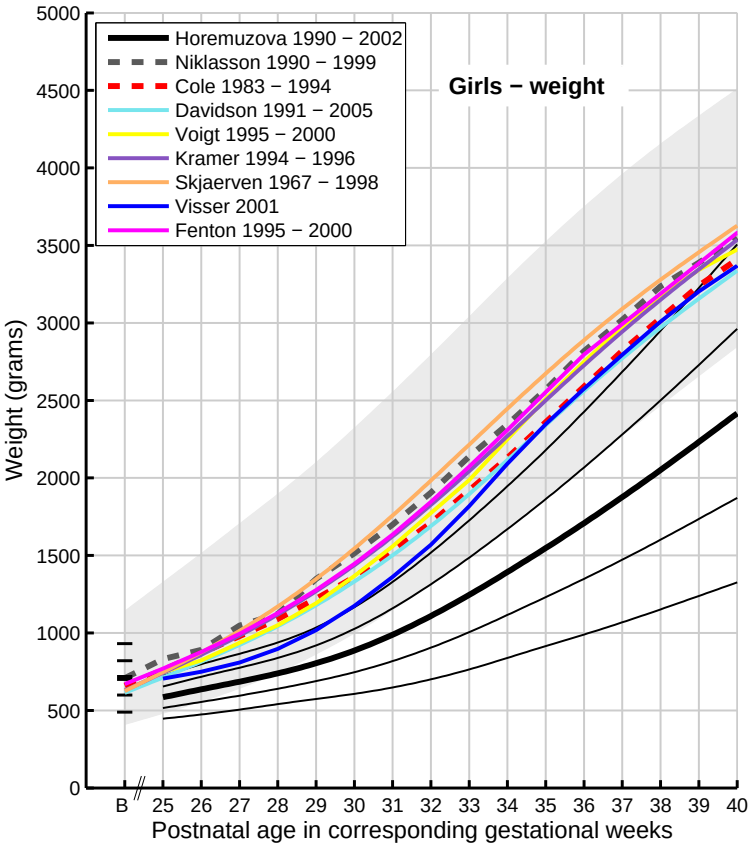
The postnatal growth until full-term age of almost all EPB infants grossly deviated from the mean of new Swedish birth-size reference (Niklasson and Albertsson-Wikland 2008). Therefore birth size or estimated fetal size references should not be used to monitor postnatal growth of EPB population (Paper I) which supports what has been suggested by others (Sauer 2007, Bertino 2008, Cole 2011).
In the EPB population extrauterine growth patterns in weight, height and HC was vastly different from cross-sectional birth size reference by Niklasson and Albertsson-Wikland 2008 (Paper I) as well as from the other published international birth-size references (Cole 2011, Davidson 2008, Voigt 2006, Visser 2009, Skjaerven 2000, Kramer 2001, Davidson 2008 and Fenton 2007); see Figures 7ABC, the reference populations were born 1983-2005.

Swedish reference on estimated fetal weight is based on ultrasonographical follow-up of pregnancies with normal outcome, thus birth of a full-term newborn (Marsal 1996). Comparison between extrauterine (Horemuzova 2012, Hansen-Pupp 2011) and intrauterine (Niklasson and Albertsson-Wikland 2008, Lawrence1989/Niklasson 1991, Marsal 1996) growth is presented in Figure 1 (in the section what is normal or optimal growth). Hansen-Pupp cohort was born 2005-2007 when current nutritional guidelines were applied and represent 52 infants corresponding to 30 % of total material. The presented Hansen-Pupps' weight curve in gram is derived from published SDS values (calculated from Marsal 1996 reference) at only four postmenstrual ages (25.7 weeks;

29.8 wks; 35 and 40 wks). Mean weight of the selected cohort is higher than Horemuzovas EPB cohort (Paper I).

7A





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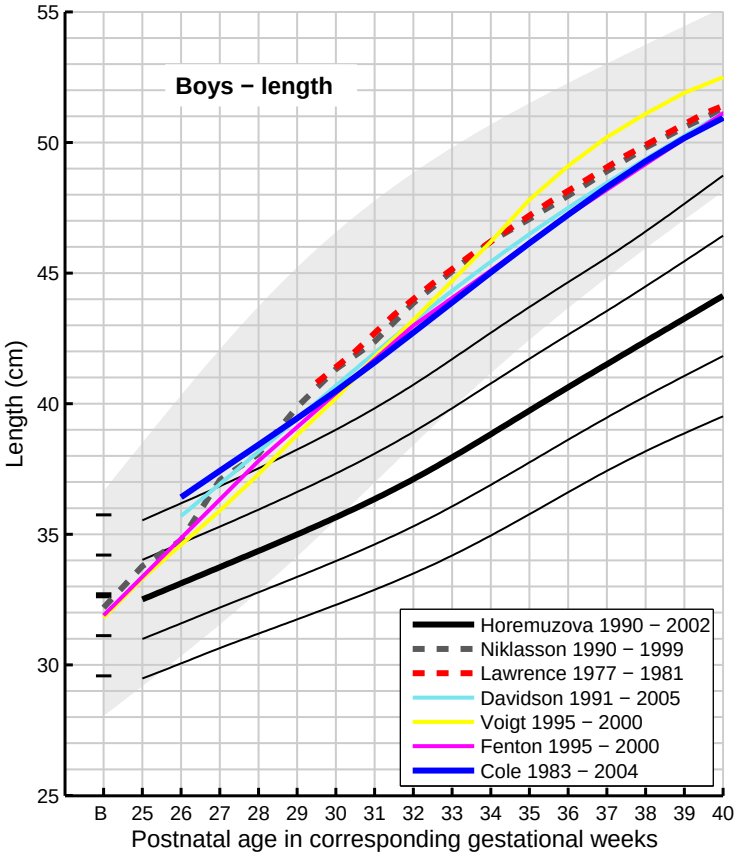
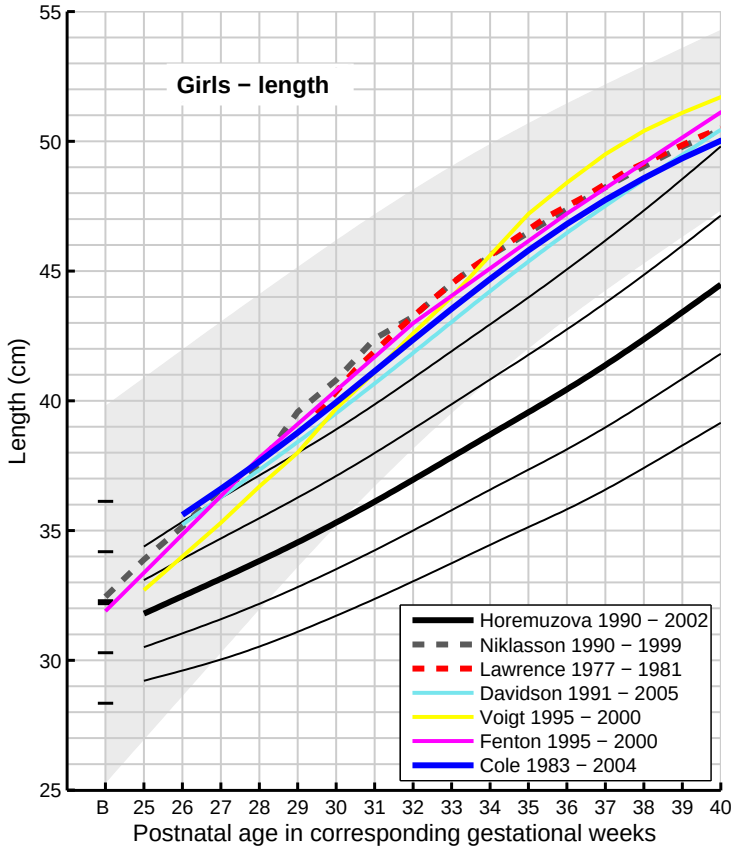

Boys − length
Length (cm)
55
50
45
40
35
30
25
B 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Postnatal age in corresponding gestational weeks
Horemuzova 1990 − 2002
Niklasson 1990 − 1999
Lawrence 1977 − 1981
Davidson 1991 − 2005
Voigt 1995 − 2000
Fenton 1995 − 2000
Cole 1983 − 2004


Girls − length
Length (cm)
55
50
45
40
35
30
25
B 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Postnatal age in corresponding gestational weeks
Horemuzova 1990 − 2002
Niklasson 1990 − 1999
Lawrence 1977 − 1981
Davidson 1991 − 2005
Voigt 1995 − 2000
Fenton 1995 − 2000
Cole 1983 − 2004

7C

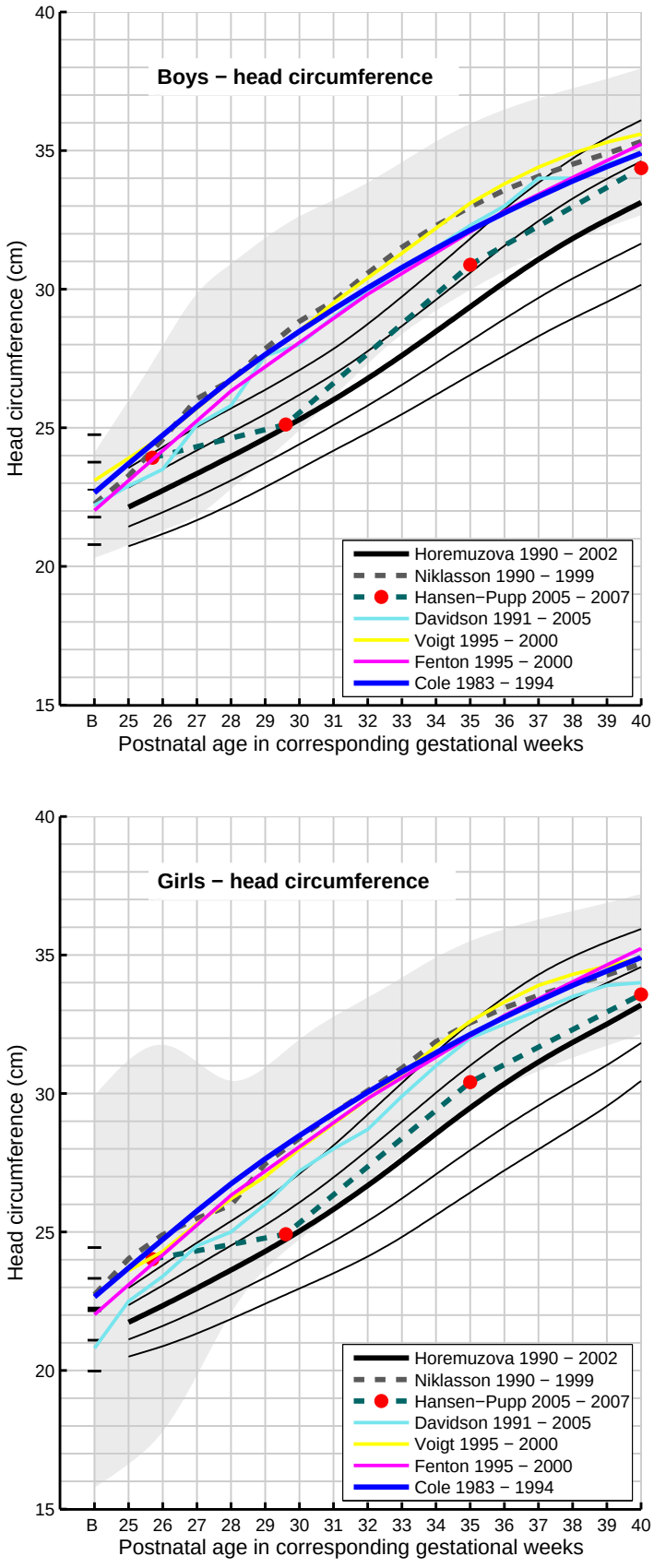


Figure 7ABC. Comparison between extrauterine (Horemuzova 2011, Hansen-Pupp 2011) and intrauterine (Niklasson and Albertsson-Wikland 2008, Cole 2011, Davidson 2008, Voigt 2006, Kramer 2001, Skjaerven 2000, Visser 2009 and Fenton 2007)

growth. (a) Weight-for-age, (b) Length-for-age (c) Head circumference-for-age as until full-term age in a cohort of extremely preterm born (EPB) infants (mean±2SD) as mean±2SD compared to the Niklasson and Albertsson- Wikland 2008 birth size reference (grey area showing mean±2SD) and other published international birth size references. Boys up, girls down.

We suggest that the poor growth of our studied EPB cohort is due to the combination of profound neonatal morbidity due to extreme prematurity and limited energy intake. None of the study infants were treated according to the current nutritional guidelines for the EPB population and even though the nutritional policy has slightly changed during the period (1990-2002), the limited number of infants in each subgroup prevents identification of any trends (Paper I). As the number of patients hospitalized at NICU at 40 weeks was quite small, there is a possibility of a negative selection bias of the measurements presented at that age due to overrepresentation of infants with significant morbidity. The other infants had left NICU for follow up care at secondary hospital units.

However, the previous focusing on EPB infants' survival and not early nutrition should not be switched to a situation of overnutrition in order to reach the intrauterine growth reference position since overfeeding might jeopardize the infant´s metabolic health later in life. It is not obvious if promoting the goal of complete catch-up growth is desirable or even achievable (Martin 2009) but there may be a trade-off between optimizing neurocognitive outcomes and increased metabolic problems in later life. We still do not know to what extent extrauterine growth failure can be minimized with the introduction of current nutritional guidelines. It remains to be evaluated in future long-term studies on EPB population treated according to the current nutritional guidelines whether the progressive postnatal growth failure is inevitable or not.

Thus we still do not know what optimal growth of the EPB population is but if birth size/fetal weight estimate references are perceived as unattainable and thus not relevant or feasible, we might wish to settle for a more appropriate reference that is closer to achievable growth of this population. Neither the charts based on birth-size nor the charts presented in this study are supposed to be used as a prescriptive standard for EPB population. The use of these two in combination can help the neonatologist to directly compare the growth of the individual infant with the intrauterine norms as well as with the 1990-2002 cohorts' growth, which probably represent the two extreme ends of the scale (Paper I).

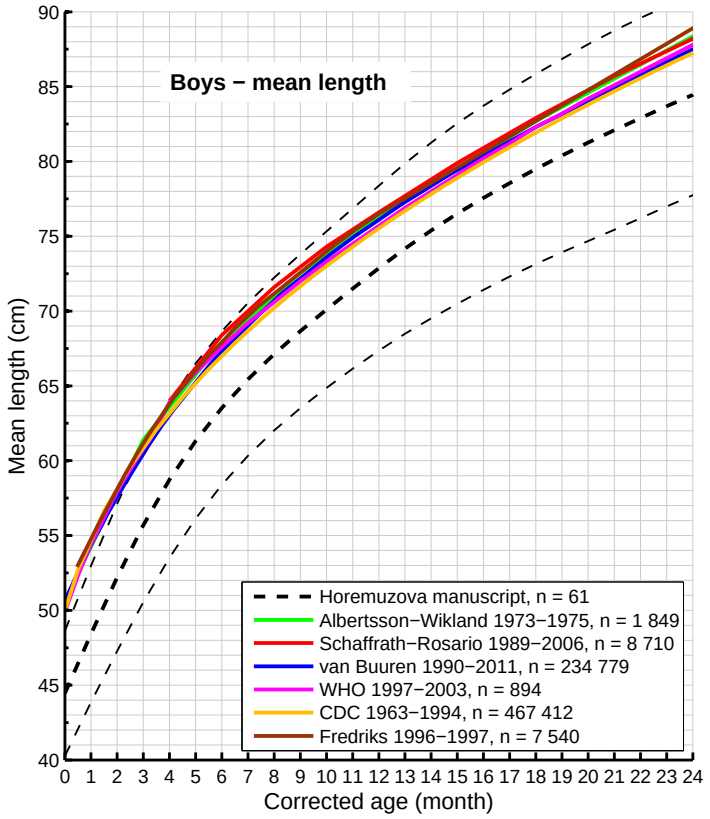
6.5 WHICH REFERENCE IS SUITABLE FOR EVALUATION OF POSTNATAL GROWTH IN EPB INFANTS?

As "healthy" EPB infants born before 26 weeks of gestation can hardly be found it should be considered that specific growth charts for EPB infants cannot be a prescriptive standard. This contrasts to the proposal by International Fetal and Newborn Growth Consortium (INTERGROWTH-21st) (Villar 2010) to conduct a growth standard for the preterm population but at the same time to exclude subjects with complications of prematurity. Instead, an international growth reference, including all EPB survivors, irrespectively of prematurity complications, should be considered, as it

will mostly depict the target population, and several sub cohorts with respect to severity of prematurity complications can thereafter be analyzed separately. Such growth reference would portray the typical/possible/"healthy" growth instead of aiming to an "ideal" target described by a highly selected group.

It is better to fit the curve to the population of interest than to fit the population to an "ideal" curve. Our attempt to fit the EPB population to an "ideal" curve might be a trade-off for future metabolic complications. Although mathematical modeling of the reference is important for construction of growth curves, there is no mathematical formula which defines how children should grow and what is the normal variation of growth in a certain population. Using different advanced formulas to the measured data means "forcing" this data to a predefined assumption and is not correct mathematical modeling. It is of importance that clinicians dealing with growth assessment in children are aware of limitations of the used growth reference.

After reaching full-term age, EPB infants can be monitored on country-specific growth charts for full-term infants but these charts are poor substitutes for monitoring growth in EPB population (Bocca-Tjeertes 2012). It is important to recognize that preterm born population´s growth tempo is slower (but not during the period of catch-up growth when the growth tempo is higher) and thus growth below median is a "physiological" variation of infants' intrauterine and early postnatal growth pattern, and not necessarily signaling pathology. Comparison between mean length of EPB children and Swedish reference (Paper III) or other full-term references is documented in Figure 8 (from full-term age to 2 years) and Figure 9 (from 2 years to 10 years). Being born before 26 weeks of gestation substantially lowers the height attained by 2 years' corrected age but the differences decrease up to the age of 10 years depending of the used reference, as documented in Table 11-12AB.



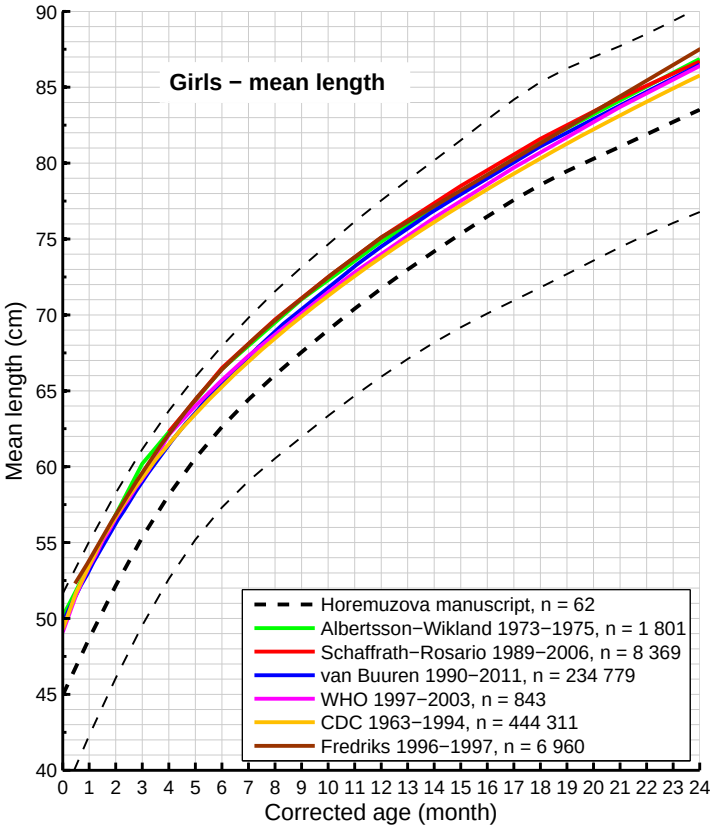
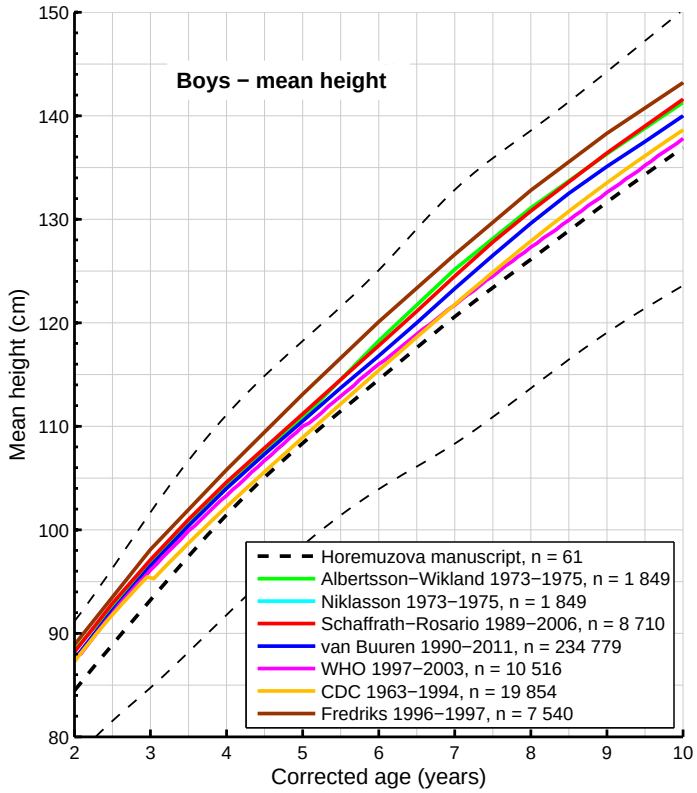


Figure 8. Comparison in postnatal growth between EPB infants (Horemuzova manuscript) and full-term references (Albertsson-Wikland 2002, Schaffrath-Rosario 2011, van Buuren 2012, WHO 2006, CDC 2000, Fredriks 2005) according to year of data collection. Length-for-age development (mean±2SD, black dashed lines,

Horemuzova) 2 years after full-term age in a cohort of EPB infants as compared to the mean of references. Boys up, girls down.
Inclusion criteria for the full term references were healthy infants, excluding those with chronic diseases, medications or conditions interfering with growth. They were born between 1963 and 2006 as compared to Horemuzovas' cohort that was born between 1990 and 2002.



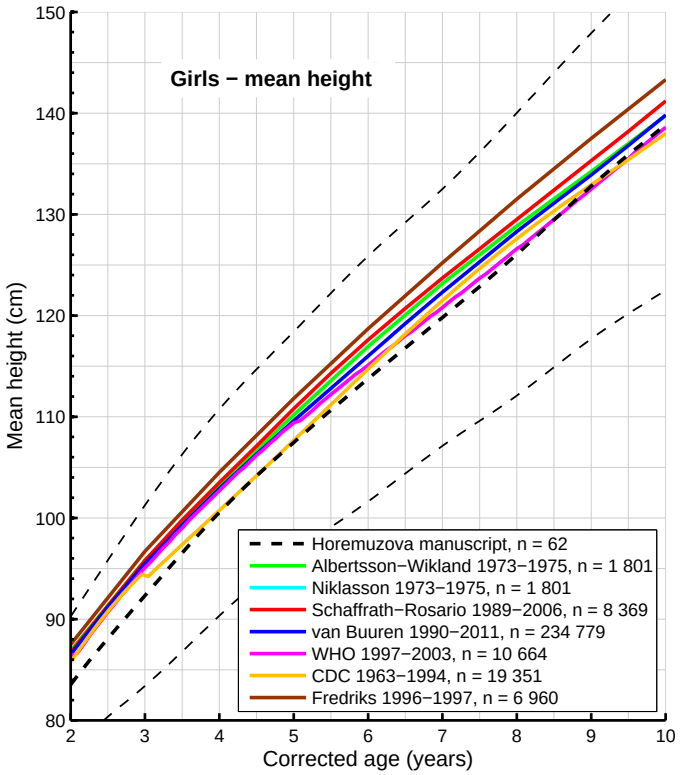


Figure 9. Comparison in postnatal growth between EPB infants (Horemuzova manuscript) and full-term references (Albertsson-Wikland 2002, Schaffrath-Rosario 2011, van Buuren 2012, WHO 2006, CDC 2000, Fredriks 2005) according to year of data collection. Length-for-age development (mean±2SD, black dashed lines, Horemuzova) from 2 years to 10 years after full-term age in a cohort of EPB infants as compared to the mean of references. Boys up, girls down.

The median growth of EPB differs from that of full-term children. Being born before 26 weeks of gestation substantially lowers the height attained by infants at 2 years corrected age but the relative differences are decreasing. On average, both EPB boys and girls are 2 years after full-term age significantly shorter compared to full-term references but the difference is decreasing from 5-7 cm in boys and 4-6 cm in girls at full-term age to 2.5-3.5 cm in boys and 2-3.5 cm in girls at one year and thereafter remains constant during the second year in both genders. The differences are presented in Table 11A and 11B for boys and girls separately. At 2 years, EPB boys are 3-4.5 cm shorter and EPB girls 2.0-4.0 cm shorter compared to the full-term references. In boys, length at +2 SD in EPB is similar to the mean of the full-term references until 5 months; thereafter, the +2 SD level clearly exceeds the references means. In girls, length at +2SD is slightly above the mean of the references and this difference after 5 months corrected age further increases with age. The differences between median length of EPB and full-term references expressed in SDS (Z-scores) are presented in Table 12A and 12B.

Table 11A: Difference in mean height (cm) in boys between full-term references, according to year of data collection, and Horemuzovas' EPB cohort

ΔHeight (cm)	Albertsson-Wikland 1973-1975		Niklasson 1973-1975	Schaffrath-Rosario 1989-2006	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997	Van Buuren 1990-2011
	Table 2	Table 3	Table 4					
Full-term age	+6.3	+6.2	+7.1	-	+5.4	+5.3	-	+6.2
1 year	+3.3	+3.4	+3.2	+3.7	+2.8	+2.6	+3.6	+3.2
2 years	+3.6	+3.9	+3.8	+3.7	+3.3	+2.8	+4.4	+3.1
5 years	+2.8	+2.4	-	+2.8	+1.6	+0.5	+4.7	+2.1
6 years	+3.2	+3.7	-	+3.3	+1.5	+0.9	+5.6	+2.3
7 years	+4.1	+4.6	-	+3.9	+1.1	+1.2	+6.0	+2.7
8 years	+4.5	+5.0	-	+4.7	+1.2	+1.8	+6.7	+3.5
9 years	+4.1	+4.7	-	+4.7	+0.9	+1.9	+6.6	+3.4
10 years	+4.4	+4.4	-	+4.7	+0.9	+1.7	+6.3	+3.1

Table 11B: Difference in mean height (cm) in girls between full-term references according to year of data collection and Horemuzovas' EPB cohort

ΔHeight (cm)	Albertsson-Wikland 1973-1975		Niklasson 1973-1975	Schaffrath-Rosario 1989-2006	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997	Van Buuren 1990-2011
	Table 2	Table 3	Table 4					
Full-term age	+5.1	+5.2	+5.8	-	+4.1	+4.7	-	+4.7
1 year	+3.0	+3.1	+3.0	+3.4	+2.3	+2.0	+3.4	+2.8
2 years	+3.6	+3.3	+3.7	+3.2	+2.9	+2.3	+4.0	+3.0
5 years	+2.2	+2.7	-	+3.3	+1.9	+0.2	+4.3	+2.1
6 years	+3.8	+3.2	-	+3.8	+1.3	+1.0	+5.0	+2.2
7 years	+4.1	+3.4	-	+3.9	+1.0	+1.7	+5.4	+2.5
8 years	+3.8	+2.8	-	+3.4	+0.5	+1.5	+5.4	+2.2
9 years	+2.4	+1.4	-	+2.5	-0.3	+0.1	+4.7	+1.1
10 years	+2.3	+0.9	-	+2.4	-0.2	-0.8	+4.5	+1.0

Table 12A: Z-score for mean height in boys in full-term references according to Horemuzovas' EPB cohort

Height (SDS)	Albertsson-Wikland 1973-1975		Niklasson 1973-1975	Schaffrath-Rosario 1989-2006	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997	Van Buuren 1990-2011
	Table 2	Table 3	Table 4					
Full-term age	+3.0	+3.0	+3.5	-	+2.6	+2.6	-	+3.0
1 year	+1.2	+1.2	+1.1	+1.3	+1.0	+0.9	+1.3	+1.2
2 years	+1.1	+1.2	+1.1	+1.1	+1.0	+0.8	+1.3	+0.9
5 years	+0.6	+0.5	-	+0.6	+0.3	+0.1	+1.0	+0.4
6 years	+0.6	+0.7	-	+0.6	+0.3	+0.2	+1.1	+0.4
7 years	+0.7	+0.7	-	+0.6	+0.2	+0.2	+1.0	+0.4
8 years	+0.7	+0.8	-	+0.8	+0.2	+0.3	+1.1	+0.6
9 years	+0.7	+0.7	-	+0.8	+0.2	+0.3	+1.1	+0.5
10 years	+0.7	+0.7	-	+0.7	+0.1	+0.3	+0.9	+0.5

Table 12B: Z-score for mean height in girls from full-term references according to Horemuzovas' EPB cohort

Height (SDS)	Albertsson-Wikland 1973-1975		Niklasson 1973-1975	Schaffrath-Rosario 1989-2006	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997	Van Buuren 1990-2011
	Table 2	Table 3	Table 4					
Full-term age	+1.5	+1.5	+1.7	-	+1.2	+1.3	-	+1.4
1 year	+1.0	+1.1	+1.0	+1.2	+0.8	+0.7	+1.2	+1.0
2 years	+1.1	+1.0	+1.1	+0.9	+0.8	+0.7	+1.2	+0.9
5 years	+0.6	+0.5	-	+0.6	+0.3	0	+0.8	+0.4
6 years	+0.6	+0.5	-	+0.6	+0.2	+0.2	+0.8	+0.4
7 years	+0.6	+0.5	-	+0.6	+0.2	+0.3	+0.8	+0.4
8 years	+0.5	+0.4	-	+0.5	+0.1	+0.2	+0.8	+0.3
9 years	+0.3	+0.2	-	+0.3	0	0	+0.6	+0.1
10 years	+0.3	+0.1	-	+0.3	0	-0.1	+0.5	+0.1

A Dutch growth study of EPB infants was published in 2012. In that study 1690 preterm children with GA of 25 to 36 weeks were compared with 634 full-term children. The median growth of early (GA<32 weeks) and moderately preterm (GA 32-36 weeks) children differed from that of full-term children. Being born before 37 weeks gestation substantially lowered the height, weight and HC attained by a child at age 4 years; the lower the GA, the lower was the median value (Bocca-Tjeertes 2012). Similar finding were reported from a hospital-based cohort from Prague (Kytnarova 2010). Interestingly, the variability was greater in boys than in girls, particularly for the lower GAs, which contrasts to our findings (Paper III, IV).

Referrals based on a fixed centile or SD curve in this population might lead to unnecessary medical attention in contrast to referrals based on clinical judgment. It is unknown how many of these referrals actually would have a diagnostic accuracy of detecting growth pathology, or how many of those having been detected with growth pathology is being identified by the applied criteria (van Dommelen and van Buuren 2013).

6.6 SHORTEST PARENTS' Z-SCORE FOR HEIGHT MIGHT BE PREDICTIVE OF INFANTS' GROWTH PATTERN

A combination of "short for target height", "very short" and "height deflection" rules are the most sensitive for detecting growth disorder in children between 3 and 10 years of age (Grote 2008, van Dommelen 2013) with the highest influence of "short for target height" (Grote 2008).

Mid-parental target height (MPH) is not a method for predicting adult height but is necessary to assess whether the child's height is lower than expected for its genetic

potential. However, the genes do not follow arithmetical law of mean value between parental genes and childs' growth most often mimics the growth pattern of one of the parents, mothers' or fathers'. Mothers height is associated with the child's (target) height and short mothers (below -1SD) are more likely to have short children (Bocca Tjeertes 2011) in a general population (Luo 1998) but short fathers can have short children too. Powls in 1996 reported that mothers of preterm born/SGA children were shorter than mothers of full-term controls indicating an impact of fetal programming between generations. In this study children's height Z scores (-0.48) were lower than those of their fathers (-0.27) but similar to those of their mothers (-0.57) in contrast to infants with normal BWs whose height Z scores were higher (+0.11) than those of either their mothers (-0.22) or fathers (-0.20).

In the EPB cohort (Paper III) we used Z-score for MPH as a measure of children's genetic potential for height, based on measured parental heights. At birth there was only a minimal difference between Z-score for length and MPH (0.2/0.0 in boys/girls respectively), in contrast to the difference at full-term age (-3.5/-3.0). Thereafter, at 1, 2 and 10 years this difference decreased to -0.9/ -1.1, -0.9/ -0.9 and -0.3/ -0.3, in boys and girls respectively.

6.7 GROWTH PROPORTIONS IN WEIGHT AND HEIGHT

It is often of interest to identify individuals whose anthropometric measurements are not in proportion to each other, as height in relation to weight, since persistence of the infant body proportions to childhood might signal impaired metabolism and/or growth pathology caused by growth hormone deficiency.

A significant catch-up (CU) growth in EPB children occurred for both weight and height already during the first year after full-term age with the most rapid tempo observed during the first 3 months. The CU growth was followed by growth plateau during the second year of life (Paper IV) that continued in boys to 10 years but in girls only to 7 years; thereafter the girls' growth tempo for height increased (Table 11-12AB). During the period from 1 to 10 years growth in weight was more pronounced compared to height in both genders. The leanness of the EPB population decreased from 1 year to 10 years indicating that at 10 years this cohort was clearly more "round" as compared to infancy period (Paper IV). More pronounced weight gain compared to height development following the 2 years after full-term age was also described by Kytnarova 2011, and the Swedish national historical cohort born 1990-1992 (Farooqi 2006) at 11 years of age was relatively heavy, with mean Z-score in BMI +0.30 compared to Z-score of -1 at full-term age.

Associations between weight gain in infancy and the truncal to peripheral fat distribution in adulthood was described in the POPS-19 collaborative study (Euser 2005) with 403 participants (45% men) born before 32 weeks of gestation. The ratio of subscapular-to-triceps-skinfold thickness was calculated as an index of truncal to peripheral adiposity. The periods three months after birth and from three months to one year were studied. Greater weight gain during these periods was associated with greater height, weight, BMI and a higher percentage of body fat at 19 years of age but BW

SDS was not associated with higher adult waist circumference and fat mass when adjusted for current height SDS (Euser 2005).

Differences in weight development between published growth references and EPB infants in the present study are presented in Table 13-14AB. There is a relatively constant weight difference between EPBs and the references, from full-term age to 5 years; the highest difference seen in Swedish and Dutch cohorts (minus 1-2 kg) compared to WHO and CDC references. Interestingly 7 years after full-term age, EPBs have similar weight as CDC reference and the WHO highly selected group of healthy infants, but continue to be lighter (minus 1.5-2 kg) compared to the Swedish and Dutch cohorts. However, at 10 years EPB boys are heavier by +0.7 kg compared to CDC, +0.2 kg for WHO references but still lighter by -1.2 kg and -1.9 kg for Swedish and Dutch reference, respectively. Situation in EPB girls is +0.2 kg for CDC, +1.1 kg for WHO but -0.2 and -1.4 kg for Swedish and Dutch references.

Table 13A: Difference in mean weight (kg) in boys between full-term references according to year of data collection and Horemuzovas' EPB cohort

ΔWeight (kg)	Albertsson-Wikland 1973-1975	Niklasson 1973-1975	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997
Full-term age	+1.2	+1.3	+0.9	+1.1	+0.9
1 year	+1.9	+1.7	+0.9	+1.6	+0.8
2 years	+2.2	+2.1	+0.9	+1.3	+1.0
5 years	+1.4	-	+0.7	+0.2	+1.0
6 years	+1.6	-	+0.2	+0.3	+1.5
7 years	+1.6	-	0	+0.2	+1.8
8 years	+1.9	-	-0.2	+0.1	+2.2
9 years	+1.1	-	-1.1	-0.6	+1.8
10 years	+1.2	-	-0.2	-0.7	+1.9

Table 13B: Difference in mean weight (kg) in girls between full-term references according to year of data collection and Horemuzovas' EPB cohort

ΔWeight (kg)	Albertsson-Wikland 1973-1975	Niklasson 1973-1975	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997
Full-term age	+0.9	+1.1	+0.7	+0.9	+0.8
1 year	+1.7	+1.5	+0.7	+1.3	+1.2
2 years	+2.1	+1.9	+0.7	+1.2	+1.5
5 years	+1.7	-	+0.7	+0.4	+1.7
6 years	+2.0	-	+0.5	+0.5	+2.1
7 years	+2.2	-	+0.3	+0.7	+2.6
8 years	+1.8	-	-0.4	+0.2	+2.4
9 years	+0.9	-	-1.1	-0.3	+1.7

10 years	+0.2	-	-1.1	-0.2	+1.4

Table 14A: Z-score for mean weight in boys in full-term references according to Horemuzovas' EPB cohort

ΔWeight (SDS)	Albertsson-Wikland 1973-1975	Niklasson 1973-1975	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997
Full-term age	+3.3	+3.6	+2.5	+3.1	+2.0
1 year	+1.6	+1.5	+0.8	+1.3	+0.7
2 years	+1.4	+1.4	+0.6	+0.9	+0.6
5 years	+0.5	-	0	+0.1	+0.3
6 years	+0.5	-	0	+0.1	+0.4
7 years	+0.4	-	0	0	+0.4
8 years	+0.4	-	0	0	+0.4
9 years	+0.2	-	-0.2	-0.1	+0.3
10 years	+0.2	-	-0.2	-0.1	+0.3

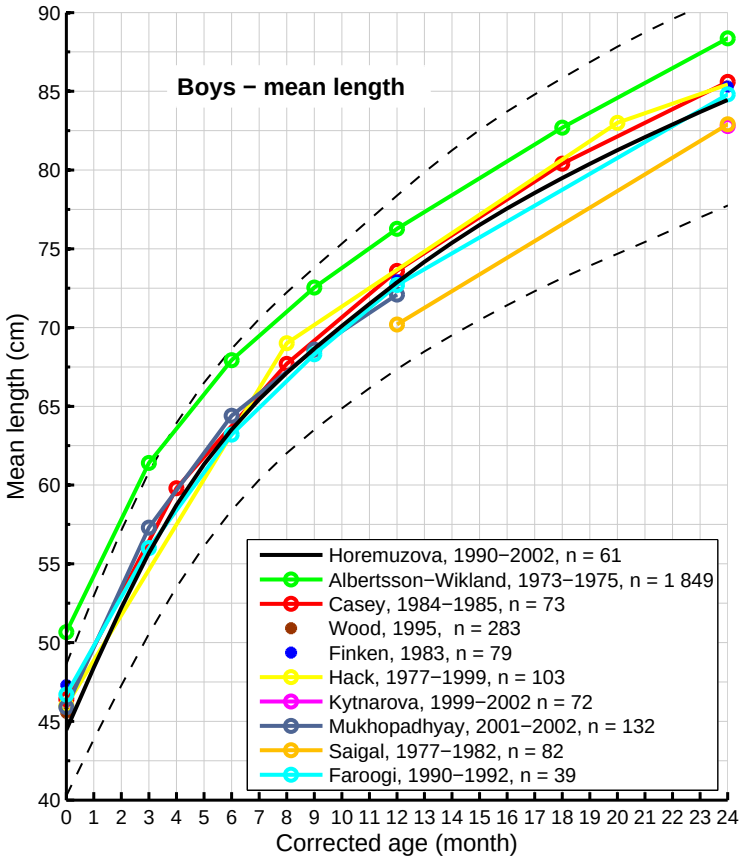
Table 14B: Z-score for mean weight in girls in full-term references according to Horemuzovas' EPB cohort

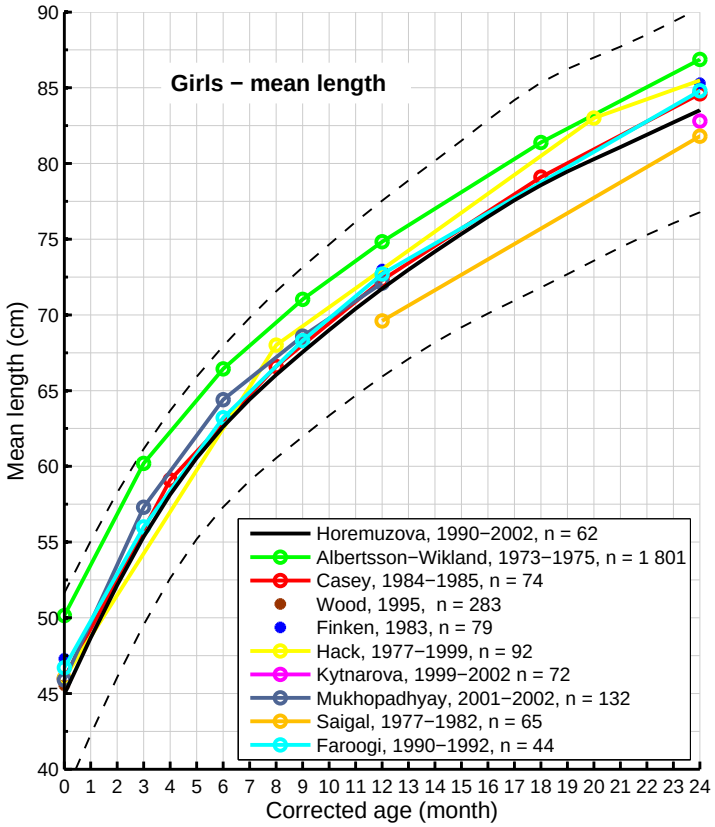
ΔWeight (SDS)	Albertsson-Wikland 1973-1975	Niklasson 1973-1975	WHO 1997-2003	CDC 1963-1994	Fredriks 1996-1997
Full-term age	+1.7	+1.9	+1.3	+1.6	+1.4
1 year	+1.4	+1.3	+0.6	+1.1	+1.1
2 years	+1.4	+1.3	+0.4	+0.8	+1.0
5 years	+0.6	-	+0.2	+0.1	+0.5
6 years	+0.5	-	+0.1	+0.1	+0.6
7 years	+0.5	-	+0.1	+0.2	+0.6
8 years	+0.3	-	-0.1	0	+0.5
9 years	+0.1	-	-0.2	0	+0.2
10 years	0	-	-0.1	0	+0.2

6.8 COMPARISON OF POSTNATAL GROWTH BETWEEN DIFFERENT PRETERM BORN/VLBW COHORTS

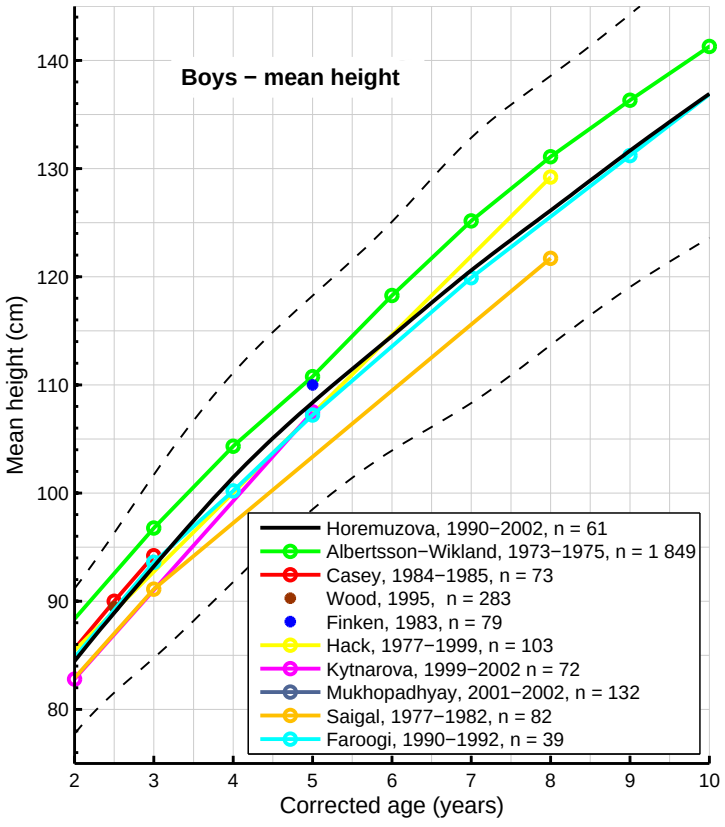
Fair comparison of length between our EPB cohort (Paper I, III, IV) and other published preterm born/VLBW cohorts have several limitations. The inclusion criteria of the historical populations are mostly based on BW rather than GA and thereby resulting in inclusion of probably more growth-restricted but biologically older children who might have a different growth pattern compared to EPB children. These populations are mostly hospital-based cohorts born from 1977 to 2002 presented without neurosensory impairment data; growth assessment covers different age periods and is often presented by sparse measurements on weight, height and HC during infancy and childhood. Comparison in Ht between EPB children from this study, Swedish full-term reference (Paper III) and the other references is documented in the Figure 10A (from full-term age to 2 years) and Figure 10B (from 2 years to 10 years), the differences are presented in detail in Tables 15-16AB. The average Ht of EPB children does not substantially differ from that of other preterm/VLBW surveys. However, being born before 26 weeks of gestation slightly lower the height attained at full-term age and at 1 and 2 years corrected age.

10A




Girls − mean length
Mean length (cm)
Corrected age (month)
Horemuzova, 1990−2002, n = 62
Albertsson−Wikland, 1973−1975, n = 1 801
Casey, 1984−1985, n = 74
Wood, 1995, n = 283
Finken, 1983, n = 79
Hack, 1977−1999, n = 92
Kytnarova, 1999−2002 n = 72
Mukhopadhyay, 2001−2002, n = 132
Saigal, 1977−1982, n = 65
Faroogi, 1990−1992, n = 44

10B


Boys − mean height
Mean height (cm)
Corrected age (years)
Horemuzova, 1990−2002, n = 61
Albertsson−Wikland, 1973−1975, n = 1 849
Casey, 1984−1985, n = 73
Wood, 1995, n = 283
Finken, 1983, n = 79
Hack, 1977−1999, n = 103
Kytnarova, 1999−2002 n = 72
Mukhopadhyay, 2001−2002, n = 132
Saigal, 1977−1982, n = 82
Faroogi, 1990−1992, n = 39

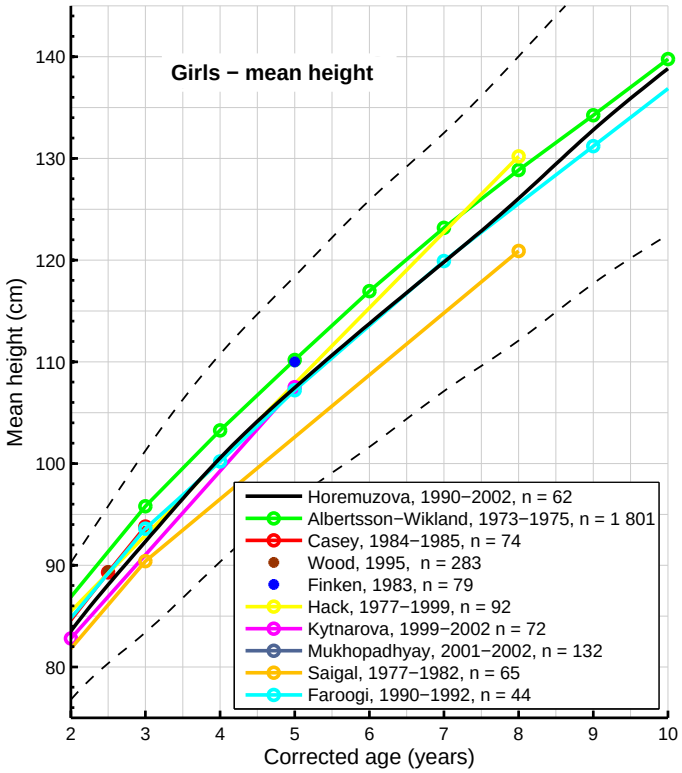


Figure 10. Comparison in length-for-age between EPB infants (Horemuzova manuscript, mean±2SD, black dashed lines) and published preterm born (PB)/ VLBW cohorts (Cassey, Wood, Finken, Hack, Kytnarova, Mukhopadhyay, Saigal, Farooqi) and the full-term reference (Albertsson-Wikland 2002, light green line) according to year of data collection (**A**) 2 years after full-term age (**B**) from 2 to 10 years. Preterm /VLBW cohorts were born between 1977 and 2002 as compared to Horemuzovas' cohort born between 1990 and 2002 and full-term cohort in 1973-1975.
Boys up, girls down. Dots represent time-point for available length in cm (Cassey, Hack, Farooqi, Kytnarova) and are calculated from available SDS-values (Wood, Finken, Mukhopadhyay). The gender-adjusted length is published in all presented surveys except for Finken, Mukhopadhyay and Kytnarova.

Table 15A: Difference in mean height (cm) in boys between preterm/VLBW surveys and Horemuzovas' EPB cohort

ΔHeight (cm)	Cassey 1984-1985	Wood 1995	Finken 1983	Hack 1977-1983	Kytnarova 1999-2002	Mukhopadhyay 2001-2002	Saigal 1977-1982	Farooqi 1990-1992
Full-term age	+1.9	+1.1	+2.8	+1.6	-	+1.4	-	+2.2
1 year	+0.7	-	+0.1	-	-	-0.8	-2.7	-0.2
2 years	+1.1	-	+0.8	-	-1.6	-	-1.6	+0.3
2.5 years	-	+0.6	-		-	-		
5 years	-	-	+1.6	-	-0.9	-	-	-1.2
8 years	-	-	-	+3.1	-	-	-4.4	
9 years	-	-	-	-	-	-		-0.4

Table 15B: Difference in mean height (cm) in girls between preterm/VLBW surveys and Horemuzovas' EPB cohort

ΔHeight (cm)	Cassey 1984-1985	Wood 1995	Finken 1983	Hack 1977-1983	Kytnarova 1999-2002	Mukhopadhyay 2001-2002	Saigal 1977-1982	Farooqi 1990-1992
Full-term age	+1.1	+0.6	+2.3	+1.1	-	+1.0	-	+1.8
1 year	+0.6	-	+1.3	-	-	+0.4	-2.1	+1.0
2 years	+1.1	-	+1.8	-	-0.7	-	-1.7	+1.3
2.5 years	-	+1.4	-		-	-	-	-
5 years	-	-	+2.5	-	0	-	-	-0.3
8 years	-	-	-	+4.1	-	-	-5.2	-
9 years	-	-	-	-	-	-	-	-1.6

Table 16A. Z-score for mean height in boys from preterm/VLBW surveys according to Horemuzovas' EPB cohort

Height (SDS)	Cassey 1984-1985	Wood 1995	Finken 1983	Hack 1977-1983	Kytnarova 1999-2002	Mukhopadhyay 2001-2002	Saigal 1977-1982	Farooqi 1990-1992
Full-term age	+0.9	+0.5	+1.4	+0.7	-	+0.7	-	+1.1
1 year	+0.3	-	0	-	-	-0.3	-1.0	-0.1
2 years	+0.3	-	+0.2	-	-0.5	-	-0.5	+0.1
2.5 years	-	+0.1	-		-	-		
5 years	-	-	+0.3	-	-0.2	-	-	-0.2
8 years	-	-	-	+0.5	-	-	-0.7	
9 years	-	-	-	-	-	-	-	-0.1

Table 16B: Z-score for mean height in girls from preterm/VLBW surveys according to Horemuzovas' EPB cohort

Height SDS	Cassey 1984-1985	Wood 1995	Finken 1983	Hack 1977-1983	Kytnarova 1999-2002	Mukhopadhyay 2001-2002	Saigal 1977-1982	Farooqi 1990-1992
Full-term age	+0.3	+0.2	+0.7	+0.3	-	+0.3	-	+0.5
1 year	+0.2	-	+0.4	-	-	+0.1	-0.7	+0.3
2 years	+0.3	-	+0.5	-	-0.2	-	-0.5	+0.4
2.5 years	-	+0.4	-		-	-		
5 years	-	-	+0.5	-	0	-	-	0
8 years	-	-	-	+0.6	-	-	-0.7	
9 years	-			-	-	-	-	-0.2

6.9 LONG-TERM SEQUELAE AFTER BEING BORN EXTREMELY PRETERM

Although the majority of EPB children today escape gross disabilities, there is still significantly increased prevalence of multiple disabilities and functional limitations in motor, communicative, learning and behavioural skills compared to term born population, despite the presence of normal neonatal brain ultrasound scans (Msall 2000, Saigal 2003, Hack 2005, Delobel-Ayoub 2009). Thus, longitudinal monitoring of neurological development is necessary for all infants being born extremely preterm. Although functional disabilities are quite common, the growth of EPB infants might be well-preserved, as documented by similar mean weight, height and HC at birth, full-term, 1, 2 and 10 years between infants with and without significant morbidity (Paper III). However, boys with significant sequelae were shorter at 10 years (-4.5 cm) and had smaller head size at follow-up during childhood (-1.3 cm) compared to those without sequelae; while in girls no difference was observed in height but larger head size by +1.3 cm in 10 girls with sequelae compared to 23 girls without sequelae (Paper II, III).

It is possible that a high grade of morbidity early in life results in insufficient brain and retina development that is followed by neurological/visual functional deficits. EPB infants with severe ROP had smaller head size at one year of age compared to children with milder forms of ROP or without sequelae (Paper III). Although the treatment for ROP has long been in focus, all treatment options are in fact destructing the avascular retina (Jacobson 2009) and are a balance between preserving the visual acuity on the expense of visual field defects. Population-based studies of preterm-bon children with follow-up up to 10 years of age have shown subnormal visual acuity, visual field defects, an increase of myopia and strabismus and visual perceptual deficiencies that used to contribute to significant difficulties in everyday life and therefore long-term ophthalmological follow-up is warranted (Holmström and Larsson 2008, Jacobson 2006, Jacobson 2009). In general, boys seem to be more vulnerable to pre- and perinatal insults compared to girls as documented by higher mortality rate after birth, lower body weight at full-term age, higher frequency of severe ROP development and visual impairment (Paper I, II).

Although follow-up rate was high (Paper I- IV), we still cannot exclude the possibility of higher rates of significant long-term sequelae in non-participants suggested by the presence of severe perinatal insults and parent information of significant motor, cognitive and/or social difficulties in their children leading to parental decision of non-participation in these studies. Many parents of EPB children expressed they were abandoned with their child's health problems, after the difficult start in life, due to a limited follow-up by specialists after discharge from NICU.

7 SUMMARY AND CONCLUSIONS

7.1 SUMMARY

Prospective monitoring of growth and morbidity in extremely preterm born survivors should be a clinical routine in any health care system. In order to reliably capture growth patterns in extreme preterm born survivors, comprehensive growth data based on frequent measurements, including head circumference, until final height are needed. Growth charts for this population should be created on a national or international basis to increase the sample size in age category. Gender-neutral curves are an option as extrauterine growth in weight, height and head circumference are rather similar during prepubertal years in boys and girls born extremely preterm. Regular follow up by pediatric ophthalmologist, pediatric neurologist and pediatrician is warranted although most of these children escape from significant or severe disabilities and growth disorders. Children with mild disabilities can be offered support from school services when needed. Inclusion of growth data from child health records and school health services improves the quality of obtained data and gives more objective, accurate and cost-effective measurements than what can be obtained in any other study setting.

7.2 CONCLUSIONS

Paper I

1. Extremely preterm infants show a postnatal continuous growth restriction in weight, length and head circumference as compared to birth size references.
2. Neither the birth-size derived growth curves nor the presented charts should be used as a single prescriptive standard to evaluate extra uterine growth in extreme preterm born children. Using these two references in combination can help neonatologists to directly compare the growth of an individual infant with the intrauterine norms and with the growth pattern in the 1990-2002, references probably representing two extreme ends of the scale.
3. The presented postnatal growth data elucidates growth patterns in infants born from 1990 to 2002, and can be used to investigate whether infants born in e.g. 2002-2012 grow better.

Paper II

All children, especially boys, born at the limit of viability, are at high risk for visual impairment, often in combination with additional functional deficits, as a consequence of brain dysfunction. Rehabilitation of these children with multiple disabilities is a challenge. Improved preventive measures are urgently needed.

Paper III

1. Both boys and girls who are born extremely preterm had by 10 years of age reached normal or near-normal height and weight and were close to their midparental height.
2. Boys seem to be more vulnerable to perinatal insults.
3. The most challenging is growth between preterm birth and full-term age, a critical time for the development of central nervous system.

Paper IV

1. Extremely preterm born infants reach by 10 years of age normal or near normal height independently of the tempo of initial catch-up growth.
2. A lean body constitution at full-term age changed to BMI increase after 2 years and thus an increased weight for height development at 10 years.
3. Being heavier and taller at 2 years, after rapid initial catch-up growth, leads probably to a disadvantageous metabolic constitution in high-food exposition environment and may be a risk factor with negative metabolic consequences.

8 FUTURE PERSPECTIVES

Growth charts for extremely preterm born infants from birth to discharge from NICU should describe – and not prescribe- the infants' growth, as 'healthy' extremely preterm born infants can hardly be defined or found.

Although the number of survivors with extreme prematurity is increasing, the number of infants at each neonatal center is a too small to allow for development of local growth references. Multicenter, national and international studies to further describe the growth pattern in this population are needed.

The presented postnatal growth data, describing growth pattern in extremely preterm born infants during 1990-2002, can serve as a comparison database to investigate whether growth patterns in preterm infants during e.g. 2002-2012 show improvements.

The cohort described in the present study can be used to various long-term follow-up studies, including

1. Assessment of growth after age10 years, timing of puberty and characteristics of pubertal growth spurt, morbidity and metabolic characteristics during adolescence and adulthood and impact of catch-up growth on various metabolic outcomes.
2. Evaluation of prevalence, characteristics and natural course of long-term morbidities, including retinopathy of prematurity.
3. Analyzing whether long-term outcomes can be predicted by patterns of early growth.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: Under senare år har överlevnaden för barn som föds mycket för tidigt (här definierat som före fullbordade 26 graviditetsveckor) dramatiskt förbättrats men majoriteten av barnen har minst en svår medicinsk komplikation (svår lungsjukdom, hjärnblödning eller ögonskada) som kan påverka den framtida utvecklingen. Bestående funktionshinder är förhållandevis ovanliga medan kognitiva problem och perceptionsstörningar som påverkar barnets framtida liv är vanliga hos extremt för tidigt födda barn. Ur somatiskt tillväxtperspektiv, kvarstår sannolikt delvis en fosterrelaterad tillväxtfysiologi även postnatalt, dvs. regleringen av den postnatala tillväxten kan styras av fetala mekanismer under tiden fram till motsvarande fullgångenhet. Detta kan öka sannolikheten för att händelserna under den initiala postnatala perioden ger en prägling av ämnesomsättning samt av tillväxtpotentialen. Att vara lättare och kortare jämfört med barn som föds i fullgången tid, skapar incitament för intensifierad nutritionstillförsel för att främja tillväxten. Orsaken till det är användning av födelsestorlekstillväxtkurvor för bedömning av postnatal tillväxt hos extremt för tidigt födda barn. Tillväxten efter ålder motsvarande fullgången tid, bedöms med hjälp av tillväxtkurva avsedd för fullgångna barn eftersom specifik tillväxtreferens för barn födda för tidigt saknas.

Avhandlingens syfte är att beskriva tillväxt och sjuklighet hos extremt för tidigt födda barn från födelsen till 10 års ålder. Barnen är födda 1990-2002 och vårdade vid neonatalintensivvårdsavdelningarna på Karolinska Universitetssjukhuset i Stockholm och/ eller Sahlgrenska sjukhuset i Göteborg. Den beskrivna tillväxten skall inte användas som rekommenderad tillväxt utan som en bas för jämförelse med tillväxten för framtida grupper av barn vårdade med moderniserade metoder.

I **arbete I** samlade vi data på 162 barn, födda före 26:e graviditetsveckan och förutom sjuklighet studerade vi utvecklingen av kroppsvikt, längd och huvudomfång från födelsen till ålder motsvarande fullgången tid och jämförde med svensk födelsestorleksreferens. Vi fann att en uttalad tillväxthämning för vikt, längd och huvudomfång utvecklades hos majoriteten av barnen. Vid utskrivningen från neonatalintensivvårdsavdelningen var 75 % av barnen med normal kroppsstorlek vid födelsen betydligt kortare, lättare eller hade betydligt mindre huvudomfång jämfört med referensen. Tillväxten hos barn efter en extremt för tidig födelse är annorlunda än tillväxten som predikteras av den ”ideala” intrauterina referensen och därför är denna referens inte lämplig att använda för tillväxtuppföljning av dessa barn.

I **arbete II** samlade vi data för 114 barn, födda före 25:e graviditetsveckan, och som följdes av ögonläkare för en vanlig komplikation av för tidig födsel, prematuritetsretinopati (ROP), på Karolinska och Sahlgrenska sjukhuset. Vi studerade förekomst av ROP och synfunktion hos pojkar och flickor separat. Vi fann att nästan alla barn (97%) utvecklade ROP; 75 % av barnen utvecklade svår ROP (grad≥3) och ofta i kombination med andra funktionsnedsättningar som kan vara orsakade av skador i hjärnan (sammanhängande med periventrikulär leukomalaci). Normal synfunktion kunde finnas hos hälften av alla barn, mer vanligt hos flickor medan grav synnedsättning förekom oftare hos pojkar.

I **arbete III**, samlade vi data på 123 barn födda före 26:e graviditetsveckan och studerade deras sjuklighet och tillväxt i vikt, längd och huvudomfång från födelsen till 10 års ålder och jämförde tillväxtmönstret med svensk tillväxtreferens baserat på födelse vid fullgången tid. Vi fann att vid födelsen alla barn hade normal kroppsstorlek för sin graviditetslängd. Efter en grav tillväxthämning från födelsen till ålder motsvarande fullgången tid följde en uttalad kompensatorisk ökning av tillväxttakten för vikt och längd. Vid 10 års ålder hade barnen vuxit till sina genetiska förutsättningar men 48 % av pojkarna och 34 % av flickorna hade betydande sjuklighet.

I **arbete IV**, studerade vi närmare den kompensatoriskt ökade tillväxttakten i vikt och längd hos barnen, beskrivna i arbete III, och dess betydelse för den uppnådda tillväxten under senare barndom. Vi fann att den mest uttalade tillväxtökningen i både vikt och längd hade skett första året efter fullgången tid, med den mest intensiva tillväxtperioden de första tre månaderna. Den intensiva tillväxten under första året följdes av en tillväxt-platå mellan ett och två års ålder men med mer uttalad vikt- än längdutveckling, vilket mönster fortsatte till 10 års ålder. Barnen med den mest uttalade kompensatoriska tillväxten 3 månader efter fullgången tid var längre och vägde mer vid 1 år och 2 års ålder men de var inte längre vid 10 års ålder jämfört med barnen med långsammare tillväxttakt under samma period.

Slutsatser i avhandlingen är att mycket för tidigt födda barn har annorlunda tillväxtmönster jämfört med födelsestorleksreferensen och därför skall denna referens inte tillämpas för deras tillväxtuppföljning. Varken födelsestorleksreferens eller de presenterade tillväxtkurvorna bör användas som en normativ standard för tillväxtuppföljning av extremt för tidigt födda barn. En kombination av de två tillväxtkurvorna kan vara till hjälp; d.v.s. man kan jämföra det individuella barnets tillväxt både med födelsestorleksreferensen och med den beskrivna barnpopulationen född under perioden 1990-2002.

Vid 10 års ålder har de flesta barn uppnått sin genetiska tillväxtpotential. Extremt för tidigt födda barn, särskilt pojkar, har högre risk för utveckling av synskada och andra bestående funktionshinder och därför bör noggrann uppföljning och habilitering av alla dessa barn prioriteras. Den mest utmanande perioden är den mellan födelsen och fullgången tid, sannolikt ett kritiskt fönster för utvecklingen av centrala nervsystemet.

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