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THE ASSOCIATION BETWEEN GROWTH AND NEURODEVELOPMENT IN VERY PRETERM INFANTS –

A Follow-up Study in the PIPARI Study

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Kaunis pieni ihminen,
sä olet ainutlaatuinen.
Mitä vastaan tuleekaan,
toista sua ei milloinkaan.

-Johanna Kurkela-

To small newborn infants

ABSTRACT

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The Association between Growth and Neurodevelopment in Very Preterm Infants – A Follow-up Study in the PIPARI Study

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Placental insufficiency is one major cause of intrauterine growth restriction and also relates to neurodevelopment. Preterm infants with very low birth weight are at risk of postnatal growth restriction as well as neurodevelopmental impairments. However, the optimal postnatal growth for long-term neurodevelopment is still unclear.

The objective of this study was thus to investigate the association between growth and neurodevelopment in very preterm infants. The study populations consisted of 83 (I), 55 (II), 36 (III) and 181 (IV) infants with very low birth weight (below 1501 grams), and very or extremely low gestational age (below 32 and 26 weeks). Foetal blood circulation in relation to two-year neurodevelopment and the association between early growth and brain maturation at term age were studied. Postnatal growth, and its association with five-year cognitive outcome, was analysed.

Changes in foetal blood circulation related to placental insufficiency associated with an adverse two-year cognitive outcome. Early postnatal growth in extremely preterm infants was comparable to a similar Swedish cohort. Preterm infants with slow intrauterine growth had less mature brains at term age; rapid catch-up growth until term age did not eliminate this difference. Weight gain and head circumference growth from birth until two years of age associated positively with five-year cognitive outcome in appropriate for gestational age infants. In small for gestational age infants, head circumference growth from term age to four months (corrected age) associated positively with their five-year cognitive outcome.

The association between postnatal growth and neurodevelopment was different for prenatally normally grown versus slow grown preterm infants.

Key words: antenatal Doppler; brain white matter maturation; cognition; diffusion tensor imaging; extreme preterm infants; growth; neurodevelopment; premature infant; small for gestational age; very preterm infant; very low birth weight.

TIIVISTELMÄ

Marika Leppänen

Pikkukeskosen kasvun ja neurologisen kehityksen välinen yhteys – PIPARI-projektin seurantatutkimus

Lastentautioppi ja kansanterveystiede, Turun yliopisto; Turun yliopistollinen sairaala

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Istukan vajaatoiminta on yksi merkittävä syy sikiöajan kasvuhäiriölle ja on yhteydessä myös neurologiseen kehitykseen. Hyvin pienipainoisten keskosten syntymänjälkeinen kasvu ja myös neurologinen kehitys ovat riskissä häiriintymiselle. On vielä epäselvää minkälainen syntymänjälkeinen kasvu on optimaalinen neurologisen pitkäaikaisennusteen kannalta.

Tämän tutkimuksen tavoitteena oli tutkia pikkukeskosen kasvun yhteyttä neurologiseen kehitykseen. Tutkimusryhmät koostuivat 83 (I), 55 (II), 36 (III), 181 (IV) hyvin pienipainoisista (syntymäpaino alle 1501 grammaa) sekä hyvin ja erittäin ennenaikaisista keskosista (raskausviikot alle 32 ja 26). Työssä tutkittiin sikiön verenkierron yhteyttä neurologiseen kehitykseen kahden vuoden iässä sekä varhaisen kasvun ja lasketun iän aivojen kypsyyden välistä yhteyttä. Syntymänjälkeistä kasvua tutkittiin ja selvitettiin sen yhteyttä älylliseen tasoon viiden vuoden iässä.

Istukan vajaatoimintaan liittyvät sikiön verenkierron muutokset olivat yhteydessä huonompaan älylliseen tasoon kahden vuoden iässä. Erittäin ennenaikaisesti syntyneiden keskosten kasvu oli yhtenevä ruotsalaisen aineiston kanssa. Keskosilla, joilla sikiöaikainen kasvu oli ollut hidasta, oli aivojen kypsyminen jäljessä lasketussa iässä. Nopea kiinniottokasvu laskettuun aikaan mennessä ei korjannut tätä eroa. Raskausviikkoihin nähden normaalikokoisilla keskosilla syntymänjälkeinen kasvu kahteen ikävuoteen saakka oli positiivisessa yhteydessä älylliseen tasoon viiden vuoden iässä. Raskausviikkoihin nähden pienikokoisilla keskosilla ainoastaan pään kasvu lasketusta iästä neljän kuukauden (korjattuun) ikään saakka oli positiivisesti yhteydessä älylliseen tasoon viiden vuoden iässä.

Syntymänjälkeisen kasvun ja neurologisen kehityksen välinen yhteys oli erilainen sikiöaikana normaalisti kasvaneiden ja hitaasti kasvaneiden keskoslasten välillä.

Avainsanat: aivojen valkean aineen kypsyminen, diffuusiotensorikuvaus; erittäin pienipainoinen, erittäin ennenaikainen, hyvin pienipainoinen, kasvu, keskonen, kognitio, neurologinen kehitys, raskaudenaikaiset virtausmittaukset, syntymäviikkoihin nähden pienipainoinen

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ABBREVIATIONS

AD	Axial Diffusivity
AGA	Appropriate for Gestational Age
AREDF	Absent or Reversed End Diastolic Net Blood Flow
BPD	Bronchopulmonary Dysplasia
BW	Birth Weight
BSID-II	Bayley Scales of Infant Development, 2nd edition
CA	Corrected Age
CI	Confidence Interval
CLD	Chronic Lung Disease
CP	Cerebral Palsy
d	Day
D	Glass' Delta
DAo	Descending Aorta
DTI	Diffusion Tensor Imaging
ELBW	Extremely Low Birth Weight
ELGA	Extremely Low Gestational Age
EUGR	Extrauterine Growth Restriction
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FA	Fractional Anisotrophy
FLAIR	Fluid-Attenuated Inversion Recovery
FSIQ	Full-Scale Intelligent Quotient
FSL	Functional MRI of Brain Software Library
FTT	Failure-To-Thrive
GA	Gestational Age
GW	Gestational Weeks
HC	Head Circumference
HINE	Hammersmith Infant Neurological Examination
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
IVH	Intraventricular Hemorrhage
IQ	Intelligence Quotient
L	Length
LBW	Low Birth Weight
MCA	Middle Cerebral Artery
MD	Mean Diffusivity

MDI	Mental Developmental Index
Mhz	Megahertz
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NEC	Necrotizing Enterocolitis
NDI	Neurodevelopmental Index
NICU	Neonatal Intensive Care Unit
PI	Pulsatility Index
PDA	Patent Ductus Arteriosus
PIPARI	PieniPAinoisten RIskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään
RD	Radial Diffusivity
ROI	Region of Interest
PVL	Periventricular Leucomalasia
r	Spearman Correlation Coefficient
SD	Standard Deviation
SE	Standard Error
SGA	Small for Gestational Age
T	Tesla
TBSS	Tract Based Spatial Statistics
T1	Spin-Lattice (Longitudinal Relaxation Time)
T2	Spin-Spin (Transverse) Relaxation Time
UA	Umbilical Artery
US	Ultrasound
UV	Umbilical Vein
VLBW	Very Low Birth Weight
VLGA	Very Low Gestational Age
VON	Vermont Oxford Network
W	Weight
WHO	World Health Organization
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence – Revised

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I–IV, and on some supplementary unpublished data.

I. Leppänen M, Ekholm E, Palo P, Maunu J, Munck P, Parkkola R, Matomäki J, Lapinleimu H, Haataja L, Lehtonen L, Rautava P and the PIPARI Study Group. Abnormal antenatal Doppler velocimetry and cognitive outcome in VLBW infants at two years of age. Ultrasound in Obstetrics and Gynecology 2010; 36(2): 178-185.

II. Leppänen M, Lapinleimu H, Lehtonen L, Rautava P and the PIPARI Study Group. Growth of extremely preterm infants born in 2001- 2010. Acta Paediatrica 2013; 102(2):206-208.

III. Lepomäki V*, Leppänen M*, Matomäki J, Lapinleimu H, Lehtonen L, Haataja L, Komu M, Rautava P, Parkkola R and the PIPARI Study Group. Preterm infants' early growth and brain white matter maturation at term age. Pediatric Radiology 2013; 43(10): 1357-1364.

IV. Leppänen M, Lapinleimu H, Lind A, Matomäki J, Lehtonen L, Haataja L, Rautava P on behalf of the PIPARI Study group. Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. Pediatrics 2014; 133(1):63-70.

* Equal contribution in publication.

1. INTRODUCTION

The decreasing mortality of premature infants, especially extremely preterm infants, during the last 15–20 years (Fanaroff et al., 2007, Hintz et al., 2011) has turned the focus of interest onto their long-term neurodevelopment. In Finland, very preterm infants (with a birth weight (BW) below 1500 grams (g) and/or gestational age (GA) below 32 weeks) represent 1.6% of all newborn infants (National Birth Register 2013, National Institute for Health and Welfare). Thus, this small subgroup presents a significant number of infants with disabilities in neurodevelopment (Mikkola et al., 2005, Larroque et al., 2011) who need special care and support (Larroque et al., 2008). In particular, cognitive, behavioural and educational impairments are common in very preterm infants (Bhutta et al 2002, Larroque et al., 2008, Saigal and Doyle 2008, Aarnoudse-Moens et al., 2009). Better understanding of the aetiologies and mechanisms behind neurodevelopmental impairments, with the aim to improve treatment policies and to target corrective treatment strategies, is needed.

Both a low BW (Bhutta et al., 2002, Guellec et al., 2011, Morsing et al., 2011) and low GA (Bhutta et al., 2002, Larroque et al., 2008) may increase the risk for adverse neurodevelopment. Placental insufficiency and related antenatal growth restriction associate with impaired neurodevelopment (Scherjon et al., 2000, Vossbeck et al., 2001, Baschat et al., 2009). The long-term consequences, however, are still unclear and the underlying pathophysiological mechanisms for impaired neurodevelopment remain unknown. In very preterm infants, a common finding is diffuse white matter injury combined with neural connectivity disruption (Volpe 2009), which may associate with later neurodevelopment (Lubsen et al., 2011, Woodward et al., 2012). New techniques of neuroimaging enable detailed assessment of white matter and different brain areas connecting neural tracts and may provide answers for how disabilities in neurodevelopment originate.

It has been shown that good postnatal growth in very preterm infants associate with improved neurodevelopment (Lucas et al., 1998, Franz et al., 2009, Belfort et al., 2012). However, it is still unclear what the optimal postnatal growth is for neurodevelopment in very preterm infants. Treatment for preterm infants may never replace intrauterine conditions, but by understanding the mechanisms and causes of problems in neurodevelopment, treatment strategies can be improved to protect brain development.

2. REVIEW OF LITERATURE

2.1 Antenatal growth restriction

2.1.1 Normal foetal growth

Foetal growth is dependent on the nutrition and oxygen supply from the mother via the umbilical cord and placenta. External factors, such as placental insufficiency, may restrict the growth of the foetus even more than endocrine factors (Mullis and Tonella 2008). Parental physical size and parity also have a significant effect on birth size (Sankilampi et al., 2013). At the end of the third trimester there is a growth spurt, especially in weight gain; foetal weight triples during the last trimester (Horemuzova et al., 2012). The mean birth weight (BW) for Finnish girls and boys born in 2012 was 3436 g and 3559 g, respectively (National Institute for Health and Welfare 2013, available from: http://urn.fi/URN:NBN:fi-fe201309276347), which is about three to four times the mean of BW for very low BW (VLBW) infants. The mean birth length for healthy term born Finnish girls and boys is 50.3 centimetres (cm) and 51.1 cm (Saari et al., 2011), respectively. And correspondingly, head circumference (HC) is 34.8 cm and 35.3 cm (Karvonen et al., 2012).

2.1.2 Definition of growth restriction

Definitions like intrauterine growth restriction (IUGR), small for gestational age (SGA), and VLBW all may indicate intrauterine malnutrition and growth restriction, although these definitions differ remarkably. The terms SGA and IUGR are not synonymous (Ott 2000); even the definition of these terms varies between countries. Usually, IUGR is based on the estimate of intrauterine measures, mostly used to describe growth restriction before birth, and SGA refers to deviation of birth size from the mean for the same gender and age. Antenatal evaluation of growth is usually based on a weight estimate by ultrasound (US) (Abele et al., 2010); some definitions of growth restriction also include estimate of length. But because of the position of foetus, estimation of length is technically difficult and it is used crown-rump length.

IUGR is the pathological intrauterine slowdown of genetically programmed growth potential often caused by some defect in the bio-physiological process (Tideman et al., 2007, Morsing et al., 2011). IUGR is usually defined as estimated weight below the 10th percentile of the mean weight for the same GA and gender (Latal-Hajnal et al., 2003, Ehrenkranz et al., 2006), where the 10th percentile equals -1.28 SD. However, other definitions also appear (Baschat et al., 2009). Growth is compared to ‘normal’ foetal growth, yet the reference varies in different countries and centres.

The definition of SGA describes growth status at birth and is usually classified as a z-score of BW and/or birth length more than 2.0 standard deviations (SD) (equal to the 2.3th percentile) below the mean weight/height for the same GA and gender (Hack et al., 2003, Franz et al., 2009). The SGA definition is based on the normal distribution of growth variation and also includes genetically small infants without pathology. Ideally, SGA definition should take parity and parental height into account (Sankilampi et al., 2013). However, a limit of the 10th percentile is also used in the definition of SGA (Brandt et al., 2003 and 2005).

Small newborn infants can also be classified according to BW in grams as follows: low BW (LBW) = BW less than 2500 g, very low BW (VLBW) = BW less than 1500 g, extremely low BW (ELBW) = BW less than 1000 g. Out of all Finnish newborn infants in 2012, 4.2% had LBW, 0.7% VLBW and 0.3% ELBW (National Birth Register 2013, National Institute for Health and Welfare).

2.1.3 Aetiology of antenatal growth restriction

Antenatal growth restriction can start at any time period during pregnancy and it can vary from mild to severe. Symmetrical and proportional IUGR in weight, length and HC occurs frequently in syndromes and in genetic smallness, and also in pathologies occurring in the early stage of pregnancy, for example in viral infections and exposure to drugs. Asymmetrical IUGR, in which weight is more affected than length and especially head circumference, is caused for example by placental insufficiency and can be less severe on the brain. This means that HC can be normal even if weight and length are small for GA. (Militello 2009.)

Intrauterine conditions, endocrine and genetic factors are determinants of foetal growth. However, malnutrition, morbidity and placental disorder have major effects on foetal growth (Resnik et al., 2002, Ergaz et al., 2005). Additional factors like multiple pregnancy and parity (Sankilampi et al., 2013) affect the growth potential. Substance abuse (Wouldes et al., 2010), alcohol and smoking (Räisänen et al., 2014) can restrict growth potential; for example, of the brain (Rivkin et al., 2008, Ekblad et al., 2010). Syndromes and chromosomal disorders of the foetus, as well as congenital infections, also associate with IUGR (Ergaz et al., 2005). In this thesis, the focus is on placental function as an antenatal growth-restricting factor, and its association with neurodevelopment.

2.1.3.1 Placental insufficiency

Placental insufficiency is a vascular disorder that results in multi-vessel cardiovascular signs, and which can progress to foetal growth restriction. In its most severe forms, it also increases the risks of morbidity and mortality (Valcamonico et al., 1994, Baschat et al., 2000, Soregaroli et al., 2002, Hartung et al., 2005). Manifestations of placental

insufficiency vary from mild to severe and from stable to progressive and it can begin in the early or late stages of pregnancy (Hecher et al., 2001, Turan 2008).

During placental insufficiency, resistance increases in the umbilical artery (UA). Autoregulation of foetal blood circulation protects essential organs, like the heart and brain, from long-term hypoxia by redistributive changes in blood flow. Based on longitudinal studies, decreased umbilical venous (UV) blood flow velocity (Rigano et al., 2001) is followed by a redistribution of blood flow towards the foetal heart and a decrease of blood flow to the liver (Kiserud 2006), which in turn is related to growth restriction (for review please see Baschat 2011). Furthermore, blood flow resistance in the middle cerebral artery (MCA) decreases to ensure oxygen supply to the brain. In prolonged conditions of hypoxia, blood flow of the descending aorta (DAo) becomes reversed and blood flow to the brain and heart enhanced. Later, blood flow to the ductus venosus becomes pathological (Hecher et al., 2001) and this is found to be a strong predictor of stillbirth (Baschat et al., 2000, Turan et al., 2011).

Foetal well-being and growth are assessed quite reliably by antenatal US. Inclusion of feto-placental blood flow analysis increases the predictability of antenatal US for later health and neurodevelopment outcome (Valcamonico et al., 1994, Ley et al., 1996, Soregaroli et al., 2002, Tideman et al., 2007, Eixarch et al., 2008, Chabulinski et al., 2012).

2.2 Preterm birth and preterm infant

Preterm birth is defined as birth at less than 37 completed weeks of gestation (the WHO). In previous decades when estimation of gestational age was more uncertain, the BW was used to determine prematurity; for example, Arvo Ylppö (1920) used a BW limit of 2500 g. Low BW can be a natural consequence of preterm birth, but the growth of a foetus can already be restricted before birth, or both can occur. According to the WHO, an infant who is born below 32 weeks of GA is defined as very low GA (VLGA), and an infant born at GA less than 26 weeks as extremely low GA (ELGA). Worldwide, 5 to 13% of children are born prematurely (Saigal and Doyle 2008, Zeitlin et al., 2013). In Finland, in 2012, 2997 preterm infants were born, which was 5.1% of all newborns (National Birth Register 2013, National Institute for Health and Welfare). The aetiology of preterm birth varies, and the incidence seems not be decreasing (Goldenberg et al., 2008).

Globally, prematurity is still one leading reason for neonatal mortality (Liu et al., 2012). In Finland, 11% of VLBW/VLGA infants die before their first birthday (Rautava et al., 2007). Immaturity of the lungs and also infections present limitations on survival (Lundqvist 2009). Improvements in neonatal care since the 1960s have influenced the

increased survival of very preterm infants, especially of the most immature ones (Hintz et al., 2011). GA has a determinant role both in morbidity (Rautava et al., 2007) and also for neurodevelopment (Inder et al., 2003, Rautava et al., 2010, for meta-analysis please see for Bhutta et al., 2002). However, the maturity of preterm infants in cohorts is markedly varied making the interpretation of the result difficult. For example, preterm infants born at 24–28 weeks of GA are at greater risk for adverse neurodevelopment than those born at 29–32 weeks of GA (Larroque et al., 2008).

2.2.1 Postnatal growth restriction and growth references

During the first postnatal weeks an immature child is struggling for life. High morbidity (Clark et al., 2003) and coexisting nutritional problems are common (Hulst et al., 2004, Ehrenkranz et al., 2011). This presents challenges to growth for LBW preterm infants at a time when these infants are in need of plentiful energy and protein, both to maintain weight and also for catch-up of growth. The concept of optimal nutrition has been unclear for years (Ehrenkranz et al., 2007, Joosten and Hulst 2011). However, since many years there have been recommendations for nutrient intakes for preterm infants by the European Society for Gastroenterology and Nutrition (ESPGHAN) (Koletzko et al., 2005, Agostoni et al., 2010).

There is no common consensus about the evaluation of postnatal growth in very preterm infants and, most importantly, in very preterm infants the definition of "optimal" postnatal growth is unclear. It has been thought that preterm born infants should imitate intrauterine growth in growth velocity. However, preterm infants do commonly not achieve intrauterine growth (Ehrenkranz et al., 2006, Horemuzova 2012, Stoltz Sjöström et al., 2013).

There are various known determinants for postnatal growth such as GA, antenatal growth, nutrition, morbidity, glucocorticoid treatment, gender, and genetic growth potential (Clark et al., 2003, Dusick et al., 2003, Pierrat et al 2011, Bocca-Tjeertes et al., 2011, Ramel et al., 2012, De Jesus et al., 2013). Clinically, the most significant factors may be insufficient nutrition, high morbidity and prematurity itself. It has been difficult to achieve recommended intakes of nutrients for preterm infants (Embleton et al., 2001, Dabydeen et al., 2008). However, recently it was found that recommended intake is possible to fulfil and thereby intrauterine growth rate could be achieved (Rigo and Senterre 2013). As mentioned, severe morbidity increases the risk of postnatal growth restriction (Ehrenkranz et al., 1999 and 2006, Cooke 2006, Ranke et al., 2007, Pierrat et al., 2011, Mitha et al., 2013). Also the endocrine regulation of growth in preterm infants is immature; for instance, concentrations of insulin-like growth factors remain at a low foetal level after birth. In preterm VLBW infants the circulating insulin-like

growth factor level has been found to be low, at least during the first nine weeks, and that the low concentration relate to poor postnatal growth (Kajantie 2003).

2.2.2 Postnatal growth restriction in very preterm infants

Postnatal growth restriction in preterm born infants begins directly after birth. All newborn infants lose weight, presumably due to the fluid shift between intra- and extracellular compartments and loss of extracellular fluid. However, the percentage of weight loss is usually greater and it also takes longer to achieve BW in VLBW infants than in larger infants (Ehrenkranz et al., 1999, Steward et al., 2002, Franz et al., 2009). Early nutrition deprivation has long-term consequences (Ehrenkranz et al., 2006) and even though treatment and nutritional strategies have advanced, postnatal growth restriction is still common in very preterm infants (Horemuzova et al., 2012). However, the incidence of growth restriction may be decreasing as, for example, it was found less often in later born ELBW infants: that is, in infants born 2000–2001 compared to infants born in 1995–1996 (Dusick et al., 2003). Extrauterine growth restriction (EUGR) is most commonly measured at 36 weeks of GA and is usually still present at discharge from hospital (Hack et al. 1991, Ehrenkranz et al., 1999, Embleton et al., 2001, Steward et al 2001, Clark et al., 2003, Dusick et al., 2003, Horemuzova et al., 2012). In a recent study by Stoltz Sjöström and co-authors (2013), where postnatal growth was followed carefully during the first 70 days, it was found that EUGR was most pronounced at four to five weeks after birth. Further, despite the catch-up growth in these preterm born children, they still remain smaller than their term born peers in childhood (Cooke and Foulder-Hughes 2003, Dusick et al. 2003, Hack et al., 2003, Franz et al. 2009, Roberts et al., 2013) and in preadolescence, at the age of 11 years (Farooqi et al., 2013).

ELGA infants are at a higher risk for postnatal growth restriction (Ehrenkranz et al., 1999, Franz et al., 2009, Horemuzova et al., 2014) than later born preterm infants. Even at the age of 18, ELGA survivors are shorter than term born controls, although the difference in weight is diminishing (Roberts et al., 2013). In a recent Swedish publication, 75% of ELGA infants born between 1990 and 2002 were under -2.0 SD (2.3 percentile) at least in one growth parameter at discharge. This was found even though BW was appropriate for gestational age (AGA) (Horemuzova et al., 2012). Those who are less than 29 weeks of GA at birth have a higher risk for postnatal growth restriction than those who are born at 29 weeks of GA or later (Clark et al., 2003, Franz et al., 2009, Pierrat et al., 2011).

Postnatal growth failure is also related to BW − the lower the weight, the higher the risk (Clark et al., 2003, Dusick et al., 2003). Cooke and Foulder-Hughes (2003) found that very preterm infants (<32 weeks of GA) with a mean weight of 1467 g were smaller at

seven years of age compared to term born children. SGA status predicts a short stature at four to five years of age (Bocca-Tjeertes et al., 2011, Pierrat et al., 2011); indeed, it takes many years to "recover" from intrauterine growth delay (Niklasson et al., 2003). Postnatal growth in very preterm infants varies, including a catch-up growth and a catch-down growth in former SGA infants (Hack et al., 1991, Ehrenkranz et al., 1999, Brandt et al., 2005, Neubauer et al., 2013). It has been discussed that the definition of SGA excludes infants with a milder form of growth restriction (Pierrat et al., 2011). However, even postnatal growth in AGA born very preterm children can be slow and growth may drop from normal growth variation more than 2.0 SD (Pierrat et al. 2011, Horemuzova et al., 2012).

For unknown reasons, boys are at higher risk for EUGR than girls born at the same GA (Clark et al., 2003, Cooke and Foulder-Hughes 2003).

2.3 Neurodevelopment in the preterm infant

Many developmental processes are accelerated just before birth; therefore, preterm birth and preceding hypoxia can interrupt maturational processes, especially in the brain (Ment et al., 2009, Lubsen et al., 2011). This is probably because the late second and third trimesters are found to be important for neural connectivity and also for the maturation and growth of axons and synaptic connections, as well as for brain volume growth per se (Limperopoulos et al., 2005). Maturation interruption in premyelinating cells and oligodendroglial precursor cells is thought to be one key factor in brain injury connected to preterm birth (Volpe et al., 2011). Pathologies related to prematurity, such as intraventricular hemorrhages (IVH) and periventricular leucomalacia (PVL) occur in 3–10% of VLGA infants (Zeitlin et al., 2008). Preterm encephalopathy is a diffuse white matter injury combined with axonal deficits. It is speculated that this connectivity disorder may explain the neurodevelopmental deficits in preterm infants (Lubsen et al., 2011, Marret et al., 2013).

2.3.1 Neurodevelopmental disabilities

Mild disabilities, including learning disabilities, attention-deficit/hyperactivity disorders, and impaired executive functions, exist in the very preterm population more often than in term born children (Saigal and Doyle 2008, Aarnoudse-Moens et al., 2009, Larroque et al., 2008 and 2011). The conclusion in the meta-analysis by Bhutta and co-authors (2002) was that preterm infants (either BW <2500 g or GA below 33 weeks) have 10.9 points lower IQ compared to full-term born controls. Also, the presence of minor neuromotor dysfunction is found to be higher in preterm infants

(GA below 33 weeks) than in term born infants, at 41% and 22%, respectively (Arnaud et al., 2007). Correspondingly, the prevalence of impairment in cognitive performance in preterm (GA below 33 weeks) and term born infants is 44% and 14%, respectively (Larroque et al., 2008). Cognitive impairments are reported as more common than neuromotor impairments in preterm infants: at 31% and 14%, respectively (Marret et al., 2013). Major disabilities, including cerebral palsy (CP), deafness, blindness, and mental retardation are becoming rarer, most likely reflecting the favourable changes in treatment (Platt et al., 1996, Saigal and Doyle 2008). The incidence of CP varies in different study cohorts, between 5 and 10% (Larroque et al., 2008, Mitha et al., 2013), and when reported it relates to GA and age, with the greatest incidence being in the ELGA population (Saigal and Doyle 2008, Marret et al., 2013). Some kind of neurologic disability is reported in about a quarter of VLGA infants, again with the risk being highest in the most immature infants (Larroque et al., 2008, Saigal and Doyle et al., 2008). Neuromotor functions remain delayed until adulthood, and VLWB preterm-born adults perform slower and poorer in fine and gross motor functions compared to match term controls (Kievet et al., 2009, Husby et al., 2013). Again, it is found that even minor disabilities can potentially influence life quality and educational achievements and increase the need for special support (Larroque et al., 2011, for meta-analysis please see Aarnoudse-Moens et al., 2009).

However, comparing neurodevelopmental outcomes among different studies is complex. Preterm infant groups are heterogenic and children vary among studies in factors such as GA, BW, background factors, morbidity and neurosensory disabilities. For instance, neurosensory limitations have a determinant role in neurodevelopment outcome (Streimish et al., 2012). Follow up protocols and treatment strategies also differ remarkably between cohorts.

2.3.2 Placental insufficiency and neurodevelopment

The time period during which placental malfunction manifests and the severity of the malfunction have a determining role for neurodevelopmental outcome (Baschat et al., 2011); the brain is most vulnerable during the most immature stages. Many studies show that IUGR with the presence of abnormalities in in feto-placental blood circulation associate with an increased risk for impaired neurodevelopment (Valcamonico et al., 1994, Ley et al., 1996, Tideman et al., 2007, Morsing et al., 2011). However, it is also found that IUGR alone without detected abnormality in UA can also be an independent risk factor for later adverse neurodevelopment (Figueras et al., 2008, Llurba et al., 2013, Savchev et al., 2013). It is thought that mild placental insufficiency and hypoxia might be disadvantageous even before it can be detected by Doppler US waveforms (Cruz-Martinez et al., 2009).

Preferential blood flow to the brain in chronic hypoxia is a protective mechanism but it might also be a sign of risk, as it is associated with adverse neurodevelopment (Scherjon et al., 2000, Eixarch et al., 2008). This phenomenon is called for brain sparing and is defined as a foetal middle cerebral artery (MCA) pulsatility index (PI) below the 5th percentile (Eixarch et al., 2008, Figueras et al., 2008) or as UA/MCA PI ratio above the 95th percentile (Arduini and Rizzo 1990). The latter is used in this study.

PI = systolic – diastolic velocity/mean velocity

Intrauterine conditions are optimal for the maturation of organs (Walker et al., 2011) but in suboptimal conditions it is unclear when exactly the baby should be delivered. Therefore, there are many studies that have attempted to correlate time sequences of feto-placental abnormalities with infant health outcomes (Hecher et al., 2001, Turan et al., 2008, Chabulinski et al., 2012). Still, the threshold for when hemodynamic conditions have more effect than GA is unclear (Chabulinski et al., 2012, for review please see Baschat 2011). However, ongoing study projects are investigating this threshold, for example 'The Trial of Umbilical and Fetal Flow in Europe' (available from: https://trufflestudy.org/truffle/index.htm).

2.3.3 Low gestational age, low birth weight and neurodevelopment

Low GA and LBW are the primary definers of neurodevelopmental outcome (Bhutta et al., 2002, Baschat et al., 2009, Beaino et al., 2011). As the inclusion criterion of very preterm infants varies in different studies, the findings below are separated for VLGA and VLBW infants.

Preterm born children perform less well in cognitive tests than term born control children at the same age (Cooke and Foulder-Hughes 2003, Larroque et al., 2008, Roberts et al., 2010, Woodward et al., 2012, Månsson and Stjernqvist 2014, for meta-analysis see Bhutta et al., 2002). Even though in studies previously published within the PIPARI study (Munck et al., 2010, Lind et al., 2011), the cognitive outcome in childhood was in the normal range, the statistically significant difference, compared to the selected term control group, was still present in VLBW/VLGA population.

Those who are born extremely preterm (in the studies, GA <27 weeks) have the highest risk for deficiencies in neurodevelopment (Wolke et al., 2007, Saigal and Doyle 2008, Larroque et al., 2011). Referring to Marret and co-authors (2013) only 36% of ELGA infants were free of any kind of disability (motor or cognitive) at age of eight years compared to 66% of later born preterm infants (from 31 to 32 weeks of GA). But even

more mature preterm infants (from 32 to 35 weeks of GA), considered to have low risk for neurodevelopmental disabilities (without major neonatal morbidities or brain pathology), are at risk for impaired global intellectual performance at nine years of age (Sonia-Pastor et al., 2009).

Inferiority in neuropsychological functions in VLBW infants compared to term born controls is still found in adulthood (Pyhälä et al., 2011). LBW associates with an increased risk for suboptimal neurological outcome (Franz et al., 2009, Guellec et al., 2011). However, even though many studies have shown SGA status to be one potential risk factor for adverse neurodevelopment (Baschat et al., 2009, Guellec et al., 2011, Morsing et al., 2011, Streimish et al., 2012, de Jesus et al., 2013, Kerstjens et al., 2013), SGA status in itself is not necessarily a cause of adverse neurodevelopment (Latal-Hajnal et al., 2003, Casey et al., 2006, Ehrenkranz et al., 2006, Ranke et al., 2007). There seems to be a relation between SGA status and neurodevelopment if head growth is affected (Frisk et al. 2002) and especially if postnatal growth is also poor (Frisk et al., 2002, Lundgren et al., 2003, Casey et al. 2006).

2.4 Postnatal growth and neurodevelopment

There have been suggestions about a sensitive period of growth and development of the brain in late pregnancy and early neonatal life since the 1970s (Dobbing 1971). Yet, it is still unclear whether this sensitive period indeed exists. Lucas and co-authors (1994 and 1998) performed a randomized controlled trial into the association between nutrition and growth and, later, also with neurodevelopment. They found that the preterm infants who received more energy during NICU care grew more rapidly and also had higher cognitive scores at follow-up (Lucas et al., 1994 and 1998). The positive association between postnatal growth and neurodevelopment has been established (Brandt et al., 2003, Ehrenkrantz et al., 2006, Stephens et al., 2009). In addition, there are ongoing attempts to locate a critical period of growth for brain development (Franz et al., 2009, Belfort et al., 2011).

Problems in the comparability of studies emerge from differences in their study designs. Some studies only report the size at birth and at discharge, and postnatal growth at a few later age points. The majority use the z-score (standard deviation from the mean in same age and gender) either as a measure in one point or as a sum of change during a certain period instead of quartiles of growth velocity in the evaluation of growth. Also, the used growth references vary, making the results less comparable.

It is speculated that postnatal growth may affect brain development more greatly than intrauterine growth (Casey et al., 2006, Kan et al. 2008, Franz et al. 2009). Only a few studies have compared SGA and AGA children separately regarding postnatal growth and

neurodevelopment (Frisk et al., 2002, Brandt et al. 2003, Latal-Hajnal et al., 2003, Casey et al., 2006). Belfort and co-authors (2011) discovered a stronger association to rapid weight gain between the ages of one week to term age in SGA than in AGA born VLGA infants. However, cognitive outcome at 18 months of CA was not reported for these groups. It is difficult to compare different preterm cohorts by different definitions of growth restriction; also, neurodevelopment outcome is assessed at varying ages by different methods. But in summary, preterm infants with poor antenatal and also poor postnatal growth have a less optimal outcome compared to infants with normal growth and term infants. In addition to which, boys are at a greater risk of EUGR than girls; EUGR, especially in boys, also increases the risk for adverse neurodevelopment (Frondas-Chauty et al., 2014).

2.4.1 Factors related to postnatal growth and neurodevelopment

During postnatal growth, the demand for nutrients is high. Since the beginning of the 2000s, nutrition has changed dramatically. Parenteral nutrition by amino acids is started earlier and the importance of breast milk is further emphasized; it is not just energy (Brandt et al., 2003) but also the quality of nutrition that matters for growth and neurodevelopment (Lucas et al., 1994 and 1998, Diekmann et al., 2005, Ehrenkranz et al., 2006, Kramer et al., 2008, Stephens et al., 2009, Rozé et al., 2012, Stoltz Sjöström et al., 2013).

Prematurity itself by immature endocrine regulation (Kajantie 2003) and related pathological abnormalities, such as immaturity of the lungs and gastrointestinal tract, increase risk of infections and feeding problems. And these problems associate with both growth and neurodevelopment (Ehrenkranz et al., 2006, Mitha et al., 2013). For instance, advanced (surgically managed) necrotizing enterocolitis (NEC) is considered a risk factor for both EUGR (Clark et al., 2003) and neurodevelopment (Hintz et al., 2005). Ventilation problems and a prolonged need for oxygen therapy associate with an increased risk of EUGR (Ehrenkranz et al., 1999, Cooke 2006, Ranke et al., 2007, Pierrat et al., 2011) and for cognitive delay (Ehrenkratz et al., 2006, Beaino et al., 2011). Also, treatment by postnatal corticosteroids relates to an increased risk of EUGR (Clark et al., 2003, Pierrat et al., 2011) and motor developmental delay (Ehrenkranz et al., 2006). Anaemia relates to severe cognitive deficiency in very preterm infants (Beaino et al., 2010). Maternal education relates positively to the cognitive performance of a child (Beaino et al., 2011). Interestingly, Bocca-Tjeertes and co-authors (2011) found that maternal education may also associate with HC growth. Other environmental factors, like kangaroo care, have a positive effect on the neurodevelopment of a preterm born child (Feldman et al., 2014).

2.4.2 Growth in weight and neurodevelopment

Rapid weight gain and head growth in ELBW infants during the time spent at a neonatal intensive care unit (NICU) associates with better cognitive and motor neurodevelopment

at 18 months (Ehrenkranz et al., 2006). A growth spurt in weight from 36 to 40 gestational weeks was the most significant growth parameter during the first year to predict motor and cognitive neurodevelopment at 18 months CA (Belfort et al 2011). In another study, early weight gain, between birth and discharge, was predictive for both motor and cognitive outcomes at five years of age in very preterm infants (<30 weeks of GA and <1500g) (Franz et al., 2009). Rapid weight gain until two years of CA is found to associate with better neurodevelopment both in SGA and AGA (VLBW) infants. However, in SGA infants, this association was found only in the motor outcome, whereas in AGA infants it was found both in motor and cognitive performance (Latal-Hajnal et al, 2003).

2.4.3 Length/height growth and neurodevelopment

It is thought that growth in length relates more to organ growth (such as the brain) than that of weight, and would be important for the prediction of neurodevelopment (Ramel et al., 2012). However, growth in length associates less with neurodevelopment compared to weight and HC; moreover, most often, a short stature in itself, rather than change in z-score, is related to outcome (Cooke and Foulder-Hughes 2003, Ramel et al., 2012). Ranke and co-authors (2007) found that VLBW children who were short in height at the mean of 3.7 years more often had a delay in motor development. A short stature at four and 12 months of CA associates with a lower cognitive level at two years of CA (Ramel et al., 2012). A short stature at age of 7 years in very preterm (below 32 GA) born boys correlates to poor performance in motor and cognitive tests (Cooke and Foulder-Hughes 2003). A lack of catch-up in height in SGA preterm males also associates with impaired IQ in adulthood (Lundgren et al., 2003).

2.4.4 Growth of head and neurodevelopment

Rapid head growth during the first year of life has a significant positive effect on both motor (Cooke 2006, Franz et al., 2009, Belfort et al., 2011) and cognitive (Hack et al., 1991, Neubauer et al., 2013) neurodevelopment in VLBW infants. This effect is easily understood, as HC is an indirect measure of brain size (Maunu et al., 2009). Franz and co-authors (2009) found in very preterm children that HC growth from birth until discharge associates positively with motor outcome. From week one to term age, rapid HC growth associates with better motor and cognitive outcomes (Belfort et al., 2011). The same association is also found over a longer period, between birth and four months of CA (Stathis et al., 1999). HC at birth, four, and 12 months of CA is linked to cognitive outcome at 24 months of CA in very preterm infants (Ramel et al., 2012).

Even later HC growth at very preterm is significant for neurodevelopment. Microcephaly at two years of age in ELGA born children associates with motor and cognitive impairments at the age of two years (Kuban et al., 2009). Cooke (2006) found that the

association between HC and neurodevelopment was different for motor and cognitive outcomes; after adjustments for IUGR, only HC at four and 15 years of age correlated to IQ. Catch-up growth of HC from birth until the age of five years associates with better cognitive outcome (Franz et al., 2009). Cooke and Foulder-Hughes (2003) showed that small HC at seven years of age associates with poor motor and cognitive performance at the same age both in boys and girls. But that HC growth rate between birth and seven years of age also correlates positively to cognitive tests.

In SGA preterm infants, it has also been found that HC growth during the first year associates positively with intelligence (Brandt et al., 2003). Frisk et al. (2002) reported that SGA infants who had both poor prenatal and postnatal (between birth and nine months) HC growth had the worst outcomes in school-age cognitive tests compared to infants with normal growth and IUGR infants with catch-up growth.

However, it is still unclear how much can be rescued by brain plasticity after early growth restriction. The side effects of early efficient nutrition and rapid growth are also increasingly discussed, which in term infants are shown to relate to adverse metabolic outcomes in later life (Singhal et al., 2010).

2.4.5 Brain imaging in neurodevelopment follow-up of very preterm infants

Knowledge about the development of the preterm brain is increasing as brain imaging techniques have advanced and can provide additional data of the aetiologies and mechanisms of impairments. Pathologies, like ischemic and haemorrhagic brain lesions, and volume loss and maturational processes (myelination, sulcation, increased coherence of diffusion in neural tracts), can all be detected and followed using brain imaging techniques. However, the clinical significances are not yet clear (for review please see Ment et al., 2009, Rutherford et al., 2010).

Ischemic insults, cystic or non-cystic PVL and IVH can be detected by bedside brain US. Brain US is a useful and easily available method to study brain pathology for very preterm infants. Abnormalities in brain US associate with neurodevelopmental impairments (De Vries et al., 2004, Leijser et al., 2010). Recently, Bolicetty and co-authors (2014) reported that even I-II grades of IVH increase the risk of adverse neurodevelopment; previously, it was thought that predictability is quite low in less severe brain abnormalities seen by sequential brain US (Leijser et al., 2010).

White matter injury including, for example, volume loss and delayed myelination is a common finding in preterm infants (Inder et al., 2003). White and grey matter pathologies can be detected more accurately in the whole brain with brain magnetic resonance imaging (MRI) (Leijser et al., 2010, Woodward et al., 2012), although diffuse injuries are still hard to find (Inder et al., 2003). Obvious neuropathological findings in brain MRI such as white

matter volume loss or white matter signal abnormality are related to impaired cognitive outcome (Woodward et al., 2012) and severe neuropathology increases the risk of severe cognitive impairment. Normal brain MRI, at term age, has a 92% negative predictive value for cognitive delay and MRI with major pathology had a 44% positive predictive value for cognitive delay at the age of five years (Setänen et al., 2013). Setänen and co-authors (2013) found that major pathologies seen in brain MRI at term age had a positive predictive value of 75% for neurological impairment (Cognitive score < 85, CP, severe hearing impairment and severe visual impairment). Preterm infants can have either regional or total brain volume loss (Kievet et al., 2012). Previous studies have shown that regional brain volumes, either in grey or white matter, correlate to neurodevelopment (Beauchamp et al., 2008, Sonia-Pastor et al., 2009, Lind et al., 2011).

However, brain MRI may not reveal all diffuse injuries that may have an effect on later brain functions, for example more subtle findings that may relate to cognitive functions (Lubsen et al., 2011, Marret et al., 2013). Diffusion tensor imaging (DTI) is a new technique that is based on the diffusion of free water molecules in tissues. As the diffusion of water is restricted by tissue membranes and fibres, water diffuses more rapidly in the direction aligned with neural axons (LeBihan et al., 2003). Thus, DTI has a spatial resolution of white matter, maturation and pathology (Arzoumanian et al., 2003, Volpe 2003, Counsell et al., 2008, Ment et al., 2009). Myelination, for example, can be detected by DTI before it can be by conventional MRI (LeBihan 2003). With increasing GA microstructures also becoming more organized, anisotropy (directionally dependent diffusion) increases describing increasing coherence and integrity of axons (Hüppi et al., 1998, Ment et al., 2009). Fractional anisotropy (FA) describes axonal integrity. Axial diffusion (AD) is the rate of diffusion along the principal axis and radial diffusion (RD) along the two minor diffusion axes vertical to fibre bundles. Mean diffusivity (MD) is the sum of the diffusivity along the principal axis (AD) and the diffusivities in the two minor axes (RDs) divided by three. It is also thought that an increase in FA is driven by RD (Patridge et al., 2004, Thompson et al., 2011).

DTI is not yet established in clinical practice to assess white matter maturation in preterm infants, as results are inconsistent regarding findings linking DTI and preterm birth (Anjari et al., 2007) and later neurodevelopment (Arzoumanian et al., 2003, Patridge et al., 2004, Counsell et al., 2008, Van Kooij et al., 2012, De Bruïne et al., 2013). It has also been discussed that complications related to prematurity, like brain pathology, have an effect on DTI parameters but not necessary GA itself (Bonifacio et al., 2010, Feldman et al., 2012). Also, environmental factors associate with maturation; findings by Gimenez and co-authors (2008) suggest that early extra uterine sensory neural stimuli, for example visual stimuli, can accelerate the maturation of white matter connections.

3. AIMS OF THE STUDY

The objective of this study was to determine the association between growth and neurodevelopment in VLBW/VLGA infants.

The specific aims of this thesis are:

I To study the association between feto-placental blood flow and neurodevelopment of VLBW infants at two years of CA (Study I).

II To compare early postnatal growth in Finnish ELGA infants (born between 2001 and 2010) to 'new' growth reference based on similar Swedish ELGA cohort (born between 1990 and 2002) (Study II).

III To determine if improved early postnatal growth in VLBW/VLGA infants associates with maturation in white matter connections of the brain at term age, assessed by DTI (Study III).

IV To investigate the effect of intrauterine growth on future growth and to assess whether there is a specific growth period(s) that associates with improved cognitive abilities at five years of age in the VLBW/VLGA cohort (Study IV).

4. MATERIALS AND METHODS

4.1 Participants

The study sample consisted of VLBW (defined in this study as BW ≤1500 grams) preterm (GA <37 weeks) infants born between January 2001 and December 2006 – and after April 2004 and until the end of December 2006 also VLGA (<32 GA, regardless of BW) infants – born at Turku University Hospital (Study I, III, and IV).

The inclusion criteria were that families were living in the catchment area of Turku University Hospital. Otherwise, the inclusion criteria were similar to the Vermont Oxford Network (VON). Totally 291 VLBW/VLGA infants were born in Turku University Hospital in 2001–2006, five infants were excluded because families did not speak two of official languages (Finnish or Swedish), eight of families lived outside of catchment area of Turku University Hospital and four of infants were excluded because of syndrome or severe congenital anomalies. In Study II, ELGA infants (GA <26 weeks) born between 2001 and 2010, and treated in Turku University Hospital, were studied. Figure 1 (Flow chart) presents the study infants used in this thesis.

Very preterm infants (VLBW and/or VLGA) born between 2001 and 2006 were participants in a large multidisciplinary follow-up study called: "Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age" ("PIeniPAinoisten RIskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään, PIPARI").

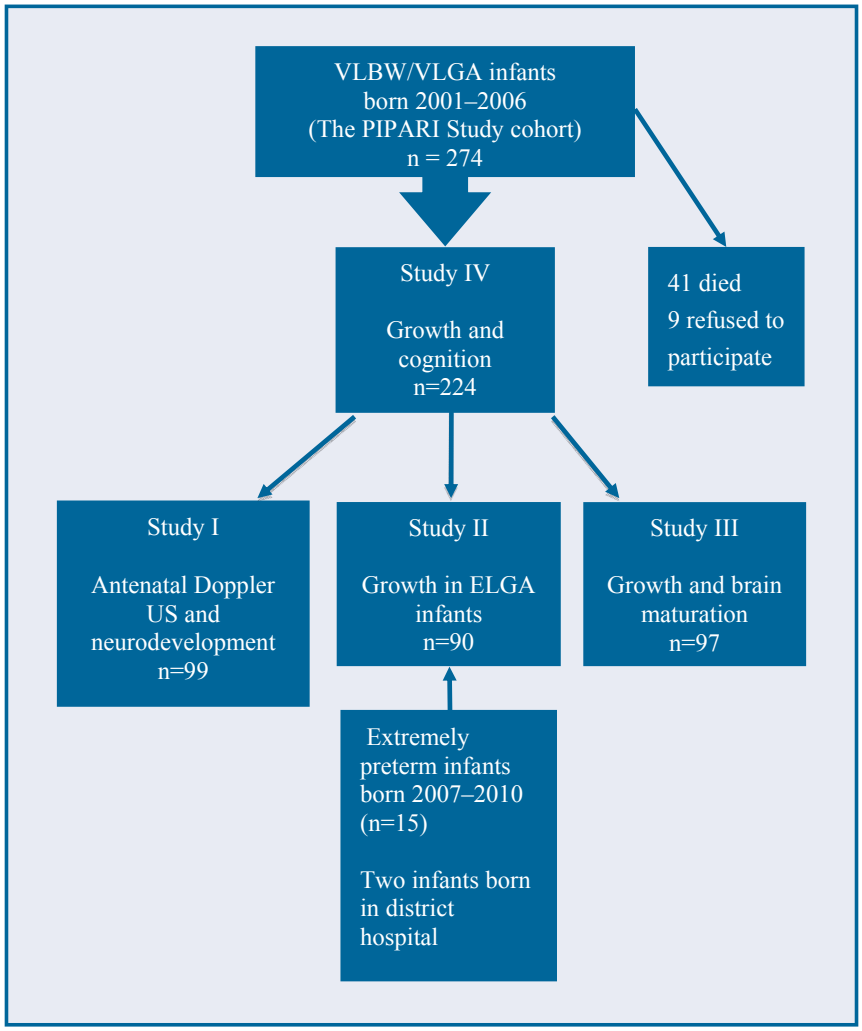


Figure 1. Flow chart of participants. Additional inclusion and exclusion criteria and the final number of the participants for each study are described in text.

Study I consisted of VLBW and VLGA infants born between 2001 and 2006 at Turku University Hospital. All pregnancies in which the delivery was expected before 32 weeks of GA or with BW below 1501 g were studied by antenatal Doppler US within the week prior to delivery. As the blood flow studies were the basis of further assessments, to increase the reliability of the procedure only US examinations conducted by two experienced perinatologists were accepted (altogether 99 cases). Additional inclusion criteria for Study I were: 1) serial brain US examinations, 2) brain MRI at term age, and 3) neurological and 4) psychological assessment at two years CA. The exclusion criteria were: 1) the infant had died during the neonatal period (n=11), 2) infants were not included in the follow-up (n=4) and 3) neonatal follow-up was refused (n=1). The final study population consisted of 83 infants; in this study, all infants had VLBW.

Study II consisted of ELGA infants born between 2001 and 2010, who were admitted to the NICU at Turku University Hospital. Out of these 90 infants, those were excluded who died before term age (n=33) or those with missing information (n=2). The final study population consisted of 55 ELGA infants.

Study III consisted of VLBW and VLGA infants born between 2004 and 2006, and who were examined with a 1.5 Tesla (T) MRI system, including DTI at full-term equivalent age. The exclusion criteria were that the infant had: 1) died during the neonatal period (n=17); 2) major congenital anomalies or recognized syndromes (n=2); 3) major brain pathology in MR images (n=16); 4) DTI that was incorrectly imaged or not imaged at all (n=21); and 5) movement artefacts in DT images (n=20). A total of 40 preterm infants were accepted for the study. The data analysis registration process failed for three infants and one infant had missing clinical data. The final study population consisted of 36 preterm infants.

Study IV included a total of 274 VLBW infants born between 2001 and 2006 and VLGA infants born between 2004 and 2006. The exclusion criteria were: 1) infants died during the neonatal period/follow-up (n=41); 2) families refused to participate in the study (n=9); 3) dropouts (n=23); 4) an infant with per oral corticosteroid therapy was excluded from the study because of a possible adverse effect of the medication on growth (n=1); 5) neuropsychological tests were done too late (n=2); 6) the tests were unsuccessful or outcomes were missing (n=11); 7) infants who had severe congenital anomalies or a diagnosed syndrome affecting their growth and development were excluded (n=6). The final study population consisted of 181 VLBW infants.

4.2 Methods

4.2.1 Collection of demographic data

Neonatal background data were collected during the NICU care. This background data included maternal age, the presence of pre-eclampsia, GA and physical measures at birth, gender, the use of antenatal and postnatal corticosteroids BPD, sepsis, meningitis, and NEC. The diagnostic criteria were similar to the ones in VON (Manual of operation for infants born in 2012). A diagnosis of CP was confirmed by a paediatrician at the two-year follow-up visit. At follow-up, the weight, height and HCs of parents were measured by a research nurse.

4.2.2 Antenatal Doppler US

In Finland, all pregnancies are followed using antenatal US to determine the duration of gestation. In this study, all pregnancies in which the delivery was expected before 32

GA or BW below 1501 g were studied by antenatal Doppler US within the week prior to delivery. These antenatal Doppler US examinations were performed by two experienced perinatologists using a 3.5 to 5 Megahertz (Mhz) convex transducer (Acuson Sequia, Mountain View, California, USA). Blood flow velocity waveforms were assessed from the UA, the MCA, the DAo, the aortic isthmus and the ductus venosus. PI was calculated for the UA, the MCA and the DAo flow as described by Gosling and King (1975) from the mean of three consecutive waveforms. Ratios between the PI in UA and MCA and in DAo and MCA were calculated and were used as continuous variables in further analyses. The direction of the net blood flow of the aortic isthmus and end-diastolic flow of the ductus venosus was determined to be antegrade, retrograde or absent, and the blood flow of each vessel was classified as normal or abnormal. Abnormal blood flow was defined as a UA PI value and UA /MCA PI ratio above the 95th percentile for the appropriate GA according to Arduini and Rizzo (1990). The UA/MCA PI ratio above the 95th percentile was considered to be brain sparing. Absent or revised end diastolic flow (AREDF) of the UA and the ductus venosus, and absent or retrograde net blood flow of the aortic isthmus were classified as abnormal (Maunu et al., 2007). The managing clinicians were not blinded to the Doppler US velocity measurements (Study I).

4.2.3 Nutrition regimen used at Turku University Hospital

In this study intravenous glucose was started immediately after birth, and was followed by parenteral nutrition. From the year 2000 the clinical nutrition regimen began to improve, and the amount of parenteral protein was increased, incrementally, from 1 g per kilogram (kg) from day 1 (during the first 24 hours), to 2 g/kg on day 2 and to 3 g/kg on day 3. At the end of 2005, protein intake was already at 2 g/kg from day 1, but this was increased to 3 g/kg the next day. Parenteral nutrition was administered until the daily breast milk intake was 120 millilitres (ml) per kg.

The amount of breast milk, either the mother's or donated (pasteurized), was gradually increased up to 150 ml/kg per day, when fortification of breast milk was started; 0.8 g protein was added per 100 ml of breast milk. This fortification was continued until the infant reached the weight of 3.5 kg. All infants were given breast milk at least until discharge. Maternal breast milk or preterm formula if maternal breast milk was not available was recommended as the only diet until four months of calendar age.

Retrospectively, from the patient data it was found that breast milk was given on day 1 for 29% of the infants born in 2001 and 2002. However, for infants born between 2009 and 2010, this proportion had already increased to 60% of infants. The rest of the infants had a later start for enteral feeding.

The babies were given solid food at four months of calendar age, in addition to the breast milk or formula. This was followed by meat at five months of calendar age to ensure iron and protein intake. Baby food was replaced with normal family food at approximately one year after birth. In the case of problems with growth or nutrition, a dietician and a speech-therapist were consulted (Leppänen et al., 2014).

In terms of micronutrients, iron was supplemented for all infants from three weeks of age by 2.5 milligrams per day, and increased to 5 milligrams after a weight of 5 kg was reached until the first tooth appeared. Vitamin D was supplemented from two weeks of age until two years of age by 10 micrograms per day and then until three years of age by 7.5 micrograms. Vitamin supplements for preterm infants (a mix of vitamin A, B12 = cobalamin, E and folic acid) were started at one week after birth if breast milk was not fortified. Phosphorus and calcium were included in this supplementation, if needed.

4.2.4 Growth assessment

The nurses working in NICU measured the infants in the hospital and at the follow-up clinic until two years of CA, and thereafter the nurses at the well-baby clinics continued with these measurements. After birth, weight was recorded daily, the crown–heel length twice a month and the HC weekly until discharge. The weight was measured to the nearest 0.01 kg by a baby scale (MeWa GmbH, Schwerin) until the age of two years of CA and thereafter to the nearest 0.1 kg. The child was usually lying supine (a fully extended position) for length measuring up to 24 months CA; thereafter, the child was measured in a standing position. The length/height and HC were measured to the nearest millimetre (mm). HC was measured by a soft inflexible measure, which was checked and changed regularly. The National Institute for Health and Welfare provides a detailed manual of methods for measuring a child (available from: http://urn.fi/URN:NBN:fi-fe201205085455). Available data were collected from hospital records, the measurements at five years of age were determined by a questionnaire from nurses at the well-baby clinics. Growth data in the present study was checked, and deviations in the growth curve were checked again, using other growth measures around the doubtful measuring points to get a reliable value (Study II, III and IV).

Growth was assessed using the measures of weight, length/height and HC at birth, 36 weeks of GA (GA) (±seven days), 40 weeks of GA (±seven days, term age), one month, (±seven days), two months (±seven days), four months (±seven days), one year (±seven days), two years (±seven days), and five years (±two months). Age was corrected for prematurity until two years.

The growth parameters were converted to the z-scores that correspond the age and gender adjusted standard deviation scores (SDS) according to two Finnish Growth references between 24 and 40 weeks of GA (Pihkala 1989, Sorva 1990 a+b). The WHO growth curves were used from 40 weeks of GA to five years of age (Study IV).

In the present study, SGA status was defined as a z-score for BW below -2.0 SD from the mean of same GA and gender, AGA status as a z-score for BW above -2.0 SD. In Study IV, the term non-SGA was used as two infants with z-scores of +2.2 and +2.6 were included in the AGA group. For clarity, the term non-SGA was replaced by AGA in this thesis.

The z-score change rate was used as a continuous variable in Study III and IV. Additionally, in Study III, rapid growth was defined as growth velocity where the z-score change between two time points exceeded 0 SD. And, conversely, slow growth was defined as growth velocity where the change in growth measure remained under 0 SD. In Study IV catch-up growth in SGA infants was defined as growth measure above -2.0 SD at the time point and catch-down as a z-score of body measure below -2.0 SD.

As intrauterine growth was not followed systematically in this project, the SGA status was used to determine possible intrauterine growth restriction, assuming that SGA infants have not reached their full growth potential before birth. Syndromes and chromosomal disorders were excluded from the study.

4.2.5 Brain imaging

At Turku University Hospital, both brain US and MRI are included in the postnatal follow-up protocol of very preterm infants.

4.2.5.1 Brain ultrasound

Study infants were scanned by brain US at 3−5 days, 7−10 days, one month of age and monthly thereafter, until discharge from the hospital according to clinical practice at Turku University Hospital. The brain US was performed, in a blinded method, by the attending NICU neonatologist, except at term age when it was performed by a paediatric radiologist. US examinations assessed IVH and cystic PVL. At term age, the brain US scan was performed in order to assess the ventricular/brain ratio, the widths of the ventricular horns and brain lesions. From January 2001 to August 2002, a 7.5-MHz vector transducer (Aloka SSD 2000, Aloka Co, Ltd, Tokyo, Japan), and from September 2002 to March 2007 an 8-MHz vector transducer (General Electric Logic 9, GE Medical Systems, USA), was used (Study I, IV).

4.2.5.2 Brain magnetic resonance imaging

At term equivalent age, brain MRI was performed during postprandial sleep without pharmacological sedation or anaesthesia. The MRI equipment was an open 0.23-T Outlook GP (Philips Medical Inc.,Vantaa, Finland) until 2004 and, thereafter, a 1.5 T Philips Gyroscan Intera (Philips Medical Systems, Best, The Netherlands). The infants were swaddled to calm them and to reduce movement artefacts in the images. During MRI, a pulse oximeter was used to follow the infant. A physician attended the examination to monitor the infant, if necessary. Ear protection was used. On both MR field strength systems, axial T2-weighted and coronal T1-weighted sequences were optimized to image term infant brains. Using 1.5 T equipment, additional T2-weighted sagittal sequences were obtained. The MR images were clinically analysed by a neuroradiologist, who used a blinded method to assess both the clinical information and the US examination results. MRI was used to assess brain pathology, volume and maturation (please see below).

4.2.5.3 Brain pathology assessment by brain US and MRI

The infants were categorized into three groups according to the most pathological brain findings, either from brain US or MRI: 1) the normal group consisted of infants with normal brain anatomy and extracerebral space ≤ 4 mm in width (McArdle et al., 1987); 2) the intermediate group consisted of infants with IVH grades 1 to 2, dilation of no more than one of the four horns of the lateral ventricles or caudothalamic cysts in any cranial US examination and extracerebral space of 5 mm in width or caudothalamic cysts or IVH grades 1 to 2 on MRI; 3) infants included in the major pathology group were those with IVH grades 3 to 4, white matter cysts or ventriculomegaly with 2–4 horns dilated, abnormal T1 or T2 signals in cortex, basal ganglia, thalamus, cerebellum or internal capsule, abnormal corpus callosum, increased width of extracerebral space (>5 mm), ventriculitis, or a ventricular/brain ratio greater than 0.35 (Study I and IV, Maunu et al., 2007 and 2009). In Study III, major brain pathology was assessed only using MR images, and defined as IVH grades 3–4, haemorrhage of the brain parenchyma, white matter cysts, abnormal signal intensities in the T1- or T2-weighted images in the cortex, the basal ganglia, the thalamus, the cerebellum or the internal capsule, abnormality of the corpus callosum, an extracerebral space width of 6 mm or more, or ventriculitis (Study III, Lepomäki et al., 2013).

4.2.5.4 Brain volume measurement by MRI

The volume measurement was performed on a GE workstation (GE AW1.0, GE Medical Systems, Milwaukee, Wisconsin) and the coronal T1-weighted images were analysed with Functool 1.0 post processing software (GE Medical Systems, Milwaukee, Wisconsin). The volume measurements were performed manually using the slice by slice technique.

4.2.5.5 Diffusion tensor imaging

The sequence used for diffusion-weighted imaging was a single-shot echo planar imaging with SENSE. SENSE reduction was 2. The slice thickness was 5 mm, with gaps between the slices of 1 mm. A 200 mm square field of view was used. The imaging matrix was 111×89 and the reconstructed voxel size was 0.78 mm×0.78 mm. The number of signal averages was 2 and the Echo Planar Imaging factor was 47. Repetition time was the shortest possible (minimum of 2264 milliseconds) and echo time was 68 milliseconds. The b values were 0, 600, and 1200 second per square mm with 15 directions. Fat suppression was conducted using spectral presaturation with inversion recovery. In addition to the DTI data set, the imaging protocol included conventional images. Data processing was performed using FSL 4.1.7. Data was corrected for eddy currents and motion. FA, MD, AD and RD maps were calculated using applications of the FSL 4.1.7. (Lepomäki et al., 2012). Tensor is a mathematical construct of diffusion and describes the linear relation between vectors in each voxel (3-dimensional pixel). As the direction of diffusion depends on the angle of observation, it is used in many directions in DTI. Using post-processing techniques (mathematical models), reconstruction of neural connectivity can be achieved (Johansen-Berg et al 2006). By quantifying the MD, the orientation dependence of diffusion (FA, RDs), and also maximum diffusion at each brain voxel, the model can be calculated. Tract-based spatial statistics (TBSS) is an automated observer-independent method that provides group-wise comparisons of diffusion tensor imaging data from multiple subjects (Anjari et al., 2007), and was performed as described by Smith and co-authors (2006). Images were analysed by a neuroradiologist and hospital physicist.

4.2.6 Assessment of neurodevelopment

4.2.6.1 Bayley Scales of Infant Development

Cognitive development was assessed by a psychologist using the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development (2nd edition) (BSID-II) at 2 years of corrected age (from -1 week to +1 month) (Bayley 1993). The MDI scale assesses memory, habituation, problem solving, early number concepts, generalization, classification, vocalization, language and social skills. The MDI scale, which has a mean value of 100 (1 SD = 15), was translated for the purposes of the present study (Study I, Munck et al., 2010).

4.2.6.2 Wechsler Preschool and Primary Scale of Intelligence

A psychologist assessed the cognitive outcome of the children at five years (-1 week to 2 months) with the short version of the Wechsler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R). The WPPSI-R test is standardized in Finland (Wechsler

1995). The subtests' information, sentences, arithmetic, block design, geometric design, and picture completion were used and the Full Scale Intelligence Quotient (FSIQ) was estimated. The FSIQ was used as a continuous variable (mean 100, SD 15) (Study IV).

4.2.6.3 Hammersmith Infant Neurological Examination

The neurological examinations were performed either by a physician or by a physiotherapist. The Hammersmith Infant Neurological Examination (HINE) assesses the neurological status of infants between 2 and 24 months of age (Haataja et al., 1999). HINE has been standardized in term infants at the age points of 12 and 18 months (Haataja et al. 1999) and the method has also been applied to preterm infants (Frisone et al., 2002). The examination assesses cranial nerve function, posture, movements, tone and reflexes, development of motor functions, and behaviour. The global score, a sum of all the individual item scores, is used to quantify the results. Scores below 74 are regarded as suboptimal at 18 months in a low-risk population of term infants. Normal references are not available for preterm infants, so the global scores were used as continuous variables in the statistical analyses (Study I).

4.2.7 Confounding factors

In Study I, the potential confounding factors were neonatal morbidity: BPD, sepsis, meningitis, and NEC requiring surgery, GA at birth, gender, the use of antenatal corticosteroids and maternal education (classified as <9 years, ≥9 and <12 years, and ≥12 years). Preliminary analysis indicated that SGA status was not a significant predictor of MDI in the data. In Study III, the z-score of BW was statistically adjusted for. In Study IV, the association between growth and five-year cognitive outcome were adjusted for GA, gender and mother's educational level. Further, GA, gender, brain pathology, BPD and NEC were studied for their association with postnatal growth.

4.2.8 Statistical analysis

In all statistical analyses, $p < 0.05$ was considered to be significant.

Study I: The associations between the antenatal Doppler US blood flow velocity waveforms and the outcome variables (MDI and HINE scores) were studied using regression analysis. Each Doppler US parameter was considered separately in all analyses. Univariate associations were first studied using a simple linear regression model, before adjusted analysis was performed by adding potential confounding factors to the multiple regression models. Finally, brain pathology and cerebral volume were added to the regression model, one at a time. Regression analysis was used to study the associations between Doppler measurements and cerebral volume controlling for GA.

GA was controlled for when the associations between the ordinal dependent variable, brain pathology and Doppler measurements were studied using cumulative logit models. Using an independent-samples t-test, continuous variables were compared between the study infants. The data analysis was performed using SAS for Windows, version 9.2 (SAS Institute, Cary, North Carolina, USA). Continuous variables were described using the mean, SD and range. The results of the regression analysis are presented using estimated regression coefficient (b) and standard error (SE). The intraclass correlation coefficient (2, 1) for cerebral volume was calculated to describe reliability and was found to be 0.99.

Study II: Early postnatal growth (z-scores) was compared between Finnish and Swedish infants using an independent samples t-test. In trend analysis, Spearman's correlations were calculated for birth year and each growth measure at 36 and 40 weeks of GA to study the effect of nutritional changes. ELGA infants' measures were transformed to z-scores according to Swedish growth curves for ELGA infants.

Study IIII: The z-score change rate was calculated between birth and term age and divided by postnatal age, in weeks, in order to create a growth rate which takes into account the variation in gestational ages at birth. (For example, infants born at 23 weeks of GA have a longer time to grow until term age than those born at 32 weeks of GA).The z-score change rate was used as a continuous variable and the z-score of BW was used as a confounding covariate in the statistical analysis to study the association between early postnatal growth and brain maturation measured by DTI at term age. To further assess growth, two groups were formed based on early postnatal growth velocity between birth and term age. In the first group, infants had rapid postnatal growth in weight, length or HC (z-score change >0) and in the other group, infants had slow postnatal growth (z-score change <0).

Tract-based spatial statistics (TBSS) was performed as described by Smith and co-authors (2006). A detailed description of the TBSS analysis, performed by a medical physicist, is found in Study III. In addition to TBSS, the comparisons between two categorical variables were performed using a Fisher exact test. Continuous variables were compared between the two groups based on different postnatal head circumference growth rate and between included and excluded infants using an independent sample t-test.

Study IV: To determine the particular growth period, growth was evaluated in short periods, in sequential order, from each age to following age points; for example, between 36 GA and term age and between one and two months. Growth was also evaluated over longer periods systematically, for example from birth and then from 36 GA to all measure points. The z-score change rate was used as a continuous variable. Associations between the categorical predictors and the continuous response variables were studied using the Kruskal-Wallis test. Univariate associations between two continuous variables

were studied with Spearman's correlation coefficient (r). The association between the background variables – GA, gender, NEC, BPD, brain pathology, and the mother's education – and growth was analysed. Associations between the z-score change of growth and FSIQ were further studied using regression analysis.

4.2.9 Ethical consideration

The PIPARI Study protocol was approved in December 2000 by the Ethics review committee of the Hospital District of South-West Finland. All participating parents received written and verbal information about the study and provided their informed consent (Study I, III, IV). Study II was a register study, T76/2012, and was performed according to Finnish law without ethical review.

5. RESULTS

5.1 Relation of Antenatal Doppler US findings to two-year neurodevelopment

In the total cohort of Study I (n=83), AREDF was seen in UA in 8% and ductus venosus in 4%. Retrograde net blood flow in the aortic isthmus was found in 2% of the followed foetuses. Abnormal blood flow patterns were found in the UA in 20% and MCA in 22% of the foetuses. In addition, UA/MCA PI ratio was abnormal in 19% of the followed foetuses.

The mean value of MDI was 102 (SD 14). Ten infants (12%) had an MDI below 85 (-1.0 SD) and one (1%) had an MDI below 70 (-2.0 SD). The mean HINE score was 74 (SD 4). CP was clinically diagnosed in five infants (6%).

Pathological flow in the UA and abnormal UA/MCA PI ratio were found more often in SGA infants than in AGA infants: 45% versus 7% and 50% versus 6%, respectively. Antenatal blood flow parameters are presented separately for SGA and AGA very preterm infants (Table 1). The number of observations varied from various veins and arteries.

Table 1. Pathological blood flow velocities in SGA and AGA infants.

	SGA infants (n=39)	AGA infants (n=60)
AREDF in UA	8/39 (21%)	2/55 (4%)
AREDF in the ductus venosus	1/37 (3%)	2/55 (4%)
Retrograde blood flow in the aortic isthmus	1/27 (4%)	1/43 (2%)
Abnormal UA PI	17/38 (45%)	4/59 (7%)
Abnormal UA/MCA PI	18/36 (50%)	3/48 (6%)
UA PI/MCA PI ratio	1.19 ± 0.70	0.64 ± 0.40
DAo/MCA PI ratio	1.43 ± 0.77	0.95 ± 0.30

In the present study no relation was found between feto-placental blood flow and motor outcome at two years of CA. However, cognitive outcome at two years of CA was related to antenatal Doppler US parameters. In the univariate analysis, abnormal UA PI and UA/MCA PI ratio, as well as increases in both the DAo PI and in the DAo/MCA PI ratio, were associated with adverse cognitive outcome (Figure 2). When one or several of the confounding factors (BPD, sepsis, meningitis, NEC requiring surgery, GA at birth, gender, the use of antenatal corticosteroids and maternal education) were controlled for,

the DAo PI and UA/MCA PI ratio remained significant, SE -12.1 (p=0.003) and -6.5 (p=0.03) respectively (Figure 2 and Table 3).

As pathological UA/MCA PI ratio, known also as brain sparing, was strongly associated with two year cognitive outcome, background characteristics are divided separately for infants with abnormal and normal UA/MCA PI ratio (Table 2). SGA status itself did not relate to the adverse neurodevelopment at two years of CA.

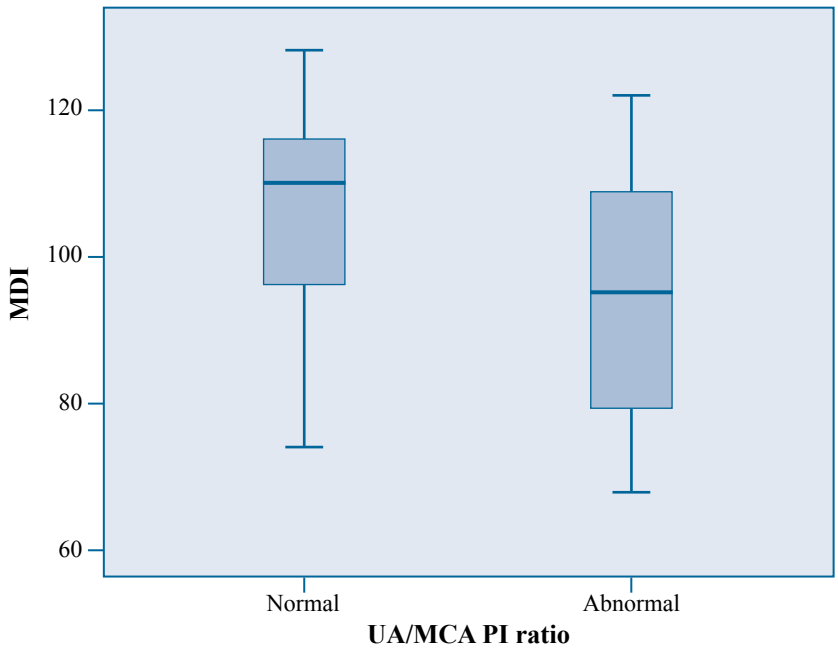


Figure 2. Association between normal versus abnormal UA/MCA PI ratio and cognitive outcome at two years of CA. The median, interquartile range and range of mental developmental index (MDI) for infants with normal (n=52) and abnormal (n=15) UA/MCA PI ratio are shown (unpublished).

Table 2. Characteristics of infants with normal versus abnormal UA/MCA PI ratio. Data are expressed as mean (range), or n (%). UA/MCA PI was measured in 70 infants.

Mean [min, max] (SD) or n (%)	Infants with abnormal UA/MCA PI (n=16)	Infants with normal UA/MCA PI (n=54)
Prenatal characteristics		
Age of mother	31 (20, 39)	31 (16, 40)
Mother's education level		
<9 years	3/15 (20%)	6/53 (11%)
9–12 years	3/15 (20%)	15/53 (28%)
>12 years	9/15 (60%)	32/53 (60%)
Nulliparous*	5/16 (31%)	31/46 (67%)
Pre-eclampsia*		
None	7/15 (47%)	39/52 (75%)
Mild	5/15 (33%)	1/52 (2%)
Severe	3/15 (20%)	12/52 (23%)
PROM*	0%	20/54 (37%)
Antenatal steroids*	12/16 (75%)	54 (100%)
Multiple birth	1/16 (6%)	15/54 (28%)
At birth		
Mode of delivery*		
Vaginal	1/16 (6%)	21/54 (39%)
Caesarean		
Elective	6/16 (40%)	10/54 (19%)
Non-elective	9/16 (60%)	20/54(37%)
Emergency	0%	3 (6%)
GA, w + d	29 + 4 (25 + 6, 34 + 6)	28 + 3 (23 + 6, 33 + 4)
Male	7/16 (44%)	30/54 (56%)
BW, g	968 (580−1420)	1071 (565−1500)
SGA	13/16 (81%)	16/54 (30%)
Umbilical artery pH	7.27 (7.06−7.35)	7.33 (7.19−7.45)
Postnatal characteristics		
Sepsis/meningitis/NEC	5/16 (31%)	10/54 (19%)
BPD	3/16 (19%)	10/54 (19%)
Postnatal steroids	1/16 (6%)	6 /54 (11%)
Outcome		
Brain volume (ml)	330 (233 - 391)	371 (261 - 466)
Brain pathology		
Normal	2/16 (13%)	14/52 (26%)
Intermediate	5/16 (31%)	18/52 (33%)
Major	9/16 (56%)	20/52 (38%)
MDI	94 (68−122)	106 (74−128)
HINE	73 (68−78)	74 (52−78)

* Statistically significant difference.

5.1.1 The possible pathophysiological mechanism

To find a possible pathophysiological mechanism for association between pathological feto-placental blood flow pattern and adverse cognitive outcome the effect of brain pathology and brain volume was studied.

Brain volume was considered as a mediating factor for cognitive outcome. This is based on the finding that infants with abnormal UA/MCA had reduced cerebral volume, and that abnormal UA/MCA PI ratio associated with adverse cognitive performance, and when the effect of brain volume was controlled for in multivariate analysis, association between UA/MCA PI ratio and cognitive outcome was no longer significant (Table 3). Brain pathology was not found to be a mediating factor. The definition of mediating factor bases on theory by Baron and Kenny (1986).

Table 3. Association between feto-placental blood flow patterns and cognitive outcome at 2 years CA. Results are expressed as estimated regression coefficient and SE. Estimated regression coefficient describes change in MDI when UA PI and UA/MCA PI ratio are abnormal and when DAo/MCA PI ratio, DAo PI and MCA PI are elevated by one unit; minus symbol indicates decrease in MDI. (Study I, picture republished with the permission of the publisher).

Doppler US flow	Univariate analysis	Multivariate analysis		
		Confounding factors	Confounding factors and brain pathology	Confounding factors and brain volume
Abnormal UA PI	-7.9; (3.8)*	-6.6; (4.2)	-6.1; (4.4)	-5.6; (4.2)
Abnormal UA/ MCA PI ratio	-12.1;(3.9)*	-11.4; (4.4)*	-10.6; (4.7)*	-8.2; (4.6)
DAo/MCA PI ratio	-7.6;(3.1)*	-5.6; (4.1)	-4.8; (4.4)	-3.9; (5.6)
DAo PI	-6.5;(2.9)*	-7.5; (3.3)*	-6.8; (3.5)	-6.1; (3.4)
MCA PI	3.9; (3.5)	3.0; (3.8)	3.0; (4.0)	2.8; (3.7)

* Statistically significant difference.

Cerebral volume at term age measured by MRI was reduced in those infants with abnormal UA PI compared to those infants with normal UA PI, the mean reduction being 33 ml. An abnormal UA/MCA PI ratio was also associated with a smaller cerebral volume in MRI compared to those infants with normal UA/MCA PI ratio; the mean reduction was 41 ml, total cerebral volumes are presented in Table 2.

5.2 Early growth of extreme immature infants at the beginning of 2000s

The Finnish extremely preterm infants were born during 2001 to 2010. In addition to the ELGA group of the PIPARI Study cohort, infants born between 2006 and 2010 and two infants treated in a district hospital (postnatal growth did not differ) were also included in the ELGA study cohort.

Early growth in weight, length, and HC of ELGA infants, born at Turku University Hospital between 2001 and 2010, was compared to the Swedish growth charts for ELGA infants (Horemuzova et al., 2012). These charts were based on data from ELGA infants born at Karolinska University Hospital between 1990 and 2002. Table 4 presents the background data of both the present and the Swedish ELGA study cohorts.

Table 4. Perinatal characteristics of ELGA study infants compared to reference study cohort (Study II, picture republished with the permission of the publisher).

Finnish study infants (n=55) n/ mean, (range) / %		**Swedish study infants (n=162) n/ mean, (range) / %**	
Participants of each GA (n)		Participants of each GA (n)	
22	0	22	1
23	8	23	14
24	21	24	53
25	26	25	94
Female	47%	Female	53%
Birth weight of each GA (g)		Birth weight of each GA (g)	
23	537 (485 - 585)	23	617 (519 - 700)
24	717 (600 - 975)	24	720 (462 - 875)
25	760 (560 - 956)	25	781 (426 - 1005)
Birth length of each GA (cm)		Birth length of each GA (cm)	
23	33 (28 - 48)	23	31 (27 - 33)
24	33(31 - 37)	24	32 (27 - 35)
25	34 (30 - 37)	25	33 (29 - 37)
Birth HC of each GA (cm)		Birth HC of each GA (cm)	
23	21 (20 - 22)	23	21 (20 - 23)
24	23 (21 - 27)	24	22 (20 - 24)
25	24 (22 - 30)	25	23 (21 - 26)
PROM	35	PROM	35%
Antenatal steroids	100%	Antenatal steroids	70%
PDA	51%	PDA	77%
BPD	51%	CLD	73%
Postnatal steroids	53%	Postnatal steroids	20%
NEC	14%	NEC	17%
IVH > grades III	16%	IVH > grades III	14%

Figure 3 shows that in the female neonates, there was no difference in weight between the Finnish and Swedish cohorts at a GA of 36 and 40 weeks (Glass's delta (D) = 0.1, p = 0.93 and D = 0.0, p = 0.72, respectively). In comparison with the reference cohort, the male infants from the present study seem to be heavier at 40 weeks of GA, but not at 36 weeks of GA (Figure 3, D = 0.7, p = 0.01 and D = 0.4, p = 0.13, respectively).

Length and HC were compared in the combined data of both genders. The study infants were taller at 36 and at 40 weeks of GA (D = 0.7, p = 0.001 and D = 0.7, p = 0.002, respectively), and the HC was bigger at 40 weeks of GA (D = 0.5, p = 0.01) compared with the reference population. There was no difference in HC at 36 weeks of GA (D = 0.3, p = 0.10) (Figure 4 and 5). In the following figures – 3, 4 and 5 – are presented growth parameters in weight, length and HC for female and male infants at 36 and 40 weeks of GA in a box plot. Grey ± 2, ± 1 and 0 SD-lines are based on Swedish ELGA growth charts. Regarding the study cohort, the weight median is marked as a thick black line, and a mean as a triangle. Quartiles are presented as a large square, and the lowest measure is within the 1.5 interquartile range (IQR) of the lower quartile and the highest measure is within the 1.5 IQR of the upper quartile in the study cohort, marked as vertical lines

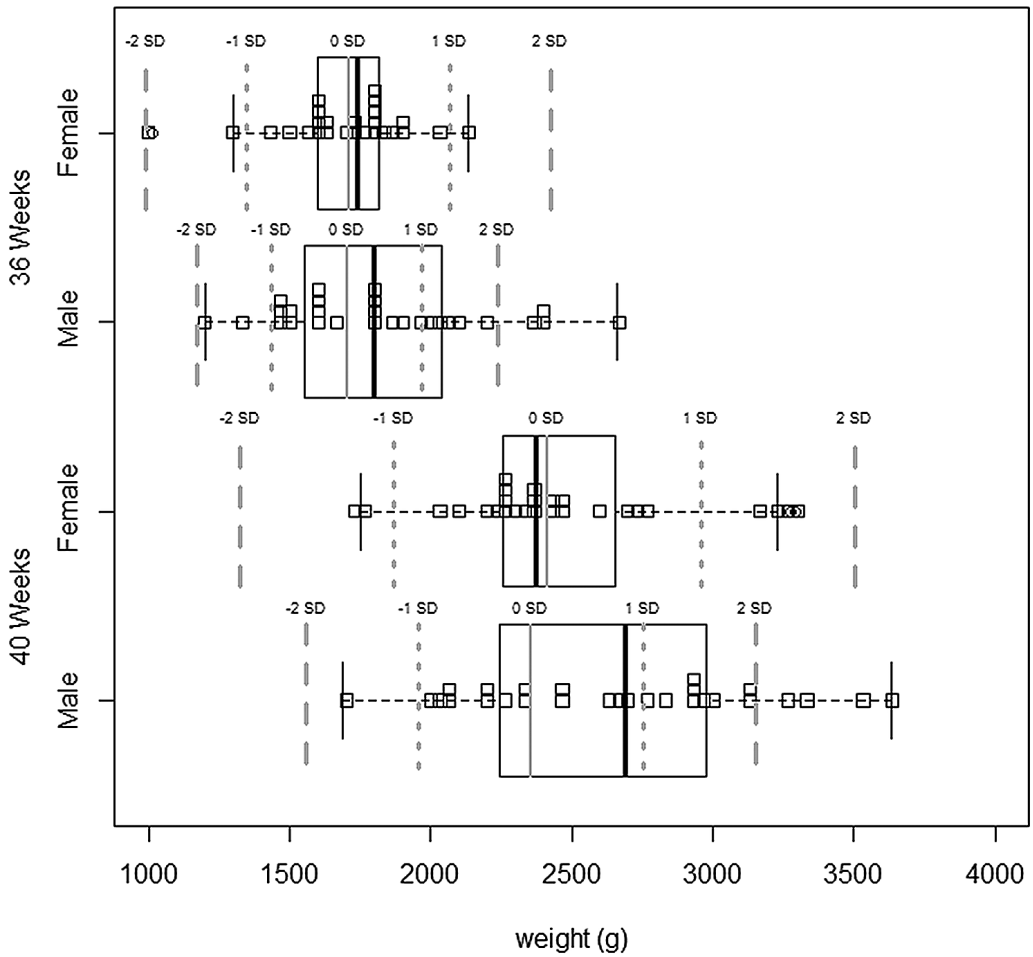


Figure 3. The weights in grams at 36 and at 40 weeks of GA for female and male study infants compared to the Swedish reference population. (Study II, picture republished with the permission of the publisher).

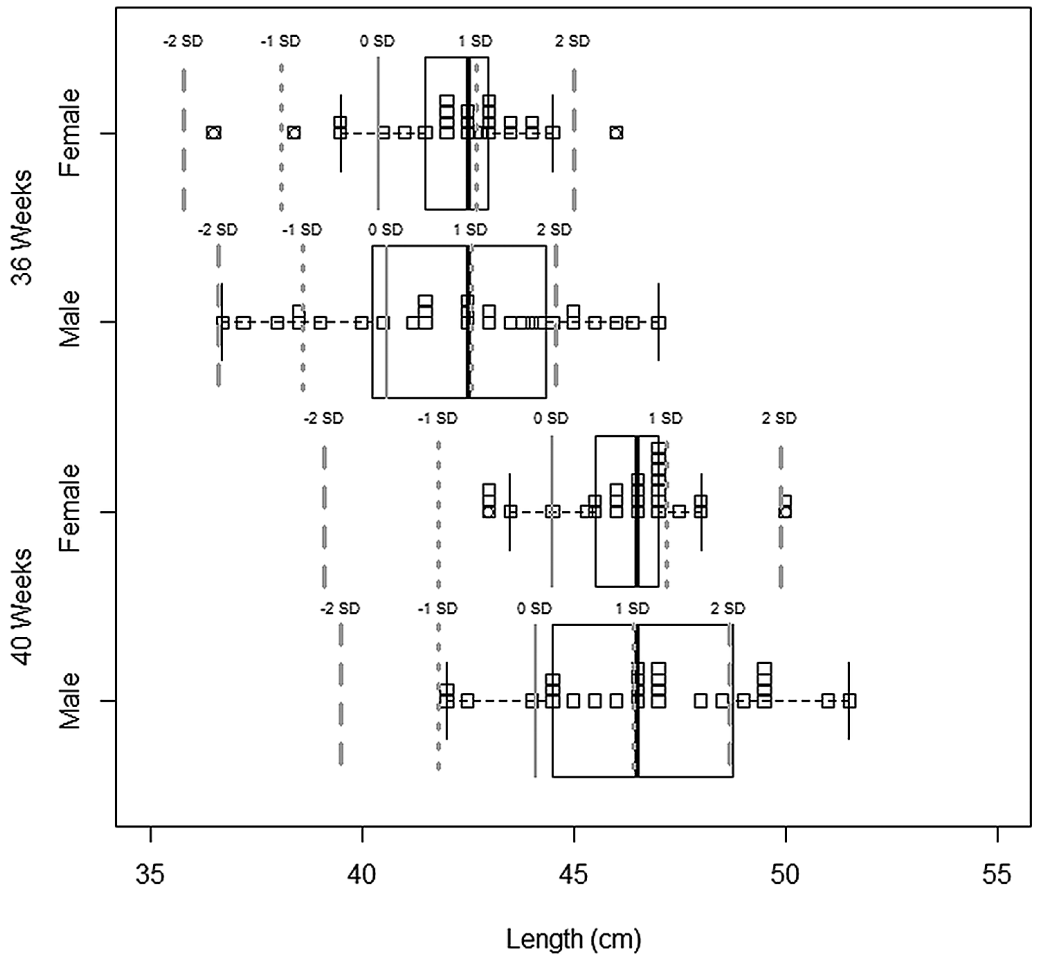


Figure 4. Length in centimetres at 36 and at 40 weeks of GA for female and male study infants compared to the Swedish reference population. (Study II, picture republished with the permission of the publisher).

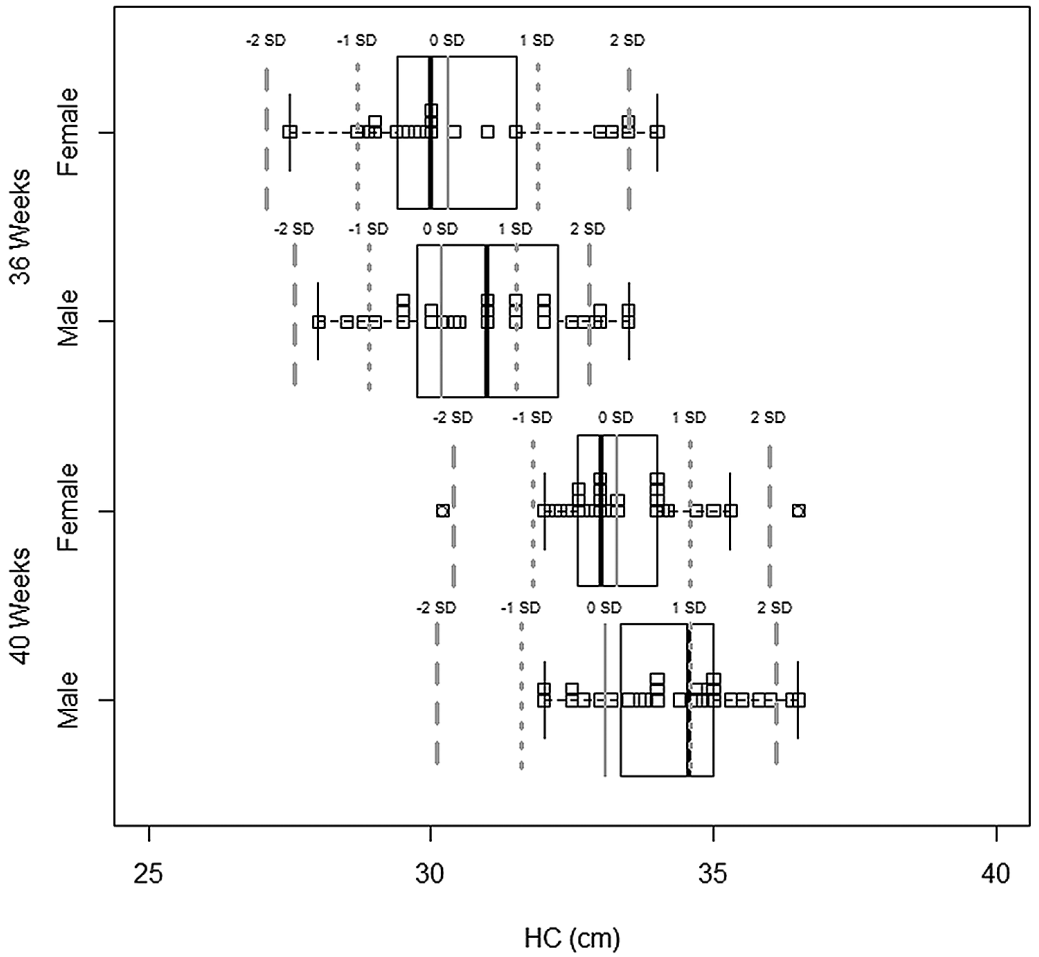


Figure 5. The HC in centimetres at 36 and at 40 weeks of GA for female and male study infants compared to the Swedish reference population. (Study II, picture republished with the permission of the publisher).

It was also studied whether early growth has changed since the beginning of the 2000s, and it was found that in the end of study period (2001–2010), the infants were bigger. The birth year correlated with measures at 36 weeks of GA: weight ($r = 0.49$, $p = 0.001$), length ($r = 0.36$, $p = 0.01$) but not with HC ($r = 0.44$, $p = 0.11$). At 40 weeks of GA, only weight correlated with birth year ($r = 0.35$, $p = 0.01$).

5.3 Early growth and maturation of brain white matter

It was studied whether postnatal growth velocity in this study cohort (n=36) relates to brain maturation at term age as assessed by DTI parameters. No significant associations were observed between early postnatal growth (between birth and term age) in weight or length and DTI parameters: FA, MD, AD, or RD (please refer to the explanation of parameters on page 24).

Instead, catch-up growth in HC associated negatively with FA (Figure 6). Significant positive associations were observed between the catch-up growth in HC and MD (Figure 7), AD, and RD. In all these parameters (FA, MD, AD, RD) associations with z-score change in HC were found in the whole brain: in the forceps major, forceps minor and bilaterally in the anterior thalamic radiation, corticospinal tract, cingulum (cingulate gyrus, hippocampus), inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinated fasciculus and superior longitudinal fasciculus (temporal part). Each of these results (low FA, high MD, high AD and high RD) indicates less matured white matter tracts in infants with more rapid catch-up growth.

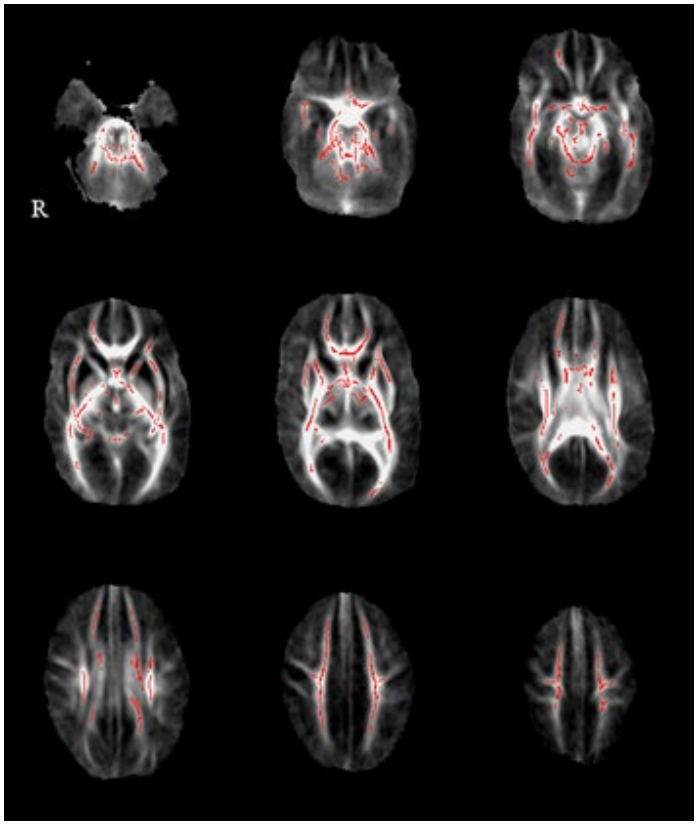


Figure 6. Fractional anisotropy and catch-up growth in HC. A negative association was found between catch-up growth in HC and fractional anisotropy. Areas with a significant difference ($p < 0.05$), between groups are shown in red (Study III, picture republished with the permission of the publisher).

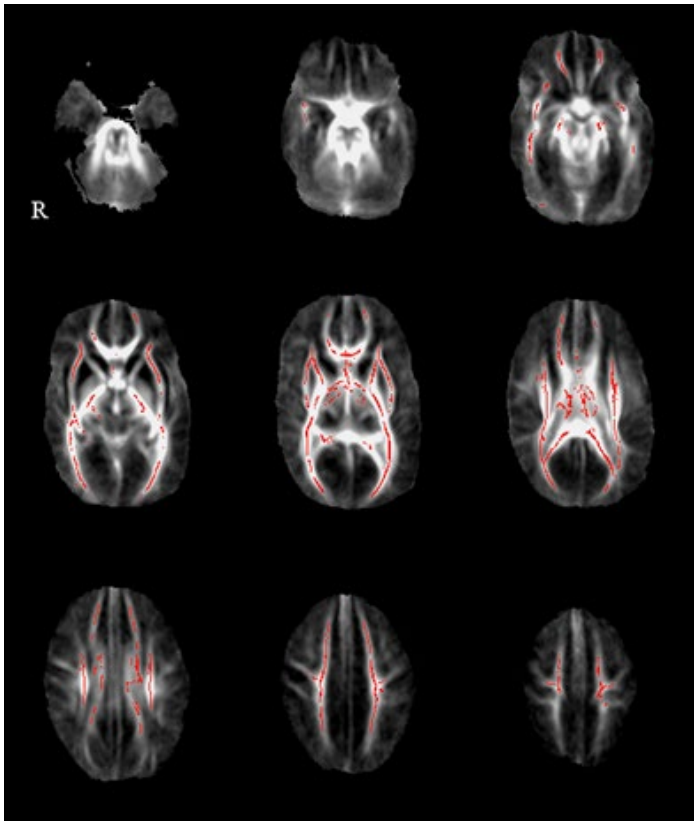


Figure 7. Mean diffusivity and catch-up growth in HC. A positive association was found between catch-up growth in HC and mean diffusivity. Areas with a significant difference ($p < 0.05$), between groups are shown in red (Study III, picture republished with the permission of the publisher).

Further analysis of postnatal growth revealed that study infants with catch-up growth (z-score change > 0 SD between birth and 40 weeks of GA) were smaller at birth compared to infants who grew more slowly (z-score change < 0 SD between birth and 40 GA). Study infants were divided in two subgroups based on postnatal growth pattern (Table 5) and this table reveals differences in BW and HC status. No differences were found in other descriptive statistics.

Table 5. Descriptive statistics for VLBW/VLGA infants with rapid and with slow growth in HC. (Study III, picture republished with the permission of the publisher).

	Rapid growth (n = 25) mean (min, max) or %	Slow growth (n = 11) mean (min, max) or %
Gestational age (weeks+days)	30 + 5 (26 + 1, 33 + 6)	27 + 6 (26 + 5, 31 + 4)
BW (g)	1426 (840, 1970)	1454 (790, 2120)
Birth length (cm)	41 (35, 45)	41 (35, 46.5)
Birth HC (cm)	28 (23.5, 30.5)	29 (23, 32)
BW z-score*	-1.4 (-4.1, 1.1)	- 0.1 (-1.8, 2.6)
Birth length z-score	-0.2 (-3.6, 2.8)	0.5 (-1.4, 3.0)
Birth HC z-score*	-0.9 (-3.7, 1.9)	0.8 (-1.3, 2.2)
SGA (SD <-2.0)	24%	0%
LGA (SD >2.0)	0%	9%
Weight z-score at 40 GA	-1.1 (-4.4, 1.3)	-0.5 (-2.5, 0.9)
Length z-score at 40 GA	-0.4 (-3.3, 2.0)	-0.4 (-1.9, 0.7)
HC z-score at 40 GA	0.1 (-2.4, 2.4)	0.0 (-1.9, 1.4)
HC z-score change between birth and 40 GA*	0.9 (0.1, 2.2)	-0.8 (-1.8, 0.0)

* Statistically significant difference between these differently grown subgroups.

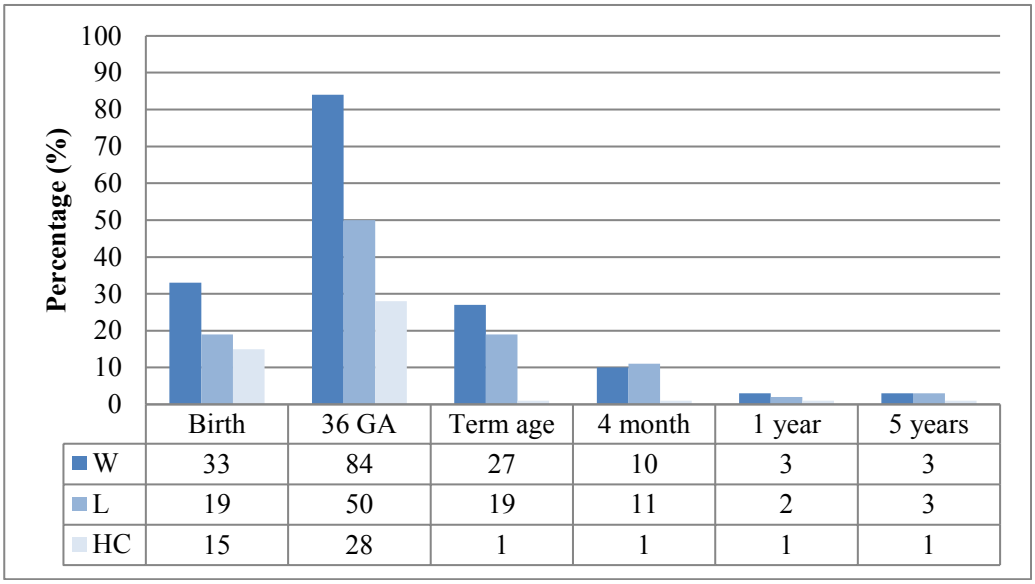
Additional analysis revealed that early growth in HC in this study population did not associate with neurodevelopmental outcome at two years of CA, MDI ($r = -0.03$, $p = 0.88$) and HINE ($r = -0.08$, $p = 0.66$) (unpublished data).

5.4 Growth of very preterm infants until five years of age

5.4.1 Postnatal growth in the whole VLBW/VLGA study cohort

Gender, GA, and brain pathology significantly determined the long-term growth pattern in the whole study cohort. Girls gained more weight from birth to one year ($p = 0.006$) and two years of CA ($p = 0.007$) than boys. Higher GA correlated to better growth before term equivalent age (weight: $r = 0.73$, $p < 0.0001$, length: $r = 0.56$, $p < 0.0001$, HC: $r = 0.42$, $p < 0.0001$) and also up to five years of age (weight: $r = 0.55$, $p < 0.0001$, length: $r = 0.44$, $p < 0.0001$, HC: $r = 0.25$, $p = 0.02$). Infants with normal brain MRI at term age gained more weight between birth and five years of age than the infants with brain pathology ($p = 0.02$). There was a trend that infants with BPD had slower weight ($p = 0.05$) and length growth ($p = 0.05$) until five years of age than infants without BPD (unpublished). The education of mothers and fathers did not correlate to postnatal growth, and neither did diagnosis of NEC (unpublished).

Also AGA born very preterm infants had postnatal growth restriction; approximately 78% of all VLBW/VLGA infants had a z-score of weight below -2.0 SD at 36 weeks of GA. However, growth restriction was rare after that, only 15% were growth restricted at 40 weeks of GA (Figure 8).



	Birth	36 GA	Term age	4 month	1 year	5 years
W	33	84	27	10	3	3
L	19	50	19	11	2	3
HC	15	28	1	1	1	1

Figure 8. Postnatal growth restriction (SD <-2.0) in weight (W, dark grey column), length (L, light grey column), and head circumference (HC, mid grey column) between birth and five years of age in the combined data of both SGA and AGA infants (unpublished).

5.4.2 Postnatal growth in SGA and AGA infants

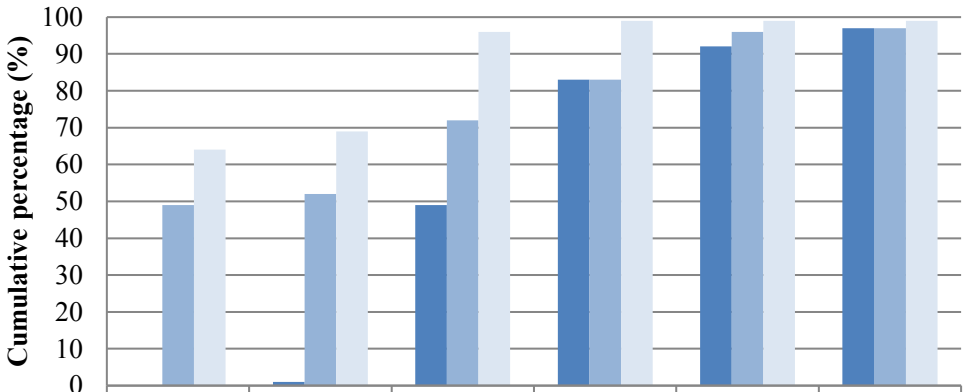
In this cohort 33% were SGA infants and 67% AGA infants, and a further 68% of SGA infants had disproportional growth failure with head sparing, reflecting those infants who might have had growth restrictions before birth. In this study pathological UA/MCA PI ratio associated with risk of intrauterine growth restriction (SGA), $p < 0.0001$, numbers presented in Table 1. However, pathological UA/MCA PI ratio did not associate with disproportional growth failure. Background information separately for SGA and AGA children in Study IV is presented in Table 6. These infants differed in addition to z-score of BW in GA, in percentage of getting antenatal corticosteroids and in Apgar scores, but not for example in body measures of parents.

Table 6. Descriptive data of the VLBW/VLGA study cohort (n=181) for SGA and AGA children. (Study IV, picture republished with the permission of the publisher).

	SGA children (n = 59) Mean (min, max) or %	AGA children (n = 122) Mean (min, max) or %
Multiple birth	29%	34%
Gestational age*	30 + 6 (25+5, 35+6)	28 + 2 (24, 31 + 6)
Male	51%	60%
BW		
(g)	1090 (400, 1500)	1162 (610, 2025)
z-score*	-3.0 (-5.0, -2.0)	-0.6 (-2.0, 2.6)
Birth length		
(cm)	38 (27, 38)	38 (31, 44)
z-score*	-2.3 (-7.8, 1.0)	0.2 (-3.8, 3.7)
Birth HC		
(cm)	27 (20, 31)	26 (21, 31)
z-score*	-1.9 (-5.3, 0.3)	-0.2 (-2.4, 2.8)
Antenatal corticosteroids *	86%	99%
Apgar Score at 5 minutes *	7.2 (2 , 10)	6.7 (1, 10)
Sepsis or meningitis	20	15
BPD	10	16
NEC	2	5
Brain Pathology		
Normal	29%	26%
Minor	32%	36%
Major	39%	37%
FSIQ	99 (42, 133)	101 (39, 140)
CP	3%	3%
Height of mother (cm)	166 (153, 181)	165 (128, 190)
HC of mother (cm)	55 (52, 58)	55 (48, 59)
Height of father (cm)	180 (154, 197)	181 (161, 198)
HC of father (cm)	58 (54, 63)	58 (50, 62)

*A statistically significant difference.

The cumulative percentage of infants reaching ‘normal growth variation’ (>- 2.0 SD) is presented in Figure 9. Catch-up growth was, especially in HC, very early and 96% had normal HC at term age (Figure 9). Despite catch-up growth in the first year, children born as SGA remained smaller at five years of age than children with normal BW for GA (Table 7); in weight $p<0.001$, HC $p<0.001$, and length $p=0.02$ (unpublished).



	Birth	36 GA	Term age	4 month	1 year	5 years
W	0	1	49	83	92	97
L	49	52	72	83	96	97
HC	64	69	96	99	99	99

Figure 9. The cumulative percentage of SGA infants whose body growth exceeded -2.0 SD in each growth measure to describe the catch-up growth of these growth-restricted infants. W = weight, L = length, and HC. (Study IV, picture republished with the permission of the publisher).

Table 7. Growth measures and percentage for postnatal growth restriction (<-2.0 SD) in SGA and in AGA born children from birth to five years of age. (Study IV, picture republished with the permission of the publisher).

Age	SGA children n=59* Mean in g/cm/cm, St. dev., (mean of z-score)	%	AGA children n=122* Mean in g/cm/cm, St. dev., (mean of z-score)	%
At birth				
weight	1089, 285, (-3.0)	100	1162, 308, (-0.6)	0
length	38, 3.6, (-2.3)	53	38, 3.2, (0.2)	3
HC	27, 2.4 (-1.9)	39	26, 2.7, (-0.2)	4
At 36 GA (n=59/120)				
weight	1618, 248, (-4.0)	98	2019, 302, (-2.7)	78
length	42, 2.5, (-3.0)	71	44, 2.2, (-1.8)	39
HC	31, 1.3, (-1.9)	47	32, 1.2, (-1.1)	17
At term age (n=59/119)				
weight	2497, 408, (-1.9)	51	2999, 493, (-0.7)	15
length	46, 2.3, (-1.6)	39	49, 2.3, (-0.4)	8
HC	34, 1.4 (-0.2)	2	35, 1.3, (0.7)	1
At 2 months (n=59/122)				
weight	4446, 658, (-1.5)	27	5031, 732, (-0.6)	11
length	55, 2.7, (-1.6)	27	57, 2.3, (-0.7)	8
HC	39, 1.5, (-0.2)	3	39, 1.3, (0.4)	0
At 1 year (n=59/121)				
weight	8816, 1016, (-0.5)	5	9539, 1088, (0.1)	3
length	74, 2.7, (-0.3)	2	76, 2.7, (0.3)	2
HC	46, 1.7, (0.4)	2	47, 1.5, (1.0)	0
At 2 years (n=59/122)				
weight	11230, 1271, (-0.5)	9	12186, 1393, (0.2)	2
height	87, 3.1, (-0.2)	3	88, 3.1, (0.2)	1
HC	48, 1.8, (0.4)	2	49, 1.5, (1.0)	1
At 5 years (n=53/90)				
weight	16611, 2267, (-0.8)	8	18412, 2310, (0.0)	0
height	108, 5.4, (-0.4)	4	110, 4.4, (0.0)	2
HC	50, 5.1, (-0.4)	0	52, 1.6, (1.0)	2

*Number of observations varies at different ages, presented in first row after age.

5.5 Association between growth and five-year cognitive outcome

Growth in length did not associate with cognitive outcome at five years of age in this VLBW/VLGA study cohort. In AGA children, but not in SGA children, rapid growth in weight and HC from birth until two years of CA was positively associated with cognitive outcome. In SGA infants, growth of HC in SGA infants between 36 weeks of GA and four months of age was positively correlated to better fives-year cognitive outcome.

Table 8. All significant correlations between growth in weight (W), length, and HC and cognition at five years in detailed and separate analyses for SGA, AGA, and all VLBW/VLGA study children (both SGA and AGA children) controlling for gender, gestational age, and the mother's educational level. (Study IV, picture republished with the permission of the publisher).

Time period	SGA r, (p-value)	AGA r, (p-value)	All r, (p-value)
Birth – 36 GA		W 0.22, (0.02), HC 0.23, (0.02)	
36 GA – one month	HC 0.36, (0.009)		
36 GA – two months	HC 0.36, (0.008)		
36 GA – four months	HC 0.33, (0.03)		HC 0.19, (0.003)
Birth – 40 GA		W 0.21, (0.02), HC 0.22, (0.02)	
40 GA– four months			HC 0.17, (0.04)
Birth – two months		HC 0.23, (0.01)	HC 0.16, (0.03)
Birth – four months		HC 0.28, (0.004)	HC 0.18, (0.02)
Birth – one year		HC 0.23, (0.01)	HC 0.15, (0.04)
Birth – two years		W 0.18, (0.04), HC 0.25. (0.006)	HC 0.15, (0.04)
36 GA – five years		HC -0.35, (0.04)	

When the study infants were studied as one group, only HC growth between birth and two years of CA associated with cognitive outcome at five years of age. Analysed in separate time intervals, FSIQ at the age of five years increased by 2.5 (95% confidence interval, CI=0.67 to 4.33, p = 0.008) for each z-score increase in the HC between birth and one year CA, by 3.6 (CI=0.95 to 6.15, p = 0.007), between term equivalent age and one year of CA, by 2.5 (CI=0.65 to 4.31, p = 0.008), between birth and two years of CA, and by 3.1 (CI=0.45 to 5.70, p = 0.02) between term equivalent age and two years of CA after adjustments for GA, gender and the mother's education. The FSIQ according to the z-score change between birth and two years of CA (without adjustments) is presented in Figure 10.

Further, study infants were divided according to the size of HC at birth to two groups (Birth HC < -2.0 and > -2.0 SD), and studied again in detailed if particular growth period in weight, length or HC is significant for 5-year cognitive outcome (unpublished, Table 9). These results are a little bit different than results when comparing SGA and AGA infants (weight < -2.0 or > 2.0, respectively). Growth in HC was the most significant for both groups. Again, in growth restricted infants early growth, beginning already since 36 weeks of GA was significant when in normally grown significant period started after birth. But infants with small HC at birth did benefit of HC growth also after birth and even until five years of age.

Table 9. All significant correlations between growth in weight (W), length (L), and HC and cognition at five years in detailed and separate analyses for study infants that had birth HC below - 2.0 SD and for infants that had birth HC above -2.0 SD (unpublished).

Time period	Birth HC < - 2.0 (n=28) r, (p-value)	Birth HC > -2.0 (n=153) r, (p-value)
Birth – 36 GA		HC 0.19, (0.04)
36 GA – 40 GA	L -0.46, (0.01)	
36 GA – one month	L -0.42, (0.03) HC 0.47, (0.02)	
36 GA – two months	HC 0.51, (0.007)	
36 GA – two years	HC 0.39, (0.04)	
Birth – 40 GA	L -0.41, (0.03)	HC 0.17, (0.04)
40 GA– two months	L 0.44, (0.02) HC 0.56, (0.002)	
Birth – one month	HC 0.48, (0.01)	
Birth – two months		HC 0.20, (0.02)
Birth – four months		HC 0.24, (0.006)
Birth – one year	HC 0.43, (0.02)	HC 0.23, (0.004)
Birth – two years	HC 0.43, (0.02)	HC 0.21, (0.008)
Birth – five years	HC 0.49, (0.04)	

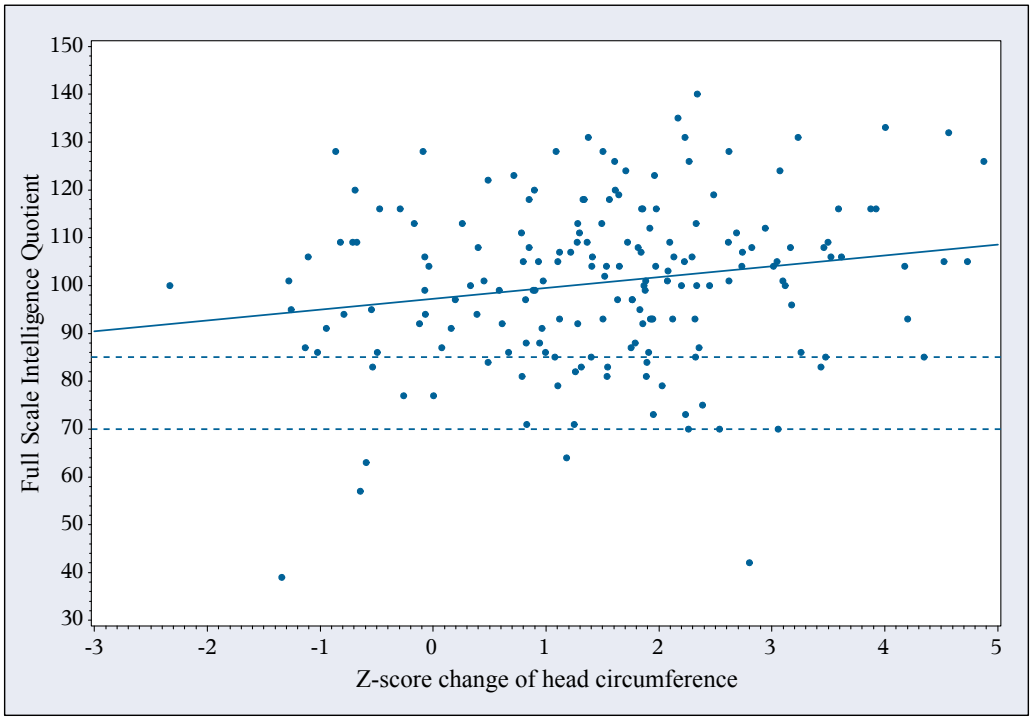


Figure 10. Correlation between head circumference (HC) growth and cognitive outcome. The x-axis presents the z-score change of head circumference between birth and two years of corrected age. The y-axis shows the FSIQ. The horizontal lines at FSIQ 85 (-1.0 SD) mark slightly below normal and at FSIQ 70 (-2.0 SD) mark significantly below normal (Study IV, this picture is republished with the permission of the publisher)

The time when infants had catch-up growth (>-2.0 SD) in weight, length, and HC did not correlate to cognitive outcome at five years of age. It was also found that AGA infants with and without catch-down growth in weight at 36 weeks of GA did not differ in cognitive outcome at five years. There was no difference in cognitive outcome (FSIQ) at five years of age between SGA and AGA children. There was also no divergence in the presence of neurodevelopmental impairment at five years of age (FSIQ below 70); it was 9% in AGA and 12% in SGA children (unpublished data).

6. DISCUSSION

This prospective follow-up study in the PIPARI Study cohort provides new information about early growth and its influence on the neurodevelopment of very preterm infants born in the beginning of the 2000s. Antenatal hemodynamic circumstances that have an effect on growth were also studied. The growth and development of the brain was studied in relation to blood circulation and growth.

6.1 Feto-placental blood flow and neurodevelopment in very preterm infants

Here, blood flow changes in foetal circulation combined with decreased umbilical artery blood flow were related to impaired cognitive outcomes in very preterm infants. These redistributive changes try to compensate for foetal distress due to placental insufficiency and ensure blood flow to the foetal heart and brain. However, the clinical significance of these changes has remained controversial (Scherjon et al., 1998 and 2000, Tideman et al., 2007, Eixarch et al., 2008, Roza et al., 2008, Baschat et al., 2009). Moreover, it is thought that these changes may not protect brain development sufficiently during instances of placental insufficiency; this is supported by the findings of Study I. Brain sparing (an increase of blood flow in the MCA when the flow in UA is diminished) and increased resistance in the DAo were found to be the risk factors for adverse cognitive outcome at two years of age (CA). No association was found between antenatal Doppler US flow patterns and motor outcome. Therefore, it can be assumed that the maturation of motor and cognitive brain functions may occur separately.

Regarding the possible pathophysiological mechanisms, based on the present study, the total brain volume loss detected at term age may be a mediating factor for the association between brain sparing and adverse neurodevelopment. A negative association between placental insufficiency and brain volume has been previously reported in animal studies (Dobbing et al., 1971) and also in clinical studies, for example by Tolsa and co-authors (2004) and in a previous study by Maunu and co-authors (2007) within the PIPARI study. Hypoxia in placental insufficiency is usually less severe but may be long lasting. However, even a mild deficiency of nutrients and oxygen may slow down the growth of organs, including the brain, despite the body's attempts to increase blood flow to the brain and heart. In this study, intrauterine growth was not followed systematically in relation to Doppler US findings. But it was found that the pathological blood flow patterns in UA and MCA were more common in SGA than in AGA infants. In Study IV, 68% of the SGA infants had a disproportional growth failure with head sparing, which

may be related to growth restriction in late gestation (Militello et al., 2009). Thus, the aetiology of the growth restriction in these infants may have been placental insufficiency.

On the contrary, brain pathology was not found to mediate the association between pathological feto-placental blood flow and adverse neurodevelopment. It is speculated that acute hypoxia poses a higher risk for brain pathology than chronic hypoxia (Bolisetty et al., 2014), which may partly explain the result of this study, as acute hypoxia was rare. On the other hand, only brain US and MRI were used to determine brain pathology in this study, so it can be discussed whether other imaging modalities like for example, DTI, could have revealed more delicate white matter pathologies not seen here (Counsell et al., 2008, Woodward et al., 2012).

The most pathological flow indices, absent or retrograde net flow, were rare in this VLBW/VLGA study population when compared to observational studies in IUGR infants (Chabulinski et al., 2012). It can be remarked that in most cases, the foetuses were delivered before any obvious abnormality in the feto-placental blood flow was anticipated. This may also be one reason why the motor outcome of these children was good and why most of the infants had normal cognitive outcome. The results of this study support the clinical practice of delivering these babies before less severe abnormalities like abnormal UA/MCA PI and DAo PI are seen if other risks such as prematurity are not problematic. However, more studies are needed to obtain information about this phenomenon and its long-term consequences.

6.2 Postnatal growth

In the present study, postnatal growth was analysed in three separate studies. Firstly, early postnatal growth between birth and term age in ELGA infants was compared to the Swedish cohort of ELGA infants (Study II). Secondly, early postnatal growth between birth and term age was analysed in association with brain maturation in a small proportion of the PIPARI study infants (Study III), as discussed in the next chapter. Moreover, growth was followed longitudinally until five years of age in the whole PIPARI study cohort (Study IV), and growth was also studied in relation to neurodevelopment in SGA and AGA born children – see Chapter 6.4.

In order to evaluate postnatal growth in very preterm infants treated in Turku, the growth of the ELGA infants was compared to the Swedish ELGA growth charts (Horemuzova 2012). As ELGA infants do not achieve an ideal intrauterine growth rate (Ehrenkrantz et al., 1999 and 2006, Clark et al., 2003, Horemuzova et al., 2012) cross-sectional growth charts that describe intrauterine growth (data collected either by birth measures or by the antenatal US estimation) may not be a practical tool to assess postnatal growth in

preterm infants. Therefore, it was considered that the Swedish ELGA growth chart based on extrauterine growth rate could be comparable as treatment policies in Finland and Sweden do not differ markedly. However, it is important to notice that cohorts were born at different times and therefore the Swedish growth chart was already likely to be 'old' for describing the extrauterine growth of preterm infants born in the 2000s.

ELGA boys grew differently than the girls in the present study. The early growth of Finnish ELGA boys was faster than the Swedish cohort, whereas in girls it was quite similar. It has previously been concluded that preterm born boys are for some reason more vulnerable to insufficient nutrition, and even despite equal nutrition, boys have a higher risk for EUGR (Hack et al., 2003, Brandt et al., 2005). However, in this cohort, boys grew better than girls compared to the Swedish ELGA cohort. One explanation for better growth in the present study can be that cohorts were born at different time periods: the Swedish between 1990 and 2002 and the Finnish cohort later, between 2001 and 2010. Thus, improvements in nutrition or treatment may explain this finding. It can be speculated, for example, that growth in boys has improved because of increased early intake of energy, protein or lipids. This was also speculated by Horemuzova and co-workers (2012), as HCs of boys were found to be bigger compared to previous growth chart (Niklasson et al., 2003). However, nutrition was not included in the study design and therefore information was not collected systematically. But it is known that the start of breast milk on the day of birth, even for these small ELGA infants, was more common during the end of study period than in the beginning. Also, the intake of amino acids has increased since the beginning of the 2000s (Study IV, Leppänen et al., 2012). In the present ELGA cohort, growth was better at the end of the study period (weight and length at 36 GA and weight at 40 GA), which is possibly explained by these improvements in nutrition.

In Study IV, growth in SGA and AGA infants were analysed separately as antenatal growth may have a determinant effect on postnatal growth. Results of catch-up growth in SGA born children differ in different studies (Brandt et al., 2003, Hack et al., 2003, Diekmann et al., 2005, Pierrat et al., 2011, Bocca-Tjeertes et al., 2013). In the present study, postnatal growth, overall, even in SGA born children, was better when compared to the results in earlier studies (Frisk et al., 2002, Brandt et al., 2003, Franz et al., 2009, Bocca-Tjeertes et al., 2013). However, it is difficult to compare this result to other studies because of the differences in cohorts: for example, GA, birth weight, morbidity and also the years in which the cohorts were born vary. Importantly, cohorts also may include different percentages of SGA infants: for example, in the present study the number is 33, yet there were only nine in the study by Belfort and co-authors (2011). Indeed, different growth references and definitions of growth restriction make such a comparison almost impossible.

In the present study, EUGR was most obvious at 36 weeks of GA both in SGA and AGA infants, as it is reported in many earlier studies (Steward et al 2001, Clark et al., 2003, Dusick et al., 2003, Horemuzova et al., 2012). However, growth between birth and 36 weeks was not investigated in the current study. It should be noted that EUGR in ELGA infants peaks at 28–35 days after birth (Stoltz Sjöstrom et al., 2013) and thereafter some catch-up growth is observed, suggesting that an evaluation at 36 weeks probably underestimates EUGR. But growth in this study cohort was rapid after 36 weeks of GA, and weight, length, and HC were in the "normal range" (between -2.0 and + 2.0 SD) by one year of age. HC was already within the normal range at term age, even in SGA infants. Similarly, Horemuzova and co-authors (2012) found the catch-up growth in HC before term age in ELGA infants born 1992–2002. In many previous studies, later catch-up growth of HC has been reported (Hack et al., 1991, Brandt et al., 2003). For example, in a study by Franz and co-authors, the mean z-score of HC was still -1.9 at five years of age in very preterm infants (GA below 30 weeks and BW below 1500 g, born 1996–1999).

Regarding factors that may have influenced on postnatal growth, unfortunately nutritional data were not collected systematically in the current study and relation to growth was not studied. Earlier for example, Stoltz Sjöström and co-authors (2013) found that energy, protein and fat intake related positively to postnatal growth, but the latter only for HC. It is known also that morbidity relates to increased risk of EUGR (Ehrenkranz et al., 1999 and 2006, Cooke 2006, Ranke et al., 2007, Pierrat et al., 2011, Mitha et al., 2013), for instance to ventilation problems, infections and corticosteroid treatment (Stoltz Sjöström et al., 2013). Infants in the current study with detected brain pathology grew more slowly until five years of age than infants without pathologies, which is in line with previous studies (Ehrenkranz et al., 1999, Dusick et al., 2003, Cooke 2005, Franz et al., 2009, Frondas-Chauty et al., 2014). It can be speculated that growth restriction in infants with brain abnormality may relate to feeding problems. However, information about feeding problems was not systematically collected in this study. Here, the diagnosis of BPD or NEC (surgically treated) was not associated with growth. Earlier, NEC (Ehrenkranz et al., 1999, Hintz et al., 2005) and chronic lung disease (BPD) (Ehrenkranz et al., 1999, Pierrat et al., 2011) have been related to the increased risk of delayed growth in very preterm infants. But there is also a linear finding to the current study regarding the effects of BPD on postnatal growth (Frondas-Chauty et al., 2014). In this cohort, morbidities were quite rare; for example, of the SGA study infants 10% had a diagnosis of BPD and 2% had NEC. In turn, low morbidity may relate to a high percentage of breast milk intake (Arslanoglu et al., 2013). Higher GA at birth correlated to more rapid growth both before term age and also from birth up to five years of age. Indeed, GA is shown to be major determinant of postnatal growth pattern (Clark et al., 2003, Dusick et al., 2003). Girls gained more weight between birth and two years of CA than boys. This finding

that girls grow better after birth than boys is in line with earlier studies (Marlow et al., 2005, Farooqi et al., 2013, Frondas-Chauty et al., 2014). About the gender difference, the greater morbidity of boys compared to girls has been considered as one explanation for postnatal growth restriction in boys (Marlow et al., 2005).

6.3 Relation of postnatal growth to brain maturation

Relation of postnatal growth to brain maturation has not been studied earlier as I know, so there are no comparable results. In contrast to the primary hypothesis, catch-up growth between birth and term age did not associate positively with markers of brain maturation, as assessed by DTI at term age. A matured brain is defined as one with better integrity of neural tracts within the white matter that connect the different areas of the brain. Instead, catch-up growth of HC was associated with less matured white matter connections at term age.

Further evaluation of the results revealed an important factor: the infants with catch-up growth were smaller at birth than infants with catch-down growth. Based on this result, IUGR, even if not yet as severe as in SGA, may delay brain maturation in very preterm infants. However, based on the present results, this catch-up growth until term age might not fully compensate for the brain maturation delay that was found between smaller and larger study infants. Yet, this result remains unclear because maturation was not studied longitudinally in this study. It can be discussed that compensation may have occurred but it was not seen in this cross-sectional study.

According to results from animal models (Dobbing et al., 1971) and clinical studies (Lepomäki et al., 2013, Padilla et al., 2014), foetal brain growth is vulnerable to hypoxemia and placental insufficiency. Moreover, volume loss in specific layers indicates a reduction in growth of the axons, dendrites, and also oligodendrocytes, which produce the myelin sheath (Mallard et al., 2000). Regarding the pathophysiological mechanism, DTI parameters indicate organizational arrangements and the maturation of the developing brain, not just myelination but also axonal growth and integrity (LeBihan 2003). In this cohort, the myelination stage was assessed at term age by conventional MRI by visual grading. Myelination was not delayed and does not offer an explanation for the observed difference. There is similar finding by DeBruine and co-authors 2013. Therefore, it can be speculated that the difference may be in growth of neural tracts and axons.

This cross-sectional DTI study does not offer an answer regarding the sensitive period in brain development and growth. Nevertheless, earlier results support the theory of a sensitive period in brain growth. It is supported by the finding in a follow-up study of

SGA infants – prenatal growth restriction is associated with impaired cognitive outcome at school age despite rapid postnatal growth (Frisk et al., 2002). Placental insufficiency induced brain growth delay is also found to relate to less mature behaviour at term age assessed by a specialized neurobehavioral assessment (Tolsa et al. 2004). However, not only antenatal growth alone, but also postnatal growth, influences neurodevelopment (Casey et al., 2006, Latal-Hajnal et al., 2003, Franz et al., 2009). A considerable amount of compensation may happen after birth as the development and growth of the brain is slow compared to other organs, and it continues into adulthood (De Graaf et al., 2006).

Previously, DTI parameters at term age have been shown be predictive for later neurodevelopment at two years (Counsell et al., 2008, Van Kooij et al., 2012, De Bruïne et al., 2013). Van Kooij and co-authors found positive association between FA values in part of the corpus callosum and cognitive outcome at two years of age. De Bruïne and co-authors (2013) found that low FA in the posterior limb of the internal capsule could predict risk of motor delay and CP at two years of age in very preterm born children. However, in the present study, even if a more immature development of white matter was found in small infants, for example in part of the internal capsule (corticospinal tract), at term age these infants scored normally in neurodevelopmental tests at two years of CA (unpublished). It can be postulated that this is explained by the cohort selection as infants with major brain abnormalities were excluded from this study.

6.4 Antenatal and postnatal growth and relation to neurodevelopmental outcome

Optimal postnatal growth in very preterm infants has been a significant issue in recent years, with both later neurodevelopment and metabolic consequences (Singhal and Lucas 2004) having been in focus. To study if there is a sensitive physical growth period for five-year cognitive outcome, and whether antenatal growth patterns relate to this association, the neurodevelopment of SGA and AGA born very preterm infants were analysed separately controlling for gender, gestational age, and the mother's educational level. Previous analysis of postnatal growth separately for SGA and AGA born children in order to study the association between growth periods and cognitive outcomes (Frisk et al., 2002, Brandt et al., 2003, Latal-Hajnal et al., 2003, Casey et al., 2006, Belfort et al., 2011) have not used such extensive growth data.

Here, early growth until term age was not found to associate with better brain maturation assessed by DTI (Study III, discussed in previous chapter), but postnatal growth over longer periods associated with better cognitive outcome at five years of age (Study IV). More specifically, especially weight gain and growth of HC associated positively, with the cognitive level at five years of age. The results indicate also that a significant time

period for postnatal growth for neurodevelopment seems to be different for SGA and AGA born very preterm infants.

Earlier, an association was found between length growth and neurodevelopment (Belfort et al., 2011, Ramel et al., 2012) and, especially in boys, a lack in height catch-up has been related to adverse neurodevelopment (Cooke and Foulder-Hughes 2003, Lundgren et al., 2003). However, in the present study growth in length did not relate to cognitive outcome at five years of age. Except the found positive association of length growth between 40 weeks of GA and two months of CA in infants with birth HC below – 2.0 SD.

Contrary to earlier results (Belfort et al., 2011), weight gain in SGA infants did not correlate to neurodevelopment. Interestingly, only HC growth in a short period, between 36 weeks of GA and four months of CA, associated positively with five-year IQ in SGA infants. This is nearly at the same age when catch-up growth in HC occurred in SGA infants, as at four months of CA 99% (cumulative) of SGA infants had HC above -2.0 SD. Similarly, Stathis and co-authors (1999) found that poor HC growth between birth and four months of CA associated with impaired six-year cognition in ELBW infants, but SGA and AGA infants were not separated in this analysis.

Weight gain and growth in HC between birth and two years of CA have related positively to a five-year cognitive outcome in AGA born very preterm infants. Some earlier findings support the idea that AGA born very preterm children benefit from rapid postnatal growth during their first year (Latal-Hajnal et al., 2003, Casey et al., 2006) but not after one year. However, the opposite conclusion has also been presented (Beyerlein et al., 2010). Belfort and co-authors (2011) also found that rapid HC growth between the age of one week and term age related to better neurodevelopment in VLGA infants (the mean z-score of birth weight -0.2), but not later in the first year.

However, in many studies the time frame for significant postnatal growth varies and in HC this has been even wider: from nine months (Frisk et al., 2002) to one year (Brandt et al., 2003) or five years (Franz et al., 2009). It is important to note that how exactly ‘the critical time window’ can be defined depends on the research design; for example, Franz and co-authors used measures only from birth, discharge and five years of age. In the present study, the growth evaluation was intensive at the beginning but measures between four months and one year were not used. So, it can be speculated that ‘the critical time frame’ in SGA infants in the present study could have lasted longer than four months, but not longer than one year.

When the association between postnatal growth and five-year cognitive outcome was analysed using the combined data of SGA and AGA, only HC growth associated positively with a five-year outcome. Furthermore, cognitive outcome measure (FSIQ) at

the age of five years increased by 3.6 for each z-score increase in the HC between term equivalent age and one year of CA after adjustments for GA, gender and the mother's education.

In separate analysis, (unpublished, Table 9), it was compared if infants with small birth HC (< 2.0 SD) and normal birth HC (> -2.0 SD) have difference in particular growth periods for cognitive outcome. There were some differences compared to the analysis where SGA and AGA infants were compared. For example, in HC growth the significant period was longer in infants with small birth HC compared to SGA (birth weight < 2.0 SD) infants. These results strengthen the conclusion that growth of HC is the most significant of physical growth parameters for cognitive outcome.

In the present study it was also studied whether the catch-down growth at 36 weeks of GA associates with five-year cognitive outcomes. However, there were no differences in outcome between infants with and without catch-down growth, and the time point when catch-up happened did not associate with cognitive outcome at five years.

Interestingly, the mean cognitive outcome was in the normal range and did not differ between SGA and AGA born very preterm children when they were tested by a standardized and commonly used measures: BSID at the age of two years and by WPPSI-R at the age of five years. Yet, the difference to term born cohort exist (Munck et al., 2010, Lind et al., 2011). The neurodevelopment process is multifactorial and, for example, stimulation, education and environment also have important roles. It can be speculated that postnatal growth (Casey et al., 2008) and possibly other factors like nutrition, which were not studied, could have been compensative for the identified early brain injury: brain volume loss (Study I) and lower maturation in DTI at term age (Study III). For example, one explanatory factor could be the proactive perinatal treatment at Turku University Hospital. This treatment includes antenatal steroids, early delivery before gross abnormalities in antenatal Doppler US, surfactant, effective resuscitation, early feeding with breast milk, and gentle treatment, which might support the developmental plasticity of brain. Breast milk is a good source of long-chain polyunsaturated fatty acids, and long-chain polyunsaturated fatty acids may play an important role in neurodevelopment (Colombo et al., 2013). However, concentration of these fatty acids varies in breast milk depending for example on maternal diet (Brenna et al., 2007). The role of the family was not studied in this thesis but families are increasingly taken into account during care. In Turku University Hospital, for example, kangaroo care and skin-to-skin contact is recommended for all VLBW infants as early as possible. The education level of the mothers relates to cognitive outcome (Beaino et al., 2011, Bocca-Tjeertes et al., 2011), and was taken into account as a confounding factor in Studies I and IV.

6.5 Limitations and strengths

The aetiology of LBW is multi-factorial, and in most of cases determining the aetiology of growth restriction and the genetic growth potential is difficult. Unfortunately, in the present study foetal growth was not systematically followed and a lot about the foetal growth restriction is still unknown. One further limitation is that antenatal Doppler US assessment within one week before delivery was not always possible, for example if the delivery began unexpectedly or the assessment was technically impossible, so the number of observation varied between different veins and arteries. Yet, a major strength of the antenatal Doppler US examinations was that they were conducted by two experienced perinatologists, which increases the reliability of the data.

A significant limitation of this study was that nutrition was not studied systematically for its association with growth and neurodevelopment. For example nutrition at NICU and at home after discharge may differ as intake of milk may be more self-regulated by infant at home. However, nutritional practices are described in this thesis. Recommendations for nutrition were similar for all very preterm infants, but of course intakes may have varied between individuals and years, for example due to morbidities. Nevertheless, one of strengths of the nutrition policy in Turku University Hospital is that breast milk was given to all infants until discharge from hospital, as is recommended (Arslanoglu et al., 2013). Also it can be discussed that a follow-up study may not provide any explanation for causal relation and some other factors, not studied here, may also have had an influence on both growth and neurodevelopment.

It can be discussed whether the measuring of children is error-sensitive. Also, measures especially at five years of age were measured by various nurses. However, the reliability of growth monitoring is assumed to be good as Finnish nurses are experienced in monitoring child growth. Second, a detailed manual exists from the Finnish National Institute for Health and Welfare to standardize the methods of measuring children.

Growth charts, which play a significant role in the evaluation of growth, are an important issue when discussing limitations. Firstly, a single recommendation or standard for growth evaluation in preterm infants does not exist. Thus, there are many options and different studies and countries use different growth charts. Also, as the treatment of preterm infants is advancing, growth references of preterm infants are not up to date. Secondly, one big problem related to growth charts is that many of them are cross-sectional, beginning from term age (the WHO charts), or they only last for short time periods (Diekmann et al., 2005, Niklasson et al., 2008). Therefore, a need exists for the use of many different growth charts in longitudinal studies, like in the present study.

Thirdly, there are different opinions over whether the WHO or national growth charts are optimal for growth follow-up. ESPGHAN recommends the use of the WHO growth charts for preterm infants as the growth of breast-fed infants should be a standard for growth in all infants (Turck et al., 2013). The WHO growth chart includes a weight-for-age chart, which is helpful in identifying growth-restricted infants. The WHO charts also enable the comparison of growth between studies. The WHO charts are taken into clinical practice in many countries, or then some use growth references from developed countries which are combined with the WHO charts (Fenton and Kim 2013). However, national growth charts are also considered to be suitable for growth follow-up as genetic background has an influence on growth (Sankilampi et al., 2013). The strength of the Finnish curves used here is that they are based on birth measures not on estimates of growth done by antenatal US, the latter being less accurate. Unfortunately, both of the Finnish growth charts are old, with the reference measures taken from infants born between 1959 and 1983. Therefore, they might not describe the optimal growth of very preterm infants in general or the very preterm born in the 2000s (Sankilampi et al., 2013). In Finland, new growth charts are also available for children (beginning from term age) (Saari et al., 2011) but the growth data of infants born during 1983 and 2008 was not available at the time of this analysis.

Furthermore, one significant problem in the growth follow-up of preterm infants generally is the lack of reliable growth data for the most immature preterm infants. The number of observations in the most immature infants is small, and growth curves based on birth measures of very preterm infants may present growth of unhealthy and growth-restricted infants, not optimal growth. Moreover, some growth references are selected and others un-selected. It has also been discussed that cross-sectional growth charts describe growth in general, and may not represent individual growth (Sankilampi et al., 2013).

However, in the present study, postnatal growth was studied in relation to neurodevelopment, and as such it can be speculated that the choice of growth charts was not so determinative. Regarding Study II, it can be also discussed that ethnic variability may be larger in the Swedish than in the Finnish cohorts, as Finland has less population diversity, which might reduce the comparability of Finnish and Swedish ELGA cohorts.

Regarding strengths, this study included both VLBW and VLGA infants and only children with syndromes or chromosomal disorders and one child with postnatal corticosteroid treatment were excluded from the growth study. Thus, this cohort represents well the very preterm population born in the beginning of the 2000s, the differences between VLBW and VLGA cohorts were noticed, as the first is likely to include more growth restricted and more mature infants.

Also, a wide range of imaging techniques (both longitudinal and cross-sectional) for brain imaging was used in this thesis. Brain MRI and serial brain US are part of clinical practice and enable early detection of brain injury or volume loss. DTI is a new method, which may be useful in the future to identify white matter injury related to prematurity. However, more studies are needed to determine its clinical utility potential. One major limitation was only one DTI at term age; the cross-section images may not provide information about dynamic brain maturation in relation to growth. In the future, study into brain maturation longitudinally, in relation to growth, is needed. DTI could be done, for instance, at birth and then monthly or in later age. Generally, imaging of very preterm infants is challenging, because of the difficult balance between the technical quality of the images and the health risks of the imaging procedure for an immature body. In the present study, sedation was not used and the artefacts caused by movements restricted the size of the data (Study III). Also, major pathologies were excluded from the study (Study III) because factors such as haemorrhages restrict the diffusion and these images thus do not provide reliable data. As the data was selected in this way, the results may not be representative generally for all very preterm infants. On the other hand, two evaluators examined the DTI data to increase the reliability of the interpretation.

It would have been interesting to have a third group for comparison in the association between growth and neurodevelopment. In the PIPARI Study there is a healthy and selected term-born cohort for cognitive outcome (Munck et al., 2010, Lind et al., 2011), but growth was not followed intensively in this group. The strength of this study is that assessments of cognitive outcomes at two and five years of age were done by validated and widely used methods and by a psychologist. On other hand, a detailed perspective of neurodevelopment can be acquired more reliably later, at school age, using neuropsychological methods.

One of the most important strengths of this thesis is the strict follow-up starting before birth and lasting until five years of age, with only a small number of dropouts, providing extensive data on the growth and development of very preterm infants. The background information was also extensive, for example, parental height and weight and information about maternal education were collected.

7. SUMMARY, CONCLUSIONS AND FUTURE RESEARCH

Naturally, it is essential to prevent children being born with LBW or IUGR. One way to do so is to provide pregnant women with the best treatment possible. Globally, for example, nutritional intervention for pregnant women has decreased the number of LBW and SGA infants (Bhutta and Das 2014). However, preterm birth is not always preventable because of its spontaneous nature (Goldenberg et al., 2008); postnatal treatment should thus be developed to achieve the best possible outcome. Monitoring growth and following up neurodevelopment in very preterm infants is an existing part of health care, but practices differ between centres because of a lack of data about the optimal timetable for monitoring. Thus, the optimal postnatal growth for neurodevelopment in VLBW and VLGA infants is a major issue. Also to know the early origin of the structural and functional development of the brain is momentous for clinical practice in neonatology. In this study, both antenatal and postnatal growth related to neurodevelopment, the latter possibly being compensative for antenatal growth restriction. This study thus has clinical implications.

Both pathological DAo and UA/MCA PI ratios are redistributive changes of blood circulation when the oxygen and nutrient supply of the foetus is threatened, but it seems that these compensatory changes are insufficient to protect the development and growth of the foetal brain. When considering that the risks of preterm birth are tolerable, these infants should be delivered when there are signs of blood flow redistribution, as listed above.

Antenatal growth restriction, even in a milder form than SGA, may delay brain maturation, based on the results of DTI-study. The significance of the results regarding an association between postnatal growth and brain maturation remains unclear and warrants more investigation.

This study highlights that it is essential to recognise SGA and AGA children separately in growth and neurodevelopment follow-up and also in treatment. The significant time periods of postnatal growth were different for these groups of VLBW preterm infants. Growth in AGA born very preterm infants in weight and HC until two years of CA was predictive for a five-year cognitive outcome. However, in SGA infants only HC growth between 36 weeks of GA and four months of GA was determinant for five-year cognitive performance. Nutrition and growth of very preterm infants should be followed up at least until two years of CA. By closely monitoring growth it is possible to influence growth, for example through nutrition. Parents should have easy access to support and advice when needed, and the personnel following growth should be educated in the specific

issues related to nutrition in preterm infants, which is possible at the follow-up clinic for preterm infants.

It can be speculated that the postnatal treatment and nutrition policy is protective for brain growth and development, as at five years of age there was no difference in cognitive performance between SGA and AGA children even there was difference in brain maturation at term age between growth restricted and normally grown infants. There is still a need for further studies to determine if there are critical periods in growth for brain development and what all the factors may relate to the recovery of the brain.

DTI is a potential method to assess brain microstructures in vivo. In future it would be interesting to assess brain maturation by serial imaging as it may give more answers about maturation of brain and its association with growth. Nutrition has a large role in growth and neurodevelopment but there is still a need for more studies: for example, there is no clear explanation why the nervous system of preterm born boys is more vulnerable to insufficient nutrition. It would be also interesting to study whether there are metabolic effects of the rapid early growth in this study cohort.

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