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HUMANIORA

**COGNITIVE DEVELOPMENT OF VERY  
LOW BIRTH WEIGHT CHILDREN  
FROM INFANCY TO PRE-SCHOOL AGE**

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*To tiny fighters and their families*  
*To the staff of NICU*

## ABSTRACT

The survival of preterm born infants has increased but the prevalence of long-term morbidities has still remained high. Preterm born children are at an increased risk for various developmental impairments including both severe neurological deficits as well as deficits in cognitive development. According to the literature the developmental outcome perspective differs between countries, centers, and eras. Definitions of preterm infant vary between studies, and the follow-up has been carried out with diverse methods making the comparison less reliable. It is essential to offer parents up-to-date information about the outcome of preterm infants born in the same area. A centralized follow-up of children at risk makes it possible to monitor the consequences of changes in the treatment practices of hospitals on developmental outcome.

This thesis is part of a larger regional, prospective multidisciplinary follow-up project entitled “Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age” (PieniPAinoisten Riskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään, PIPARI). The thesis consists of four original studies that present data of very low birth weight (VLBW) infants born between 2001 and 2006, who are followed up from the neonatal period until the age of five years. The main outcome measure was cognitive development and secondary outcomes were significant neurological deficits (cerebral palsy, CP, deafness, and blindness). In Study I, the early crying and fussing behavior of preterm infants was studied using parental diaries, and the relation of crying behavior and cognitive and motor development at the age of two years was assessed. In Study II, the developmental outcome (cognitive, CP, deafness, and blindness) at the age of two years was studied in relation to demographic, antenatal, neonatal, and brain imaging data. Development was studied in relationship to a full-term born control group born in the same hospital. In Study III, the stability of cognitive development was studied in VLBW and full-term groups by comparing the outcomes at the ages of two and five years. Finally, in Study IV the precursors of reading skills (phonological processing, rapid automatized naming, and letter knowledge) were assessed for VLBW and full-term children at the age of five years. Pre-reading skills were studied in relation to demographic, antenatal, neonatal, and brain imaging data.

The main findings of the thesis were that VLBW infants who fussed or cried more in the infancy were not at greater risk for problems in their cognitive development. However, crying was associated with poorer motor development. The developmental outcome of the present population was better than has been reported earlier and this improvement covered also cognitive development. However, the difference to full-term born peers was still significant. Major brain pathology and intestinal perforation were independent significant risk factors for adverse outcome, also when several individual risk factors were controlled for. Cognitive development at the age of two years was strongly related with development at the age of five years, stressing the importance of the early assessment, and the possibility for early interventions. Finally, VLBW children had poorer pre-reading skills compared with their full-term born peers, but the IQ was an important mediator even when children with mental retardation were excluded from the analysis.

The findings suggest that counseling parents about the developmental perspectives of their preterm infant should be based on data covering the same birth hospital. Neonatal brain imaging data and neonatal morbidity are important predictors for developmental outcome. The findings of the present study stress the importance of both short-term (two years) and long-term (five years) follow-ups for the individual, and for improving the quality of care.

**KEYWORDS:** infant, crying behavior, prematurity, neonatal morbidity, cognitive development, neurological outcome, brain imaging, pre-reading skills, follow-up

## TIIVISTELMÄ

Pienenä keskosenä syntyneiden lasten selviytyminen on parantunut, mutta keskosuuteen liittyvän pitkäaikaissairastavuuden esiintyvyys on pysynyt edelleen korkeana. Pienillä keskosilla ovat riski kehityksellisille ongelmille, joita ovat muun muassa vaikeat neurologiset vammat sekä kognitiivisen kehityksen poikkeavuudet. Kirjallisuuden mukaan keskosten kehitykselliset näkymät vaihtelevat eri maiden ja eri sairaaloissa syntyneiden lasten välillä, kuten myös eri aikakausina syntyneiden lasten välillä. Eri tutkimuksissa on tarkasteltu eri tavoin määriteltyjä keskosryhmiä vaihtelevilla arviointimenetelmillä, mikä vaikeuttaa luotettavaa vertailua. Keskosien vanhemmille olisi tärkeää pystyä tarjoamaan ajantasaista ja alueellisesti kerättyä tietoa keskosten kehityksellisestä selviytymisestä. Keskitetty riskilasten seuranta antaa sairaaloille mahdollisuuden arvioida hoitokäytännöissä tapahtuvien muutosten vaikutusta keskosten kehityssuuntaukseen.

Väitöskirja on osa laajaa alueellista, prospektiivista ja moniammatillista seurantaprojektia "PieniPAinoisten RIskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään", PIPARI. Väitöskirja koostuu neljästä alkuperäisestä tutkimuksesta, jotka esittävät seurantatietoa vuosina 2001-2006 hyvin pienipainoisena (<1500 grammaa) syntyneistä keskosista imeväisiästä viiden vuoden ikään. Ensisijainen kehitystä kuvaava mittari on lasten kognitiivinen kehitys ja toissijaisesti väitöskirjassa kuvataan lasten merkittäviä neurologisia vammoja (CP-vammaisuus, kuurous ja sokeus). Ensimmäisessä osatyössä keskosten varhaista itkukäyttäytymistä tutkittiin vanhempien täyttämän itkupäiväkirjan avulla ja suhteessa kognitiiviseen ja motoriseen kehitykseen kahden vuoden iässä. Toisessa osatyössä arvioitiin kognitiivista ja neurologista kehitystä kahden vuoden iässä suhteessa taustamuuttujiin, raskauden ja imeväisiän aikaisiin tekijöihin sekä varhaisiin aivokuvantamislöydöksiin. Kehitystä verrattiin samassa sairaalassa täysiaikaisena syntyneiden lasten kehitykseen. Kolmannessa osatyössä arvioitiin keskosten ja täysiaikaisena syntyneiden lasten kognitiivisen kehityksen pysyvyyttä kahdesta viiden vuoden ikään. Viimeiseksi neljännessä osatyössä arvioitiin 5-vuotiaiden keskosten ja täysiaikaisena syntyneiden lasten lukemaan oppimista edeltäviä valmiuksia (äänteiden prosessointi, nopea sarjallinen nimeäminen ja kirjaintuntemus). Lukivalmiuksia arvioitiin suhteessa

taustamuuttujiin, raskauden ja imeväisiän aikaisiin tekijöihin sekä varhaisiin aivokuvantamislöydöksiin.

Väitöskirjan päälöydöksiä olivat, että imeväisiässä itkuiset keskokset eivät olleet korkeammassa riskissä kognitiivisen kehityksen ongelmille. Itkuisuus oli kuitenkin yhteydessä heikompaan motoriseen kehitykseen. Keskosten kehitys oli parempaa verrattuna aiemmin kirjallisuudessa esitettyihin tuloksiin, ja kehityksen parantuminen näkyi myös kognitiivisen kehityksen osalta. Ero täysiaikaisena syntyneisiin verrokkeihin oli kuitenkin merkitsevä. Vaikea aivopatologia, samoin kuin suoliperforaatio, olivat itsenäisiä riskitekijöitä kehityksellisille ongelmille silloinkin, kun monia muita riskitekijöitä oli huomioitu. Kahden vuoden iässä arvioitu kognitiivinen kehitys oli vahvasti yhteydessä kognitiiviseen kehitykseen viiden vuoden iässä, mikä korostaa varhaisen kehitysseurannan ja mahdollisten varhaisten interventioiden mahdollisuuden merkitystä. Keskosilla oli heikommat lukemista ennakoivat valmiudet viiden vuoden iässä kuin täysiaikaisena syntyneillä lapsilla. Keskosten lukivalmiuksiin vaikutti kuitenkin huomattavasti yleinen kognitiivinen kehitystaso siitäkin huolimatta, että kehitysvammaiset lapset eivät olleet mukana analyysissa.

Tutkimusten tulosten perusteella voidaan suositella, että keskosten vanhemmille tulisi tarjota tietoa keskosten kehityssuunnusteesta, joka perustuu samassa sairaalassa saatuihin seurantatuloksiin. Varhaiset löydökset aivokuvantamistutkimuksessa ja imeväisiän sairastavuus ovat kehityksen keskeisiä ennustekijöitä. Tutkimustulokset korostavat sekä lyhyen (2 vuoden) että pitkän (5 vuoden) kehitysseurannan tarpeellisuutta niin yksilön kuin palvelujärjestelmän laadun näkökulmasta

**AVAINSANAT:** vauva-ikä, itkukäyttäytyminen, keskisuus, neonataalisairastavuus, kognitiivinen kehitys, neurologinen kehitys, aivokuvantaminen, lukemista ennakoivat taidot, seurantatutkimus

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## **ABBREVIATIONS**

<b>BSID-II</b>	<b>Bayley Scales of Infant Development, 2nd edition</b>
<b>BDD</b>	<b>Baby Day Diary</b>
<b>BW</b>	<b>Birth weight</b>
<b>CA</b>	<b>Corrected age</b>
<b>CLD</b>	<b>Chronic Lung Disease</b>
<b>CP</b>	<b>Cerebral Palsy</b>
<b>CUS</b>	<b>Cranial Ultra Sound</b>
<b>ELBW</b>	<b>Extremely Low Birth Weight, &lt; 1000 grams</b>
<b>ELGA</b>	<b>Extremely Low Gestational Age, &lt; 28 weeks</b>
<b>FSIQ</b>	<b>Full-scale Intelligent Quotient</b>
<b>GA</b>	<b>Gestational Age</b>
<b>IVH</b>	<b>Intraventricular Hemorrhage</b>
<b>MDI</b>	<b>Mental Development Index</b>
<b>MRI</b>	<b>Magnetic Resonance Imaging</b>
<b>NDI</b>	<b>Neurodevelopmental Impairment</b>
<b>NEC</b>	<b>Necrotising Enterocolitis</b>
<b>NICU</b>	<b>Neonatal Intensive Care Unit</b>
<b>NIDCAP</b>	<b>Newborn Individualized Developmental Care and Assessment Program</b>
<b>PDI</b>	<b>Psychomotor Development Index</b>
<b>PIQ</b>	<b>Performance Intelligence Quotient</b>
<b>PVL</b>	<b>Periventricular Leucomalasia</b>
<b>SGA</b>	<b>Small for Gestational Age</b>
<b>VIQ</b>	<b>Verbal Intelligence Quotient</b>
<b>VLBW</b>	<b>Very Low Birth Weight, &lt;1500 grams</b>
<b>VLGA</b>	<b>Very Low Gestational Age, &lt;32 weeks</b>
<b>WPPSI-R</b>	<b>Wechsler Preschool and Primary Scale of Intelligence – Revised</b>

## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on four original publications; they are referred to by Roman numerals.

- I** Munck P, Maunu J, Kirjavainen J, Lapinleimu H, Haataja L, Lehtonen L; PIPARI Study Group (2008). Crying behaviour in early infancy is associated with developmental outcome at two years of age in very low birth weight infants. *Acta Paediatrica*;97(3):332-336.
  
- II** Munck P, Haataja L, Maunu J, Parkkola R, Rikalainen H, Lapinleimu H, Lehtonen L; PIPARI Study Group (2010). Cognitive outcome at 2 years of age in Finnish infants with very low birth weight born between 2001 and 2006. *Acta Paediatrica*;99(3):359-366.
  
- III** Munck P, Niemi P, Lapinleimu H, Lehtonen L, Haataja L; the PIPARI Study Group (2012). Stability of Cognitive Outcome From 2 to 5 Years of Age in Very Low Birth Weight Children. *Pediatrics*;129(3):503-508.
  
- IV** Munck P, Niemi P, Väliäho A, Lapinleimu H, Lehtonen L, Haataja L; PIPARI Study Group (2012). Prereading skills of very-low-birth-weight prematurely born Finnish children. *Child Neuropsychology*;18(1):92-103.

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## INTRODUCTION

### 1. Preterm infant

A preterm infant is born before the 37th gestational week. A very low gestational age (VLGA) is defined as a gestational age less than 32 weeks, and an extremely low gestational age (ELGA) as less than 28 weeks. A birth weight (BW) of less than 2500g is considered low (LBW), less than 1500g very low (VLBW), and less than 1000g extremely low (ELBW). An infant's birth weight can be appropriate (AGA), small (SGA, -2 SD), or large (LGA, + 2SD) for gestational age (GA). Both GA and BW inclusion/exclusion criteria have been used in studies of prematurity. When the GA criteria are used, it is possible to study the effect on immaturity, and additional BW criteria allow for the study of the mixed effect of immaturity and growth failure.

In Finland, 5.7% of infants are born preterm, the prevalence of LBW births is 4.4%, VLBW births 0.9%, and ELBW births 0.4% (National Centre for Health, Statistics 2010. Available from: [www.stakes.fi/tilastot/tilastotiedotteet/2010/Tr06\\_10.pdf](http://www.stakes.fi/tilastot/tilastotiedotteet/2010/Tr06_10.pdf)). These percentages are among the lowest in European countries (EURO-PERISTAT Project, European Perinatal Health Report 2008. Available from: [www.euoperistat.com](http://www.euoperistat.com)), and significantly lower in comparison to the rates of preterm deliveries in the United States (Beck et al., 2010).

The survival rate of preterm infants has increased dramatically due to progress in care practices (Fanaroff, Hack, & Walsh, 2003; Platt et al., 2007; Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005). However, the progress seems to have slowed down recently (Doyle, Roberts, Anderson, & the Victorian Infant Collaborative Study Group, 2011; Fanaroff et al., 2007). Mortality and developmental outcome vary between countries, and between different centers within countries (Fanaroff et al., 2003; Fanaroff et al., 2007; Larroque et al., 2004; Rautava et al., 2007). This together with the varying prevalence of preterm births makes it important to study the effects of preterm birth in the context of the birth country and the birth hospital, rather than to draw conclusions from studies conducted in other countries and centers.

## 2. Morbidities of preterm birth that affect development

Preterm infants are at risk for multiple morbidities. Immaturity affects innate self-regulation systems and preterm infants are vulnerable to ventilation problems, digestion problems, severe infections, and brain insults. These in turn affect development. It has been shown that prolonged ventilator treatment is a risk for poor developmental outcome (Vohr et al., 2004). Similarly, the risk for developmental problems increases if the infant needs postnatal glucocorticoids to mature the lung (Yeh et al., 2004). Severe infections have been shown to negatively affect the development (Stoll et al., 2004). Necrotizing enterocolitis (Rees, Pierro, & Eaton, 2007; Shah et al., 2008), and especially intestinal perforation (Mikkola et al., 2005) have been shown to associate with poorer developmental outcome.

Recent research has increased the knowledge about neuroprotective factors in obstetric and perinatal care. One important preventive treatment is the application of antenatal glucocorticoids in order to mature the lung of the preterm infant. It has been shown to reduce the risk for neurodevelopmental impairments (Vohr, Wright, Poole, & McDonald, 2005). Another protective factor for better developmental outcome is better nutrition that has lead to improved postnatal growth of preterm infants (Ehrenkranz et al., 2006).

Among environmental factors, lower level of both maternal (Luu et al., 2009; Potharst et al., 2011; Wood et al., 2005), and paternal (Böhm et al., 2002; Potharst et al., 2011) education have shown to associate with poorer development.

## 3. Findings from brain imaging in preterm infants

The brain of a very preterm infant is vulnerable to many assaults both because of immaturity and intensive care. The most common pathological brain finding is diffuse injury in white matter. Preterm infants are also at high risk for intraventricular hemorrhages (IVH) of different degrees (Inder & Volpe, 2000). Periventricular leucomalasia (PVL) is a typical severe white matter lesion.

The two main methods in imaging the brain of very preterm infants are cranial ultrasound (CUS) and magnetic resonance imaging (MRI). CUS provides a view into the central parts of the brain, ventricles, and periventricular areas. It has been shown to accurately diagnose IVH (Horsch et al., 2009; Maalouf et al., 2001) and hemorrhagic parenchymal infarctation (Maalouf et al., 2001). MRI provides an anatomical view into the whole brain, including the cerebellum, and it covers structures that cannot be seen with CUS. The MRI detects white matter and grey matter abnormalities (Inder, Wells, Mogridge, Spencer, & Volpe, 2003), and cerebellar and extracerebral abnormalities (McArdle et al., 1987). However, compared to CUS, the MRI is more expensive and not as widely used. On the other hand, Rademaker et al. (Rademaker et al., 2005) found that MRI was superior to CUS in detecting those children whose brain pathology was related with poorer cognitive outcome later in their development.

#### 4. The crying and fussing behavior of the preterm infant

The duration of crying in a full-term born infant has been suggested to follow a developmental pattern during the first months of life, as shown by Brazelton (Brazelton, 1962). The duration of crying has been suggested to increase gradually from birth, peak during the second month of life (typically around 6 weeks of age), and to reduce thereafter (Barr, 1990; Brazelton, 1962; St James-Roberts & Halil, 1991). Interestingly, preterm infants follow this same developmental pattern when their age is corrected for the degree of prematurity (Barr, Chen, Hopkins, & Westra, 1996). Crying is one reflector of the infant's behavioral characteristics called reactivity and regulation. Infants that are highly reactive start to cry more often, and the duration of the crying bouts reflects the infant's ability to regulate their behavior.

The significance of the duration of crying, and the frequency of started crying bouts on later development has not been studied extensively. In term born infants, excessive crying during the first three months of life has not been shown to associate with the infants' later adverse outcome (Lehtonen, Gormally, & Barr, 2000). In addition, the duration of crying at six weeks of age was unrelated to infant negativity, temperament or behavioral problems (St James-Roberts I, Conroy S, Wilsher C., 1998). In that study, the duration of early crying was not associated with later cognitive development either. In one study, however, infants who cried excessively at six weeks of age

showed higher reactivity, and excessively crying boys had also lower regulation capacity at the ages of five and 10 months (Papousek & von Hofacker, 1998).

According to a normal crying curve, the amount of crying is typically reduced at the age of three months (Barr, 1990; Brazelton, 1962; St James-Roberts & Halil, 1991). Excessive crying continuing beyond this age is called prolonged excessive crying, and it has been shown to relate to later developmental and behavioral problems in full-term infants. In one study, children who cried excessively for more than three months had a lower mean IQ, poorer fine motor abilities and more behavioral problems at the age of five years compared to infants whose duration of crying decreased after three months (Rao, Brenner, Schisterman, Vik, & Mills, 2004). It has also been shown that persistent crying (exceeding three hours per day) is related to behavioral problems at the age of 8-10 years (Wolke, Rizzo, & Woods, 2002), as well as to problems in neuromotor functioning, adaptive behavior (Papousek & von Hofacker, 1995), and cognitive development (Wolke, Schmid, Schreier, & Meyer, 2009). However, the significance of early crying behavior for later development has not been studied among preterm infants.

##### 5. The neurological and cognitive development of the preterm infant

Despite the fact that the survival rate of prematurely born infants has increased dramatically during the past decades (Fanaroff et al., 2003; Fanaroff et al., 2007), the prevalence of neurological and cognitive impairments has continued to be high and they are common causes of long-term morbidity in preterm born children (Taylor, Minich, Klein, & Hack, 2004; Taylor, 2006; Wilson-Costello, 2007). According to the literature, the risk for these problems increases with decreasing GA and BW (Foulder-Hughes & Cooke, 2003). Typical adverse consequences of preterm birth include cerebral palsy (CP), cognitive impairments (Doyle, Anderson, & Victorian Infant Collaborative Study Group, 2005; Johnson, Hennessy et al., 2009; Vohr et al., 2005; Wilson-Costello et al., 2005), and vision and hearing impairments (Johnson et al., 2009). In a recent Finnish study on the VLBW/VLGA population, the prevalence of CP was 6.1%, hearing loss 2.5%, and visual impairment/ophthalmic problems 13.4% (Korvenranta et al., 2009).

It is reassuring that the increasing survival rate among preterm children has not occurred at the cost of a higher percentage of children with severe handicaps. However, the increasing survival rate with a relatively stable prevalence of impairments has resulted in an increased actual number of preterm born children with disabilities. The prevalence of CP first started to increase with the growing survival rate of preterm infants (Hintz et al., 2005; Vohr et al., 2000; Wilson-Costello et al., 2005), but more recent observations show that it has started to diminish (Groenendaal, Termote, van der Heide-Jalving, van Haastert, & de Vries, 2010; Himmelmann, Hagberg, Beckung, Hagberg, & Uvebrant, 2005; Platt et al., 2007; Robertson, Watt, & Yasui, 2007; Vohr et al., 2005). In Europe, the prevalence of CP fell to a level of 4 % in 16 centers for children born with VLBW (Platt et al., 2007). Similarly, also the rates of blindness and deafness have lowered recently (Doyle et al., 2011; Wilson-Costello et al., 2007).

The prevalence of cognitive impairments has, however, remained high among preterm children. This review covers studies with developmental follow-up data up to school age as this thesis focuses specially on that period. A second focus is on recent articles presenting results mostly on infants and children born in the 1990's and later.

Very preterm birth has been shown to associate strongly with cognitive impairments throughout childhood (Aarnoudse-Moens, Oosterlaan, Duivenvoorden, van Goudoever, & Weisglas-Kuperus, 2011; Beaino et al., 2011; Johnson, Hennessy et al., 2009; Larroque et al., 2008; Pritchard et al., 2009; Taylor, 2006; Wilson-Costello, 2007; Woodward et al., 2009). Since very preterm children are at risk for developmental problems, many hospitals have follow-up programs, including assessment of cognitive abilities. However, the timing of the follow-up, length of the follow-up period, as well as method repertoire used, vary between countries and centers making international, or even national comparison difficult. The reported prevalence and severity of cognitive impairments vary significantly across the countries, centers, and eras, as well as between the differently selected study populations. It is impossible to describe the cognitive outcome of preterm populations if one does not take into account several contributing factors. Firstly, varying inclusion and exclusion criteria are applied in studies; secondly, there are large differences in the outcomes between the countries and centers; and thirdly, application of different



methods, as well as timing and the length of the follow-up, vary greatly. The era when the preterm population was born is also significant and most likely reflects the change in care practices.

There has been, however, an attempt to describe the differences in cognitive outcomes between very preterm and term born controls in a meta-analysis (Bhutta, Cleves, Casey, Cradock, & Anand, 2002). The authors included 15 studies with different inclusion criteria, including also children born close to the term age, as well as low birth weight (LBW, <2500g) children. The conclusion was that the difference in the intelligence quotient (IQ) between the preterm and full-term born groups was 10.9 points, which equals to about 0.7 SD. A lower gestational age, as well lower birth weight, were related with poorer outcome.

#### a. Cognitive development of ELBW/ELGA children

In research practice, the two main criteria for the inclusion and exclusion of preterm children are gestational weeks or birth weight. A number of large studies have focused on extremely low birth weight (ELBW, <1000g), and extremely low gestational age (ELGA, <28 weeks) infants (Doyle & Victorian Infant Collaborative Study Group, 2001; Doyle, Casalaz, & Victorian Infant Collaborative Study Group, 2001; Doyle, Roberts, Anderson, & Victorian Infant Collaborative Study Group, 2010; Doyle et al., 2011; Kobaly et al., 2008; Wilson-Costello et al., 2007; Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000; Woodward et al., 2009), even though these criteria cover only a small subgroup of all preterm infants. The overall developmental outcome prospect of these populations has been very pessimistic. There are some differences between the countries, but the main message from the studies is that a large percentage of ELBW/ELGA children suffer from significant developmental problems.

In Australia, The Victorian Infant Collaborative Study Group followed up ELBW/ELGA infants born across different eras. They have found that the cognitive development of these children is poor in comparison to their full-term (FT) peers, and that the prevalence of delay in cognitive development (- 1 SD criterion) has been over 40 percent for cohorts born in the 1980's, 1990's, and in 2000's at the age of two years

(Doyle et al., 2011). Also, the prevalence of severe ( $< -2SD$ ) delay in cognitive development has been shown to be high (about 20%).

In the USA, a large NICHD Neonatal Research Network multicenter study has followed up infants born before 25 GWs during a long period (Hintz et al., 2005; Hintz et al., 2011; Vohr et al., 2004). Significant differences in the developmental outcomes between centers have been noted (Vohr et al., 2004), but the main message also from these studies has been that a high percentage of children suffer from deficits in their cognitive development. For infants born between 1993-1999, the prevalence of severe cognitive delay (Mental Development Index of Bayley Scales of Infant Development, II, MDI  $<70$ ) rose from an already high 40% up to 47% (Hintz et al., 2005). For infants born between 1999-2004, the prevalence of severe cognitive delay rose further up to 51% (Hintz et al., 2011). Percentages are high despite of the fact that these studies covered the most immature infants. In another longitudinal single-center study, ELBW infants born in three different decades (the 1980's, 1990's, and 2000's) were followed up (Wilson-Costello et al., 2007; Wilson-Costello, 2007). In spite of the increasing survival and decrease in the rate of neurodevelopmental impairments the cognitive outcome of these infants was stable. The mean MDI of this population was 86, 84, and 86 for infants born in the 1980's, 1990's, and 2000's, respectively. The prevalence of significant delay (MDI  $<70$ ) was 20%, 24%, and 21%, and a mild delay was found in 25%, 19%, and 22%, respectively.

In Canada, a large number of infants born  $\leq 800$  grams between 1983-2003 were followed up before entrance to school (Synnes et al., 2010). During that 20-year period, the survival of infants improved significantly (from 46% to 71%). The cognitive development of the children was assessed in four 5-year periods, and the prevalence of significant impairment ( $< -2SD$ ) rose gradually from 11% to 21% during that time.

In Europe, the large population-based EPICure study has followed up all preterm infants born before 26 gestational weeks in the UK. The cognitive development of this population has been reported to be pessimistic, as 30 % of infants had a severe cognitive delay ( $< -2 SD$ ) at the age of 30 months, and the mean value of MDI was 84

(Wood et al., 2000). Almost 50% of the EPICure population had some form of disability, and almost half of these were rated severe. At the age of six years, over 40 % of the population had cognitive delay when their development was compared with classmate controls (Marlow, Wolke, Bracewell, Samara, & EPICure Study Group, 2005). At the age of 11 years, almost 2/3 of the population were in need of additional support in school and the prevalence of various learning difficulties was high compared to classmate controls (Johnson, Hennessy et al., 2009).

As a response to the very pessimistic message of the EPICure study, an analogous follow-up study with similar inclusion criteria and outcome measures was carried out in Germany as a single-center study (Kutz, Horsch, Kuhn, & Roll, 2009). The population was very small in comparison to the EPICure population, but the authors were able to show a higher survival rate, as well as a lower prevalence of developmental delays (including lower rates of cognitive delays) in their inborn cohort born less than a decade after the EPICure cohort.

In a recent study from the Netherlands, infants with a BW of  $\leq 750$  grams born between 1996-2005 were assessed with either Bayley-II or Griffiths Mental Development Scale at the age of 2 years (Claas et al., 2011). Their mean MDI/General Quotient (GQ) was relatively high (95), and 21% of the infants had a mild delay, and 5% a severe delay. Unexpectedly, however, infants born earlier (1996-2000) had a better cognitive development (mean MDI/GQ 98) compared with those born later (2001-2005), (mean MDI/GQ 93).

In the Nordic countries, there is a long tradition of follow-up studies of preterm infants. In Finland, a birth-cohort of ELBW infants born between 1996-1997 was followed up at the age of two years, and a subgroup of infants born in one hospital (covering about 1/3 of the national cohort) was assessed, also for cognitive development with MDI of Bayley-II (Tommiska et al., 2003). Among these children, the difference, in comparison to controls, was 11 points, although the mean MDI was 95 for the ELBW group. The national Finnish cohort was followed up at the age of five years, and the mean IQ was 96, and the prevalence of severe ( $< -2SD$ ) cognitive delay was only 9 % (Mikkola et al., 2005). However, the mean IQ was significantly lower in comparison to the control group. For the smaller sub-group assessed, also at

the age of two years (Tommiska et al., 2003), the mean IQ was 100 at the age of five years (Mikkola et al., 2005). In Denmark, an ELGA/ELBW cohort born between 1994-1995 was assessed at the age of five years. Danish preterm children performed 12 points (10 points when disabled children were excluded) lower than controls, even if their mean IQ (measured with WPPSI-R) was also 95 (Hoff Esbjorn, Hansen, Greisen, & Mortensen, 2006). In Norway, an ELBW/ELGA cohort born between 1999-2000 was assessed at the age of five years. The authors reported the cognitive outcomes separately for those children who had CP (11%), and for those without CP (Leveresen et al., 2011). The mean IQ was 93 for those without CP, and 78 for those with CP. Severe (-2SD) delay in cognitive development was found in 6%, and mild delay (-1 SD) in 14 %, and 44 % of the study population did not have any developmental problems.

#### b. Cognitive development of VLBW/VLGA children

There are other large follow-up studies from several continents that cover also VLBW/VLGA infants. The message concerning cognitive development from these studies is also rather pessimistic. In Australia/New Zealand, in a cohort of children born before 30 gestational weeks, the percentage of cognitive delay was almost 50%, with one fifth of the delays being significant (Woodward, Anderson, Austin, Howard, & Inder, 2006). These infants were born between 1998-2002. In another study from New Zealand, a cohort of children born before 33 gestational weeks between 1998-2000 was followed up at the age of four years (Woodward, Clark, Pritchard, Anderson, & Inder, 2011). Here, the prevalence of cognitive delay was 34 % but the prevalence of severe delay was only about 10 %. Interestingly, the mean IQ of these children was 95 (mean 100 in standardization population), although 10 points lower than in the control group.

In the USA, two regional cohorts of infants born before 30 GWs between 1985-1986 and 2005-2006 were followed up at the age of 2 years (Bode et al., 2009). The mean MDI of these cohorts was 94 and 92, respectively, and the prevalence of severe cognitive delay (MDI <70) decreased from 17% to 10% during that time.

In Canada, a cohort of infants born before 32 GWs was assessed with MDI at the age of 18 months, and their mean MDI was only 88, even when very ill infants were excluded (Grunau et al., 2009). Similarly, in a study assessing the efficacy of NIDCAP treatment on the development of infants born with VLBW the mean MDI at the age of 18 months was 85 for the NIDCAP group, and 80 for the control group (Peters et al., 2009).

There are also many European studies on VLBW/VLGA infants. In France, the EPIPAGE study followed up a large sample of preterm infants (<33GW) born in 1997. In that population, the mean developmental quotient was 94 at the age of two years (Fily et al., 2006). At the age of five years, the same children were assessed with the Mental Processing Composite (MPC) of Kaufman Assessment Battery for Children (K-ABC). MPC was delayed in 32 % of the children, and delay was severe in 12 % (Larroque et al., 2008).

In Germany, the Bavarian Longitudinal Study followed up preterm children born before 32 gestational weeks and under 1500 grams. They found that at the age of six years, the mean MPC of the K-ABC test was 85, and 24 % and 26 % of children had a mild and a severe developmental delay, respectively (Wolke & Meyer, 1999), and the development was very similar still at the age of eight years (Schneider, Wolke, Schlagmüller, & Meyer, 2004).

In the Netherlands, very positive results on the developmental outcome of very preterm born infants have been reported. A VLBW/VLGA cohort born between 1991-1993 was followed up at the age of 8 years, with the mean IQ being as high as 100, and only 16% of the children had a mild (-1 SD) delay (Rademaker et al., 2005). However, their population included only infants born at least at 25 gestational weeks, and 22% of the population was lost in the follow-up. Very similar outcome data were found also in another Dutch study, in which two groups (trial for nutritional supplement) of VLBW infants were followed up at the age of two years. The mean value of MDI was 96, and 101 in a group receiving glutamine supplementation, and not receiving supplementation, respectively (van Zwol et al., 2008). The prevalence of mild cognitive delay (-1SD) was 27%, and 19%, respectively. Also in another treatment trial of Newborn Individualized Developmental Care and Assessment

Program (NIDCAP) for infants born before 32 GW between 2002-2006, the mean MDI was close to 100 at the ages of 1 and 2 years, but the authors had excluded some ill infants (Maguire et al., 2009). However, in another NIDCAP-trial, infants born before 30 GW had a mean MDI of 86 in the NIDCAP group, and 90 in the group not receiving NIDCAP care (Wielenga et al., 2009). In a recent study on a group of children born before 30 GWs between 2002-2004, the mean IQ was 92 at the age of five years, and the prevalence of mild and severe cognitive delay was 16% and 11%, respectively (Potharst et al., 2011).

In the Nordic countries there are some follow-up studies on VLBW/VLGA children. In Finland, a small cohort of preterm children born between 1985-1986 and under 1750 grams was assessed at the age of eight years, and the IQ difference to control group was only six points with the mean IQ being 98 (Olsén et al., 1998). In Sweden, a VLBW cohort born between 1988-1993 had a relatively high mean IQ of 96 at the age of five years, but their assessment age had been corrected for prematurity (Böhm et al., 2002). When the development was studied according to the chronological age, the mean IQ was 91, and the difference to the control group was nine points. Another VLBW population from Sweden, born between 1987-1988, was assessed at the age of 15 years, and their mean IQ was lower, 85 (Samuelsson et al., 2006). Yet another Swedish VLBW population had a mean IQ of 90 at the age of 10 years, and the difference to controls was seven points. It is important to notice that even if some studies have shown that the mean IQ is within the normative range the difference to full-term controls has been significant, and that the control population has typically performed above the test norms.

A notable feature of recent studies of VLBW/VLGA infants is a clear difference in inclusion/exclusion criteria. Some studies have included only infants who are free of major brain pathology or significant neurological problems. On the other hand, it is common to exclude infants with severe syndromes and disorders of assumed genetic origin. In general, the recent literature about the cognitive outcome of very preterm infants offers answers, but it also raises many questions. There are large differences in outcomes between continents, countries, and centers.

The relevance of early cognitive measures (usually around two years of corrected age) for the prediction of long-term outcome is unclear. Because of a lack of resources, many centers only offer follow-up for a short period of time. On the other hand, many developmental problems only become evident with increasing age, and the demands of the school system. It would, however, be useful for both families, as well as for centers having responsibility over the early intensive care, to offer as accurate information about the developmental prognosis of the infant as possible. However, because of diverging findings, the reliability of early cognitive measures has been questioned. Some longitudinal studies have suggested that early measures give too pessimistic view of the long-term cognitive outcome, and it has been suggested that preterm children would gradually catch up the gap to full-term born peers, at least to some degree (Hack et al., 2005; Ment et al., 2003). It has also been suggested that the number of preterm children without any cognitive deficits would decrease over the years, and at the same time the number of children having early moderate to severe disabilities would diminish, both increasing the number of children with minor problems (Roberts, Anderson, De Luca, Doyle, & Victorian Infant Collaborative Study Group, 2010). It has also been suggested that early assessments would show a good stability of the scores measuring cognitive development over time (Claas, de Vries et al., 2011; Marlow et al., 2005; Mikkola et al., 2005; Samuelsson et al., 2006).

## 6. Precursors of reading acquisition

At school age, very preterm born children are at risk for various learning difficulties and academic failure (Finnström, Gäddlin, Leijon, Samuelsson, & Wadsby, 2003; Hansen & Greisen, 2004; Larroque et al., 2008; Luu et al., 2009; Pritchard et al., 2009; Saigal et al., 2003; Taylor, Burant, Holding, Klein, & Hack, 2002; Wolke, Samara, Bracewell, Marlow, & EPICure Study Group, 2008). In a recent meta-analysis, VLBW/VLGA children showed poorer performance in all crucial academic measures of reading, spelling, and mathematics in comparison to full-term born peers (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). Especially children born with ELBW/ELGA are at most elevated risk for learning problems (Saigal et al., 2003; Taylor et al., 2002).

Because the academic problems of preterm children are widely recognized, it is rather surprising how little is known about the precursors and developmental trajectories of the learning difficulties of preterm born children. For example, reading acquisition has not been studied much. Failure in the ability to read and to comprehend written language profoundly affects all academic achievement, and it comprises a bottleneck in learning. On the other hand, there is a growing body of evidence suggesting that identifying children at risk for reading problems already before their entrance into school, and offering them appropriate support, predictably diminishes the prevalence of dyslexia (Lyytinen, Erskine, Ahonen, Aro, Eklund, & Guttorm, et al., 2008).

Very little is known about the development of pre-reading and reading abilities of preterm children. There is only one study on the pre-reading skills of very preterm born children studied at the age of six years (Wolke & Meyer, 1999). The authors showed that Bavarian preterm born children had a three-to-five time higher risk for problems in reading acquisition in comparison to the full-term born control group. The risk status found at the age of six years was significantly related with reading difficulties at the age of eight years, and also with problems in academic achievement up to the age of 13 years (Schneider et al., 2004).

In Sweden, one longitudinal study has assessed the reading ability in detail. The authors found that VLBW children at the age of nine years had poorer reading abilities in comparison to the normal birth weight controls (Samuelsson, Bylund, Cervin, Finnström, Gäddlin, Leijon, et al., 1999). However, of greater interest was the qualitative analysis of the poor reading ability. It was suggested that VLBW children with reading problems were not typical dyslectics, that is, poor word readers despite an at least average IQ. Instead, their reading problems were accompanied with low IQ (Samuelsson et al., 1999). It was also found that the reading problems of preterm born children were more often related to orthographic word decoding (i.e. the ability to recognize the word quickly as one unit) than to phonological decoding (i.e. deciphering the word by using the grapheme-phoneme route in translating letters to sounds). Therefore, preterm children were more likely to suffer from problems in (fast) whole-word decoding than in (slow) letter decoding (Samuelsson et al., 2000). Again, the problems found in orthographic decoding were accompanied with low IQ (Samuelsson et al., 2000). In the follow-up study at the age of 15, VLBW children no



longer differed from controls in most of the reading variables (Samuelsson et al., 2006). However, significant differences in orthographic reading and in IQ persisted.

It is unclear to what extent reading problems of very preterm children are specific, and how much can be explained by the poor over-all cognitive development. There is evidence that, in comparison to controls, learning difficulties are not more common in preterm children whose cognitive development is within the normal range (Finnström et al., 2003; Frye, Landry, Swank, & Smith, 2009). However, higher prevalence of learning difficulties has been reported also in the absence of intellectual deficits (Taylor et al., 2002). Also in an Australian study including children born before 30 gestational weeks, 29% of the children had reading difficulties at the age of eight years despite their normal cognitive performance (Wocadlo & Rieger, 2007). Similarly, as seen in full-term children, the phonological awareness, rapid naming, and expressive vocabulary of these children were independently related to reading accuracy (Wocadlo & Rieger, 2007).

Reading difficulties have also been studied in relation to risk factors associated with prematurity. VLBW children with bronchopulmonary dysplasia (BPD) have been shown to be at risk for problems in word reading and reading comprehension (Short et al., 2003). In another study, significant neonatal risk factors for reading problems were mechanical ventilation and low Apgar scores, but not, for example, a low BW or gestational age (Finnström et al., 2003). In a LBW population, a large number of neonatal, maternal, and developmental factors were associated with low reading scores, but most of these factors were related to low achievement in other academic scores, as well (Roberts, Bellinger, & McCormick, 2007). There is evidence that IVH would not associate with reading problems (Finnström et al., 2003). However, in another, study IVH was negatively associated with reading (Luu et al., 2009).

The facility of learning to read differs between languages. The Finnish language has a highly consistent orthography with a nearly perfect grapheme-phoneme correspondence at a single-letter level. From a phonological point of view, it is relatively easy for Finnish-speaking children to learn to read (Seymour, Aro, & Erskine, 2003). However, complex morphology increases the number of different words that can be derived from each word stem, which makes the orthographic

decoding of written language very complex. The precursors of reading acquisition in the Finnish language are well documented in the Jyväskylä Longitudinal Study of Dyslexia (Lyytinen et al., 2008). Many language skills are strongly correlated with reading acquisition, and have been shown to predict it (Lyytinen et al., 2006). Letter knowledge, rapid automatized naming, phonological processing, and inflectional morphology measured at five years of age appear to be excellent predictors for reading skills at the end of the 2nd grade (Lyytinen et al., 2008). From the age of 3.5 years on, phonological awareness, short-term verbal memory, rapid automatized naming, expressive vocabulary, repetition of nonsense words, performance intelligence quotient (PIQ), and familial risk for dyslexia are related to later reading achievement (Puolakanaho et al., 2007). These skills explain 55% of the variation in reading accuracy, but are not equally strongly related to reading fluency. In another Finnish longitudinal study, early measures of the size and composition of the vocabulary, use of inflections, and phonological awareness were found to be important precursors for reading (Silvén, Poskiparta, & Niemi, 2004). Rapid automatized naming is associated with fast decoding (reading), and phonological processing with accuracy of reading. A deficit in both of these separable predictors of reading difficulty is called a double deficit, and it is associated with a complex and intervention-resistant type of reading disability (Wolf & Bowers, 1999; Wolf et al., 2002).

## AIMS AND HYPOTHESES

Preterm born children are at an elevated risk for neurological and cognitive deficits. Since a large variability of outcomes from different countries is evident, it is important to establish a regional follow-up that is up-to-date and longitudinal enough to identify individuals at risk, the possible risk factors, as well as protective factors that may affect the outcome. In this study the developmental outcome of VLBW children from infancy to the age of five years was studied, taking into account several different aspects assumed to affect the development.

The specific aims of four publications are presented below.

In **Study I**, the *aim* was to study the significance of the duration and frequency of crying in early infancy for later cognitive and motor development at the corrected age of two years in VLBW children. The *hypothesis* was that early crying behavior is one additional prognostic marker for the developmental outcome.

In **Study II**, the *aim* was to assess the cognitive and neurological development of VLBW children at the corrected age of two years in relation to prenatal, neonatal, and brain imaging data, and to compare development to that of full-term born control children born in the same hospital. The *hypotheses* were that current treatment practices and centralized care would result in improved developmental outcomes, and that there is a relationship between neonatal morbidity and developmental outcomes.

In **Study III**, the *aim* was to delineate the clinical significance of the cognitive outcomes measured at the age of two years for the cognitive outcomes at the age of five years by assessing the stability of development. The developmental level and its stability were compared to full-term born control children. The *hypotheses* were that assessments between these two time-points would correlate with each other and that the classification of developmental outcome would be relatively stable across the time-points.

In **Study IV**, the *aim* was to study the pre-reading skills of VLBW children at the age of five years and to compare their skills to a full-term born control group in order to

identify children at risk for failure in reading acquisition. Pre-reading skills were studied in relation to parental and neonatal factors, as well as to IQ. The *hypotheses* were that preterm children would have poorer pre-reading skills and that they would be more often at risk for failure in reading acquisition. It was also hypothesized that neonatal and parental factors, as well as IQ, would associate with pre-reading skills.

## **PARTICIPANTS AND STUDY DESIGN**

### **1. Participants**

The study sample consisted of very low birth weight (VLBW, birth weight  $\leq$  1500 grams and gestational age  $<$ 37 weeks at birth) infants. The infants participated in a larger 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). The PIPARI study included several study questions covering different aspects of prematurity and developmental outcome. In PIPARI, data were collected systematically and with validated methods about the prenatal period, delivery, neonatal morbidities, mother-infant interaction, and developmental outcome (including language, cognition, neuropsychological, and neurological development).

All preterm VLBW infants born at Turku University Hospital, Finland, in the period between 2001 and 2006, and living in the catchment area were eligible. All high-risk pregnancies are centralized to this level IV hospital from a larger catchment area. Infants with severe congenital anomalies or a diagnosed syndrome affecting their development were excluded. Inclusion criteria were adopted from the Vermont-Oxford Network. Due to differences in study designs and timetables, the number of participants varied somewhat in Studies I-IV.

Study I concerned VLBW infants born between January 2001 and July 2004 (151 altogether). Of them, 22 (15%) died during the neonatal period and six of the surviving infants (5%) did not participate (three had moved away from the area, and the parents of three other infants spoke neither Finnish nor Swedish, the two official languages of Finland). The final study population consisted of 117 VLBW infants with complete data.

Study II covered the whole PIPARI Study cohort of VLBW infants born between 2001 and 2006 (261 altogether). Of these, 41 (16%) died during the neonatal period and four (2%) lived outside the catchment area. Finnish and/or Swedish were not the only languages of the families of 20 infants (8%), and these infants were excluded from the

analysis (follow-up was offered to all infants). One infant was excluded because of multiple anomalies, and one because of osteogenesis imperfecta. The parents of 11 of the 194 eligible infants (6%) refused to participate or withdrew from the study. One infant did not attend the psychologist's examination within the time limit. The final study population consisted of 182 VLBW infants.

In Studies II-IV, there was a control group of 200 healthy full-term (FT) infants born at the same hospital between 2001 and 2003. These FT infants were born at or above 37 gestational weeks into Finnish and/or Swedish-speaking families (except for Study IV where only Finnish-speaking children were included). Because only healthy infants were included into the control group, strict criteria were applied in recruitment. Only those parents whose infant was not admitted into the neonatal intensity care unit (NICU) during their first week of life were approached. The exclusion criteria were congenital anomalies or syndromes, mothers' self-reported use of illicit drugs or alcohol during the pregnancy, and the infant's birth weight being small for the gestational age ( $<-2.0$  SD, SGA) according to age and gender-specific Finnish growth charts. The FT group was recruited by asking the parents of the first boy and the girl who met the inclusion criteria born on each week to participate. If they refused, the parents of the next boy/girl born on that week were approached. In Study II, families of eight FT infants (4%) refused to participate in the follow-up, and the control group consisted of 192 FT infants.

Study III concerned 184 VLBW infants born between 2001 and 2004. Of them, 28 (15%) died during the neonatal period. Finnish and/or Swedish were not the only languages of the 15 families (10%). One infant was excluded because of multiple anomalies. The families of four of the 140 eligible infants (3%) refused to participate or they withdrew from the study. A total of 136 VLBW infants were assessed at the corrected age of two years. Of these, 124 children (91%) were also assessed at the age of five years. Four children were too severely handicapped to be assessed at the age of five years, but they were included in the analysis of the categorized data and were classified as having a significant cognitive delay. Families of eight FT infants (4%) refused to participate in the follow-up at the age of two years. Of the remaining 191 FT children, 168 (88%) were assessed at the age of five years.

Pre-reading skills were examined in Study IV. Because reading acquisition differs significantly between languages, only Finnish-speaking children born were included. Between January 2001 and July 2003, there were 151 VLBW infants born. Of them, 22 (14.6 %) died during the neonatal period. Families of 13 children (9 %) did not speak Finnish as the only native language and were not included in this study. One child was excluded because of a Bloom syndrome, one because of Goldenhaar syndrome, and one because of a hearing deficit requiring a hearing aid. Eight (5 %) children were not included in the analysis because of a significant cognitive delay (intelligence quotient,  $IQ < 70$ ). Of the families of 105 eligible VLBW children, four (4 %) lived outside the catchment area, and seven (7 %) withdrew from participation. Two children (2 %) did not participate in the psychologist's examination within the time limit of two months. The family of one child could not be reached. There were 186 Finnish-speaking FT children. Attrition for the FT children was nine (5 %), and three children did not complete all tasks. Because the focus was to assess the pre-reading skills, fluent readers were excluded (two readers in the FT group, and none in the VLBW group). The final study population consisted of 89 VLBW, and 152 FT children.

The characteristics of the children and parents, along with the neonatal data of VLBW infants, are shown in Table 1. Data of FT infants and their parents are shown in Table 2. Data are presented separately for Studies I-IV for the VLBW population and for Studies II-IV for the FT population.

**TABLE 1.** Characteristics of very-low-birth-weight infants and their parents. Number and (percentage) are presented if not otherwise indicated. SGA is defined as the birth weight of <-2.0 SD according to the age and gender specific Finnish growth charts. CLD is defined as a need for supplemental oxygen at the age of 36 gestational weeks.

	Study I	Study II	Study III	Study IV
	n=117	n= 182	n=124	n=89
Prenatal corticosteroids		167 (92)	117 (94)	85 (96)
Multiple birth		55 (30)	38 (31)	26 (29)
Birth weight (g)	1053 (278)	1083 (280)	1061 (260)	1064 (257)
Mean (SD) [min, max]	[400, 1500]	[400, 1500]	[400, 1500]	[400, 1500]
Gestational age (weeks), Mean (SD) [min, max]	28.5 (2.8) [23.0, 35.9]	29.0 (2.8) [23.0, 35.9]	28.7 (2.8) [23.3, 35.9]	28.7 (2.6) [24.3, 35.9]
Small for gestational age, SGA	43 (37)	74 (41)	49 (40)	32 (36)
Male	58 (50)	102 (56)	67 (54)	47 (53)
Apgar <6 at 5 minutes	31 (27) missing n=2	40 (22) missing n=2	28 (23) missing n=2	19 (22) missing n=1
Days on ventilator	9.9 (12.4)	8.4 (12.3)	9.4 (12.7)	8.7 (11.1)
Mean (SD) [min, max]	[0, 51]	[0, 51]	[0, 50]	[0, 49]
Postnatal steroids		25 (14)	21 (17)	14 (16)
Chronic lung disease, CLD	19 (16) missing n=1	28 (15)	19 (15)	12 (13)
Ductal ligation		22 (12)	17 (14)	12 (14)
Sepsis or meningitis		34 (19)	30 (24)	20 (22)
Intestinal perforation (NEC included)		12 (7)	7 (6)	3 (3)



Retinopathy of prematurity $\geq$ grade III		6 (3)	3 (2)	2 (2)
Hydrocephalus with shunt	3 (3)	5 (3)	4 (3)	1 (1)
Days in hospital mean (SD) [min, max]	59.4 (32.3) [3, 182]	59.7 (32.6) [3, 183]	59.6 (32.8) [3, 183]	54.9 (26.4) [3, 114]
Maternal education	Missing n=2	Missing n=1	Missing n=1	Missing n=1
Nine years	1 (1)( $<9$ years)	19 (10)	14 (11)	11 (12)
> 9-12 years	47 (41) (9-12)	50 (28)	36 (29)	20 (22)
>12 years	67 (58)	112 (62)	123 (59)	57 (64)
Paternal education	Missing n=2	Missing n=1	Missing n=1	
Nine years	10 (9)( $<9$ years)	15 (8)	12 (10)	8 (9)
> 9-12 years	69 (60) (9-12)	108 (60)	69 (56)	50 (56)
>12 years	36 (31)	58 (32)	42 (34)	31 (35)

**TABLE 2.** Characteristics of full-term born control infants and their parents. Number and (percentage) are presented if not otherwise indicated.

	Study II	Study III	Study IV
	n=192	n=168	n=152
Multiple birth	1 (1)	1 (1)	1 (1)
Birth weight (g)	3665 (449)	3659 (454)	3651 (457)
Mean (SD) [min, max]	[2570, 4980]	[2570, 4980]	[2570, 4980]
Gestational age (weeks)	40.0 (1.2)	40.1 (1.2)	40.0 (1.2)
Mean (SD) [min, max]	[37.1, 42.3]	[37.1, 42.3]	[37.1, 42.3]
Male	94 (49)	81 (48)	72 (47)
Maternal education	Missing n=27	Missing n=20	Missing n=17
Nine years	9 (6)	6 (4)	6 (4)
> 9-12 years	59 (36)	53 (36)	49 (36)
>12 years	97 (59)	89 (60)	80 (59)
Paternal education	Missing n=34	Missing n=25	Missing n=22
Nine years	15 (10)	15 (10)	14 (11)
> 9-12 years	69 (44)	59 (41)	55 (42)
>12 years	74 (47)	69 (48)	61 (47)

## 2. Methods

### a. Collection of demographic data

The number of children who received prenatal corticosteroids was recorded during pregnancy. Neonatal data were collected systematically and prospectively by a research nurse during the NICU treatment period. The length of ventilation and C-PAP treatment were recorded, as well as all neonatal morbidities. These included ventilation problems (bronchopulmonary dysplasia, BPD, and chronic lung disease, CLD), the need for postnatal corticosteroids, gastrointestinal problems (necrotizing enterocolitis, NEC, and intestinal perforation), ductal ligation, a shunt for hydrocephalus, and severe infections (meningitis and sepsis).

The length of parental education was categorized in 9 years, >9-12 years, and >12 years, except for Study I in which the categorization was <9 year, 9-12 years, and >12 years of education. Additional data of parents' self-reported reading difficulties were collected for Study IV.

### b. Brain imaging (Studies II and IV)

Brain morphology and possible brain pathology were assessed with two distinct methods during the neonatal period for VLBW infants. In Study IV, the results of the methods were combined, and the categorization was made according to the most pathological finding either in a cranial ultrasound, or in magnetic resonance imaging. No brain imaging was performed on the control group.

#### i. Cranial ultrasound (CUS)

CUS was performed serially by the attending neonatologist, or radiologist (term age scan author Rikalainen) in the NICU. All scans were video recorded. First CUS scan was performed at the post-conceptual age of three to five days, at seven to ten days, at one month, and thereafter monthly until discharge. All VLBW infants were scanned at term age. The scans (except the term age scan) were performed with a 7-MHz vector transducer (Sonos 5500 Hewlett-Packard, Andover, Mass). The term age scan

was performed with a 7.5-MHz vector transducer (Aloka SSD 2000, Aloca Co, Ltd, Tokyo, Japan) during the time period of 1/2001 to 8/2002, and after that with an 8-MHz vector transducer (General Electric Logic 9). The scans were analyzed by the radiologist (author Rikalainen). The severity of intraventricular hemorrhage (IVH) was classified according to Papile (Papile, Burstein, Burstein, & Koffler, 1978). Multiple cysts with a typical location were classified as cystic periventricular leukomalacia (cPVL).

The infants were categorized into three groups based on the most pathological finding in any CUS scan. The categories were normal, minor brain abnormality, and major brain abnormality. Brain pathologies were categorized according to Rademaker et al. (2005). According to their classification, cysts in the germinal layer/plexus, subependymal pseudocysts, and calcifications were categorized into the normal group, along with no brain abnormalities. Minor brain pathologies were IVH grades I-II, germinal layer necrosis, and ventricular dilatation. Major brain pathology included IVH grades III-IV, cPVL, thalamic lesion, focal infarction, convexity hemorrhage, and ventricular dilatation following a hemorrhage with need for the therapeutic intervention.

## ii. Magnetic Resonance Imaging (MRI)

Brain MRI was performed on the same day as the term CUS examination. The imaging took place during postprandial sleep without pharmacological sedation or anesthesia. Ear protection was used (3M Disposable Ear Plugs 1100, 3M, Brazil; and Würth Hearing protector Art.-Nr. 899 300 232, Würth, Austria). The MRI equipment was an open 0.23 Tesla Outlook GP (Philips Medical Inc., Vantaa, Finland) for infants born between 2001 and 2003, and a 1.5 Tesla Philips Intera (Philips Medical Systems, Best, The Netherlands) thereafter.

A neuroradiologist (author Parkkola) analyzed the MR images according to a scoring system modified after Maalouf (Maalouf et al., 1999; Maalouf et al., 2001), and the width of the extracerebral space was classified according to McArdle (1987). The infants were categorized into three groups according to the most pathological finding

in the MRI. The normal group included normal brain anatomy with the width of extracerebral space  $\leq 4$ mm. The minor brain abnormality group included IVH grades I-II, caudothalamic cysts, and an extracerebral space width of 5mm. In the major brain abnormality group were IVH grades III-IV, hemorrhage of the brain parenchyma, white matter cysts, abnormal T1 or T2 signals in cortex, basal ganglia, thalamus, cerebellum or internal capsule, abnormalities of corpus callosum, an extracerebral space width of 6 mm or more, and ventriculitis.

c. Baby Day Diary (Study I)

Baby Day Diary (BDD) (Barr, Kramer, Boisjoly, McVey-White, & Pless, 1988) was filled in when the infant was at term, at six weeks of corrected age (CA), and at five months of CA for three days at each time-point. The 24-hour day was divided into five-minute sections in which the parents recorded the following mutually exclusive infant behavior states: sleeping, awake content, fussing, crying, and feeding. Parents were instructed on the use of the BDD (or nurses if the parent was not present while the infant was still hospitalized) by the research physician (author Maunu). Crying was defined as continuous crying (“periods of prolonged distress vocalization”), and fussing as non-continuous negative vocalization that is not crying (“the infant is unsettled and irritable and may vocalize negatively, but not continuously crying”). Different symbols were used for each type of behavior.

The parents (or nurses) were asked to complete the diaries during typical days for the infant. The diary day was omitted if the infant was febrile (temperature above 38.0°C), had received a vaccination, or had gone through an invasive procedure on the same day, or if the diary was incompletely filled in. The parents were instructed to fill in the diary when convenient, usually using the feeding intervals.

d. Neurological examination (Study II)

The attending neonatologist and research physician (author Maunu) carried out a neurological examination on all VLBW infants serially up to the CA of two years. The Dubowitz neurological examination (Dubowitz, Mercuri, & Dubowitz, 1998) was used

at the age of 36 gestational weeks, at term, and at 1 and 2 months of CA, along with the Hammersmith Infant Neurological Examination (Haataja et al., 1999) at 12 and 24 months of CA. However, the data presented here were based on a clinical evaluation of cerebral palsy (CP) as defined after the classification of Mutch et al. (Mutch, Alberman, Hagberg, Kodama, & Perat, 1992), and hearing and vision deficit. Hearing and vision were screened as a part of the follow-up and suspected deficits were confirmed by an audiologist/ophthalmologist, as appropriate.

e. Assessment of cognitive development

i. Bayley Scales of Infant Development, 2nd edition (Studies I, II, and III)

At two years of age (CA for VLBW infants), the development of VLBW and FT infants was assessed using the Finnish translation of Bayley Scales of Infant Development, 2<sup>nd</sup> edition (BSID-II) (Bayley, 1993). The BSID-II scales were translated for the purposes of the present study. No changes were made in the scales and original norms were applied. A time frame of -1 week to +1 month from birthday was applied, because particularly the language development may be very rapid at the age of two years. Cognitive development was assessed with the Mental Development Index (MDI, Studies I, II, and III), and motor development with the Psychomotor Development Index (PDI, Study I). MDI and PDI were used as a continuous variables in Study I, and MDI was used both a continuous variable (mean 100, SD 15), and as a categorized variable in Studies II, and III. A significant delay was defined as a MDI of <70 (<-2SD), and a mild delay as 70-84 (-2SD <MDI<-1SD). A MDI of at least 85 (>-1SD) was considered average. In Study II, neurodevelopmental impairment (NDI) was defined as an MDI below 70, CP, hearing loss requiring a hearing aid, or blindness.

The psychologist (primarily author Munck) was aware of the prematurity versus full-term birth status of the infants, but she was blinded to other background variables, including crying and neonatal data.

ii. Wechsler Preschool and Primary Scale of Intelligence-Revised  
(Studies III and IV)

At the age of five years (from -1 week to + 2 months), cognitive development was assessed with a short version of the Wechsler Primary and Preschool Scales of Intelligence – Revised (WPPSI-R), Finnish translation (Wechsler, 1995). Because the time used for the assessment was limited and also other tests were administered, three verbal (Information, Sentences, Arithmetic), and three performance (Block Design, Geometric Design, Picture Completion) subscales of WPPSI-R were selected. The selection was based on these subscales' strongest correlation with the full-scale intelligence quotient (FSIQ). FSIQ was used both as a continuous variable (mean 100, SD 15), and as a categorized variable. A significant delay was defined as a FSIQ of <70 (<-2SD), and a mild delay as 70-84 (-2SD <FSIQ<-1SD). A FSIQ of at least 85 (>-1SD) was considered average. In Study III, different psychologists assessed the children at the age of two and five years to avoid the bias potentially resulting from the first assessment. In Study IV, a significant delay in FSIQ was used as an exclusion criterion because reading skills are strongly related to overall cognitive level.

iii. Precursors of reading acquisition (Study IV)

Phonological awareness, rapid automatized naming, and letter knowledge are known as predictors for successful reading acquisition. Therefore, two NEPSY-II (Korkman, Kirk, & Kemp, 2008) subtests (Phonological processing and Speeded naming), and a letter knowledge test were chosen to measure these abilities. The standardization edition of the Finnish NEPSY-II was used, because at the time of the study the final version had not yet been published. Because of the lack of the normative data of NEPSY-II, standard scores were calculated from the results of the FT control group. Similar scoring was used for both VLBW and FT groups (range from 1 to 19, mean 10, SD 3).

The Phonological Processing subtest of NEPSY-II assesses phonemic awareness. In the first part, the child is asked to identify words from word segments. In the second part, the child is first asked to repeat a word and then utter a new word by omitting or substituting a syllable or a phoneme.

The Speeded Naming subtest of NEPSY-II assesses the speed and accuracy of the semantic access to over-learned items. The child is asked to name arrays of figures according to their colors, shapes and sizes as quickly as possible. In this study, the Size/Color/Shape Naming condition was administered. It is meant for children from the age of seven and older in the final version of NEPSY-II. The scoring was slightly different from the final version (in shapes, the child was allowed to use the word “ball” in addition to “circle”). The changes made were accepted by one of the authors of the NEPSY-II (Marit Korkman). Total time and errors were scored separately, as well as the sum score of these.

The children were presented with 19 capital letters (Poskiparta, Niemi, & Lepola, 1994) and they were simply asked to name those letters they knew. All letters were presented irrespective of the performance of the child.

Because pre-reading skills were studied, precocious readers were excluded from the analysis. Reading skills were assessed by presenting children with four short written words and asking them to say the word. If the child was able to recognize the words s/he was also presented with a short written sentence.

#### f. Statistical analysis

In all the studies, associations between two continuous normally distributed variables were studied using Pearson’s correlation coefficient. Normally distributed response variables were compared between two groups using independent sample t-tests. Comparisons between two categorical variables were performed using the Chi square test or Fisher’s exact test, as appropriate. Statistical analyses were done using SAS and SPSS for Windows.

In Study I, the distributions of duration on fussing, crying, and fuss/cry, and of the frequency of fuss/cry bouts were positively skewed, and therefore a square root transformation was used to normalize the distribution before data analysis. Significant correlations were further described by presenting regression coefficients from simple linear regression. The MDI and PDI were used as dependent variables and the square



root of duration in minutes (crying, fussing, fuss/cry) or the square root of frequency of fuss/cry bouts was used as an independent variable. Significant associations were also tested using multiple regression analysis controlling for possible contributing factors. The factors included in this adjusted analysis were infants' birth weight, gestational age, gender, Apgar score at five minutes, as well as dichotomized mothers' education in years ( $\leq 12$  years and  $>12$  years).

The VLBW group was also divided into infants with moderate (Moderate Group) or excessive (Excessive Group) duration of fuss/cry. The excessive Group was defined as the average duration of fuss/cry of at least 180 minutes, and the Moderate Group as fuss/cry for less than 180 minutes per day. This cut-off point has been used earlier and it captures the highest end of excessively crying infants (Kirjavainen, Lehtonen, Kirjavainen, Kero, & 24-Hour Ambulatory Sleep Polygraphy study, 2004).

In Study II, a hierarchical regression analysis was performed for VLBW infants in order to study the association of demographic and neonatal data with MDI. The variables were independently correlated with the MDI before being chosen. After significant risk factors were identified, the variables were entered into the model in temporal order (parental education, prenatal care, infants' characteristics at birth, and postnatal morbidities). In the first stage of the regression analysis, the length of maternal and paternal education was used as independent variables with both being classified into three groups ( $<9$  years, 9 to 12 years,  $>12$  years of education). The use of prenatal corticosteroids was added to the equation in the second stage, while infants' birth weight, gestational age, and gender were entered in the third stage. Neonatal conditions (chronic lung disease, retinopathy of prematurity  $\geq$  gradus III, use of postnatal steroids, sepsis or meningitis, intestinal perforation, ductal ligation, and minor and major brain pathology, either in the brain MRI or in US) were added in the last stage.

Because intestinal perforation, which was associated with lower MDI, slows down neonatal growth a post-hoc analysis of weight gain was made by calculating the difference between the z-scores of the infants' birth weight and the weight at term. A one-way analysis of variance was used to investigate whether the mean MDI value differed between the brain finding groups (normal, minor, major). Tukey's pair-wise

comparisons were performed to investigate which groups differed significantly from each other. The analysis of covariance was used to identify potential differences between the MDI values of VLBW and FT infants after adjusting for parental education.

In Study III, Cohen's weighted kappa was calculated to estimate the agreement between categorized MDI and categorized FSIQ. A ROC curve analysis was performed to study the sensitivity and specificity of MDI on FSIQ. Both severe delay and the combination of severe, and mild delay, were used as categorized variables.

In Study IV, the Kruskal-Wallis test was used when the associations between categorical variables and bimodal outcomes, that is, the number of letters recognized was studied. The associations between continuous predictors and the number of letters recognized were studied using a Spearman correlation. Univariate analyses of the association between continuous normally distributed outcome variables (speeded naming and phonological processing) and nominal predictors were studied using a one-way analysis of variance. Differences in these outcome variables between VLBW infants and the control group were further studied using an analysis of covariance controlling for FSIQ.

g. Ethical considerations

The PIPARI study protocol was approved by the Ethics Review Committee of the Hospital District of South-West Finland in December 2000. All parents who agreed to participate gave an informed consent after the written and oral information. The families did not receive money for participating in this study. They were offered written information about their child's development after each assessment. If the child had any developmental or behavioral problems s/he was sent to the appropriate communal services.

## RESULTS

### 1. The crying and fussing behavior of VLBW infants (Study I)

The Baby Day Diaries were completed and returned by almost all of the families (94-97%) at all the time-points, which makes the sample well representative. Only two families did not return any diaries. A total of 121 infants with at least one completed diary remained in the study. At term age, 10% of the diaries were completed in the hospital, but at later time points the rate was less than 1%. Therefore, these data represent the crying behavior in a natural setting. Less than 3% of the diary days had to be excluded because the strict inclusion criteria were not met. Of infants with at least one completed diary, 117 participated in a developmental assessment.

In the analysis, the total duration of fussing and crying in minutes (both combined and separately) were summed up and divided by the number of days (3) to get the average duration per day. In addition, the frequency of started fuss/cry bouts was calculated. The duration of crying and fussing at term, at six weeks and at five months of corrected age, the total duration of gaps due to missing data (duration of 'do not recall' in the diary) and the number of fuss/cry bouts are shown in Table 3.

**TABLE 3.** The mean duration of crying, fussing, and missing data in minutes per day, and number of started fuss/cry bouts at term, at 6 weeks and 5 months of corrected age. Average per day (standard deviation), [min, max] are presented.

Crying/day at term	44 (42.7) [0; 193]
Crying/day at 6 weeks	34 (30.6) [0; 183]
Crying/day at 5 months	15 (15.6) [0; 95]
<hr/>	
Fussing/day at term	100 (62.4) [0; 285]
Fussing/day at 6 weeks	88 (57.8) [3; 378]
Fussing/day at 5 months	68 (40.7) [0; 210]
<hr/>	
Missing data at term	9.9 (24.1) [0; 157]
Missing data at 6 weeks	7.1 (18.5) [0; 135]
Missing data at 5 months	6.3 (13.8) [0; 73]
<hr/>	
Bouts at term	9.8 (6.2) [0; 37]
Bouts at 6 weeks	10.5 (7.1) [0; 36]
Bouts at 5 months	7.9 (5.6) [0; 25]

## 2. Developmental outcome

### a. In relation to early crying and fussing behavior at the corrected age of two years (Study I)

In Study I, the mean MDI of VLBW infants was 103 (SD 15) [range 50-128], and mean PDI was 98 (16) [50-121] at two years of CA. The longer duration of crying at term was negatively associated with both MDI and PDI ( $r=-.195$ ,  $p=0.040$ , and  $r=-.231$ ,  $p=0.015$ , respectively). Fussing was not associated with developmental measures at any time point. After term age, the duration of crying was no longer associated with development. Including the background variables (infants' birth weight, gestational age, gender, Apgar score at five minutes, and mothers' education in years) did not appreciably alter the statistical significance on PDI ( $b= -1.23$ , CI  $-2.24; -0.22$ ,  $p=0.018$ ). In contrast, for the adjusted analysis for duration of crying at term and MDI, there was no statistically significant association ( $b= -0.37$ , CI  $-1.28; -0.55$ ,  $p=0.426$ ). Therefore, only the association between duration of crying, and PDI is specific.

Infants were divided into two groups to study whether an excessive amount of crying is a risk sign for adverse developmental outcome. The Excessive group ( $\geq 180$  minutes of fuss/cry per day) and the Moderate group ( $< 180$  minutes of fuss/cry per day) were compared for MDI and PDI scores. At term, the Excessive group ( $n=30$ ) had lower PDI compared to the Moderate group ( $n=81$ ) (101 vs. 92,  $t(108)=2.87$ ,  $p=0.005$ ). At six weeks of corrected age, the Excessive group ( $n=18$ ) had lower scores in both MDI, and PDI (105 vs. 96,  $t(113)=2.29$ ,  $p=0.024$ , and 100 vs. 90,  $t(112)=2.54$ ,  $p=0.012$ , respectively) compared to the Moderate group ( $n=97$ ). At five months of corrected age, the analysis was not performed because of a small number (3) of infants in the Excessive group.

The number of started crying and fussing bouts, which reflects the reactivity of the infant, was not related to development until the age of five months. Then, the lower frequency of bouts was associated with better PDI ( $r=.191$ ,  $p=0.045$ ). The association remained significant after adding the background variables to the model ( $b= 3.60$ , CI  $0.61; 6.60$ ,  $p=0.019$ ).

b. In relation to prenatal, neonatal, and parental factors at the corrected age of two years (Study II)

In Study II, the cognitive development of the whole PIPARI cohort was studied. The mean MDI was 101.7 (SD 15.4). This score is high compared with the normative data of BSID-II (mean 100, SD 15). Nevertheless, VLBW infants' MDI was significantly lower in comparison to FT controls (mean 109.8, SD 11.7,  $p < 0.001$ ). The estimated difference between the groups was similar after adjusting for parental education. Therefore, it can be concluded that the difference between the groups was specific to the prematurity instead of social factors.

The percentage of severe cognitive delay was low in the VLBW group. MDI was significantly delayed ( $< 70$ ) in six (3.3 %) VLBW infants, and 28 (15.4%) had a significant delay according to the FT groups' distribution ( $-2$  SD, MDI  $< 86.4$ ). There were, however, differences between VLBW infants. Infants born on GW 23 were at highest risk for adverse development, but from GW 24 onward, the mean MDI was constantly over 95. Data according to the gestational age are shown in Table 4.

**TABLE 4.** Mean values and (SD) of Mental Developmental Index (MDI) by gestational weeks (GW). MDI below -2.0 SD according to the full-term norms (<86.4) is presented next. The total prevalence of neurodevelopmental impairment (NDI), and the components of NDI (MDI <70, cerebral palsy, and the use of hearing aid) are shown separately by gestational weeks. There were no blind children. Data are shown as frequencies (percentages).

<b>GW</b>	23	24	25	26	27	28	29
	n=3	n=10	n=18	n=19	n=14	n=29	n=24
<b>MDI</b>	<hr/>						
mean	72.7	92.2	98.4	100.0	95.3	103.7	105.4
(SD)	(22.0)	(15.7)	(13.4)	(18.0)	(17.2)	(16.3)	(15.5)
<b>MDI</b>	2	1	4	3	4	7	3
<b>-2SD</b>	(66.7)	(10.0)	(22.2)	(15.8)	(28.6)	(24.1)	(12.5)
<b>NDI</b>	2	2	3	1	2	4	1
	(66.7)	(20.0)	(16.7)	(5.3)	(14.3)	(13.8)	(4.2)
MDI	1	1	0	1	1	1	1
<70	(33.3)	(10.0)		(5.3)	(7.1)	(3.4)	(4.2)
Cerebral	1	1	3	1	2	3	0
palsy	(33.3)	(10.0)	(16.7)	(5.3)	(14.3)	(10.3)	
Hearing	1	2	0	0	0	0	0
aid	(33.3)	(20.0)					

**TABLE 4**, continued.

<b>GW</b>	30	31	32	33	34	35	Total
	n=26	n=12	n=10	n=8	n=6	n=3	n=182
<b>MDI</b>							
mean	108.8	104.5	100.8	102.4	105.7	96.0	101.7
(SD)	(12.0)	(12.7)	(8.0)	(12.4)	(7.9)	(9.2)	(15.4)
<b>MDI</b>	2	1	0	1	0	0	28
<b>-2SD</b>	(7.7)	(8.3)		(12.5)			(15.4)
<b>NDI</b>	0	0	1	1	0	1	18
			(10.0)	(12.5)		(33.3)	(9.9)
MDI	0	0	0	0	0	0	6
<70							(3.3)
Cerebral	0	0	0	1	0	1	13
palsy				(12.5)		(33.3)	(7.1)
Hearing	0	0	1	0	0	0	4
aid			(10.0)				(2.2)

Also birth weight was significantly associated with cognitive outcome. The BW of 76 prematurely born infants (41.8%) was  $\leq 1000$ g (ELBW). The mean MDI among this ELBW population was 96.7 (SD 17.3), which was significantly lower than the MDI of the 106 infants with a birth weight of 1001 to 1500g (MDI 105.4, SD 12.6,  $p < 0.001$ ). Most of the infants with MDI  $< 70$  (4/6) were born with ELBW.

To study further which demographic and neonatal factors were independently associated with low MDI of VLBW infants, a hierarchical regression analysis was performed. In the first step, parental education was studied. In the second step, the effect of prenatal corticosteroids was added to the model. Then in the third step, the infant's neonatal data, and in the final step, neonatal morbidities were added. Postnatal corticosteroids ( $p=0.04$ ), intestinal perforation ( $p=0.03$ ), and major brain pathology, either in MRI or in CUS ( $p=0.02$ ), were all independently negatively associated with MDI. Before entering the neonatal conditions into the model in the last stage, the use



of prenatal corticosteroids was positively associated with MDI ( $p < 0.001$ ). This is clinically significant, because prenatal corticosteroids are regarded as an important factor in preventing postnatal brain damage. Interestingly, parental education, the infant's birth weight, gestational age, gender, or many of the neonatal morbidities were not associated with poor MDI when other factors were taken into account.

The prevalence of neurodevelopmental impairment (NDI) was low in this VLBW population. Altogether 18 infants (9.9%) had some form of NDI. Cerebral palsy was diagnosed in 13 infants (7.1%), MDI was  $< 70$  in six infants (3.3%), and four infants (2.2%) were using a hearing aid. There were no blind infants. The previous Table 4 shows the prevalence of NDI by GA. Infants born on GW 23 were at the highest risk for NDI, but otherwise the significance of GW was not as evident as for MDI. Most of the infants with NDI (11/18) were born with ELBW.

Cognitive and neurological development was also studied in relation to the brain imaging findings. Table 5 shows the severity of the brain imaging findings in relation to the MDI and NDI.

**TABLE 5.** Mean Mental Development Index (MDI), severe delay in MDI according to full-term controls (<86.4), and the prevalence of neurodevelopmental impairment (NDI) according to brain magnetic resonance imaging (MRI) and cranial ultra sound (CUS) findings in three categories of severity. The components of NDI are MDI <70, cerebral palsy, the use of a hearing aid, and blindness. There were no blind children. Data are shown as frequencies (percentages).

	MDI mean (SD)	MDI <86.4	NDI	MDI <70	Cerebral palsy	Hearing aid
MRI Major (n=48)	92.8 (20.1)	16 (33.3)	16 (33.3)	6 (12.5)	11 (22.9)	4 (8.3)
MRI Minor (n=28)	105.3 (12.3)	3 (10.7)	0	0	0	0
MRI Normal (n=104)	104.9 (11.7)	9 (8.7)	2 (1.9)	0	2 (1.9)	0
CUS Major (n=15)	86.5 (15.0)	5 (33.3)	9 (60.0)	2 (13.3)	7 (46.7)	2 (13.3)
CUS Minor (n=76)	102.1 (16.1)	13 (17.1)	7 (9.2)	2 (2.6)	6 (7.9)	2 (2.6)
CUS Normal (n=91)	104.0 (13.4)	10 (11.0)	2 (2.2)	2 (2.2)	0	0
Full-term (n=192)	109.8 (11.7)	7 (3.6)	1 (0.5)	1 (0.5)	0	0

Major brain abnormality found either in CUS or in MRI was a significant risk factor for cognitive development. Infants with major brain abnormality differed significantly from infants with either minor brain abnormalities or normal brain findings. On the other hand, the significance of minor findings was less evident as these infants did not differ from those with normal brain finding on MDI. A similar pattern of findings was found when major brain abnormality, either in CUS or in MRI, was studied in relation to NDI. Infants with major brain abnormality had a significantly higher risk for NDI compared to those with minor brain abnormality or normal brain finding. The latter two groups did not differ from each other on the prevalence of NDI.

### c. Stability of cognitive development from two to five years (Study III)

The cognitive development of the VLBW group was relatively good at the corrected age of two years. However, the significance of early measures and the stability of cognitive development has been questioned. Here, high stability was found from two to five years of age. In the VLBW group, mean MDI at the age of two years was 101.2 (SD 16.3, range 50-128), and mean FSIQ at the age of five years was 99.3 (SD17.7, range 39-132). The correlation between MDI and FSIQ was 0.563 ( $p<0.0001$ ), indicating a good stability. In the FT group, mean MDI was 109.8 (SD 11.7, range 54-128), and mean FSIQ was 111.7 (SD14.5, range 73-150), and the correlation between MDI and FSIQ was 0.400 ( $p<0.0001$ ). VLBW children had lower mean MDI and FSIQ (both comparisons  $p<0.001$ ) compared to FT controls.

To verify the clinical significance of the high correlation found between the age points, MDI and FSIQ were studied as categorized variables. The good stability of the developmental category was found for children with severe delay, and for those who were within the normal range. A total of 83% of the children with significant delay in MDI ( $n=6$ ) had significant delay also in FSIQ. Similarly, 87% of the children in the average range in MDI ( $n=113$ ) were within the average range also in FSIQ. However, children with mild developmental delay ( $n=5$ ) showed poor stability.

There were no FT children with significant developmental delay at either age point. Of the FT children within the average range at the age of two years ( $n=164$ ), 97% were within the average range also at the age of five years. Of those four FT children who had mild delay at the age of two years, three had improved in their development and only one child remained in the mild delay group.

### 3. Precursors of reading acquisition at the age of five years (Study IV)

The VLBW group had significantly poorer phonological processing skills (mean 8.8, SD 2.3) in comparison to the FT group (10.0, 2.4,  $p < 0.001$ ). In speeded naming, there was a clear discrepancy found when the sub-components of time and number of errors were analyzed separately. The VLBW group was not significantly slower (VLBW mean 9.7, SD 3.0 vs. FT mean 10.2, SD 2.7,  $p = 0.135$ ), but they made significantly more errors in the naming process (VLBW 9.0 [2.9] vs. FT 10.7 [3.5],  $p < 0.001$ ). The VLBW group recognized significantly fewer letters (mean number of letters recognized 6.8, [6.6]) in comparison to the FT group (9.3 [6.6]), ( $p = 0.005$ ).

All pre-reading measures were also categorized to assess the clinical significance of the group differences. Children who performed below the normal range ( $-1SD$  or less according to the distribution of the FT group) were considered to be at risk for problems in reading acquisition. There were more VLBW children than FT children in the risk groups in most variables. In phonological processing, 24% of the VLBW children were at risk compared to 9% of FT children ( $p = 0.002$ ), and 27% vs. 14%, respectively, were at risk in letter knowledge ( $p = 0.017$ ). In speeded naming, there was again a difference between groups in the accuracy of naming, as the VLBW group was more often at risk for making errors in naming (26% vs. 13%,  $p = 0.020$ ), but the groups did not differ significantly in their naming speed. Interestingly, different VLBW children were at risk in phonological processing and for speeded naming, as a double deficit was found in only 5%. This was, however, a significantly higher rate than in the FT group (2%,  $p = 0.006$ ). Gender did not interact with any pre-reading skill differences found between the groups.

In the VLBW group, pre-reading skills were studied in relation to prenatal and neonatal factors. These factors included the use of prenatal corticosteroids, GA, BW, gender, status of SGA, intestinal perforation, and neonatal brain pathology shown either in CUS or in MRI. Surprisingly, none of these factors were significantly associated with the pre-reading skills or the risk status in any of them. The amount of parental education, on the other hand, was significant. In the analysis, parents with 9 years and those with  $>9-12$  years of education were combined (lower level of education), and compared with the group with  $>12$  years of education (higher level of

education). A lower level of maternal education was associated with poorer letter knowledge ( $Z = -2.10$ ,  $p = 0.040$ ), but not with other pre-reading skills. The lower level of paternal education was associated with all measures (poorer phonological processing,  $b = -1.167$ ,  $CI -2.154 - -0.180$ ,  $p = 0.021$ , speeded naming,  $b = -1.945$ ,  $CI -3.270 - -0.621$ ,  $p = 0.005$ , and letter knowledge,  $Z = -3.46$ ,  $p = 0.001$ ).

In the VLBW group, mean (SD, range) FSIQ was 101.9 (15.0, 70-132), verbal IQ (VIQ) 104.8 (14.6, 74-135), and performance IQ (PIQ) 99.1 (15.6, 74-139). In the FT group, mean FSIQ was 112.0 (14.6, 73-150), VIQ 108.2 (13.9, 65-142), and PIQ 111.7 (13.4, 84-144). As expected, VLBW children had lower mean FSIQ and PIQ (both comparisons  $p < 0.001$ ) compared to FT controls. Interestingly, the difference in VIQ was not statistically significant ( $p = 0.072$ ).

Pre-reading skills were studied in relation to the overall cognitive development, and differences found between the groups were mediated by the FSIQ. When FSIQ was controlled for, VLBW and FT groups did not differ on speeded naming (estimated difference 0.04,  $SE = 0.39$ ,  $p = 0.910$ ), or in phonological processing (estimated difference 0.57,  $SE = 0.31$ ,  $p = 0.068$ ). FSIQ was lower in the at-risk group in comparison with non-risk VLBW children for phonological processing (104.0 [SD 14.6] vs. 95.0 [SD 14.4],  $p = 0.019$ ), speeded naming (105.4 [SD 13.4] vs. 93.4 [SD 14.8],  $p = 0.002$ ), and letter knowledge (104.4 [SD 14.6] vs. 95.1 [SD 14.3],  $p = 0.012$ ). Only four children had a double deficit, and their mean FSIQ was 80.8, indicating a more global intellectual deficit rather than a specific risk for poor reading achievement.

## DISCUSSION

### *Cognitive development in relation to early crying and fussing behavior at the corrected age of two years*

Study I assessed the association between early crying behavior and developmental outcome in a cohort of non-selected preterm VLBW infants. Previous studies on full-term infants have shown that prolonged crying is correlated with less optimal cognitive outcome (Papousek & von Hofacker, 1995, Lehtonen et al., 2000). In contrast, our results with preterm infants showed that early (term age) crying was correlated with less optimal motor outcome. However, no correlation was found with cognitive development. Excessive fussing and crying that exceeds three hours per day at term age was associated with poorer motor development, and at six weeks of corrected age with both poorer motor and cognitive development. A longer duration of fussing and crying at term may reflect lower self-regulation capacity.

An unexpected finding was that an increased number of fuss/cry bouts at five months of age associated with better motor development. It has been suggested that a high frequency of fuss/cry bouts indicates high reactivity (Barr, Paterson, MacMartin, Lehtonen, & Young, 2005). Therefore, high reactivity might also be a positive prognostic sign. Another possible explanation may be found from the early communicative function of fuss/cry vocalization at five months of corrected age. Frequent attempts to communicate may be an indicator of favorable development. However, diary data using five-minute samples may not be sensitive enough to measure the number of bouts reliably.

The VLBW infants of Study I showed a longer duration of fussing and crying compared to an earlier study of preterm infants by Barr et al. (1996). Our study population, however, differed from the previous study, which included only relatively mature preterm infants without any brain complications. Our non-selected population included less mature infants, and no pre-selection was performed based on neonatal morbidities. However, our preterm infants showed a very similar prevalence of excessive fuss/cry at six weeks of corrected age (15.7%) compared to the prevalence

of colic (13%) at five weeks of age in an earlier community sample from the same regional population (Lehtonen & Korvenranta, 1995).

The strengths of Study I included the longitudinal setting, and a validated diary method. The diary data were collected at three time points over a five-month time period, thus making it possible to explore developmental trends in crying behavior. At each time point, a recording from three consecutive days was used to minimize the day-to-day fluctuation in the behavior. A further strength was that the completion and return rate of the diaries was high, making data very representative. A majority of the diaries were completed in a home environment, which is thought to best represent spontaneous behavior in a natural setting.

Although statistically significant associations were found between early crying behavior and later development, there was a large overlap in the developmental outcome of infants with lower or higher durations of fussing and crying. This limits the use of fussing and crying behavior as a predictor of poor developmental outcome in clinical work.

Our premature infants had close-to-average scores, both in MDI and PDI of BSID-II, when the results are compared to American normative data (mean 100, SD 15). However, American norms cannot be applied directly to non-American populations. Of the subscales of BSID-II, PDI offers important information about the quantitative aspects of motor development. However, PDI ignores such qualitative aspects as tone distribution, asymmetries in motor actions, and abnormal movement patterns. Therefore, more detailed qualitative aspects should be assessed using other methods.

*Cognitive development in relation to prenatal, neonatal and parental factors at the corrected age of two years*

In Study II, VLBW infants had their mean MDI at an average level compared with test norms. While the prevalence of neurological deficits was similar compared to earlier studies, the cognitive outcome was more positive.

The outcome of the ELBW/ELGA infants has been reported as relatively pessimistic. In the NICHD Neonatal Network, the average MDI of ELBW infants has remained at the level of 85 and the prevalence of severe cognitive delay has been high (20 to 24%) (Wilson-Costello, 2007). Similarly, it has been reported that the prevalence of NDI is 23% in ELBW infants born after the year 2000 (Kobaly et al., 2008; Wilson-Costello et al., 2007). In the EPICure cohort, the mean value of the MDI was at the same level as in the NICHD infants, being <70 in 30% of the ELGA infants (Wood et al., 2000; Wood et al., 2005). A total of 24% of the EPICure infants had a neuromotor disability, and less than 50% of these infants survived without any disability. In the population of Study II, infants born below 26 gestational weeks (n=31) had a mean MDI of 93.9, MDI was <70 in 6.5%, and 22.6% had some form of NDI. However, a small number of infants born <26 GWs in Study II limits comparison to large the EPICure cohort.

Recent studies of the VLBW/VLGA populations have suggested a more positive perspective for cognitive outcome. However, there is large variability in both the inclusion and exclusion criteria, as well as in the results. There are studies (Maguire et al., 2009; van Zwol et al., 2008; Walch, Chaudhary, Herold, & Obladen, 2009) that have reported a mean MDI on the same level as in Study II. Two of these studies (Maguire et al., 2009; Walch et al., 2009) have, however, excluded infants with significant neonatal risk factors. In another selected population the mean MDI was 88 (Grunau et al., 2009). In unselected study populations comparable with Study II, the mean MDI has been reported to range from 74 to 92 (Bode et al., 2009; Johnson et al., 2009; Rose et al., 2009; Westera, Houtzager, Overdiek, & van Wassenaer, 2008; Wielenga et al., 2009). In comparison to these studies, the population of Study II, which also included at-risk infants, had a relatively good cognitive outcome.

The EPIPAGE study, which included infants born below 30 weeks of gestation, reported CP in 8.2% of infants (Fily et al., 2006) and they had a mean developmental quotient (DQ) of 94 (SD 11). However, the prevalence of severe delay in DQ was not reported (Ancel et al., 2006). It should be noted that the test that was used is not directly comparable with the MDI. In the Australia/New Zealand cohort of infants born below 31 weeks of gestation, the prevalence of MDI <70 was also higher (17%) than in Study II, but the rate of CP was comparable (Woodward et al., 2006).



In Study II, poor postnatal growth was associated with a less favorable cognitive outcome. This is consistent with earlier literature (Ehrenkranz et al., 2006). A negative association was found between intestinal perforation and cognitive outcome, which also supports previous findings (Rees et al., 2007). However, many treatment strategies have not been adequately evaluated, resulting in a wide variation of care practices, and this may explain the differences in later cognitive outcomes of VLBW infants. These include medical treatments and also the avoidance and treatment of pain, and support for families to optimize the post-discharge environment. Antenatal factors predisposing to prematurity may also differ among populations with a varying prevalence of prematurity (Goldenberg et al., 2006).

The lower number of severe brain abnormalities in ultrasound did not explain the better cognitive outcome in Study II. Here, a similar prevalence of major brain abnormalities were found as in the populations of NICHD Neonatal Network (Wilson-Costello, 2007), and that of the EPICure (Wood et al., 2000), and the EPIPAGE (Larroque et al., 2008). Only the Australia/New Zealand study reported brain MRI findings (Woodward et al., 2006). The infants had a comparable prevalence of moderate/severe brain abnormalities (21% of severe findings compared to 25% in Study II). However, 50% of the Australia/New Zealand infants had mild findings compared to 16% of the minor brain abnormalities in Study II. The large variety in the criteria used for severity classification makes it difficult to compare these imaging results. No consensus has been reached for either the methods or for the classification used for brain imaging findings in very preterm infants. This makes it difficult to pursue relevant comparisons between data from different countries and centers.

Both CUS and MRI had good sensitivity for predicting NDI and a low MDI. The combination of these early brain-imaging methods provided valuable information about the risks for later development. Severe brain abnormalities also explained a share of variation in the MDI independently in the regression model. The brain MRI detected all infants with severe delay in MDI, while CUS failed to detect two out of six cases. In contrast, CUS detected all infants with CP, while MRI failed to detect two out of 12 cases.

The FT infants in the present study had a high mean MDI compared with the original BSID-II normative data. However, only healthy-born infants were included, while all preterm and SGA infants were excluded, along with those who required NICU admission for any reason (over 10% of the newborn population need NICU care) or who were antenatally exposed to alcohol or illicit drugs. In addition, the average education level in Finland is high and the variation in socio-economic background is smaller than in many other countries. Importantly, the socio-economic background factors did not differ between VLBW and FT infants, which served to differentiate the VLBW population in the present study from those of many other countries. This may partly explain the better cognitive outcome, as it makes it possible to study the impact of prematurity without the confounding effects of socio-economic factors. In Finland, antenatal clinics are free of charge for all mothers, which makes it possible to closely monitor the pregnancy. Another possible protective factor for infant development is the nine-month maternity leave period (for preterm infants count from term age) for all mothers. Among the 182 families of the VLBW infants, 177 reported their family structure two years after the infant's birth, and only 10 of these 177 families had separated, which illustrates high family stability. Although infants did not take part in any structured intervention program in this study, all of the infants who had a significant delay in motor development received physiotherapy.

The strengths of this regional cohort study include a high coverage of the VLBW infants born in one hospital with structured obstetric and neonatal treatment, and with an active treatment approach from 23 0/7 weeks of gestation. In Finland, there is an aim for a high degree of centralization of preterm births to level III-IV hospitals, and therefore this population represents a larger region rather than single center. Standardized methods were used for follow-up and a regional control group was used in addition to the normative data of BSID-II.

The limitations of the present study are that birth weight, rather than gestational age, was used as an inclusion criteria. This led to the inclusion of more mature infants and the number of SGA infants was relatively high. However, there was no difference in the MDI of the SGA/AGA infants. In addition, the MDI of BSID-II sums up several areas of development, such as language and visuo-motor functions. Furthermore, the MDI does not offer detailed information about long-term cognitive development, as

two years is not sufficient to evaluate academic performance. A translation of the original version of BSID-II was used and no Finnish norms (other than from the study's control group) were available. This should be taken into account when comparing results with the other populations. Another limitation is the low number of infants born in each gestational week. As these results only reflect the treatment practices of one hospital, they are not directly applicable to hospitals that use different treatment strategies. Multi-center research is necessary in order to compare outcome data from different centers and to identify optimal guidelines for treatment strategies. However, consensus is needed both on methods used, as well as harmonization of timing of follow-up in order to compare results. Also, the inclusion criteria should be equal. Because out-born infants were excluded, it is possible that the MDI is higher than in populations in which they are included. Infants from other than Finnish/Swedish-speaking families were excluded, because it was not possible to reliably examine the MDI (especially linguistic sub-tests). This selection may also have affected the outcome of this population. Examiners were also aware of whether the infant belonged to the VLBW or to the FT group, which is a possible source of bias.

#### *Stability of cognitive development from two years to five years*

Opinions concerning whether early measures of cognitive development show stability over time has varied considerably. Some researchers have suggested a poor predictive validity to later assessments (Hack et al., 2005; Ment et al., 2003), while others have concluded that early measures can predict the later cognitive outcome quite reliably (Claas, de Vries et al., 2011; Marlow et al., 2005; Mikkola et al., 2005; Samuelsson et al., 2006). Study III showed a strong correlation between MDI measured at two years of age and FSIQ measured at the age of five years, suggesting that early assessment of cognitive development is significantly associated with cognitive development at least up to the age of five years. The stability of the classification of cognitive outcome was high in normally developing and in significantly delayed groups of VLBW children. This implies that early assessment of cognitive development is clinically relevant.

The cognitive development of the present study population was good at the corrected age of two years in Study II, and Study III confirmed that this was not due to the

timing of the assessment, or method used. Preterm born children performed at the normative level of both BSID-II, and WPPSI-R. Despite that, the difference with the control group was approximately 10 points also at the age of five years. Our control group, however, was selected as it included only infants who were born healthy.

The strengths of Study III include a high coverage of the VLBW children with a long follow-up period. Standardized methods were used for follow-up and a regional control group was used in addition to the normative data of BSID-II and WPPSI-R. Different psychologists conducted the assessment at two different time-points to avoid bias from the previous assessment. A strong correlation was found in spite of the fact that different methods had to be used to measure cognitive development at different ages, as both methods cover only a limited age-span. However, both methods give normative information about the individual development and they are based on the same scaling. An additional strength was that all the children participated in the assessment within a very strict time limit. The timing of the assessment was chosen to be both developmentally and clinically relevant. From the developmental point of view, two years of age is interesting, as motor development is less dominant and language development is in a very active phase. Clinically, it is important to identify children with developmental problems as early, and as accurately, as possible to provide them with the appropriate services. Five years is a more reliable age for assessment considering the later school performance and there is still time for preventive interventions if the child is at risk for academic failure. In Finland, children enter school at the age of seven years.

Some limitations include the fact that BSID-II, and WPPSI-R were used instead of the new versions of Bayley Scales for Infant and Toddler Development, III and WPPSI-III, as these tests were not available in Finland at the time of the study. Also, it would be more reliable to use one method in longitudinal follow-up, but considering the ages at assessment (2 and 5) this was not possible, as neither BSID-II, nor WPPSI-R covers all of this developmental period. It is also important to stress that measures of cognitive development, such as those used here, do not allow inferences about neuropsychological deficits that can be found with more specific measures, or that may become evident only later in the development. Low cognitive capacity is usually accompanied by neuropsychological difficulties, but an average capacity does not

imply that one would be free from more specific neuropsychological problems. Therefore, also other methods are needed to complement the follow-up of at-risk preterm born children. In other studies on the same PIPARI cohort, VLBW children were at higher risk for various neuropsychological deficits in comparison to FT controls (Lind et al., 2010; Lind et al., 2011). Long-term follow-up is needed to identify specific problems that may become evident only later in the development.

#### *Precursors of reading acquisition at the age of five years*

Very little is known about the pre-reading skill of very preterm born children. In Study IV, 75% of the five-year-old VLBW children performed within the normal range in the measures of pre-reading skills (phonological processing, rapid automatized naming, and letter knowledge) that are known to be predictors for reading acquisition (Lyytinen et al., 2008). Risks in individual pre-reading skills did not cumulate as different children performed poorly, for example, in phonological processing and in rapid automatized naming. VLBW children had significantly poorer pre-reading skills than FT children, and they performed more often below the normal range, and were thus more often considered to be at risk for problems in reading acquisition later in school age. In a study by Wolke & Meyer (1999) preterm children were reported to have a 3-5 times higher risk for problems in their pre-reading skills in comparison to full-term peers. In our study, the risk was approximately 2-3 times higher in the VLBW population, indicating a smaller additional risk due to prematurity (at risk 24-27% of the VLBW population, and 9-17% of the FT population). However, Wolke & Meyer (1999) did not exclude any children on the basis of low an IQ, and here all children with IQ of <70 were excluded. Also, they used a 10<sup>th</sup> percentile cut-off point whereas in the present study the cut-off point of <-1SD (equal to the 16<sup>th</sup> percentile) was adopted. To our knowledge, only these two studies have investigated the pre-reading skills of the very preterm born children. The present study thus confirms the previous result that preterm children have a higher risk for problems in reading acquisition.

In the present study, the overall cognitive functioning showed a significant association with pre-reading skills. As controlling for FSIQ strongly reduced group differences in pre-reading skills, this study suggests that VLBW children's risk for reading problems

would be a reflection of more global cognitive problems rather than a specific problem. The strong relation of FSIQ to pre-reading skills was evident even after the exclusion of children with FSIQ <70. However, it is important to note that there was a trend for poorer performance in phonological processing in VLBW children also after controlling for FSIQ. The finding that the problems in pre-reading skills were mediated by FSIQ is consistent with the results by Samuelsson et al. (Samuelsson et al., 1999, Samuelsson et al., 2000, Samuelsson et al., 2006) As the present population and that of Samuelsson et al. represent different age groups, we cannot dispute their finding that preterm children are not at risk for phonological problems.

Somewhat surprising was the finding that the pre-reading skills of the VLBW children were not affected by any of the neonatal risk factors, including neonatal brain insults. It is possible that the selection of the sample (including only children with IQ >70) may have excluded the children with the most severe neonatal problems and brain pathology. We cannot speculate on the possible neural mechanism that may lie behind the problems in pre-reading skills, because more sophisticated imaging methods, like functional brain imaging, would be needed to further study this question. A plausible explanation for the deficit in pre-reading skills is very likely multi-factorial, including some social, and possibly also genetic factors. In the present study, paternal education was significantly related to all pre-reading skills in the VLBW population, and maternal education with letter knowledge. The self-reported reading problems of the mothers were associated with poorer phonological processing as well as letter knowledge, and reading problems of the fathers were associated with poorer letter knowledge.

The strengths of the present study are its prospective and population-based nature with a well-defined VLBW cohort together with a control group born in the same hospital. The measures used were selected on the basis of their power to predict reading acquisition later at school age. This enabled us to inform the parents of the children at risk, and allowing enough time for preventative measures. If there were any concerns about the development or the behavior of the child, s/he was referred to the appropriate local services. In Finland, there is a national pre-school curriculum as part of the communal day-care system. This system provides appropriate support for all children with developmental or behavioral concerns, and no IQ discrepancy is required

for inclusion. Trained nursery-school teachers introduce language and literacy skills in daily play-situations. Training in literacy skills is given to all children during pre-school when they are 6 years old. This program also serves as a preventive measure for children-at-risk of learning difficulties. All children also participate in formal assessment before entrance into school.

Because our focus was on pre-reading skills, the final outcome in reading acquisition is not yet known. A further limitation was the administration of a standardized, edition of NEPSY-II, which differs slightly from the version published later. Because of that, we were not able to compare the performance of the VLBW children to the unselected normative population of NEPSY-II. As a consequence, the cut-off scores for risks in pre-reading skills were derived from the healthy born FT group recruited for this study. As our control group scored about 10 points above the national WPPSI-R norms, it is possible that the cut-off scores might have been more stringent than in a non-selected normative population. Thus, the number of VLBW children actually at risk might be smaller than presented here. The distribution of the FSIQ was similar in both groups, but the VLBW group performed more than a half standard deviation below the FT group. The lowest end of the distribution was overrepresented in the VLBW population, although children with an IQ of <70 were not included. However, no statistically significant difference was found in VIQ between the groups, and the difference in FSIQ was predominantly caused by lower PIQ in VLBW children.

## **CONCLUSIONS, CLINICAL IMPLICATIONS, AND FUTURE RESEARCH**

The early excessive crying of VLBW infants was associated with a poorer developmental outcome. It is important to identify risk groups among preterm infants to target the limited resources of the follow-up. Behavioral assessment as a part of clinical evaluation might be an additional useful tool to identify infants at risk.

The cognitive outcome of this VLBW cohort was more positive than has been reported earlier. However, the difference with the full-term control was significant. The risk factors for adverse cognitive development included the use of postnatal corticosteroids, intestinal perforation, and major brain pathology. According to our findings, we suggest that preterm infants should be assessed with brain imaging, preferably with both serial CUS, and with MRI. The classifications used in the PIPARI Study successfully correlated with developmental findings.

The organization of care, along with various background factors, may explain regional differences in outcome. The cognitive outcome of extremely preterm infants can vary greatly among different populations due to differences in the causes of the prematurity, socio-economic background factors, and treatment practices. Also, the degree of centralization of preterm deliveries to level III-IV hospitals varies. Therefore, regional follow-up data are important when counseling parents about making decisions regarding the active/inactive treatment approach. We suggest that two and five years of age are relevant age points to assess the cognitive development of preterm born children. The significance of early developmental assessments of preterm born infants has been questioned on the basis of a lack of evidence about their longitudinal prognostic value. Here, cognitive outcome measured at the age of two years, was significantly associated with cognitive outcome at the age of five years. Well-conducted assessment is relevant and valuable also at an early age, making it possible to support those children with developmental problems, and to also support their families. Children with significant developmental problems should be addressed to appropriate diagnostic, etiological, and rehabilitation services as early as possible. On the other hand, also children with milder problems should be provided with parental counseling to support their child's possible specific needs. The age of two years is too early to assess neuropsychological deficits. Therefore, we stress the



importance of long-term follow-up of these at-risk children, as well as the application of methods covering both cognitive and neuropsychological development.

Very little is known about the pre-reading skills of very preterm born children, albeit reading problems later in school age are well recognized. Here, about 75% of the VLBW population showed no risk for problems in individual measures of reading acquisition at the age of five years, and only a few children had problems typical for the double deficit. However, VLBW children have poorer pre-reading skills, and these are strongly mediated by over-all cognitive capacity. Learning to read is a seminal task and it is important to anticipate and prevent problems in reading acquisition. This risk can be assessed with only three relatively simple tasks as part of the assessment of cognitive development, and we suggest that this should be part of the follow-up procedure.

More research is needed about the future academic competencies of the children studied here. Especially, many risks that have been shown here manifest themselves as possible learning difficulties in school age. The focus of the present studies was on the over-all cognitive development, and only pre-reading skills were studied in more detail. In the future, also many other academic skills, as well as neuropsychological deficits, need more attention. Especially the mathematical skills of very preterm children should be studied in more detail. Of the neuropsychological deficits, especially working memory and executive functions are of great interest, as they both form a bottleneck for learning, even if the over-all cognitive functioning would not limit learning.

Here, the birth weight criteria were adopted to include the infant in the study. Therefore, the mixed effect of prematurity and low birth weight was studied. However, many large studies have used the gestational week criteria to include infants and it makes it challenging to compare the results. Therefore, also the PIPARI study has adopted the GA criteria for infants born later in the data collection process. This enables also better international comparison. It would have been interesting to study the effect of intervention on the development of these children. In Finland, all children at risk for developmental problems are provided with communal support. However, it was not possible to offer them any additional intervention. On the other hand, also

offering the parents and daycare with relevant information about the child's development can be an important intervention.

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## **ORIGINAL PUBLICATIONS**