Preterm birth, long-term outcome: how an early start affects school-aged children

Jansen, L.

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PRETERM BIRTH, LONG-TERM OUTCOME:

How an early start affects school-aged children

Lisette Jansen

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The research described in this thesis was performed at the Willem-Alexander Children's Hospital, the Department of Neonatology, in collaboration with Curium, department of Child and Adolescent Psychiatry of the Leiden University Medical Center, the Netherlands.

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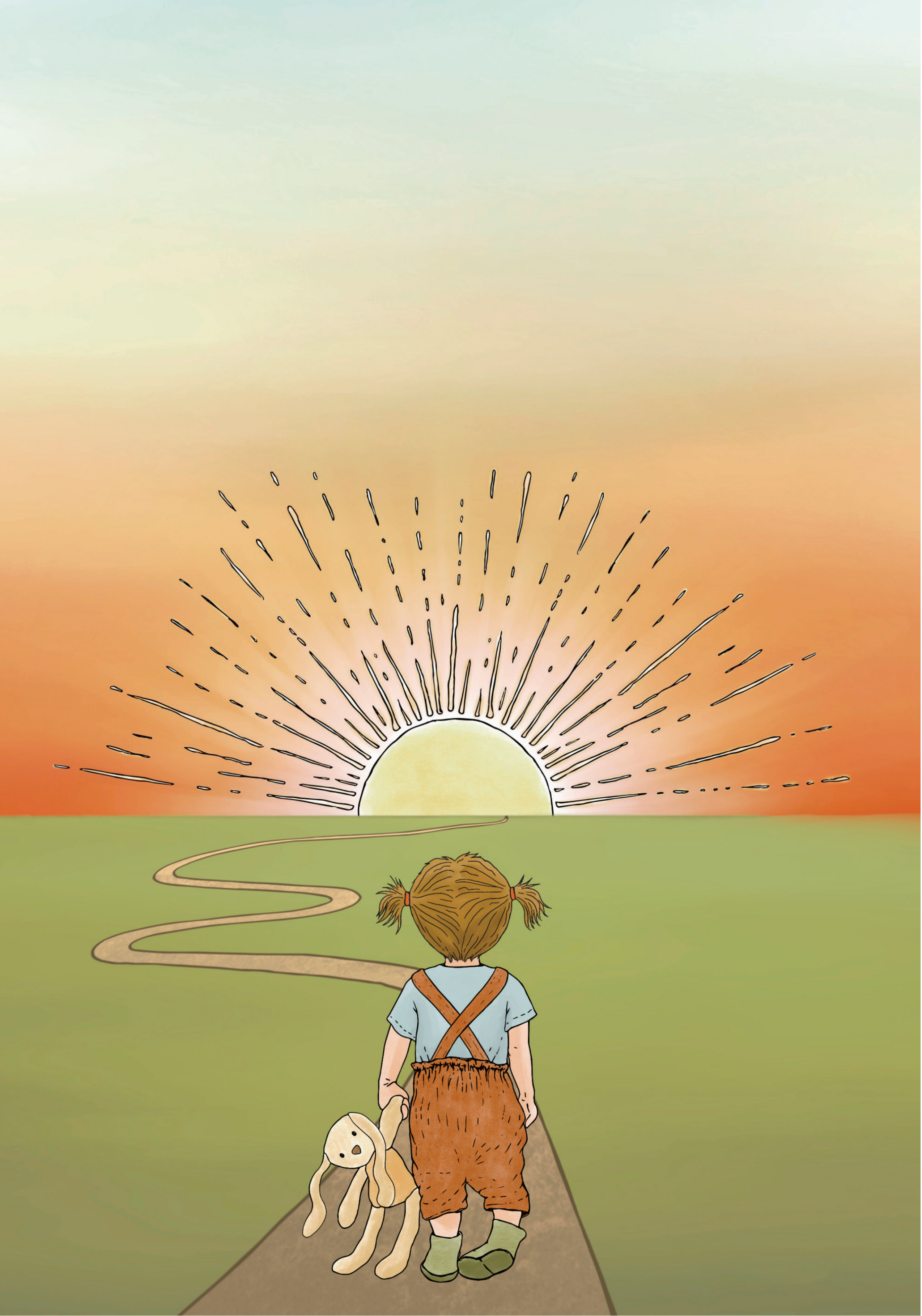

PART ONE

PATIENT JOURNEY

At first glance, Kevin (age 14) and Nizar (age 15) are two adolescent boys like any of their peers. They both attend secondary education and playing sports is an important part of their life. However, they were also both born extremely preterm, at 25 weeks' gestation, and therefore had a difficult start of their lives.

In 2007, Kevin's parents (Arjan and Annemieke), were expecting their first child. Even though the prenatal ultrasound scans and appointments were all normal, the delivery started suddenly, at 25 weeks and three days. Kevin's mother was rushed to the Leiden University Medical Center (LUMC) by ambulance. She received tocolytic medication in an attempt to stop premature contractures and corticosteroids to enhance fetal lung maturation. Parents were told that, if their baby was born before 26 weeks' gestation, he would have to show signs of viability after birth, or life-prolonging treatment would be discontinued. Unfortunately, the medication had no effect and Kevin was born after a pregnancy of 25 weeks and 4 days, weighing 950 grams. Even though Annemieke has little active memories of the delivery, she strongly believed that Kevin would survive. She remembers a staff member mentioning that their baby would have had better chances of survival if the gender would be female, a very painful comment given the circumstances. After birth, Kevin was taken to the Neonatal Intensive Care Unit (NICU) where his parents met their son several hours later. They had to wait three more days before they could hold him in their arms for the first time (figure 1).

Nizar's mother (Ilham) already had a frightening experience during her first pregnancy of Nizar's brother. She developed preeclampsia and was admitted to the intensive care after his birth at 34 weeks' gestation. It took Nizar's parents eight years to feel confident enough to get pregnant again. Due to her medical history, Nizar's mother was closely monitored at a local hospital. After five months of pregnancy, her blood pressure started to rise. She was admitted and treated with antihypertensive drugs, but despite the medication, her blood pressure reached alarming levels. After transfer to the LUMC, a cardiotocography showed that their baby was in serious distress. An emergency caesarean section was performed and Nizar was born at a gestational age of 25 weeks and 4 days, weighing 670 grams. He was intubated immediately after birth and admitted to the NICU. It took Nizar's parents a few days to realize what had happened. Due to the acute situation, parents were not counselled before birth. After birth, they felt overwhelmed when they heard about the possible risks and consequences of Nizar's extremely preterm birth.

Time in the hospital

Due to immaturity of their lungs, both Kevin and Nizar remained in need of mechanical ventilation during the first weeks after birth. Their parents were faced with the choice of treatment with Dexamethasone, a medicine that would likely benefit the development of the pulmonary system and help them to get of the ventilator. However, treatment could also have severe side effects including motor and mental retardation. Nizar's parents decided quickly that this was the only option, but, feeling overwhelmed with emotions, remember that they did not speak to each other for the rest of the day. Kevin's parents considered it a very difficult and emotional decision, but at the end also felt that there was no other option (figure 2). Besides concerns about pulmonary problems, preterm babies are also at risk for neurologic complications and both boys received weekly cranial ultrasound scans. Kevin's parents remember that the doctors talked about white flaring in his brain. This could have serious consequences for Kevin's development, especially if it became worse. Therefore, every ultrasound was nerve wracking, but luckily the results were optimistic.

As the boys remained at the NICU for over two months, their parents drove to the hospital every day, only returning home to sleep. Despite the anxious and fearful moments, their parents describe the experience with the NICU as positive as they felt supported by the medical staff and nurses. After 9-10 weeks of NICU admission and several weeks in a local hospital, Kevin and Nizar were discharged home.

Kevin's parents were told that they would have a baby with a chronic lung condition and an uncertain future due to treatment with Dexamethasone. They were concerned about their home environment, as they lived at an old farm and worried whether this would negatively affect the pulmonary problems. Nizar's parents were thrilled to take him home, but found themselves during the first weeks constantly checking whether he was still breathing. Since the doctors were not able to make any predictions on Nizar's future functioning, parents also worried about what they could expect.

The first years

During the first years, parents were supported through home visits from a physiotherapist and were regularly invited for follow-up appointments at their local hospital, the LUMC and, as is the case for all Dutch infants, a children's health care centre. During these years, Kevin's parents still worried whether the Dexamethasone treatment would affect his ability to reach age-appropriate milestones. Nizar's parents noticed early on that Nizar developed well behind his peers. This was not a concern to them, for they felt adequately informed and expected this to happen. They were happy that Nizar was home, able to see and hear, and felt confident that he would learn to walk and talk in his own pace.

At the age of two, Kevin and Nizar underwent an extensive follow-up assessment in the LUMC, where they were seen by a paediatrician, physical therapist and child psychologist. Besides a minor neurological dysfunction, Kevin's outcomes in the motor, cognitive and behavioral domain were all in the (above) average range. During this visit, parents were told that he developed well, and that no major problems were to be expected in the future. However, Kevin did experience a delay in speech development in the following years, and received support from a speech therapist on a regular basis till the age of eight. Nizar showed a normal cognitive development, but a delay in his fine motor skills and speech for which physio- and speech therapy was started. He also transferred from a regular to a medical day care for extra developmental stimulation.

Elementary school

At four years of age, Kevin started to attend mainstream education. The first two years were difficult for him, as he had struggled with unexpected change and showed difficulties in play, playing mostly with a deck of cards which he piled into little stocks. Due to Kevin's social and emotional functioning, his parents wondered whether it would be better for him to prolong preschool. However, the teachers of his school, who were aware of his difficult first period of life, thought he would be better off in first grade. To assess Kevin's functioning, he was observed at school and received a cognitive assessment, showing adequate social skills and an above average IQ score with specifically a very high processing speed. Kevin continued to first grade, where he immediately thrived within the structure. The rest of his years in elementary school were characterized by easy learning, but social difficulties. Kevin was anxious to have play dates, and his mother was concerned whether he would be able to form friendships.

When Nizar reached the age of four, his parents were advised against mainstream education due to his need of additional support. Parents decided on an elementary school specialised in language and speech problems. Three years later, Nizar no longer needed to remain at his school, and parents were faced with the choice between mainstream or special education. His parents visited several schools, but found the large group sizes of mainstream education overwhelming. Since Nizar was easily distracted and very sensitive for sensory stimuli, they decided he would be better off in a smaller class in special education. Nizar felt right at home at his new school and performed well within his level of education. He finished his assignments quickly and received additional work. His mother recognizes that this might have been different in mainstream education, since his school had enough resources to support him, mostly in terms of concentration. The transfer had however negatively affected his social contacts, as he was unable to maintain his friendships from his former school.

At ten years of age, Kevin (Figure 3) and Nizar and their parents were again invited for follow-up in the LUMC. For Kevin, the results of the neurological, cognitive, motor and behavioral assessment were almost all in line with the two-year assessment, showing (above) average outcomes in all domains. In contrast, the outcomes of Nizar's assessment at ten years of age were different compared to those at two years of age. The biggest change was within his cognitive capacities. Despite an average score at two years of age Nizar showed significant problems at ten years of age, especially with tasks relying on his visuo-spatial abilities.

Now

Nowadays both Kevin and Nizar are healthy and happy boys who are doing well according to their parents. Kevin attends the third class of general secondary education and has an interest in numbers and mathematics, plays volleyball and has a steady group of friends. He tends to be a bit shy, and still likes to know what he can expect in certain situations, but parents see him bloom and gain confidence. Nizar is also doing well at school, attending the third year of practical education and hoping to be able to transfer to secondary vocational education afterwards. He likes kickboxing, soccer and playing videogames. Although he easily connects with others, it has been difficult for him to maintain friendships over the years.

Both the parents of Nizar and Kevin mention that the history of preterm birth is a closed chapter in their life. They consider themselves lucky with how well their sons have developed over the years. As an advice to parents of preterm babies today, Kevin's mother states it was a true rollercoaster, and parents should be prepared for rapid shifts between good and bad days. She advices to write things down, and talk to others in order to process everything that happens. But her main advice would be: don't use Google as the internet is full of negative stories. Believing in your child is the most important thing to do. Nizar's mother states it is important to have faith in science and the medical staff, but also to stay connected with your feelings. If something doesn't feel right, make sure you receive all the information. And, despite the hardship, try to keep a positive spirit as negativity is not what your baby needs while fighting for its life.

Figure 1. Kevin is being held by his father for the first time, four days after birth.

Figure 2. Kevin is taken of the ventilator and able to breathe on his own for the first time.

Figure 3. Kevin at 10 years of age.

PART TWO

GENERAL INTRODUCTION

Preterm birth is defined as birth before 37 completed weeks of gestation [1]. Globally, an estimated 15 million babies are born preterm every year, with the rate of preterm birth ranging between countries from 5% to 18%. Prematurity can be divided into three groups, based on gestation:

1. Extremely preterm born infants (born below 28 weeks' gestation)
2. Very preterm born infants (born between 28 and 32 weeks' gestation)
3. Moderate to late preterm born infants (born between 32 and 37 weeks' gestation)

With the improvement of fetal and neonatal care in high-income countries, perinatal mortality after preterm birth has significantly decreased over the last decades [2]. However, the challenges following preterm birth can have a profound impact on long-term development. All preterm infants are susceptible to experiencing difficulties in a wide variety of domains, including motor skills, cognitive capacities, academic attainment and behavior [3, 4].

The purpose of this thesis is to describe a longitudinal cohort of children born below 32 weeks' gestation and study the associations between neonatal factors, early outcomes at two years and school-aged outcomes at ten years of age. In this chapter, we will start with an outline of preterm birth in the Netherlands and the Dutch neonatal follow-up program. We will give a brief overview of what is known about neurodevelopmental outcomes of very preterm infants until now and describe known risk factors of adverse outcomes. Finally, we will present the design and aims of this thesis.

Preterm birth and follow-up in the Netherlands

In the Netherlands, approximately 11.000 infants are born preterm every year, accounting for 6.5% of all live births [5]. Nearly 2500 of the preterm infants are yearly admitted to one of the Neonatal Intensive Care Units (NICU's) due to extreme or very preterm birth. Because children born preterm are at risk of neurodevelopmental impairments, all children born below 30 weeks' gestation and/or with a birthweight below 1500 grams are enrolled in the national Dutch neonatal follow-up program [6]. This program is designed to assess children in four domains, including growth and health, neuromotor development, cognitive development, and social-emotional development. Since the implementation of the national guideline [6] in 2015, children and their parents are invited for five follow-up visits; at the corrected age of six and twelve months, and at the age of two, five, and eight to nine years. All children are assessed by a neonatologist, physical therapist and child psychologist in order to capture the child's functioning.

There are several reasons why follow-up of children born preterm is important. First of all, it provides insight for parents in the development of their child. By discovering potential developmental challenges at an early stage, children might possibly benefit from early adapted intervention strategies. Furthermore, the collection of follow-up data is essential in order to increase our knowledge and our ability to adequately counsel the expectations of parents of preterm infants born today. The collection of follow-up data also allows us to assess changes in (long-term) developmental outcome over time and provides feedback about the effects of clinical practice.

Developmental outcome

The outcome of children born preterm has been a topic of interest for many years [7, 8]. Most studies have focused on neurodevelopmental outcome at 24 months of age, although the impact of preterm birth reaches far beyond toddlerhood.

Toddlerhood

During the first years of life, major abnormalities in motor, cognitive and sensory functioning will be identified, including cerebral palsy, severe mental retardation, hearing loss and visual impairment [9]. Approximately a quarter of very preterm infants shows substantial difficulties at 24 months of age, corrected for prematurity [2].

School-age

During school-age, preterm birth is associated with lower cognitive scores and difficulties in executive functioning and academic attainment [4, 7, 10]. This leads to an increase in special educational needs, including learning support and/or enrolment in special education [11]. Furthermore, children born preterm have a 2 to 4 fold higher risk for experiencing internalizing and externalizing behavioural problems, including symptoms of attention deficit hyperactivity disorder, autism spectrum disorder, and anxiety disorders [12].

Adolescence and adulthood

Adolescents born very preterm have more difficulties in establishing and maintaining social contacts [13] and have diminished social skills. Compared to the general Dutch population, very preterm adolescents are more likely to be poorly educated and/or to be unemployed or not enrolled in school activities at 19 years of age. Reassuringly, as adults, the majority of preterm infants rates their functioning similar to their term-born peers, even though they remain at risk for general health issues and anxiety and/or depressive disorders [14].

Initial studies reporting on outcomes after very preterm birth mainly focused on major impairments (sensory impairments, cerebral palsy and/or mental retardation), and found the occurrence to remain relatively stable among different birth cohorts over time[15, 16]. In contrary, the prevalence of more subtle problems, including behavioral difficulties and learning problems, seems to increase. This might be the result of more sensitive assessment tools for older children, but also because subtle problems usually don’t appear until a later stage of life.

Factors associated with developmental outcome

With increasing knowledge of the developmental challenges faced by children born very preterm, an understanding of factors associated with adverse outcome and the ability to predict who is at risk becomes clinically relevant. The aetiology of neurodevelopmental impairments is complicated and includes multiple facets such as genetic, maternal, peri- and postnatal, and sociodemographic factors. Additionally complex is that, with increasing age, environmental factors become of greater influence in predicting outcome compared to the factors known at birth [17].

One of the strongest and most consistent predictors of neurodevelopmental functioning is gestational age. With each completed week of gestation, the risk of (severe) impairment decreases [18]. Linsell and colleagues reported in multiple systematic reviews on prognostic factors for cognitive development, motor impairment and behavioural problems. Factors found to be associated with cognitive impairment were male sex, ethnicity, lower birthweight and lower levels of parental education in children younger than 5 [17]. Interestingly, only the influence of parental education sustained as a predictive factor in older children. Intraventricular haemorrhage and periventricular leukomalacia were especially predictive for cerebral palsy [19] and there was a lack of evidence concerning the prediction of general behavioural problems [20]. One of the most important and frequently seen complications in preterm infants is neonatal brain injury, a factor that has gained increasingly more attention in predicting early outcome.

Neonatal brain injury

The brain of children born very preterm is often organized differently compared to the brain of full-term born children, due to the disruption in development of brain structures and brain maturation [21]. Neonatal brain injury can be detected by either cranial ultrasound or magnetic resonance imaging (MRI). Nowadays, most children with neonatal brain damage have subtle brain abnormalities, which are difficult to detect without an MRI [22, 23]. However, as the prognostic implications of MRI are still debated, the use of neonatal MRI is currently not recommended as standard care. In particular, the associations between MRI findings and long-term developmental outcomes are still largely unknown.

Purpose and design of the study

The general aim of this thesis was to report on long-term developmental outcomes in children born very preterm and to investigate the association between outcome and brain abnormalities as seen on neonatal MRI. Because this study has been part of a broader prospective study investigating developmental outcomes after preterm birth (*PReterm brain injury, long-term Outcome and brain Development study (PROUD)*), participants were recruited from an ongoing longitudinal cohort of 113 children, born at the Leiden University Medical Center (LUMC) between May 2006 and October 2007. All infants underwent an MRI at term-equivalent age, and were invited for a follow-up study at two years of age, creating a database with perinatal outcomes and developmental outcomes in toddlerhood. For the current study, all children of the original cohort were invited at 9-10 years of age for a clinical neurodevelopmental follow-up visit, and an additional MRI and EEG. The neurodevelopmental follow-up focused on four domains and included neurological functioning, motor skills, cognition and behavior. The first three domains were assessed by a child neurologist, child physical therapist and child psychologist. Parents completed questionnaires on their child's behavior for the behavioral domain.

Outline

Chapter 1 describes the rate and stability of impairments in children born preterm by assessing early and school-age outcome in four developmental domains (neurological functioning, motor skills, cognition and behavior) at both 2 and 10 years of age. The individual change in outcome between both timepoints was also assessed. This gives an insight not only in the rates of impairment at both timepoints, but also in the course of development over the years for individual children. As early prognostic markers can have an important role in predicting development, **Chapter 2** associates neonatal neuroimaging findings with both early and school-age outcome within a cohort of very preterm children. Chapter 3 and 4 will focus on outcome measures other than those derived from standardized assessments. **Chapter 3** describes how children perform at school, by reporting their grades on reading, spelling and mathematics and comparing these to their Dutch peers. Most studies reporting on outcomes include an intelligence test. However, intelligence measured in a clinically controlled environment is not always (fully) predictive of school results, which are assessed in a classroom filled with other children and many distractions. Besides reporting on classroom-evaluated performance, we also tried to identify those children most at risk to fall behind at school. **Chapter 4** covers a qualitative study reporting on social-emotional and behavioral issues after very preterm birth. In this study we examine both the parents' and teachers' perspectives. What are the themes parents worry about and do these change between two and ten years of age? Because children of ten years of age spend much time at school, we also included teachers' perspectives and reported on differences compared to the parental view. Lastly, the main findings of this thesis are discussed and directions for future research are suggested.

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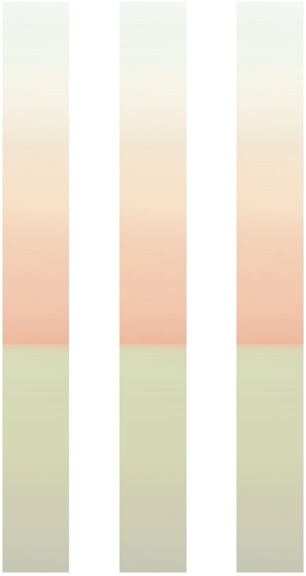
PART THREE

FOLLOWING CHILDREN BORN PRETERM OVER THE YEARS



CHAPTER 1

Longitudinal follow-up of children born preterm: Neurodevelopment from 2 to 10 years of age

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Lisette Jansen
Cacha Peeters-Scholte
Annette van den Berg-Huysmans
Jeanine van Klink
Monique Rijken
Janneke van Egmond-van Dam
Robert Vermeiren
Sylke Steggerda

Abstract

Objective: To investigate the rate and stability of impairments in children born preterm by assessing (1) early and school-age outcome in four developmental domains and (2) individual changes in outcome at both timepoints.

Design: Prospective, longitudinal cohort study in children born in 2006–2007, <32 weeks' gestation. Follow-up at 2 and 10 years of age included standardized neurological, motor, cognitive and behavioral assessments. Children were categorized as having no, mild or moderate-severe impairment in these four domains. A composite impairment score was composed and the number of domains with impairments counted. For each child, individual outcomes at both timepoints were compared.

Results: Follow-up at both time-points was available in 71/113(63%) children. At group level, there were no significant changes in the severity of impairments per domain. However, at individual level, there were less children with a mild abnormal composite score at 10 years of age (44 vs. 20%; $p = 0.006$), and more with a moderate-severe abnormal composite score (12 vs. 35%; p = 0.001). Especially children with normal/mild outcome at 2 years were likely to shift to other outcome categories over time.

Conclusions: Children with early severe impairment are likely experiencing impairments later on, but early normal/mild abnormal outcomes should be interpreted with care, considering the large individual shifts over time. Long-term follow-up in all children born very preterm should therefore be continued to at least school-age.

Introduction

Being born prematurely threatens a healthy development across the life course [1]. With developmental challenges arising, or becoming more visible with increasing age and additional demands on the child's functioning, favorable outcomes at an early age do not necessarily reflect on a child's abilities later in life [2]. In order to fully recognize the difficulties of children born preterm, it is important to follow them individually, through several developmental stages, and include a standardized assessment of multiple domains of functioning.

While studies initially reported on major handicaps, including sensory deficits, cerebral palsy and cognitive delay, the focus has shifted over the past years to a broader range of milder impairments. Alongside, the assessment of impairment across multiple domains has received more attention and led to the understanding that children born preterm are prone to develop impairments in several domains of functioning at the same time [3]. This combination of multiple (mild or severe) impairments in different domains might have a significant impact on functioning later on in life.

Several follow-up studies have now reported on outcomes in longitudinal cohorts of children born preterm at two or more time-points, however the majority of them only reported outcomes at group level, discarding the possible existing variation at an individual level [2, 4-7]. Studies that did report on individual developmental trajectories mainly focused on one specific outcome domain in cohorts of children born extremely preterm (<26 weeks gestation) and reported stable trajectories of unfavorable cognitive and behavioral outcomes, persisting into adulthood [8, 9]. Prospective studies using standardized outcome assessments of individual trajectories over time in multiple developmental domains are limited. One study reported stable numbers of children with severe disabilities (cerebral palsy, moderate to severe impairment in neuromotor function, vision, hearing and/or cognition) between 6 and 11 years of age, with considerable variation in individual trajectories [10]. Recently, a study by Taylor and colleagues [11] reported a weak relationship between neurodevelopmental impairment at 2 and 10 years of age in a large cohort of infants born extremely preterm (<28 weeks gestation). In this study, a relatively high proportion of children had an improvement of their neurodevelopmental impairment classification between infancy and childhood. Combining knowledge on the outcomes at different time-points and the individual variation in multiple domains between 2 and 10 years of age is important, not only for children born extremely preterm, but also for those born very preterm (28–32 weeks gestation). On one hand, it will benefit the counseling of parents of children born premature by potentially identifying those at risk, and, on the other hand, it may support early intervention strategies to improve outcome.

The aim of the current study was to investigate the rate and stability of impairment in a prospective cohort of children born preterm (<32 weeks' gestation) between May 2006 and November 2007, by standardized assessment of neurological, motor, cognitive, and behavioral outcomes at both 2 and 10 years of age. A second aim was to assess the composite impairment scores and to report on the co-occurrence of impairments by considering the number of affected domains for each child at both timepoints. The final aim was to assess the individual changes in outcome in the separate domains over time. This will give an insight in the rate and stability of impairments in preterm born children from toddler to school-age.

Methods

Participants

This study was performed as part of a larger single-center longitudinal study on neuroimaging and outcome after preterm birth. For this study, a cohort of 113 children born preterm (<32 weeks' gestation), who were admitted to the tertiary neonatal unit of Leiden University Medical Center (LUMC) between May 2006 and November 2007, was included. Neonatal in- and exclusion criteria of the original cohort were published previously [12, 13]. For this particular follow-up study, only the children with follow-up data at both 2 and 10 years of age were included. Children who were unable to be assessed due to severe motor, visual or cognitive disabilities were assigned the corresponding lowest score.

Outcome Assessment

Children and their parents were invited for follow-up visits at 2 years of age corrected for prematurity and at 10 years of age. Both visits consisted of a standardized pediatric, neurologic, cognitive and motor functioning examination. Parents reported on the presence of problem behavior. All tests were performed by certified professionals, as part of a regular, standardized clinical follow-up program, according to the national guideline of the Dutch working group on follow-up for preterm infants. The assessors at 10 years of age had no knowledge of outcomes at 2 years of age prior to their assessment. Outcomes of this cohort at 2 years of age, in relation to brain imaging findings, have been published previously [12, 14-16]. The institutional review board of the LUMC approved this study, and written parental consent was obtained from both parents (P06.002). For the follow-up at 10 years of age, a waiver was obtained as this is part of the national clinical follow-up program (C15.072/P17.087).

Baseline Characteristics of the Study Population

Perinatal data were available for all children, as published earlier [13]. Small for Gestational Age (SGA) was based on birth weight <10th percentile [17]. Postnatal sepsis was determined by a positive blood culture. Necrotizing Enterocolitis (NEC) was diagnosed when stage ≥2 was present [18]. Bronchopulmonary Dysplasia (BPD) was categorized as either none or mild/moderate/severe BPD [19]. Intraventricular Hemorrhage (IVH) severity was based on neonatal cranial ultrasound as low grade (grade I–II) or high grade (grade III and/or periventricular hemorrhagic infarction) [20]. White matter and cerebellar injury were classified according to a standardized MR imaging scoring system [21]. Maternal education was classified as low (primary school and lower general secondary school), intermediate, or high (higher vocational school and university) [22].

Measures

The children were seen by a certified neonatologist, pediatric physical therapist, and child psychologist at 2 and 10 years of age, and, at 10 years of age, also by a child neurologist. Neurological functioning at 2 years of age was assessed by a standardized neurological examination according to Hempel which assesses the following clusters: fine and gross motor functioning, posture and muscle tone, reflexes, and visuomotor functioning [23, 24]. At 10 years of age, neurological functioning was examined according to Touwen which assesses the following clusters: involuntary and associated movements, posture, reflexes, sensory deficits and cranial nerve dysfunction [25]. Children were classified as having simple minor neurological dysfunction (MND) with one dysfunctional cluster, or complex MND with two or more dysfunctional clusters.

The presence and grade of CP at 2 and 10 years was examined using the Gross Motor Function Classification Score (GMFCS) [26]. A GMFCS score of ≥2 was considered mild to severe CP.

Motor development at 2 years of age was examined using the fine and gross motor scale of the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) [27, 28]. At the time of assessment, American norms were used due to the lack of a Dutch norm group. Using the American norms leads to an underestimation of developmental delays at 2 years of age [29, 30], and therefore the Bayley-III motor scores were corrected for the current Dutch norms [31]. At 10 years of age, the Movement Assessment Battery for Children, 2nd Edition (M-ABC-II) [32] was administered and assessed according to Dutch norms. According to the Bayley-III, children had either a mild developmental delay with a motor score between 1 and 2 standard deviation (SD), or a moderate-severe developmental delay with a motor score of >2 SD below the mean. According to the M-ABC-II, children were classified mildly abnormal with scores between the 5th and 15th percentile, or moderate-severe abnormal with scores $\leq$ 5th percentile.

Cognitive ability at 2 years of age was assessed using the Bayley-III cognitive scale [27]. Similar to the Bayley-III motor score, the cognition scores were originally derived from American norms, and therefore corrected for the current Dutch norms to avoid underestimation. At 10 years of age, the Wechsler Intelligence Scale for Children (WISC-III) was administered [33]. Children were classified as mildly abnormal with a score between 1 and 2 SD, or moderate-severe abnormal with a score of $>$ 2 SD below the mean.

Parents reported on behavioral problems at both timepoints by means of the Child Behavioral CheckList (CBCL) [34]. Age standardized t-scores were obtained for internalizing, externalizing and total problem behavior, where higher scores indicate higher levels of problem behavior. Children were classified with mild behavioral problems, with t-scores in the borderline clinical range ($\geq$84th percentile), or moderate-severe behavioral problems with t-scores in the clinical range ($\geq$90th percentile).

Composite Impairment Score

A composite impairment score for both timepoints was created. Children were categorized into three groups: no impairment, mild impairment or moderate-severe impairment. Mild impairment was defined as having at least one mild impairment in neurological, motor, cognitive or behavioral functioning, in absence of any moderate-severe impairment. Moderate-severe impairment was defined as having at least one moderate-severe impairment in one of the above mentioned domains. The composite impairment score included children with one, as well as those with more than one abnormal domain.

Multidomain Impairment Scores

For the multidomain impairment score, the number of domains in which a child experienced impairments was counted, ranging from zero (no impairments at all) to four (impaired in the neurological, motor, cognitive and behavioral domain). Multidomain impairment was present when a child had a mild or moderate-severe outcome in two or more domains.

Developmental Change

In order to assess the developmental change, we investigated differences over time on both a group level and an individual level for each domain separately. Children were categorized as normal, mild, or moderate-severe at both timepoints for each domain, making it possible to investigate categorical shifts for each separate domain over time.

Statistical Analysis

Statistical analyses were conducted using SPSS version 23.0 (IBM, Armonk, NY, USA). Descriptive results for nominal variables were presented as number of cases and percentages. Means and SD's were reported for continuous variables. Perinatal factors of preterm children with and without follow-up were compared to assess if selective loss to follow-up occurred. To assess whether there was a difference in group distribution of the composite impairment score and multidomain impairment score, and to adjust for the effect of paired testing, the marginal homogeneity test was conducted. If so, McNemar tests were conducted *post-hoc*. A Bonferroni correction was conducted to adjust for multiple comparisons, leading to a significant p-value of < 0.013 (0.05/4). The number of domains between 2 and 10 years of age was compared with a paired t-test. The individual changes within the different domains were assessed with a Chi Square test.

Results

The original cohort consisted of 113 children. Follow-up assessment at 2 years of age was available for 86 children (76%), of whom 71 children were also assessed at 10 years of age. Baseline characteristics of the 71 participating children are shown in Table 1.

Table 1. Perinatal characteristics and level of maternal education of the study population.

Perinatal characteristics	**Participants (n=71)**	**No follow-up available at both timepoints (n=42)**	**p**
Male sex (%)	38 (54%)	29 (69%)	.106
Part of twins or triplets (%)	23 (32%)	13 (31%)	.117
GA (weeks), mean ± SD	29.2 ± 2.0	28.7 ± 2.0	.226
BW (g), mean ± SD	1234 ± 365	1178 ± 358	.435
SGA (%)	8 (11%)	4 (10%)	.585
BPD (%)			.250
Mild	13 (18%)	11 (26%)	
Moderate/severe	16 (23%)	11 (26%)	
Sepsis (%)	27 (38%)	17 (41%)	.698
NEC (%)	1 (1%)	2 (5%)	.342
Low grade IVH	12 (17%)	6 (14%)	.636
High grade IVH	7 (10%)	4 (10%)	.954
White matter injury			.965
Mild	14 (20%)	15 (36%)	
Moderate/severe	18 (26%)	9 (22%)	
Cerebellar injury			.183
Mild	9 (13%)	3 (7%)	
Moderate/severe	6 (9%)	6 (14%)	
Maternal education		n = 29*****	.860
Low (%)	18 (25%)	5 (18%)	
Intermediate (%)	22 (31%)	13 (45%)	
High (%)	31 (44%)	11 (38%)	

*****Information was available for 29 children.

There were no differences in clinical parameters between children with and without follow-up at both timepoints (no follow-up or available only at one timepoint, *n* = 42). Due to severe motor and cognitive disability, four children were unable to complete the neurological, motor, and cognitive follow-up assessment at 10 years of age, and were therefore assigned the lowest score (complex MND within the neurological domain and ≥2 SD below the mean within the motor and cognitive domain). Their parents did complete the behavioral questionnaire. Table 2 shows the outcomes of the neurological, motor, cognitive and behavioral assessments at both time points.

Table 2. Outcomes at 2 and 10 years of age.

	Two years of age	**Ten years of age**	**p**
Neurological examination	*Hempel (n = 71)*	*Touwen (n = 70)*	.662
Normal	45 (63%)	46 (66%)	
Mild MND	19 (27%)	13 (18%)	
Complex MND	7 (10%)	11 (16%)	
Motor outcome	*BSID (n = 65)*	*M-ABC (n = 69)*	.201
Mean ± SD	98.9 ± 15.5		
Standard Score ± SD		9.5 ± 3.2	
Normal	53 (81%)	56 (82%)	
Mild impairment	7 (11%)	1 (1%)	
Moderate-severe impairment	5 (8%)	12 (17%)	
Cognition	*BSID-III (n = 70)*	*WISC-III (n = 71)*	.072
Mean ± SD	98.4 ± 16.6	95.3 ± 17.0	
Normal	56 (81%)	51 (72%)	
Mild impairment	10 (15%)	15 (21%)	
Moderate-severe impairment	3 (4%)	5 (7%)	
Behavior Total	*CBCL (n = 66)*	*CBCL (n = 65)*	.182
Mean ± SD	50.1 ± 8.3	51.0 ± 11.2	
Normal	57 (86%)	51 (78%)	
Mild impairment	6 (9%)	7 (11%)	
Moderate-severe impairment	3 (5%)	7 (11%)	
CP	*(n = 71)*	*(n = 71)*	1.000
	5 (7%)	5 (7%)	

Composite Impairment Score

Figure 1 shows the composite impairment score and number of affected domains (ranging from zero to four) at 2 and 10 years of age. At both time points, a comparable number of children (31 children (44%) at 2 years of age and 32 children (45%) at 10 years of age) had a normal outcome. From 2 to 10 years of age, the number of children with a mild impairment decreased, from 31 (44%) at 2 years of age to 14 (20%) at 10 years of age ($p = 0.006$). At the same time, the number of children with a moderate-severe impairment increased, from 9 (12%) at 2 years of age to 25 (35%) at 10 years of age ($p = 0.001$).

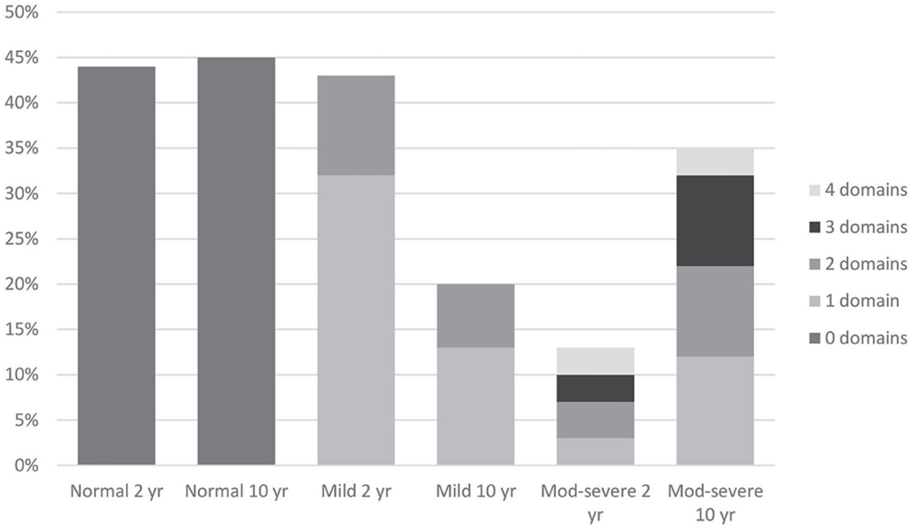

Figure 1. Composite impairment score and multidomain impairment score at 2 and 10 years. Normal 2 yr = no impairments at 2 years (44%). Normal 10 yr = no impairments at 10 years (45%). Mild 2 yr = at least one (32%) or multiple (11%) mild impairment(s) at 2 years. Mild 10 yr = at least one (13%) or multiple (7%) mild impairment(s) at 10 years. Mod-Severe 2 yr = at least one (3%) or multiple (10%) moderate-severe impairments at 2 years. Mod-Severe 10 yr = at least one (12%) or multiple (23%) moderate-severe impairments at 10 years.

Multidomain Impairment Score

Children with a mild impairment experienced, at both timepoints, difficulties in one or two domains, whilst children with a moderate-severe outcome experienced, at both time-points, difficulties in a range of one to all four domains (Figure 1). Although the number of children with a multidomain impairment increased from 15 (21%) at 2 years of age, to 21 (30%) at 10 years of age, this was not significant ($t = -1.217$, $p = 0.228$).

Developmental Change

Considering the group as a whole, there were no significant changes in the distribution of normal, mild and moderate-severe development between 2 and 10 years of age within the neurological, motor, cognitive, and behavioral domain (Table 2). When assessing the individual variation for each domain, significant changes were seen in the neurological (X2(4)X(4)2 = 18.432, $p = 0.005$), motor (X2(4)X(4)2 = 27.947, $p < 0.001$), and cognitive domain (X2(4)X(4)2 = 47.781, $p < 0.001$), but not in the behavioral domain (X2(4)X(4)2 = 7.514, p = 0.111) (Tables 3a–d).

Within the neurological domain, 40% (28/70 children) shifted in severity, of whom 46% (13/28 children) moved to a more severe category and 54% (15/28 children) to a less severe category. For the motor domain, most (84%, 53/63) children remained in the same category of severity: 16% (10/63 children) moved between categories, of whom 60% (6/10 children) from no or mild impairment at 2 years of age to a moderate-severe impairment at 10 years of age. Within the cognitive domain, 28% (19/69 children) shifted in severity. The largest change occurred in children who had a normal outcome at 2 years of age; of the 56 children who performed in a normal range at 2 years of age, 20% (11/56 children) developed a mild impairment and 3% (2/56 children) a moderate–severe impairment. Within both the motor and cognitive domain, all children with a moderate-severe impairment at 2 years of age (*n* = 5 for the motor domain, *n* = 3 for the cognitive domain) still had a moderate-severe impairment at 10 years of age. Although within the behavioral domain, the individual change of children did not differ significantly over time, parents reported higher rates of problem behavior in 22% (14/65 children) at 10 years of age, with half of them (7/14) classified as having moderate-severe behavioral problems.

Table 3a. Change in the neurological outcome from two to ten years of age.

Neurological outcome at 2 years	**Neurological outcome at 10 years**			
	None	**Mild**	**Moderate-severe**	**Total, n (%)**
None (%)	33 (75)	6 (14)[a]	5 (11)[a]	44 (63)
Mild (%)	12 (63)[b]	5 (26)	2 (11)[a]	19 (27)
Moderate-severe (%)	1 (14)[b]	2 (28)[b]	4 (58)	7 (10)
Total, n (%)	46 (66)	13 (19)	11 (15)	70 (100)

[a] Indicates a shift towards a more severe category 13/70; 19%
[b] Indicates a shift towards a less severe category 15/70; 21%

Table 3b. Change in motor outcome from two to ten years of age.

Motor outcome at 2 years	**Motor outcome at 10 years**			
	None	**Mild**	**Moderate-severe**	**Total, n (%)**
None (%)	47 (92)	0	4 (8)[a]	51 (81)
Mild (%)	4 (57)[b]	1 (14)	2 (29)[a]	7 (11)
Moderate-severe (%)	0	0	5 (100)	5 (8)
Total, n (%)	51 (81)	1 (2)	11 (17)	63 (100)

[a] Indicates a shift towards a more severe category 6/63; 10%
[b] Indicates a shift towards a less severe category 4/63; 6%

Table 3c. Change in cognitive outcome from two to ten years of age.

Cognitive outcome at 2 years	Cognitive outcome at 10 years			
	None	Mild	Moderate-severe	Total, n (%)
None (%)	43 (77)	11 (20)[a]	2 (3)[a]	56 (81)
Mild (%)	6 (60)[b]	4 (40)	0	10 (15)
Moderate-severe (%)	0	0	3 (100)	3 (4)
Total, n (%)	49 (71)	15 (22)	5 (7)	69 (100)

[a] Indicates a shift towards a more severe category 13/69; 19%
[b] Indicates a shift towards a less severe category 6/69; 9%

Table 3d. Change in behavioral outcome from two to ten years of age.

Behavioral outcome at 2 years	Behavioral outcome at 10 years			
	None	Mild	Moderate-severe	Total, n (%)
None (%)	44 (82)	6 (11)[a]	4 (7)[a]	54 (87)
Mild (%)	3 (60)[b]	0	2 (40)[a]	5 (8)
Moderate-severe (%)	2 (67)[b]	1 (33)[b]	0	3 (5)
Total, n (%)	49 (79)	7 (11)	6 (10)	62 (100)

[a] Indicates a shift towards a more severe category; 12/62; 19%
[b] Indicates a shift towards a less severe category; 6/62; 10%

Discussion

The prospective, longitudinal design of this study provided the opportunity to investigate the rate and stability of impairment over time, within multiple domains, in individual children born very preterm. With increasing age, we found more children experiencing a moderate-severe impairment in the neurological, motor, cognitive and/or behavioral domain. On a group level, these changes in the distribution of normal, mild and moderate-severe impairment in the separate domains were not significant. However, on an individual level, there was a considerable variation in all domains, showing the relevance of long-term follow-up for preterm born children and the importance to keep track of their individual development.

In our cohort, with only 3 children (4%) born below 26 weeks' gestation and 24 (34%) below 28 weeks' gestation, we still found relatively high percentages of children with long-term impairments. A moderate-severe impairment in at least one developmental domain was present in 35% of the children at 10 years of age; an almost three-fold increase compared to 2 years of age. This shows that high rates of impairment are not limited to cohorts of children born extremely preterm, and, to fully understand the extent of the difficulties experienced by children born preterm, standardized and long-term follow-up should include outcome assessment in multiple key developmental domains.

In line with the recent study by Taylor and colleagues [11] we observed large individual shifts in outcomes between 2 and 10 years of age. However, in our cohort we did not find individual improvement of moderate-severe neurodevelopmental impairment. This could possibly be explained by differences between the examined cohorts (extreme preterm vs. very preterm), but also by the use of different tests and a different specification and classification of neurodevelopmental impairment at both timepoints. Whilst we investigated neurological functioning, motor skills, cognition and behavior at both age points, Taylor and colleagues included sensory impairments, epilepsy and (symptoms of an) autism spectrum disorder. In order to truly grasp neurodevelopment impairment in children born preterm, assess the stability between infancy and childhood, and compare the outcomes within different cohorts, a standardized classification of neurodevelopmental impairment should be developed for multiple age points. Moreover, both our study and the study by Taylor experienced a relatively high loss to follow-up, which is unfortunately not uncommon in longitudinal studies and may also have contributed to the divergent results.

Although at group level there were no significant changes in the distribution of normal, mild, and moderate-severe impairments between 2 and 10 years of age within the neurological, motor and cognitive domain, there were considerable individual changes. Most changes were seen within the neurological domain, where over one third of the children shifted, mostly from mild MND at 2 years of age to no MND at 10 years of age (12/19, 63%). The early diagnosis of mild MND therefore does not seem a reliable predictor for later neurological functioning. The assessment of motor functioning was the most stable outcome measure. All children with a moderate-severe outcome at age two still had a moderate-severe outcome at age ten, and nearly all children with a normal motor outcome at age two had a normal outcome at age ten. This is in line with the positive association between Bayley motor scores and later motor functioning in children born preterm [35]. Within the cognitive domain, all children with a moderate-severe outcome at 2 years of age still had a moderate-severe outcome at 10 years of age. However, almost one fifth (19%) of the children with a normal or mild outcome at 2 years of age shifted toward a more severe category over time. For the behavioral domain, none of the children with moderate-severe behavioral problems at age two had a moderate-severe behavioral outcome at age ten. However, the number of children with reported behavioral problems at age 10 remained high (21%) and those classified with moderate-severe behavioral problems all had a confirmed psychiatric diagnosis or were under assessment for a possible psychiatric diagnosis. Problem behavior in children born preterm is negatively associated with academic performance, work outcomes and family formation later in life [36, 37]. The individual changes seen between 2 and 10 years of age support the importance of including a behavioral assessment at a later age to accurately identify those who have adjustment problems in later life.

Strengths and Limitations

Strengths of the current study are the longitudinal design, enabling us to compare early outcomes with school-age outcomes within the same cohort as well as in the individual child, the inclusion of a complete and standardized neurological examination, and the inclusion of behavioral assessment, providing a better understanding of the overall occurrence of impairments in children born preterm. Knowledge on the changes in individual development in multiple domains is important for several reasons. It can help to inform the parents of children who were born preterm about the risk of persisting problems in later life. It may also help to identify those at risk and who may benefit from early intervention. Furthermore, the awareness that individual changes are common and that outcomes at a young age may not reflect outcomes in later life is important when investigating the associations between neonatal risk factors and neonatal treatment strategies and neurodevelopmental outcome.

A limitation of our study is the lack of a healthy term-born control group in order to control for change in outcome in children born full-term. However, we used standardized assessments and compared our study population with age-appropriate normative means. The different assessment tools available for children aged two and ten, may have played a role in the variation in measured outcome. Still, the assessments used in this study reflect current clinical practice at both timepoints. Due to the original design of the study (investigating brain imaging findings in a prospective cohort of children born very preterm), no sample size or power analysis was performed for loss to follow-up at 2 and 10 years of age. This resulted in a relatively small sample size. Possibly due to the large time-interval between both assessments only 71 children of the original cohort could be assessed at both timepoints. Since previous studies reported rates up to 75% of preterm born children experiencing one impairment and a co-occurrence of impairments in up to 52% at preschool age [38-40], and others already suggested weak agreement between neurodevelopmental disabilities in infancy and early childhood [6, 7], future studies should also include follow-up assessment around 5 years of age. This will provide more information on what happens between toddlerhood, early childhood and school-age and on the critical periods of development in different domains in children. This may give more information on targeted age-points for intervention. Moreover, due to the large time-interval between both assessments and the variance in outcomes of individual children between the two time-points, we did not use multiple imputation as this may lead to an under- or over estimation of outcomes. In longitudinal cohorts with a shorter time-interval between assessments and more follow-up timepoints, multiple imputation can be used to correct for missing data. Finally, as the assessments were part of the clinical follow-up program, the assessors were not blinded to important perinatal details of the participants such as gestational age at birth and birthweight.

In conclusion, our results indicate that long-term follow-up in a broad range of developmental domains in children born very preterm is clinically relevant and should be continued up to at least school-age, and possibly also into adolescence. Children with a moderate-severe impairment at 2 years of age in the motor and/or cognitive domain are likely experiencing moderate-severe impairments within the same domain at 10 years of age. However, normal and mild abnormal outcomes at 2 years of age should be interpreted with care, since there are large individual shifts over time. As these results are a less reliable predictor for development at school age these children should therefore not be discharged from follow-up care too soon.

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IV

PART FOUR

THE ROLE OF NEONATAL BRAIN INJURY

CHAPTER 2

Associations between neonatal magnetic resonance imaging and short- and long-term neurodevelopmental outcomes in a longitudinal cohort of very preterm children

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Lisette Jansen
Andrea van Steenis
Annette van den Berg-Huysmans
Sica Wiggers-De Bruine
Monique Rijken
Linda de Vries
Robert Vermeiren
Cacha Peeters-Scholte
Sylke Steggerda

Abstract

Objective: To assess associations between neonatal brain injury assessed by magnetic resonance imaging and cognitive, motor, and behavioral outcomes at 2 and 10 years of age, in a longitudinal cohort of children born very preterm.

Study design: There were 112 children born at $<$32 weeks of gestation who participated in a longitudinal prospective study on brain injury and neurodevelopmental outcome. Using the Kidokoro score, neonatal brain injury and altered brain growth in white matter, cortical and deep gray matter, and the cerebellum were assessed. Cognitive, motor, and behavioral outcomes were assessed during follow-up visits at both 2 (corrected) and 10 years of age.

Results: After adjusting for perinatal factors and level of maternal education, the global brain abnormality score was associated with cognition ($B = -1.306$; $P = .005$), motor skills ($B = -3.176$; $P < .001$), and behavior ($B = 0.666$; $P = .005$) at 2 years of age, but was not associated with cognition at 10 years of age. In the subgroup of children with a moderate-severe global brain abnormality score, magnetic resonance imaging was independently associated with cognitive impairment at 10 years of age. For children with milder forms of brain injury, only birth weight and level of maternal education were associated with cognitive outcomes.

Conclusions: Neonatal brain injury, assessed by a standardized scoring system, was associated with short-term neurodevelopmental outcomes, but only with motor skills and behavior in childhood. Environmental factors, such as level of maternal education, become more important for cognitive development as children grow older, especially for children with relatively mild neonatal brain injury.

Introduction

Being born prematurely comprises a number of developmental challenges, especially as infants reach childhood and adolescence [1]. Children born preterm are at risk of a broad spectrum of neurodevelopmental impairments, including cognitive impairments, motor deficits, and behavioral difficulties [2-5]. For clinicians, it remains challenging to predict the short- and long-term outcomes for children born preterm and to identify those at risk for an adverse outcome.

One factor related to the developmental prognosis of children born preterm is neonatal brain injury. Owing to the disruption in development of brain structures and brain maturation caused by preterm birth, the brain is often organized differently compared with children born at full term [6]. The brain of children born preterm frequently shows white matter injury and subsequent dysmaturation of white and gray matter structures [7]. Neonatal brain injury can be assessed using magnetic resonance imaging (MRI). MRI has the ability to identify subtle forms of brain injury, especially diffuse noncystic white matter injury and small cerebellar lesions, and to precisely detect altered brain growth [8-10]. Although brain injury as seen on neonatal MRI has been related to neurodevelopmental outcomes, there is no agreement whether subtle MRI abnormalities have prognostic implications [11-13].

Although neonatal brain abnormalities have been associated with neurodevelopmental outcomes in numerous studies of children born preterm, no studies have investigated the prognostic implications on both short- and long-term cognitive, motor, and behavioral outcomes within the same cohort of children [13-17]. Children may grow into their deficits as they become older, leading to a better prediction of long-term outcomes [18]. Or environmental factors play an increasing role in development as a child grows older and may become of greater influence compared with neonatal brain injury or perinatal factors [19].

To determine if the prognostic implications of neonatal brain injury differ at different timepoints in a child's life, the aim of this study was to assess the associations between brain injury on the neonatal MRI for cognitive, motor, and behavioral outcomes at both 2 and 10 years of age, in a longitudinal cohort of children born very preterm. The Kidokoro score, a commonly used scoring system for conventional MRI at term-equivalent age, was used for this study because it incorporates the assessment of both altered brain growth and abnormalities in different brain regions [20].

Methods

This study was performed as part of a larger single-center longitudinal prospective study on neuroimaging and outcome after preterm birth (PReterm brain injury, long-term OUtcome and brain Development study; PROUD study). An unselected cohort of 112 infants (<32 weeks of gestation), who were admitted to the tertiary neonatal unit of Leiden University Medical Center between May 2006 and November 2007 and underwent an MRI at term-equivalent age, was included. Children were excluded if they had congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal disorders, metabolic disorders, or neonatal meningitis [21, 22]. All children were invited for follow-up assessments at 2 years of age corrected for prematurity and at 10 years of age (uncorrected). For this particular study, children were included if follow-up assessment was available for at least 1 timepoint.

Brain Injury Assessment on MRI

An MRI of the neonatal brain was performed around term-equivalent age using a 3.0 Tesla MR system (Achieva 3T; Philips Medical Systems), according to the procedure described previously [23]. All MRI examinations included a T1-weighted 3-dimensional turbo field-echo sequence, a T2-weighted turbo spin-echo sequence, and a T2* fast field-echo sequence. Neonatal MRI scans were reviewed by at least 2 experienced investigators. The MRI investigators reviewed the scans together, and any discrepancies in interpretation were solved by consensus or by asking the opinion of a third reviewer. They were blinded to any clinical characteristics or outcome data of the children except for their postmenstrual age (PMA) at the time of scanning. The MRI examinations were performed preferably around term-equivalent age (40-44 weeks of PMA). For infants who were in a unstable condition around that age or still on respiratory support, the MRI was performed as soon as the child was in a stable condition [21]. The median PMA during scanning of the initial cohort was 43.3 weeks (IQR, 42.3-46.0 weeks). The neonatal MRI scans were assessed using a standardized scoring system to assess abnormal brain metrics and the presence and severity of abnormalities in the cerebral white matter, cortical and deep gray matter, and cerebellum [20]. The sum of these subscores leads to a Global Brain Abnormality Score (GBAS), which can be further classified as normal (0-3), mildly abnormal (4-7), moderately abnormal (8-11), and severely abnormal (≥12).

Outcome Assessment

Children were invited for follow-up visits at 2 timepoints: at 2 years of age corrected for prematurity and at 10 years of age (uncorrected) according the national guideline of the Dutch working group on follow-up for preterm infants. During both visits, standardized cognitive and motor functioning examinations were administered, and parents reported on the presence of behavioral problems. Children were examined by a paediatrician at 2 and 10 years of age, and additionally by a child neurologist at 10 years of age. Parents were questioned on the physical and medical history of their child. Children who experienced severe illnesses or additional brain injury were excluded from the study.

At 2 years of age, cognitive and motor development was assessed using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) [24, 25]. Composite scores have a mean of 100 and a SD of 15. The motor composite score is based on fine and gross motor scaled scores with a mean of 10 and SD of 3. At the time of assessment, US norms were used owing to the lack of a Dutch norm group. Using the US norms leads to an underestimation of developmental delays at 2 years of age; therefore, Bayley-III cognition and motor scores were subsequently corrected for the current Dutch norms [26-28].

At 10 years of age, cognitive development was assessed by the Wechsler Intelligence Scale for Children (WISC-III) [29]. Full scale, verbal, and performance IQs were obtained, with a mean of 100 and SD of 15. Motor development was examined using the Movement Assessment Battery for Children, second edition (M-ABC-II), with a total scaled score based on 3 scaled subscores (manual dexterity, balance, and catch and throw), all with a mean of 10, and SD of 3 [30].

During both follow-up visits, parents reported on behavior using the Child Behavioral Checklist (CBCL) [31]. Age-standardized t-scores were obtained for internalizing, externalizing, and total problem behavior, where higher scores indicate higher levels of problem behavior.

All assessments were performed according to the national guideline of the Dutch working group on follow-up for preterm infants (<32 weeks of gestation). The institutional review board approved this prospective study and parental consent was obtained from both parents. Outcomes of this cohort at 2 years of age, in relation to brain imaging findings, have been published previously [21, 32-34].

Perinatal Risk Factors and Maternal Education

Perinatal data were retrieved for all children, as published earlier, and included the child's sex, gestational age, birth weight, small for gestational age, postnatal sepsis, necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD) [22]. Small for gestational age was based on a birth weight of <10th percentile [35]. The presence of infection/inflammation was defined as either the presence of a positive blood culture, and/or NEC stage ≥2 [36]. BPD was categorized as none/mild or moderate-severe BPD, defined as oxygen dependence at 36 weeks PMA [37]. Because of the known negative impact of a low level of maternal education on both cognitive and motor outcomes, the level of maternal education was obtained during the first follow-up visit at 2 years of age corrected for prematurity [38, 39]. It was classified as low (primary school and lower general secondary school), intermediate, or high (higher vocational school and university) [40].

Statistical Analyses

Statistical analyses were conducted using SPSS (version 23.0, IBM). To assess if selective loss to follow-up occurred, perinatal risk factors and the MRI GBAS at term-equivalent age for children with and without follow-up were compared using a $\chi 2$ or Fisher exact test for categorical variables and t test for continuous variables.

Neonatal MRI measurements of the biparietal diameter, deep gray matter area, and transcerebellar diameter were corrected for PMA at scanning using linear regression analysis (ie, corrected measurement = original measurement + slope [40 – PMA]).21 Corrected measures were used in subsequent analyses.

To assess differences within the subscores of cognitive, motor, and behavioral outcomes, paired t tests were conducted for fine and gross motor skills on the Bayley-III, verbal and performance IQ on the WISC-III, manual dexterity, aiming and catching and balance on the M-ABC-II, and internalizing and externalizing behavioral problems at both timepoints on the CBCL. If a significant difference ($P < .05$) was present, subscores, instead of total scores, were used as outcome measures in subsequent analyses.

To investigate the effect of MRI scores on cognitive, motor, and behavioral outcomes at 2 and 10 years of age, univariable linear regressions were first conducted unadjusted for any other possible contributing factors. Second, using multivariable linear regressions, the effect of MRI scores on cognitive, motor, and behavioral outcomes was adjusted for both perinatal risk factors and level of maternal education. Finally, multivariable regression analyses were conducted to determine the independent contributions of the GBAS, perinatal risk factors, and the effect of maternal education. MRI scores were used in both univariable and multivariable analyses as continuous variables. To adjust for the effect that observations in twins are not independent, the univariable and multivariable analyses were conducted in a generalized estimated equations model [41].

Results

Of the 112 children who underwent MRI at term-equivalent age, follow-up at 2 and/or 10 years of age was available for 99 children (88%). Of these, 69 (70%) underwent follow-up assessment at both timepoints and 30 (30%) at 1 timepoint (15 children [15%] at 2 years of age and 15 [15%] at 10 years of age). The baseline characteristics of the participating children are shown in Table I. The PMA at the time of the MRI was older for children with follow-up assessments (median, 43.4 weeks; IQR, 42.4-47.9 weeks) compared with those lost to follow-up (median, 42.3 weeks; IQR, 41.9-42.8 weeks); otherwise, there were no differences in clinical measures or the GBAS on MRI at term-equivalent age. Level of maternal education was registered during the first follow-up at 2 years of age. Therefore, no information on level of maternal education is available for children without follow-up.

Table I. Perinatal characteristics and level of maternal education of the study population.

Perinatal characteristics	**Participants (n=99)**	**No follow-up available (n = 13)**	**p**
Male sex (%)	60 (60%)	7 (54%)	.476
Part of twins or triplets (%)	33 (33%)	2 (15%)	.088
GA (weeks), mean ± SD	28.9 ± 2.0	29.4 ± 1.9	.660
Birth weight (g), mean ± SD	1205 ± 357	1278 ± 413	.646
SGA (%)	12 (12%)	-	.585
BPD (%)			
Moderate-severe	25 (25%)	2 (15%)	.207
Mechanical ventilation >7 days	35 (35%)	3 (23%)	.289
Sepsis (%)	37 (37%)	6 (46%)	.691
NEC (%)	3 (3%)	-	.083
High grade IVH and/or PVHI	8 (8%)	1 (8%)	.814

Table I. Continued

Perinatal characteristics	Participants (n=99)	No follow-up available (n = 13)	p
Maternal education+	(n = 97)		
Low (%)	23 (24%)	-	
Intermediate (%)	32 (33%)	-	
High (%)	42 (43%)	-	
PMA in weeks, median (IQR)	43.4 (42.4 – 47.9)	42.3 (41.9 – 42.8)	.014*
GBAS, median (IQR)	4 (2 - 6)	3 (2 – 5)	.772
Normal <4, n (%)	49 (50%)	7 (54%)	
Mildly abnormal 4-7, n (%)	34 (34%)	5 (38%)	
Moderate-severe abnormal >7, n (%)	16 (16%)	1 (8%)	

***** p <.05

+ Level of maternal education was registered during the first follow-up at two years of age. Therefore, no information on level of maternal education is available for children without follow-up.

Figure I shows the distribution of the GBAS and the subscores as seen on MRI around term-equivalent age. An abnormal GBAS was present in one-half of the children (n = 50 [50%]), with 34 children (34%) having a mild GBAS and 16 children (16%) a moderate-severe GBAS. White matter abnormalities were the most common (mild, n = 25 [25%]; moderate-severe, n = 25 [25%]), followed by cortical gray matter abnormalities (mild, n = 26 [26%]; moderate-severe, n = 19 children [19%]) and cerebellar injury (mild, n = 12 [12%]; moderate-severe, n = 11 [11%]). Three children (3%) had deep gray matter abnormalities (mild, n = 1 [1%]; moderate-severe, n = 2 [2%]), accompanied by severe abnormalities in at least one of the other subscores.

Outcomes at 2 Years of Age

Table II shows the outcome of the 2-year follow-up assessment. In 84 children (85%; mean age, 31.2 ± 4.8 months), at least one of the cognitive, motor, and/or behavioral assessments was available. Children who participated in only the 2-year follow-up assessment performed more poorly on both cognitive (t = −3.698; P = .001) and motor tasks (t = −3.730; P = .002) tasks, compared with children who participated in follow-up at both timepoints. There was no difference in behavioral outcome.

When evaluating the motor subscores, a significant difference was found between fine and gross motor outcomes on the Bayley-III (t = −2.463; P = .017), with lower scores for gross motor outcomes. There was also a difference between internalizing and externalizing behavior on the CBCL (t = −2.194; P = .031), with more reported externalizing behavior.

Figure I. Distribution of the GBAS and the subscores as seen on MRI around term-equivalent age.

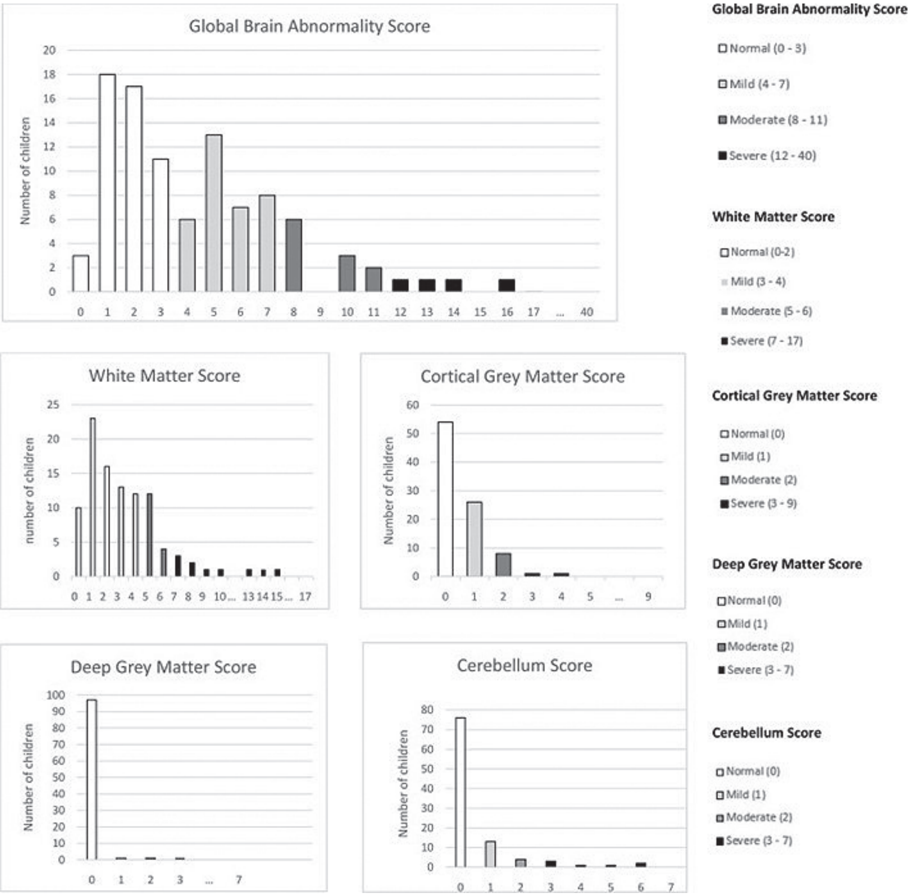

Table II. Outcome of the study population at two and ten years of age.

	Two years of age		**Ten years of age**
Age at follow-up in months	31.2 ± 4.8		117.2 ± 7.7
Cognition	*Bayley-III (n = 83)*		*WISC-III (n = 83)*
Total (m ± SD)	88.1 ± 12.4	Full Scale IQ (m ± SD)	94.7 ± 16.6
		Verbal IQ (m ± SD)	99.0 ± 16.6
		Performance IQ (m ± SD)	91.2 ± 16.8
Motor outcome	*Bayley-III (n = 74)*		*M-ABC-II (n = 79)*
Motor Composite ± SD	93.8 ± 15.0	Total (m ± SD)	9.1 ± 3.1
Fine motor (m ± SD)	9.9 ± 1.9	Manual Dexterity (m ± SD)	9.7 ± 2.2
Gross motor (m ± SD)	9.2 ± 2.0	Balance (m ± SD)	9.4 ± 2.9
		Aiming and Catching (m ± SD)	9.4 ± 3.0

Table II. Continued

	Two years of age		Ten years of age
Behavior	*CBCL (n = 77)*		*CBCL (n = 75)*
Total (m ± SD)	49.1 ± 9.1	Total (m ± SD)	51.9 ± 11.9
Internalizing (m ± SD)	48.1 ± 9.6	Internalizing (m ± SD)	54.3 ± 11.4
Externalizing (m ± SD)	50.5 ± 9.5	Externalizing (m ± SD)	48.5 ± 10.6

Table III shows the associations between brain injury (MRI) at term-equivalent age on outcome at 2 years of age. Unadjusted, both the GBAS and white matter abnormality scores were associated with lower cognitive outcomes, impaired motor composite scores, and total behavioral problems. Lower motor composite scores were further related to deep gray matter abnormality scores. When considering the motor and behavioral subscores, gross motor skills were related to white matter and cerebellar scores, and fine motor skills to deep gray matter abnormality scores. Additionally, internalizing behavior was associated with white matter and deep gray matter abnormality scores, externalizing behavior could not be predicted at 2 years of age. After adjusting for perinatal risk factors and the level of maternal education these results persisted, except for the association between gross motor skills and cerebellar scores.

Outcomes at 10 Years of Age

Outcomes at 10 years of age are reported in Table II. In 84 children (85%; mean age, 117.2 ± 7.7 months), at least one of the cognitive, motor, and/or behavioral assessments was available. Children who participated in only the 10-year follow-up assessment performed more poorly on both cognitive ($t = -2.225$; $P = .038$) and motor tasks ($t = -3.390$, $P = .002$), compared with children who participated in both follow-up timepoints. There was no difference in behavioral outcomes.

When evaluating the cognitive and behavioral subscores, there was a significant difference between verbal and performance IQ on the WISC-III ($t = 4.587$; $P \leq .001$), with lower performance IQ scores, and between internalizing and externalizing behavior on the CBCL ($t = -4.413$; $P < .001$), with higher levels of internalizing behavior. No differences were found within the different subscores of the M-ABC-II.

Table III. Unadjusted and adjusted associations between neonatal brain injury as seen on MRI at TEA and cognitive, motor and behavioral outcomes at two years of age.

	Cognition (n = 83)		Motor Composite (n = 74)		Fine motor (n = 74)		Gross motor (n = 74)		Total behavior (n = 74)		Internalizing behavior (n = 74)		Externalizing behavior (n = 74)	
	B	**p**	**B**	**p**	**B**	**p**	**B**	**P**	**B**	**p**	**B**	**P**	**B**	**p**
GBAS														
Unadjusted	- 1.458	<.001**	-3.294	<.001**	-.108	.155	-.288	.006**.016*	.721	.003**	.756	.011*	.349	.129
Adjusted	-1.306	.005**	-3.176	<.001**	-.062	.431	-.253		.666	.005**	.680	.021*	.297	.198
WM														
Unadjusted	-1.835	<.001**	-4.124	<.001**	-.123	.254	-.345	.015*	1.000	.001**	1.048	.003**	.541	.062
Adjusted	-1.707	<.001**	-4.034	<.001**	-.094	.381	-.317	.018*	.932	.001**	1.019	.002**	.446	.126
Cerebellum														
Unadjusted	-1.328	.054	-.865	.490	-.139	.347	-.637	.037*	.726	.191	.924	.374	.120	.848
Adjusted	-1.107	.120	.019	.991	.000	.998	-.525	.074	.545	.435	.195	.841	.142	.831
Cortical GM														
Unadjusted	-2.192	.238	-3.571	.202	.082	.756	-.016	.966	.790	.475	.256	.824	.540	.569
Adjusted	-1.551	.350	-2.576	.326	.244	.333	.165	.595	.553	.620	-.041	.973	.493	.617
Deep GM														
Unadjusted	-3.335	.350	-14.375	<.001**	-.851	<.001**	.245	.067	.884	.611	2.579	.008**	-.525	.813
Adjusted	-4.336	.214	-16.829	.002**	-.919	<.001**	.138	.620	1.218	.386	3.121	.050	-.886	.622

Adjusted for sex, birth weight, bronchopulmonary dysplasia, sepsis/necrotizing enterocolitis and the effect of maternal education.
* p <.05
** p <.01

Table IV. Unadjusted and adjusted associations between neonatal brain injury as seen on MRI at TEA and cognitive, motor and behavioral outcomes at ten years of age.

	Full Scale IQ (n = 83)		**Verbal IQ (n = 83)**		**Performance IQ (n = 83)**		**Motor (n = 79)**		**Total behavior (n = 75)**		**Internalizing behavior (n = 75)**		**Externalizing behavior (n = 75)**	
	B	**p**	**B**	**p**	**B**	**p**	**B**	**P**	**B**	**p**	**B**	**P**	**B**	**p**
GBAS														
Unadjusted	-1.344	.008**	-1.094	.082	-1.639	.002**	-.409	.001**	.578	.165	.413	.285	.181	.650
Adjusted	-.532	.228	-.358	.500	-.834	.108	-.304	.021*	.694	.044*	.568	.166	.275	.485
WM														
Unadjusted	-1.344	.069	-.540	.501	-2.116	.011*	-.512	.003**	1.108	.061	.895	.127	.419	.478
Adjusted	-.450	.520	.290	.668	-1.254	.139	-.431	.019*	1.304	.011*	1.143	.050	.553	.332
Cerebellum														
Unadjusted	-3.564	.008**	-4.725	.005**	-2.145	.104	-.592	.014*	-.233	.716	-.318	.584	.554	.537
Adjusted	-2.242	.036*	-3.793	.012*	-.570	.550	-.301	.200	-.097	.876	-.586	.316	.545	.552
Cortical GM														
Unadjusted	.326	.872	.320	.884	-.648	.738	-.091	.815	-.531	.716	-.491	.742	-1.256	.341
Adjusted	1.451	.361	1.343	.422	.340	.843	.225	.525	-.432	.769	-.333	.837	-1.066	.440
Deep GM														
Unadjusted	-3.873	.278	.542	.886	-8.140	.006**	-1.981	<.001**	2.759	.360	3.989	.004**	1.113	.755
Adjusted	-3.096	.053	1.124	.553	-7.021	<.001**	-2.302	.019*	3.437	.124	4.609	.001**	1.254	.693

Adjusted for sex, birth weight, bronchopulmonary dysplasia, sepsis/necrotizing enterocolitis and the effect of maternal education.
* p <.05
** p <.01

Table IV shows associations between brain injury (MRI) at term-equivalent age and outcome at 10 years of age. Unadjusted, the GBAS was associated with lower full scale IQ scores and poorer motor outcome. Lower full scale IQ scores were further associated with cerebellar scores. Poorer motor outcome was also related to cerebellar and deep gray matter abnormality scores. Considering the cognitive and behavioral subscores, lower verbal IQ scores were related to cerebellar scores, whereas lower performance IQ was related to the GBAS, white matter and deep gray matter abnormality scores. Deep gray matter abnormality scores were also related to internalizing behavior; externalizing behavior could not be predicted at 10 years of age.

Table V shows the independent contributions of the GBAS, perinatal risk factors, and level of maternal education on cognitive, motor, and behavioral outcomes. In a multivariable analysis, the GBAS and low level of maternal education predicted lower cognition scores at 2 years of age, but at 10 years of age, the GBAS predicted neither full scale, verbal, nor performance IQ. However, full scale, verbal, and performance IQ were associated with lower birth weight and low/intermediate levels of maternal education. Only the GBAS was independently associated with the motor composite score at 2 years of age (Table III). Gross motor skills were associated with the GBAS and lower birth weight at both 2 and 10 years of age. Sepsis and NEC were associated with motor skills at 10 years of age. At 2 years of age, the total CBCL scores were only associated with the GBAS (Table III). At 10 years of age, both the GBAS and male sex were related to higher CBCL scores. Additionally, internalizing behavior at 2 years of age was related to the GBAS and BPD, but at 10 years of age only to a low level of maternal education, whereas externalizing behavior, related to sepsis and NEC at 2 years of age, no longer had any associations at 10 years of age.

Table V. Independent contributions of perinatal risk factors and maternal education in a multivariable analysis on cognitive, motor, and behavioral outcomes at two and ten years of age.

Two years of age	**B**	**p**	**Ten years of age**	**B**	**p**
Cognition (n = 83)			**Full Scale IQ (n = 83)**		
GBAS	-1.306	.005**	Birth weight	.013	.013*
Low vs high Mat Edu	-7.112	.018*	Low vs high Mat Edu	-15.474	<.001**
			Int vs high Mat Edu	-11.818	.001**
			Verbal IQ (n = 83)		
			Birth weight	.014	.013*
			Low vs high Mat Edu	-17.697	<.001**
			Int vs high Mat Edu	-11.109	.002**

Table V. Continued

Two years of age	B	p	Ten years of age	B	p
			Performance IQ (n = 83)		
			Birth weight	.013	.015*
			Low vs high Mat Edu	-10.636	.020*
			Int vs high Mat Edu	-11.771	.001**
Gross motor (n = 74)			**Motor (n = 79)**		
GBAS	-.253	.016*	GBAS	-.304	.021*
Birth weight	.002	.042*	Birth weight	.003	.010*
			Sepsis/NEC	1.724	.010*
			Total behavior score (n = 75)		
			GBAS	.694	.044
			Male sex	6.530	.013
Internalizing behavior (n = 74)			**Internalizing behavior (n = 75)**		
GBAS	.680	.021*	Low vs high Mat Edu	-6.881	.035*
BPD	8.111	.003**			
Externalizing behavior (n = 74)					
Sepsis/NEC	4.955	.046*			

* p <.05
** p <.01

Discussion

We investigated the associations between neonatal brain injury on cognitive, motor, and behavioral outcomes at 2 different ages in a longitudinal cohort of children born very preterm using a comprehensive, objective scoring system to assess neonatal brain injury, and its associations with short- and long-term developmental outcomes. We showed that neonatal MRI was independently associated with cognition, motor skills, and behavior in early childhood, but at 10 years of age, neonatal MRI scores and cognition were not correlated. In the long-term, environmental risk factors, such as maternal education, were shown to exert a stronger influence on the cognitive abilities of the child.

We found, in line with other studies, that cognitive development was associated with neonatal MRI at term-equivalent age at 2 years of age, persisting after adjusting for perinatal risk factors and level of maternal education [42-44]. However, after adjusting at 10 years of age, neonatal MRI was no longer associated with cognitive abilities, except that cerebellar scores were still independently associated with lower full scale IQ scores. In a stepwise regression analysis, first adding only perinatal risk factors and then adding the level of maternal education, it was the latter with the most important influence on cognitive outcome. We showed that children of mothers with a low level of education performed on average 18 points lower on their verbal IQ and 11 points lower on their performance IQ, indicating that maternal factors are more important for cognitive development at 10 years of age compared with neonatal brain injury or other perinatal risk factors. This finding highlights the importance of maternal education. Different pathways might explain why children of mothers with higher levels of education have a higher cognitive performance. For example, genetic inheritance of maternal IQ could contribute, but mothers with a higher level of education may also be more capable of creating learning opportunities for their children than mothers with lower levels of education [38].

Within our cohort, a relatively high number of children experienced mild neonatal brain injury. It is possible that environmental factors play a more important role in determining the outcome for this group of children, whereas the more severe forms of brain injury may have a long-lasting and independent effect on outcomes. Therefore, in our cohort we evaluated cognitive development for the subgroup of children with a moderate-severe GBAS. In this subgroup, the association between neonatal MRI abnormalities and cognitive development persisted at 10 years of age, independent from perinatal factors and level of maternal education. Combining a moderate-severe GBAS with a low level of maternal education did not lead to an increased risk of an adverse development of cognitive capacities at 10 years of age. Of the 34 children in our cohort who performed ≥1 SD below the mean, there were only 3 children with both a moderate-severe GBAS and a mother with a low level of education. These findings should be confirmed in larger samples of children born preterm or with higher grades of brain injury, because this may help when counseling parents of preterm infants, and might provide opportunities for targeted interventions for mothers with lower educational levels and on the other hand for children with a moderate-severe neonatal brain injury.

Motor skills were independently associated at both 2 and 10 years of age with similar abnormality scores at term-equivalent age MRI, namely, the GBAS, white matter, and deep gray matter abnormality scores. This finding is consistent with other studies assessing the capability of the neonatal MRI to predict short- and long-term motor functioning, and is also supported by the associations between Bayley-III motor scores and later motor functioning in very preterm children [14, 43-45].

Children born preterm are at risk for developing behavioral difficulties (especially attentional deficits and internalizing problems) that persist into late adolescence [4]. However, neonatal MRI seems to play only a limited role in the prediction of these behavioral problems later on. At 10 years of age, we found an association between total reported behavioral problems with the GBAS and white matter abnormality score, but only after adjustment for perinatal factors and level of maternal education. Considering the independent contributions of the perinatal factors (Table V), behavioral problems were reported considerably more often for boys compared with girls in our cohort. Additionally, a higher level of maternal education and deep gray matter abnormalities independently contributed to more reported internalizing behavior at 10 years of age. Future research should explore the risk factors for behavioral problems in children born preterm.

The strength of this study is the use of a standardized neonatal MRI assessment tool to indicate brain injury at term-equivalent age combined with prospective long-term follow-up data at different time-points, within the same longitudinal cohort of children born very preterm. This provides valuable information for counseling of parents and the use of neonatal MRI in predicting future outcomes.

Owing to the original design of the study in 2006-2007 (investigating brain imaging findings in an unselected cohort of children born very preterm), no sample size or power analysis was performed for loss to follow-up at 2 and 10 years of age. The group of children seen at 2 years of age and the group at 10 years of age were not completely identical. However, repeating the analyses for the 69 children who were assessed at both timepoints did not change the main results or conclusions of the study. Although the outcome assessments used were age appropriate and based on the general population, the fact that this was a single-center study might affect the generalizability of our results. The use of different neurodevelopmental assessment tools for children at 2 and 10 years of age makes comparison at the 2 points in time difficult, although the tests used in this study reflect current clinical practice. When assessing the associations between outcomes at 2 and 10 years of age, we found significant, but mediocre associations. Within this study, general measures of intellectual abilities have been used. It is possible that the use of more specific measures of cognition and learning strategies, for example, executive functioning, will reveal other, possible stronger, associations with neonatal brain injury [18]. Finally, the Kidokoro scoring system was designed for infants scanned between 36 and 42 weeks of gestation and the neonatal MRI scans in our cohort were performed with a median of 43.4 weeks of gestation. Given brain growth is rapid during the first year of life, the older age at scanning in this cohort may have decreased the sensitivity of the scale, in particular with respect to the growth measures, based on the slope from linear regression. In agreement with the data of Brouwer et al, our cohort of preterm infants (gestational age of <32 weeks of gestation) consisted of a relatively large number of infants with milder forms of brain injury [44]. Therefore, it would be of interest to investigate whether the predictive ability of MRI at term-equivalent age differs for both short- and long-term outcome in other longitudinal cohorts with larger numbers of extremely preterm infants and/or higher brain abnormality scores.

With children born preterm likely to grow into their deficits, and with the increasing influence of social and environmental factors, this study showed that in this longitudinal cohort of children born very preterm, brain injury on neonatal MRI was associated with short-term cognitive, motor, and behavioral outcomes, whereas in the long-term, associations were limited and mainly restricted to the motor domain. Predicting long-term outcomes and identifying those at risk for adverse outcomes remains challenging, especially for cognitive and behavioral development. In these domains, environmental factors, such as maternal education, play an increasingly important role, particularly in children with milder forms of brain injury.

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V

PART FIVE

SCHOOL PERFORMANCE IN CHILDREN BORN VERY PRETERM

CHAPTER 3

Classroom-evaluated school performance at nine years of age after very preterm birth

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Lisette Jansen
Cacha Peeters-Scholte
Sica Wiggers de Bruine
Annette van den Berg-Huysmans
Jeanine van Klink
Andrea van Steenis
Monique Rijken
Robert Vermeiren
Sylke Steggerda

Abstract

Objective: To determine classroom-evaluated school performance nine years after preterm birth, predicted by perinatal risk factors and neonatal brain abnormalities.

Study design: Children were recruited from a consecutive cohort of 113 preterm infants (<32 weeks' gestation), participating in a longitudinal prospective study, investigating brain injury and neurodevelopmental outcome. Data on perinatal risk factors, presence of brain injury at term-equivalent age, and maternal education were collected. Information on school performance included enrolment in special (primary) education, grade repetition and school results from the nationwide standardized Dutch Pupil Monitoring System regarding reading comprehension, spelling, and mathematics.

Results: Information on school enrolment was available for 87 children (77%), of whom 7 (8%) were in special primary education and 19 (22%) repeated a grade. This was significantly higher compared to national rates ($p \leq .05$). Results on school performance were available for 74 children (65%) and showed clearly below average scores in reading comprehension ($p = .006$), spelling ($p = .014$) and mathematics ($p < .001$). Univariate analysis showed that lower performance in reading comprehension was predicted by male sex and low maternal education; spelling by male sex; and mathematics by Bronchopulmonary Dysplasia, white matter injury and maternal education. In a multivariate model, male sex and maternal education were predictive for reading comprehension and white matter injury for mathematics.

Conclusion: Preterm born children more often need special primary education and have higher grade repeat rates. They perform poorer on reading comprehension, spelling and mathematics. Regular follow-up remains important for preterm born children during school age.

Introduction

About half of preterm born children suffer from academic difficulties [1]. Because of this vulnerability, preterm born children are almost three times more likely to receive any form of special education assistance [2]. This can have important consequences as academic performance is associated with long-term health and life chances [3]. A major question for parents of a preterm infant is whether their child will be able to follow a regular educational trajectory. However, studies investigating the relation between classroom-evaluated school performance and perinatal factors are scarce.

Recent studies assessing academic performance have found lower achievements in reading and spelling, and in particular in mathematics in extreme preterm (< 28 weeks' gestational age (GA)) born children [4]. Academic functioning in children is mainly assessed by the use of standardized achievement tests, administered in a clinically controlled one-on-one environment. The results can therefore hardly be compared with school performance achieved in a regular classroom, where other conditions such as concentration and motivation are of great importance. Studies that did use other methods to assess academic performance were inconclusive on the performance in reading comprehension and spelling, but did find poorer performances in mathematics in preterm children [5, 6].

Several perinatal factors, preterm brain injury and maternal education are known to influence long-term cognitive development in children born preterm [7]. Their relation to classroom-evaluated school performance is however still unclear. One of the reasons is the diversity in educational testing between schools. In the Netherlands, however, due to the use of nationwide standardized testing, we have the unique possibility to assess actual educational attainment at school. The aim of this study was therefore to describe school performance, as assessed in a regular classroom, in a cohort of children nine years after preterm birth in relation to perinatal risk factors, brain abnormalities on neonatal magnetic resonance imaging (MRI) and maternal education.

Methods

Participants

This study was performed as part of a larger single-center longitudinal prospective study on neuroimaging and outcome after preterm birth. Participants were part of an unselected cohort of 113 very preterm born children (GA < 32 weeks) who were admitted to the tertiary neonatal unit of our hospital between May 2006 and November 2007. Preterm children were eligible when they had no congenital abnormalities, metabolic disorders or neonatal meningitis. All children underwent serial neonatal ultrasound scans according to protocol and MRI at term equivalent age (TEA) and were invited for follow-up visits with standardized neurodevelopmental assessment at two and nine years of age. Data on neonatal brain imaging findings and outcome at two years of age in this cohort have been published previously [8-11]. The institutional review board approved this prospective study and parental consent was obtained.

Outcome assessment

School enrolment and performance

Parents and teachers of the participating children were asked to fill in questionnaires on the attendance of mainstream primary education, special education or special primary education and grade repetition. Special education in the Netherlands is intended for children with severe visual impairments (cluster 1), children with severe hearing impairments, problems with speech and communication (cluster 2), physical or mental retardation and learning difficulties (cluster 3) and children with severe behavioral and/or psychiatric problems (cluster 4). Special primary education is intended for children with milder special educational needs, who are falling behind in mainstream education, but do not meet the criteria for special education. It is characterized by smaller classes and less distraction compared to mainstream education. In order to compare the results of the preterm children to their Dutch peers, reference data according to the Dutch Central Bureau for Statistics (CBS) on enrolment in special (primary) education during the school year 2015/2016 were used [12]. Most children in our study population were in 2015/2016 in the third grade (year five) of primary school.

Within the Netherlands, almost all children (98%) start their school career at age four [13]. During the first two years, children attend preschool. They start with the first year of primary school in August after they turned six between October of the previous year and the following September. Some children are not ready to continue to the first grade of primary school (third year), due to social or emotional immaturity [6]. These children will repeat the second year of preschool. Grade repetition also occurs if a child cannot keep up with its peers during primary school. In order to compare grade repeat rates with Dutch peers, reference data according to the CBS on grade repetition in 2015 were used [14].

Data on school performance were obtained directly from the children's schools. Dutch elementary schools regularly follow the learning achievements of children by administering standardized school achievement tests, according to the National Institute for Educational Measurements [15]. The Dutch National Pupil Monitoring System is designed to compare the level of an individual child to their own developmental trajectory and to their age matched peers within the Dutch population. The tests start in the second year of primary school at age 5 and are administered at specific time points during the school year. Raw tests scores are converted into ability scores and based on these ability scores, children are categorized in five levels, level A through E. Level A contains the 25% highest performing Dutch children, level B the other 25% of children who also perform above average, level C the 25% who perform slightly below average, level D the 15% of children performing clearly below average and level E are the 10% lowest performing children. For this study, the test results at the end of the third grade were obtained for reading comprehension, spelling and mathematics.

School performance in relation to perinatal risk factors, brain injury and maternal education

To investigate whether subgroups of preterm infants were more likely to develop problems in later school performance relevant perinatal and maternal data from the original database were obtained and neonatal MRI scans were reviewed. Perinatal risk factors included the child's sex, GA at birth, small for gestational age (SGA), postnatal sepsis, necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD). SGA was based on a birth weight below the 10th percentile [16]. Postnatal sepsis with a positive blood culture and/or NEC $\geq$ stage 2 [17] were taken together as one variable (sepsis and/or NEC). BPD was categorized as none or mild/moderate/severe BPD according to Banclari (2006). To determine the presence and severity of brain injury all neonatal MRI scans were reviewed by at least two experienced investigators (SS, FWB, AvS, TM), using the cerebral white matter and cerebellar abnormality scores of a standardized MR imaging scoring system [18]. The investigators had no knowledge of any clinical characteristics or outcome data of the children except the GA at the time of scanning. The severity of white matter and cerebellar injury was categorized as normal versus mild versus moderate/severe. Maternal education was classified as low (primary school and lower general secondary school), intermediate, or high level (higher vocational school and university) of education [19].

Statistical analysis

Statistical analyses were conducted using SPSS (version 23.0 IBM, Armonk, NY, USA). Descriptive results for nominal variables were presented as number of cases and percentages. Means and standard deviations (SD) were reported for continuous variables. Binomial tests for proportions were conducted to compare the percentage of children in special (primary) education, the grade repetition rate and the percentages of children in each level of school performance to their Dutch peers. To investigate the relation between perinatal factors, neonatal brain injury, maternal education and school performance, children were categorized in two groups: the lowest categories of school performance (level D and E) versus the average and higher categories of school performance (level A, B and C). Binary logistic univariate regressions were conducted to study potential risk factors for school performance on reading comprehension, spelling and mathematics. Secondly, variables from the univariate analysis with a p-value of $<.05$ were included into a multivariate regression model. To adjust for the effect that observations in twins are not independent, the multivariate analyses were conducted in a generalized estimated equations model [20]. To adjust for multiple comparisons of the three outcome variables, reading comprehension, spelling and mathematics, a p-value of $<.017$ (0.05/3) was seen as statistically significant.

Results

Information on school enrolment and grade repetition was available in 87 (77%) of the 113 children. Reasons for loss to follow-up were refusal by parents/child (n = 10), moved abroad (n = 9) and loss of contact (n = 7). Of one child, data on perinatal factors and information on school enrolment and school performance were available, but the MRI at TEA data were missing and therefore could not be reviewed. There were no differences in perinatal factors, severity of brain injury or level of maternal education between children with or without follow-up. Table 1 shows the characteristics of the study population.

Table 1. Perinatal characteristics and level of maternal education of the study population.

Perinatal characteristics	**Participants (N=87)**
Male sex (%)	50 (58%)
Part of twins or triplets (%)	31 (36%)
GA (weeks), mean ± SD	28.94 ± 2.0
BW (g), mean ± SD	1204 ± 359
SGA (%)	10 (12%)
BPD (%)	
None	47 (54%)
Mild	17 (20%)
Moderate	22 (25%)
Severe	1 (1%)
Sepsis (%)	32 (37%)
Necrotizing enterocolitis (%)	3 (3%)
White matter injury	
Normal	46 (54%)
Mild	18 (21%)
Moderate	14 (16%)
Severe	8 (9%)
Cerebellar injury	
Normal	65 (76%)
Mild	11 (13%)
Moderate	4 (4%)
Severe	6 (7%)
Maternal education	
Low (%)	20 (23%)
Intermediate (%)	30 (35%)
High (%)	37 (42%)

School enrolment and performance compared to the general population of Dutch peers

Table 2 displays the outcomes on school enrolment. Overall, 87% (76/87) of the preterm children were enrolled in mainstream primary education. Eight percent (7/87) were enrolled in special primary education, which is significantly higher compared to the 2.4% of children who are enrolled in special primary education throughout the Netherlands (p = .005). Five percent (4/87) of the preterm children were enrolled in special education, which is comparable to their Dutch peers. Within the group of children who enrolled in mainstream education, 24% (18/76) received additional assistance in the classroom, mostly through remedial teaching.

Table 2. School enrolment of the 87 children included for follow-up.

	Study population (n = 87)	**Dutch population**	***p***
Appropriate grade for age, without support (%)	43 (48%)		
Appropriate grade for age, with support (%)	18 (20%)		
One or more grades below (%)	19 (22%)	7.40%	**.000**
Grade repetition in preschool	14 (74%)		
Grade repetition in grade 1/2	5 (26%)		
Special education (%)	4 (5%)	4.73%	.879
Special primary education (%)	7 (8%)	2.41%	**.005**

***** p <.05
****** p <.01

The percentage of children who repeated a grade, in both mainstream and special education, was 22% (19/87). This is a significant higher number (p = .000) compared to the 7.4% of children within the Dutch population who repeat a grade in primary school until grade 3 (year 5). Differentiating between mainstream and special (primary) education, 20% (15/76) of the preterm children in mainstream education repeated a grade, and 36% (4/11) of the children in special (primary) education. Most children, 74% (14/19), repeated the second year of preschool education. In first grade, 21% (4/19) of the children had to repeat a grade and 5% (1/19) in second grade.

Results of the nationwide standardized achievement tests were available for 74 (65%) children, following regular and special (primary) education, of the initial cohort. Table 3 shows that preterm children more often performed within the lowest category (E) in reading comprehension, spelling and mathematics, compared to the 10% of their Dutch peers. In reading comprehension, 20% (15/74) of the children performed in level E (p = .006); in spelling, 19% (14/74, p = .014), and in mathematics 27% (20/74, p = .000).

Table 3. Academic performance based on the Dutch Pupil Monitoring System.

	(n=74)	**Dutch population**	***p***
Reading comprehension			
A	23 (31%)	25%	.142
B	11 (15%)	25%	**.025**
C	11 (15%)	25%	**.025**
D	14 (19%)	15%	.198
E	15 (20%)	10%	**.006**

Table 3. Continued

	(n=74)	Dutch population	*p*
Spelling			
A	19 (26%)	25%	.464
B	15 (20%)	25%	.232
C	18 (24%)	25%	.509
D	8 (11%)	15%	.215
E	14 (19%)	10%	**.014**
Mathematics			
A	14 (19%)	25%	.155
B	11 (15%)	25%	**.029**
C	18 (24%)	25%	.536
D	11 (15%)	15%	.534
E	20 (27%)	10%	**.000**

***** p <.05
****** p <.01

School performance in relation to perinatal risk factors, brain injury and maternal education

Univariate regression analysis (Table 4) showed that sex (B = −1.368, p = .009) and level of maternal education (B = −2.351, p = .000) both predicted the performance on reading comprehension. Males performed worse than females and children of mothers with a high level of education performed better. Males also had a poorer performance in spelling (B = −1.658, p = .007). A poorer performance in mathematics was predicted by the absence of BPD (B = 1.054, p = .031), presence of moderate/severe white matter injury on neonatal MRI (B = 1.856, p = .003) and a lower level of maternal education (B = −1.181, p = .000).

Table 5a and table 5b show the results of the multivariate regression analysis for reading comprehension and mathematics. No multivariate regression analysis was conducted for spelling, as only sex showed an effect in the univariate analysis. Both male sex (B = −1.773, p = .004) and a low level of maternal education (B = −2.737, p = .000) remained independent predictors for a lower performance in reading comprehension. The presence of moderate/severe white matter injury (B = 1.601, p = .013) remained an independent predictor for mathematics. The presence of BPD and level of maternal education did no longer have a significant effect on the performance in mathematics. Correction for multiple testing did not affect these results.

Table 4. Univariate analysis, factors affecting school performance.

	Reading comprehension		Spelling		Mathematics	
	B	*p*	B	*p*	B	*p*
Male sex	-1.368	**.009**	-1.658	**.007**	-.551	.254
GA at birth	.063	.609	.089	.497	.214	.086
SGA	.495	.510	.942	.223	.395	.612
BPD	.106	.825	.128	.803	1.054	**.031**
Sepsis/NEC	.345	.483	.811	.120	.885	.074
White matter injury						
Normal – moderate/severe	.241	.680	1.076	.075	1.856	**.003**
Mild – moderate/severe	-.922	.217	.588	.443	-.118	.880
Cerebellar injury						
Normal – moderate/severe	.799	.325	1.293	.115	1.504	.088
Mild– moderate/severe	.693	.488	1.674	.128	.511	.629
Maternal education						
Low – high	-2.351	**.000**	-1.099	.087	-1.181	**.047**
Intermediate - high	-1.216	.054	-1.019	.110	-1.076	.066

* p <.05
** p <.01

Table 5a. Multivariate regression analysis, reading comprehension.

	Reading comprehension	
	B	*p*
Male sex	-1.773	**.004**
Maternal education		
Low – high	-2.737	**.000**
Intermediate - high	-1.247	.069

* p <.05
** p <.01

Table 5b. Multivariate regression analysis, mathematics.

	Mathematics	
	B	*p*
BPD	-.579	.328
White matter injury		
Normal – moderate/severe	1.601	**.013**
Mild – moderate/severe	-.044	.959
Maternal education		
Low – high	-1.113	.107
Intermediate - high	-.655	.310

* p <.05
** p <.01

Discussion

This is, to our knowledge, the first study investigating classroom-evaluated school performance in a prospective cohort of very preterm children in relation to perinatal factors, brain injury and maternal education. Other similar studies mostly reported on academic performance as evaluated in a clinically controlled one-one-one environment or based on individual information reported by parents or teachers instead of using standardized tests in a school setting. School performance is more than being able to comply with tasks, it is also about being able to focus in a classroom full of distraction and being able to motivate yourself. Results of the few studies that did include classroom-evaluated school performance were inconclusive on performance in reading comprehension and spelling, but found poorer performances of preterm born children in mathematics. It has been known that birth weight and gestational age are associated with cognitive and academic outcomes. However, the relation between other perinatal factors, neonatal brain injury, maternal education and classroom-evaluated school performance has remained unknown.

Within our study population, a high number of preterm infants was enrolled in special primary education. This is in line with the results from other studies [7]. However, the number of children enrolled in special education, in other words, the children with severe hearing or visual impairments, learning disabilities of psychiatric disorders, was not higher compared to the general population. Within The Netherlands, the indications for special education are strict, the child's impairment or learning disability needs to be severe. Also, in 2014 the Education that Fits Act was introduced in The Netherlands, with the purpose of keeping more children with special educational needs in mainstream primary education. This has raised the threshold for children to be referred to special education [21]. In 2014, most children in our study population reached the age of seven and were enrolled in primary school. The higher threshold therefore also applied to them. This may have led to the relative high percentage (24%) of children with additional support in mainstream education within our study population. However, most children (87%) in our study population followed mainstream education, either with or without additional support or grade repetition.

Besides a higher need for special primary education, there was a higher grade repetition rate for the preterm children within our study population. The majority of these children repeated a grade in preschool, because it was considered that they were not ready for primary school. Within the Netherlands, a relatively high number of children (approximately 10%) repeat a year in preschool [22]. In our study cohort, the percentage of children who repeated a grade in preschool was 16% (14/87).

Looking at school performance, the preterm born children in our study population had lower performances in reading comprehension, spelling and mathematics, with the biggest proportion of preterm children experiencing difficulties in mathematics. Already in preschool, before the age of six, it is noticed that preterm born children have more difficulties with numerical reasoning skills [6]. Mathematical difficulties are associated with poorer internal representation of numbers, which starts early on in life [23]. It is also known that impaired executive functioning is an important predictor for poor mathematical performance in primary school, but not (already) in preschool [24]. Possibly this is due to the fact that the mathematical problems that children face become more complex and are in need of a higher level of neurocognitive abilities in order to solve them. Contrary to the early findings of difficulties in numerical reasoning skills, preterm born children do well in early linguistics in preschool [6]. However, this had in our study population no positive effect on their performance in reading comprehension and spelling.

Within the general population, there are some established factors influencing school performance, such as sex and maternal education. Studies have shown that there is a sex difference favouring girls in reading and writing achievement, possibly relating to early advantages in various language-related skills and therefor facilitating the learning process of how to read and write [25]. Maternal education within the general population is an established factor influencing IQ, executive functioning and, therefore, school performance [26]. In our study population, male sex was predictive of a lower performance in reading comprehension and spelling and a lower level of maternal education predicted a poorer performance in reading comprehension.

Some factors are known to influence neurocognitive outcome after preterm birth, like birth weight and GA [27]. The influence of other factors, such as the impact of neonatal brain injury, is still unclear, ranging from limited predictive value of white matter injury for neurocognitive and behavioral impairment [28], to the prediction of cognitive delay by white matter abnormalities [29]. GA was not a predictor of poor school performance in our study population, possibly due to the restricted range of GA [30]. Neonatal moderate/severe white matter injury was predictive of a lower performance on mathematics.

There is still a substantial unexplained residual variance when it comes to predicting school performance [31]. Literature has identified many variables that (might) influence school grades, such as factors concerning the child itself, the quality of education and parental upbringing. This suggests that there are multiple ways of facilitating cognitive development, despite the conditions in which a child is born.

Limitations

This study has limitations, one of them being the lack of reference data collected from a term-born control group, matched for example on socioeconomic status based on the level of maternal education. However, we did have reference data of the general population of Dutch peers. We experienced a relatively high loss to follow-up, due to the seven year gap between the previous follow-up at two years of age and this study's assessment. Because of the relative small number of children, some associations might be less visible.

We conclude that more than half of preterm born children need extra assistance in primary school, either through support in the classroom, grade repetition or enrolment in special primary education. Sex, white matter injury and maternal education were predictive of school performance. Nearly half of the children struggled with mathematical performance. Given the growing evidence that preterm born children already lag behind in their numerical reasoning skills in preschool, it is important that these children are carefully watched and offered additional support. Future research should therefore focus on the development of intervention programs that may help parents and teachers to support preterm born children on (pre)academic areas and on the role of other factors possibly influencing academic performance, such as parenting style and underlying dysfunctions.

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VI

PART SIX

QUALITATIVE RESEARCH

CHAPTER 4

Social-emotional and behavioural issues after very preterm birth: Parental and teachers experiences

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Lisette Jansen
Sylke Steggerda
Monique Rijken
Andrea van Steenis
Linda S. de Vries
Cacha Peeters-Scholte
Robert Vermeiren
Jeanine van Klink

Abstract

Preterm infants are at risk of developing social-emotional and behavioural difficulties. To understand the experiences of their caregivers in day-to-day life, parents (at 2 and 10 years) and teachers (at 10 years) completed a behavioural questionnaire and answered two open-ended questions addressing their concerns and the most positive aspects regarding their child and/or pupil (born <32 weeks gestation). Their answers were analysed using thematic content analysis. Parental concerns at two years related equally to themes in the clusters Developmental Milestones, Physical Development, and Development in Relation to the Self and Others. At 10 years, both parents and teachers reported mainly within the cluster Development in Relation to the Self and Others, but the underlying themes differed. While parents more often mentioned their child's emotional development, teachers were more concerned about their pupils difficulties interacting with their peers, due to a lack of social skills. In-depth qualitative analysis of what parents and teachers experience from day to day improves our understanding of the social-emotional and behavioural development of children born very preterm, revealing important topics that should be addressed during follow-up.

Introduction

Preterm-born children are susceptible to develop social-emotional and behavioural problems throughout life [1, 2]. In early childhood, they are particularly at risk for neurodevelopmental disabilities [3], while school and social-emotional difficulties, including peer relationship problems and anxiety, become more apparent from school-age onward [3, 4]. Compared to their term-born peers, they are also more prone to psychiatric disorders, including attention-deficit hyperactivity disorder (ADHD) [5]. Such disorders may lead to family distress, diminished academic performance and may, later on, have a negative impact on their careers and relationships [3, 6, 7].

Most studies investigating social-emotional and behavioural development in preterm-born children focus on quantitative measures and categorize symptoms according to classifications, for example, attention problems and ADHD or withdrawn behaviour and autism [2, 5]. Focusing solely on classified outcomes might fail to consider the full range of caregivers' main concerns and day-to-day worries, or the aspects they value most in their child after the difficult start of being born preterm. A mixed-method study showed that most parental concerns at 18-months after preterm birth relate to language and motor development [8]. Furthermore, it showed that parents are most content with their child's personality characteristics, for example, being easy going or curious. These findings would have remained undetected with a quantitative analysis of a behavioural questionnaire, even though they form relevant issues that should be addressed during follow-up assessment of preterm-born children. To our knowledge, qualitative assessments have not previously been conducted in older children.

The use of parents as a sole source of information might not be sufficient, as they, especially as parents of very preterm infants, may be more sensitive to later problems considering their early experiences [9]. As the role of teachers increases during the daily life of school-aged children, they become valuable additional source of information regarding a child's social-emotional and behavioural functioning in relation to its peers. Studies comparing the outcomes of parental and teacher questionnaires reported no differences in ratings on internalizing and externalizing behaviour [2], but this does not necessarily mean that there are no differences in how parents and teachers experience daily behavioural issues at home and in the classroom. To date, qualitative data on parent's and teacher's perspectives are lacking for school-aged children, leading to a gap in understanding which topics, both positive and/or causing concern, are predominant for caregivers in their day to day experience with children born preterm [1]. Insight in these specific experiences will enhance the knowledge of the social-emotional and behavioural development of preterm born children. Creating a broader understanding of the social-emotional and behavioural development of preterm-born children with regard to the themes parents and teachers struggle with most in daily life and over time is important. It will aid the counselling of parents of preterm-born children today in terms of what they might expect in the future, but also provides insight in topics that should be addressed by clinicians caring for preterm infants and their parents.

Aim

Our aim was to assess aspects causing the most concern in the development of very preterm-born children for parents at 2 years of age and for parents and teachers at 10 years of age. Subsequently, we wanted to identify which aspects of the child are considered most positive.

Methods

Population

This study was part of a larger single-centre, prospective longitudinal study on neuroimaging and outcome after preterm birth. It was conducted in Leiden University Medical Center, one of the ten hospitals with a Neonatal Intensive Care Unit in the Netherlands. Up to May 2017, the unit consisted of two intensive care units with room for 16 neonates, and one high-care unit that could accommodate nine neonates. Children born <32 weeks gestational age who had been admitted to our tertiary neonatal intensive care unit between May 2006 and November 2007 and underwent a MRI at term-equivalent age were included. Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal disorders, metabolic disorders, and/or neonatal meningitis.

The institutional review board of our center approved this study, and written parental consent was obtained from both parents (P06.002). For the follow-up at 10 years of age, a waiver was obtained as this is part of the national clinical follow-up program (C15.072/P17.087).

Social-emotional and behavioural assessment

All children were invited for follow-up visits at the age of 2 years, corrected for prematurity, and at 10 years. Parents completed the Child Behavioural Check List (CBCL) [10, 11] during both visits. The CBCL was standardized in a national representative sample of 4-18 year old children, who were enrolled in regular education, without recent professional care. The Dutch committee that provokes the quality of, amongst others, questionnaires (COTAN; Commissie Testaangelegenheden Nederland) has assessed the reliability and validity of the CBCL as at least sufficient.

At 2 years of age parents completed the CBCL $1^1/_2$ – 5, consisting of 100 items that describe emotional and behavioural issues of pre-schoolers. Each item contains a specific behaviour rated on a three-point Likert scale by either scoring 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true). Based on the answers eight syndrome scales are calculated: emotionally reactive behaviour (e.g., disturbed by any change in routine), anxious/depressed behaviour (feelings are easily hurt), somatic complaints (aches or pains without medical cause), withdrawn behaviour (avoids looking others in the eye), sleeping problems (does not want to sleep alone), attention problems (rapid shifts from one activity to another), and aggressive behaviour (demands must be met immediately). Together the syndrome scales form a total problem scale that is divided into the subscales internalizing problem behaviour (emotionally reactive, anxious/depressed, somatic complaints, and withdrawn behaviour) and externalizing problem behaviour (attention problems and aggressive behaviour).

At 10 years, parents completed the CBCL 6 – 18, while teachers were provided with a Teacher Report Form (TRF) 6 – 18 [12, 13]. Teachers were approached through the parents and were aware of the medical background of their pupil. Each questionnaire consists of 120 items describing the behaviour of school-aged children. Parents and teachers answered the questions on the above mentioned three-point Likert scale as in the CBCL $1^1/_2$ – 5. Based on their answers, eight syndrome scales were calculated: anxious/depressed behaviour (is afraid to go to school), withdrawn/depressed behaviour (there is very little he/she enjoys), somatic complaints (physical problems without known medical cause), social problems (clings to adults), thinking problems (cannot get his/her mind off certain thoughts), attention problems (fails to finish things he/she starts), rule-breaking behaviour (lying or cheating), and aggressive behaviour (gets into many fights). Together the syndrome scales form a total problem scale and two subscales, including internalizing problem behaviour (anxious/depressed behaviour, withdrawn/depressed behaviour, and somatic complaints) and the subscale externalizing problem behaviour (rule-breaking behaviour and aggressive behaviour).

At both ages, age-standardized *t* scores were obtained based on the percentiles of the distribution of the raw scores. Higher scores indicated higher levels of problem behaviour. For the syndrome scales, *t* scores between 65-70 were considered borderline clinical and *t* scores >70 indicated clinical behavioural problems. For the total problem, internalizing and externalizing scales, *t* scores between 60-75 indicated borderline clinical and *t* scores >65 indicated clinical behavioural problems [10, 13].

Besides the items that need to be answered on a three-point Likert scale, the CBCL and TRF provides parents and teachers with two open-ended questions: ‘What concerns you most about your child?’ and ‘Please describe the best aspects of your child’.

Statistical analyses

Statistical analyses were conducted using SPSS (Version 23.0, IBM, Armonk, NY, USA). To assess whether a selective loss to follow-up occurred, the perinatal factors of children with and without follow-up were compared using chi-square or Fisher exact (when the observed count was <10) tests for categorical variables and the *t* test for continuous variables. Descriptive statistics were computed as median and interquartile range (IQR) and proportions (n, %). To test whether there were differences in *t* scores between the two ages and between parents and teachers, a Wilcoxon signed-rank test was conducted, due to the non-normal distribution of the data. A *P* value <.05 was considered statistically significant. Answers to open-ended questions were analysed at two and ten years of age through the standard for qualitative research [14]. They were first transcribed and then analysed using the thematic content analysis method [15]. The statements of parents and teachers were coded inductively by themes, which were originally simultaneous, but independently, developed by two investigators (LJ and JK). Themes and coding definitions were further developed, agreed upon, and altered by the same two investigators using the thematic qualitative content analysis method. A third investigator was involved in case of discrepancies between coding and resolved through consensus. When statements contained more than one theme, the themes were coded separately. Frequency was calculated for each theme. Finally, themes were grouped into clusters, capturing the broader scope of a group of themes.

Results

A cohort of 113 very preterm children born <32 weeks' gestational age who had been admitted to the tertiary neonatal intensive care unit between May 2006 and November 2007 were included. Completed parental questionnaires at 2 and/or 10 years were available for 92/113 (81%) children, including 62 (67%) children at both ages (see figure 1 for the derivation of the study population). Teacher questionnaires were available for 75/113 (66%) children. There were no differences in clinical parameters between children with a behavioural assessment and those without. Baseline characteristics of the participating children, of whom 58% were boys, included a median gestational age of 28.9 weeks (IQR: 4.1) and a median birthweight of 1120 g (IQR: 548).

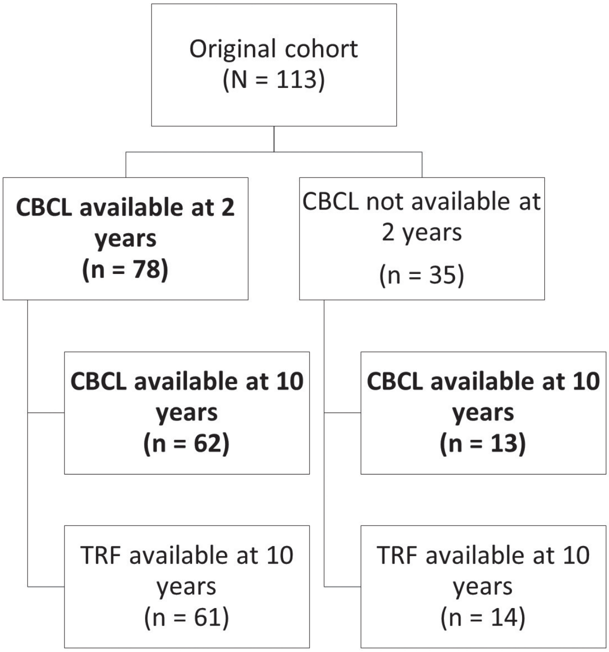

Figure 1. Derivation of the study population.

Quantitative behavioural assessment

At 2 and 10 years of age, parents reported comparable numbers of children, 17/78 (22%) vs. 16/75 (21%) with borderline-clinical externalizing problems. The number of children with borderline-clinical internalizing problems, however, tripled from 8/78

(10%) at 2 years to 24/75 (32%) at 10 years. This was a statistical significant increase, Z = -2.942, p = .003. Comparing parental and teacher ratings at 10 years, similar mean internalizing and externalizing scores were found, Z=-1.5531.607, *P*=.120 and Z=-.281, *P*=.779, respectively.

Qualitative parental assessment of daily life experiences

Table 1 and Figure 2 show the main clusters of concern and their underlying themes at 2 and 10 years.

Table 1. Qualitative assessment of social-emotional and behavioural development: main concerns of parents and teachers at 2 and 10 years.

	Concerns		
	Parents		**Teachers**
Cluster, n respondents (%) Theme, n statements	**n = 78** **2 years**	**n = 75** **10 years**	
Development in Relation to Self and Others, n (%)	**20 (26)**	**39 (52)**	**36 (48)**
Emotional development	-	28	19
Social development	-	5	17
Social and emotional development	-	2	3
Behaviour	10	13	8
Temperament - personality style	12	12	4
Mindset	-	3	3
Total statements within cluster, n	22	63	54
Developmental Milestones, n (%)	**21 (27)**	**8 (11)**	**8 (11)**
Motor skills	10	3	1
Language development	11	2	2
Potty training	3		
Planning and organizing	-	3	4
Global development	-	-	1
Total statements within cluster, n	24	8	8
Physical Development, n (%)	**20 (26)**	**12 (16)**	**4 (5)**
Health in general	6	9	2
Growth	6	2	1
Nutrition	5	-	-
Sleep	5	4	-
Respiratory	-	1	-
Disability	-	-	1
Total statements within cluster, n	22	16	4

Table 1. Continued

	Concerns		
	Parents		Teachers
Cluster, n respondents (%) Theme, n statements	n = 78 2 years	n = 75 10 years	
Family, n (%)	**2 (3)**	**2 (3)**	**1 (1)**
School, n (%)		**11 (15)**	**18 (24)**
Outcome in general		6	8
Specific subjects		3	4
Specific skills		2	6
Total statements within cluster, n		11	18
Future, n (%)	**2 (3)**	**5 (7)**	**1 (1)**
No explicit concerns, n (%)	14 (18)	4 (5)	13 (17)

Parents' main concerns at the 2-year assessment

At 2 years, 78 parents made 72 statements describing their concerns. These statements were grouped into nine themes and five clusters, which captured the broader scope of a group of themes. Parents reported three main clusters of concern: *Developmental Milestones*, with 21/78 (27%) parents making 24 statements, *Development in Relation to the Self and Others*, with 20/78 (26%) parents making 22 statements, and *Physical Development*, with 20/78 (26%) parents making 22 statements.

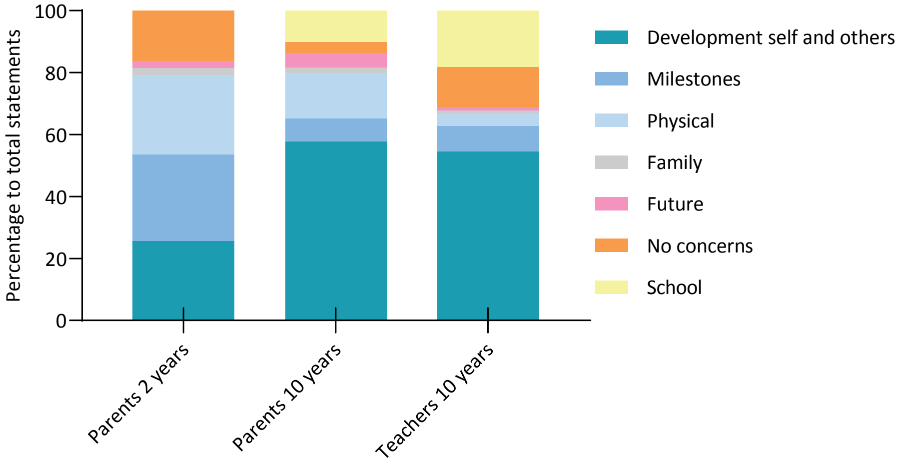

Figure 2. Statements of concern per cluster of parents and teachers.

Developmental Milestones captures three underlying themes that relate to important cognitive and motor milestones in toddlerhood: 11/24 (46%) statements related to language development and were expressed as, e.g., ‘He hasn’t started talking yet’, 10/24 (42%) related to motor skills, e.g., ‘He still falls a lot while walking’, and 3/24 (13%) related to potty training, e.g., ‘He has no interest in potty training’. In the *Development in Relation to the Self and Others* cluster, parents reported two themes: temperament, with 12/22 (55%) statements describing a child as stubborn, e.g., ‘If he wants something, he is very persistent’, and behaviour, with 10/22 (45%) statements concerning tantrums, concentration problems, and hyperactive behaviour. The *Physical Development* cluster captured four themes of concern: health in general (6/22 (27%) statements, e.g., ‘My child is susceptible to catching colds’), impaired growth (6/22 (27%) statements), nutrition (5/22 (23%) statements, e.g., ‘Eats small amounts’), and sleep (5/22 (23%) statements, e.g., ‘Not wanting to sleep on her own’). The two clusters, *Family* and *Concerns about the Future*, were mentioned least by the parents and considered the impact of a ‘broken home’ and e.g., ‘His development in the years ahead, will it continue to go well?’

Parents’ main concerns at the 10-year assessment

There was an increase from 2 to 10 years in the number of parents who explicitly reported concerns regarding their child’s development. While 64/78 (82%) parents expressed concerns at 2 years, 71/75 (95%) expressed concerns at the 10-year assessment. At 10 years, 75 parents made 101 statements that related to 18 themes and 6 clusters. The main cluster of concern was *Development in Relation to the Self and Others*, with more than half of the parents, 39/75 (52%), reporting on one or more of the 6 underlying themes in 73/101 statements. This is twice the number compared to the 2-year assessment (20/78 parents, 26%). The underlying theme emotional development (28/73 (38%) statements) included e.g., ‘His insecurity reflects in having many difficulties with his schoolwork’ and ‘His self-image is very low’. Regarding the theme behaviour, concentration problems were parents’ main concern (13/73 (18%) statements), e.g., ‘Because of his lack of focus, he is not able to give his best’. Twelve (16%) statements were related to the theme personality style (or temperament, at the 2-year assessment) and included perfectionism, e.g., ‘She sets the bar very high for herself and is not easily satisfied with her efforts’ and high sensitivity, e.g., ‘She is very sensitive, she doesn’t respond well to loud noises and cries easily’. Fewer statements related to the three underlying themes social development, 5/73 (7%), e.g., ‘Making first contact with peers’, (negative) mindset, 3/73 (4%), e.g., ‘His negative thinking’ and social-emotional development in general, 2/73 (3%). The *Physical Development* cluster covered 15 statements that expressed concerns relating to four themes: general health (8/15 (53%), e.g., 'She often does not feel well'), sleeping problems (4/15 (27%), e.g., 'Has difficulties going to bed'), growth (2/15, 13%), and respiratory problems (1/15 (7%)).

A new cluster at 10 years, *School*, contained 11 statements that were grouped into three themes: 6/11(55%) concerned general, 3/11 (27%) concerned specific learning (dis) abilities, e.g., 'Unable to remember math and spelling rules' and 2/11 (18%) statements regarding their child's attitude towards school, e.g., 'She doesn't want to go to school'. In contrast to parents' perspective at the 2-year assessment, statements of concern within the cluster *Developmental Milestones* were made less often, 24/72 (27%) vs. 8/101 (8%), respectively. At 10 years, the cluster captured three underlying themes: language development (2/8 (25%), e.g., 'Has a speech delay'), motor skills (3/8 (37%), e.g., 'Playing sports'), and the new theme planning and organizing (3/8 (37%), e.g., 'His ability to independently organize his activities'). As was the case at 2 years, at 10 years, the clusters *Family* and *Concerns about the Future* were mentioned least often.

Parents' perspectives on the best aspects of their child at 2 and 10 years

Table 2 and Figure 3 show the 6 clusters and their 16 underlying themes of what parents consider the best aspects of their very preterm-born child at 2 years (173 statements) and at 10 years (154 statements).

At both ages, most parents made positive statements relating to the cluster *Development in Relation to the Self and Others*, with 51/78 (65%) parents making 130 statements relating to four themes at 2 years and 59/75 (79%) parents making 121 statements relating to five themes at 10 years. Most positive statements regarded the theme temperament (80/130, 62%) at 2 years and personality style (64/121, 53%) at 10 years. Statements included descriptions like 'sweet', 'playful', and 'active' and character traits, such as showing perseverance, e.g., 'She always finds ways to achieve her goals'. Positive statements related to the theme social development ranged from playing with others and being affectionate, e.g., 'He loves being cuddled' at 2 years, to being caring, kind, helpful, and empathetic, e.g., 'She has a strong sense of social empathy' at 10 years. Statements relating to the theme (positive) mindset, with parents describing their child as cheerful, happy and positive, were mentioned more often at 2 years with 28/130 (22%) vs. 13/121 (11%) statements at 10 years.

Overall, being content with ‘everything’ was reported by 9/78 (12%) parents at the 2-year assessment and by 7 /75 (9%) parents at the 10-year assessment, stating, e.g., ‘He was born at 26 weeks, we are very proud of how he is developing’ and ‘We are happy with everything she knows and does’. At 10 years, *School* formed a new cluster, with seven parents making seven positive statements relating to two themes; their child’s attitude towards school (1/7, 14%), e.g., ‘He never complains about school’ and making an effort (6/7, 86%), e.g., ‘She tries her very best at school’.

Table 2. Qualitative assessment of social-emotional and behavioural development: positive aspects reported by parents and teachers at 2 and 10 years.

	Positive aspects		
	Parents		**Teachers**
Cluster, n respondents (%) Theme, n statements	**n = 78** **2 years**	**n = 75** **10 years**	
Development in Relation to Self and Others	**51 (65)**	**59 (79)**	**67 (89)**
Emotional development	-	3	-
Social development	21	40	21
Behaviour	1	1	5
Temperament - personality style	80	64	104
Mindset	28	13	12
Total statements within cluster, n	130	121	142
Developmental Milestones	**22 (28)**	**14 (19)**	**10 (13)**
Cognitive development	5	9	3
Motor skills	4	3	-
Language development	10	1	2
Making progress	7	1	4
Global development	-	-	1
Total statements within cluster, n	26	14	10
Physical Development	**4 (5)**	**4 (5)**	**-**
Health in general	3	4	-
Growth	1	-	-
Total statements within cluster, n	4	4	
School		**7 (9)**	**20 (27)**
Positive attitude		1	7
Making an effort		6	-
Contact teacher – pupil		-	6
School results		-	7
Total statements within cluster, n		7	20
Exceeding Expectations of the Past,	**4 (5)**	**1 (2)**	**-**
Everything	**9 (12)**	**7 (9)**	**-**

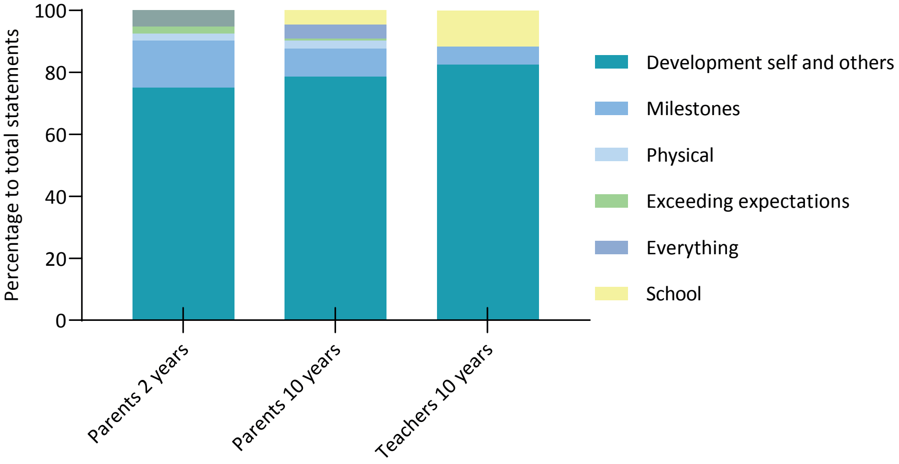

Figure 3. Positive statements per cluster as reported by parents and teachers.

Comparing parents' and teachers' perspectives at 10 years: concerns and best aspects

When comparing the parents' and teachers' perspectives (Table 1 and Figure 2), more teachers explicitly mentioned not having any concerns about their pupils, 13/75 (17%) as opposed to 4/75 (5%) parents. The main cluster of concern for both parents (39/75,52%) and teachers (36/75,48%) was *Development in Relation to the Self and Others*. However, parents' and teachers' statements related to different themes. Teachers had more concerns relating to the theme social development, 17/54 (32%) vs. 5/63 (8%) statements, and mentioned a lack of social skills, e.g., 'He's a bit awkward, socially' and 'He has trouble reading social cues', whereas parents were more concerned about their child's emotional development, e.g., 'Her self-image' and 'His insecurity'. Compared to parents, teachers reported more concerns within the cluster *School,* with 18 teachers making 18 statements relating to 3 themes. Academic achievement in general was the main theme, e.g., 'He has more difficulties understanding school assignments compared to his peers' and 'Her effort and school results do not match'. Concerns relating to the cluster *Developmental Milestones* were mentioned equally often, 8/75 (11%) by teachers and parents, where teachers were most concerned about their pupil's ability to plan and organize their schoolwork, e.g., 'Difficulties to start schoolwork and also to finish his work'.

Regarding the parents' and teachers' perspectives on the best aspects of their child/pupils (Table 2 and Figure 3), the main cluster for both parents, 59/75 (73%) and teachers, 67/75 (84%) was *Development in Relation to the Self and Others* with 121 and 142 statements relating to four themes, respectively. Most statements of both parents, 64/121 (53%), and teachers, 104/142 (73%), concerned the theme personality style. Teachers mainly praised their pupils' willingness to work hard, while parents mostly mentioned characteristics related to the self, e.g., 'He/she is very sweet/a go-getter'. Positive aspects within the cluster *School* were mentioned more often by the teachers, 20/75 (27%) vs. 7/75 (9%). Teachers praised their pupils' positive attitude towards schoolwork and the positive interactions with their pupil more often, while parents mentioned the effort their child made at school more often, e.g., 'He is very serious about school and likes to get good marks'.

Discussion

To enhance knowledge on the social-emotional and behavioral development of children born very preterm, this study provided in-depth qualitative information on what parents experience on a day to day basis during two different developmental stages (2 and 10 years of age), including both concerns and positive aspects. Due to the importance of multiple informants, the teacher perspective was incorporated at 10 years of age. At 2 years, parental concerns were equally divided between the clusters *Developmental Milestones*, *Development in Relation to the Self and Others* and *Physical Development*. The main concern at 10 years of age related to the cluster *Development in Relation to the Self and Others,* for both parents and teachers. However, underlying themes differed, with teachers reporting more social difficulties. Even though the cluster *Development in Relation to the Self and Others* was the main cluster of concern at 10 years, it was also the main cluster relating to positive statements at both 2 and 10 years of age. These findings add to our understanding of the social-emotional and behavioural development of very preterm-born children, as they give insight in what parents and teachers struggle with most in daily life and over time.

Behavior in preterm children has been mainly studied through behavioral questionnaires, showing for example that already at 6 years of age, preterm children have more behavioral problems compared to their term-born peers; a difference that remains stable throughout their school career [16]. This leads to a 3-to 4- fold higher risk for a range of psychopathology [17]. Currently, the co-occurrence of increased emotional symptoms, hyperactivity/inattention and social difficulties is described as the 'preterm behavioral phenotype', in order to distinct the risk, but also the etiology, from the broader pediatric population [18]. About 20% of children born preterm experience behavioral difficulties in line with the preterm behavioral phenotype [19]. These sorts of behaviors are imaginably challenging for caregivers, but little is known on what they truly experience on a day to day basis.

Qualitative research in relation to preterm birth has gained attention over the past decades, especially concerning parental experiences during the period at the neonatal intensive care unit [20, 21] and after early intervention programs [22, 23]. Qualitative studies after this period are scarce, potentially leading to missing outcomes that are important and meaningful to caregivers of preterm born children [24].

In line with Jaworski and colleagues (2018), we found that at 2 years the cluster *Developmental Milestones* was the main topic of concern and just as often mentioned as the most positive aspect of (the development of) the child. It might be that, even though parents are worried whether their child will reach age-appropriate milestones, they are also happy with how their child is developing after their stay at the neonatal intensive care [25].

Compared to the quantitative data at the 2-year assessment, externalizing behavior was reported most by parents. High scores of behavioral traits such as stubbornness and disobedient behavior might be in line with the normative peak of physical aggressive behavior, that increases in the second year of life [26]. However, externalizing behavioral problems were not the main reason for concern at two years of age as mentioned by parents. This underlines the importance of looking beyond the numerical outcomes of a behavioral questionnaire.

At ten years of age, parents reported quantitatively more internalizing behavior, including anxious and depressed behavior, which also showed in their answers to the open-ended questions. The mentioned themes became more complex at 10 years and included concerns regarding the child's emotional well-being, such as a sense of insecurity. Since children generally start their school careers in the Netherlands at 4 years of age, themes related to school were only mentioned at 10 years of age. School is however often not included by behavioural questionnaires, even though behavioural difficulties and school attainment are intertwined [19].

Because of the effect that very preterm birth might have on behaviour and school performance, teachers are a valuable source of information. There were substantial differences in what teachers mentioned as their main concerns and pupils' best aspects.

Not surprisingly, the answers of teachers were more often related to school and academic outcomes. Even though the main cluster of concern was similar to parents at 10 years (*Development in Relation to the Self and Others)*, the underlying themes differed. Teachers were more concerned about a lack of social skills of their pupils leading to difficulties in interactions with their peers. It could be that parents overestimate the social abilities of their child, because they are less confronted with how their child behaves with peers, while teachers have many opportunities to observe their pupils in interaction with others.

In the Netherlands, standardized follow-up of very preterm-born children ends at eight years. With increasing age, however, there appears to be a continued and perhaps even more urgent need for help and reassurance on whether a child is capable of taking care of itself in the future. For example, Dutch preterm-born adolescents were more often unemployed, not enrolled in any educational program, and boys and girls alike showed more difficulties in establishing social contacts compared to their peers [27]. This stresses the need for long-term follow-up, even after school age, to increase the understanding of the difficulties very preterm-born children face, and to provide adequate support.

The underlying themes temperament and social development, of the cluster *Development in Relation to the Self and Others,* were mentioned most related to the best aspects of a child at both ages. Considering the amount of statements made, it seemed quite easy for parents to recognize and mention the positive traits of their child. There was a clear decrease between 2 and 10 years in how often parents mentioned their child's positive mindset, with parents describing their child much more often as happy, vibrant, and lively at 2 years. High rates of a positive mindset in young children have also been found in other studies [8].

Limitations

Due to the original design of the study in 2006-2007 (investigating brain imaging findings in an unselected cohort of children born very preterm), no sample size or power analysis was performed for loss to follow-up at two and ten years of age. Because of the relatively large time interval between the two follow-up points we decided not to implement multiple imputation for missing variables. This has led to a relative small sample, with data of 62 children available at both 2 and 10 years of age. Another limitation of this study was the lack of a healthy term-born control group to assess whether the themes mentioned by parents were specific to preterm-born children, or more universally related to developmental stages.

Implications for practice

Social-emotional and behavioural development is not always included in follow-up studies after very preterm birth. Having a child without any physical concerns or intellectual problems, but with severe behavioural issues, can be equally challenging to the family in which the child is raised [24]. For clinicians working with very preterm-born children, it is important to bear in mind that the numerical outcome of a behavioural questionnaire does not always cover the full experience of parents. Structured interviews might be a valuable addition to the use of questionnaires, as is the use of multiple informants to assess social-emotional and behavioural development to the full extent. Besides generating attention to the reported concerns, it is important to ask parents about their child's successes and to celebrate these with parents. For future research, it would be interesting to add the perspective of the children themselves. Although studies have shown that self-reports of preterm-born adolescents do not show higher rates of problem behaviour compared to controls [3, 28], thematic analysis of their answers to open-ended questions might show more concerns and/or in different areas compared to their peers.

Considering the found differences in concern, teachers form a valuable source of information. This study showed that children born very preterm more often experience difficulties with their social skills, making them a possible target group for intervention focused on the development of social skills.

Conclusion

Children born very preterm are prone to develop social-emotional and behavioural difficulties. Parents of very preterm born toddlers often worry on whether their child will be able to reach age-appropriate milestones, their child's behaviour and general health. As their child grows older, the concerns of parents shift to a complex field of topics intertwined with personality, behaviour and mindset. For teachers, most concerns are related to their pupils emotional well-being, social interaction and academic attainment. This underlines the inability of behavioural questionnaires to cover the full range of experiences of caregivers as well as the importance of multiple informants. The incorporation of parental perspectives regarding their main concern and their children's best aspects within follow-up assessments will provide valuable information for clinical practice that could lead to a better understanding of very preterm-born children.

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VII

PART SEVEN

SUMMARY AND GENERAL DISCUSSION

Summary
General discussion
Nederlandse samenvatting

SUMMARY

Being born prematurely can lead to life-long neurodevelopmental challenges in multiple outcome domains [1, 2]. Therefore, children who are born very preterm (<32 weeks' gestation) are invited to outpatient departments on a regular basis to monitor their development and detect possible difficulties in everyday functioning at an early stage. However, patient follow-up often ends at two years of age, especially in research settings [3]. This is a concern, since children born very preterm are likely to grow into their deficits, the full extent of the consequences of preterm birth might not be seen until later childhood, adolescence or even adulthood.

The purpose of this thesis was to investigate a longitudinal cohort of children born before 32 weeks' gestation, and to study the associations between neonatal factors and outcomes at two and ten years of age. To contribute to the knowledge in this area, four topics were covered. First, we provided insight in the rates of impairment in multiple developmental domains at two and ten years of age, and investigated the individual trajectories between these two time-points. As it is important to have early prognostic markers that can help predict development, the second aim was to associate neonatal neuroimaging findings with both early and school-age outcome. Many studies use routine outcome measures to assess functioning, including intelligence quotients or standardized questionnaires; our goal was to increase understanding of other measures equally important when evaluating a child's daily functioning. Therefore, our third aim was to gain specific knowledge on classroom-evaluated school performance, since academic attainment depends on more than cognitive capabilities. For our fourth and final aim, we provided insight in day-to-day experiences of caregivers of preterm children over the years by asking them about their main concern and the child's best asset during two different life phases (toddlerhood and primary school). In this current chapter, the main findings of this thesis are discussed, leading to directions and opportunities for the future and future research.

Main findings

In **Chapter 1** we assessed the rate and stability of impairments in children born very preterm in the neurological, motor, cognitive and behavioral domain at two time-points (age two (corrected for prematurity) and ten). Each child was categorized as having no, mild or moderate-severe impairment for each of these domains. The individual outcomes at both timepoints were compared.

When all domains were taken together in a composite score, the number of children with a moderate-severe impairment increased almost threefold between two and ten years of age. In contrast, the number of children with a mild impairment decreased. However, when the domains were assessed separately, no differences were found in the distribution of normal, mild and moderate-severe impairment over time. So one could conclude that, on a group level, the outcome for children within the separate domains is relatively stable. But, as is reflected by the composite score, the individual trajectories revealed a considerable number of children showing changes in functioning (in the neurological, motor and cognitive, but not the behavioral domain). Within the motor and cognitive domain, all children with a moderate-severe outcome at age two still had a moderate-severe outcome at age ten. The individual shifts in functioning occurred mainly in children who had a normal or mildly abnormal early outcome, emphasizing that positive outcomes in toddlerhood should be interpreted with care and long-term follow-up is mandatory.

The considerable individual shifts in neurodevelopmental outcome as described in chapter 1, could indicate that the predictive value of neonatal prognostic parameters changes over time. Over the last decades, neonatal magnetic resonance imaging (MRI) has received increasing attention as a prognostic marker. Therefore, we investigated the associations between neonatal brain injury as shown on MRI and cognitive, motor and behavioral outcomes at both two and ten years of age in **Chapter 2**. All children within our cohort underwent an MRI scan around term equivalent age. Using the Kidokoro scoring system [4], neonatal brain injury and altered brain growth in white matter, cortical and deep gray matter and the cerebellum were assessed. Cognitive, motor, and behavioral outcomes were obtained during follow-up visits at both two (corrected) and ten years of age.

The global brain abnormality score, a general measure of neonatal brain injury, was associated with cognition, motor skills, and internalizing behavioral problems at two years of age. These associations remained after correction for perinatal factors and level of maternal education. However, at age ten, there was no longer an association with cognition (full-scale, verbal and performance IQ) and behavior. A large effect of the level of maternal education was found, affecting cognitive development at age 10. Both the average verbal and performance IQ of children of mothers with low levels of education were beneath the averages of children of highly-educated mothers (18 and 11 point respectively). The effect of maternal education on IQ was most prominent in children with milder forms of brain injury; neonatal MRI remained an independent predictor of 10-year cognitive outcome for children with moderate-severe brain abnormality scores.

During follow-up assessment of preterm born children, standardized outcome measures are often used to assess a child's functioning. It is however debatable whether these outcomes truly reflect a child's day-to-day functioning. At school, for example, the demands on behavioral regulation become greater with increasing age to engage in learning activities and expend social skills. Studies including outcome related to school performance often use standardized tests to assess a child's reading, spelling or mathematical abilities. These are generally administered by a psychologist, in a clinically controlled environment with very little distractions. Since children born preterm are likely to experience cognitive difficulties and are more prone to behavioral problems [5], we investigated in **Chapter 3** how the children within our cohort performed at school, with all the distractions that are common in an elementary classroom.

First, data on special educational needs were compared to the Dutch national average; it was more common for children born preterm to have repeated a grade and/or be enrolled in special primary education. Despite these forms of additional educational support, children within our cohort more often obtained below average scores on reading comprehension, spelling, and especially mathematics at the end of third grade (age 8-9). This is a concern, as children born preterm are unlikely to catch up with their term-born peers later on when it comes to academic attainment [6]. Factors associated with lower scores were male sex, higher rates of white matter injury and lower levels of maternal education.

With the previous chapters showing that children born preterm often experience a wide range of impairments, we aimed to provide insight in the day-to-day experiences of their caregivers. In **Chapter 4,** both the quantitative outcomes of a behavioral questionnaire and the qualitative findings based on answers of parents and teachers on two open-ended questions relating to their main concern and most positive aspect about their child/pupil, were described.

Based on the behavioral questionnaires at the corrected age of two and age ten, filled in by parents, quantitative outcomes showed a large increase in children with clinical internalizing behavioral problems over time. For externalizing problems, the number of children with normal, borderline clinical and clinical symptoms remained relatively stable over the years. Teachers reported less (borderline) behavioral problems in the clinical range, both internalizing as well as externalizing, compared to parents.

Qualitatively, main parental concerns in toddlerhood were reported across three clusters: *Developmental Milestones* (will my child be able to reach age-appropriate milestones?), *Development in Relation to the Self and Others* (mainly toddler behavior) and *Physical Development* (including their child's health). At ten years of age, the majority of parents reported concerns in the cluster *Development in Relation to the Self and Others*, capturing statements on emotional and social development, behavior, temperament, personality style, and mindset. Similar to parents, teachers mainly reported within the cluster *Development in Relation to Self and Others*, although the underlying themes differed. For example, teachers had more concerns related to their pupils social development, whereas parents worried more about their child's emotional development.

Considering the positive aspects about their child, parents made most statements within the cluster *Development in relation to the Self and Others* at both time-points. They often reported their child as being cheerful and happy at two years of age, while describing predominantly complex character traits later on, for example their child's perseverance, independence and curiosity. Teachers also mostly mentioned statements within this cluster, praising their pupils positive character traits.

GENERAL DISCUSSION

Follow-up should include more than intelligence quotients

The goal of follow-up assessment is to monitor the development of children born preterm over the years and assess their functioning at different time-points. This enables clinicians to inform caregivers about the child's strengths and weaknesses, making it possible to intervene and/or adapt the environment of the child accordingly. Data on long-term outcome provide meaningful insights in what might be expected for the future, informing the adequate counseling of parents of very preterm infants today.

One of the standardized outcome measures used during follow-up assessment is an intelligence test. However, it has been debated whether this is a reliable marker of a child's cognitive functioning [7]. Since children spend a considerable amount of time at school, evaluating outcomes like performance in the classroom can be a valuable way of monitoring a child's cognitive development in addition to standardized intelligence tests during follow-up visits. Within our cohort of children born very preterm, mean intelligence sores fell in the average range. However, preterm born children in our study had more difficulties with reading comprehension, spelling, and mathematics compared to their peers, indicating that intelligence alone is not predictive of a child's school functioning.

Over the last decades, executive functioning received increasing attention for having an important role in a child's academic performance [8, 9]. It is an umbrella-term for a broad and complex system of neurocognitive functions, including working memory and inhibitory control [10]. Impairments in executive functioning are common in children born preterm [11], and can cause difficulties in meeting the general demands of the classroom and academic attainment. In specific school tasks, such as mathematics, children who are born preterm often struggle to combine several cognitive processes including visuospatial processing and working memory [12].

The use of standardized assessments makes it possible to monitor development over time and to compare outcomes, for example between different longitudinal cohorts. However, since the main goal of follow-up assessment is to adequately assess a child's functioning, we should be aware that outcome measures such as intelligence quotients may not be the most representative of a child's day-to-day functioning.

Therefore, examining executive functioning complementary to intelligence, and the inclusion of other outcomes such as classroom-evaluated school performance, should be considered in addition to the currently used intelligence tests.

The effect of early prognostic markers (such as neonatal MRI) should be interpreted with care considering the individual changes in outcome over time

Over the past decades, research studies shifted their focus from describing outcomes at a singular time-point to multiple moments in time [13]. This is important, since, as described in chapter 1, future functioning cannot be reliably predicted by developmental assessment in toddlerhood, especially for those children with early normal or mild abnormal outcome. Therefore, assessing development at multiple timepoints provides more reliable information on the number of children experiencing difficulties in everyday functioning. Considering the limited predictive value of early developmental outcome and the individual changes in functioning over time as described in chapter 1, the question is whether other prognostic factors are better in predicting who is at risk for an adverse development.

As seen in chapter 2, although neonatal MRI showed promising associations with short-term motor, cognitive, and behavioral outcomes, these associations did not last over time. Instead, there appeared to be a stronger association with environmental factors. Currently, neonatal MRI is not considered standard care for infants born preterm and it is debatable whether it should be [14, 15]. Taken the limited value of neonatal MRI for long-term functioning into account, it should be considered to only use MRI in those infants who are expected to have higher grades of brain injury, for example based on cranial ultrasound findings, instead of all preterm born infants.

The main factors in predicting classroom-evaluated school performance in chapter 3 were the child’s sex, white matter injury and level of maternal education. For example, boys and children of mothers with low educational levels obtained lower scores on reading comprehension. This is not different from the general population, where sex differences favoring girls and a relation with maternal education are known as important factors influencing intelligence, executive functioning and, therefore, school performance [16].

Environmental factors should be taken into consideration

Since the level of maternal education was associated with school-performance and cognitive development in older children, it is important to take (multiple) environmental factors into account when trying to predict outcome. Studies have reported that, for example, sensitive parenting has a protective effect on neurodevelopment [17, 18]. This suggests that adapting early interventions for preterm born children, in terms of supporting their parents and enhancing early responsive care, will aid their development. However, the effectiveness of these intervention programs has been debated, since treatment effects that were observed on motor and cognitive outcomes in infancy and toddlerhood, did not last into school-age [19, 20].

The importance of qualitative research

Behavioral outcomes in children born preterm have been described for many years [1, 21, 22]. Most studies assess behavior through a questionnaire, and distinguish between internalizing and externalizing behavioral traits. Internalizing behavior is characterized by processes within the self, such as feelings of anxiety, depression and somatization, where externalizing behavior comprises actions that are primarily directed towards others and/or the environment [23]. In current literature, the behavior of children born preterm is classified as ‘the preterm behavioral phenotype’, comprising an unique co-occurrence of, often focused inwards, behavioral symptoms [24]. The risk of internalizing behavior is that these children often go unnoticed, since they do not draw (negative) attention to themselves. An additional difficulty is that, even though children born very preterm are more likely to be diagnosed with a psychiatric disorder such as Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder, there are many children who do not meet the requirements of an official classification but still experience great difficulties with their learning abilities and behavior [24, 25]. These children are, for example, more easily distracted, have difficulties to follow instructions and are disorganized when it comes to their schoolwork.

Even though behavioral questionnaires can provide insight in the areas children born preterm tend to struggle with, it does not take the day-to-day personal experiences of caregivers into account. Considering what parents mentioned to be their main concern, there was a clear shift in worrying about reaching age-related milestones and physical health in toddlerhood, to themes aligning with social and emotional development at a later age. The importance of multiple informants when assessing behavioral difficulties was underlined by the observation that parents and teacher expressed their concerns in different themes, where teachers more often worried about their pupils social skills. It is possible that parents are less confronted with their child's interactions with other children.

In summary, the chapters in this thesis reinforce that children born preterm are at risk for long-term impairments. Being able to predict who is at risk, by neonatal neuroimaging or early assessment, remains difficult, especially in children who have milder forms of brain injury and/or experience milder difficulties at two years of age. Currently, most follow-up assessments use standardized outcome measures that might not show the full extent of a child's daily functioning. Additional measurements and/or the implementation of qualitative research can be of great additional value.

Study limitations

The original design of the PROUD-study was to investigate brain imaging findings in a prospective cohort of children born very preterm. Over time, follow-up outcomes at two and, later on, ten years of age were added. Because follow-up was not included in the original study design, there was no sample size or power analysis conducted to account for loss to follow-up at two and ten years of age during the recruitment of the cohort. Possibly due to the large interval, we had a fair percentage of loss to follow-up, as is the case with most longitudinal studies. We acknowledge that this may have influenced the generalizability of our findings.

Other factors possibly affecting the generalizability of our findings are the limited number of children with severe neonatal brain injury and the relatively high level of maternal education, with the majority of mothers attending higher vocational school or university. Studies focusing on more severely affected or extremely preterm born children and/or including different ratios in educational level might therefore find different outcomes.

Considering the assessment tools used, especially the Bayley Scale of Infant and Toddler Development, the 3rd edition seems to underestimate, especially mild, cognitive delays [26]. The use of a more sensitive tool might have a better predictive value for later functioning and improve the detection of impairments already at an early age.

The original study design did not include the purpose of qualitative research. Future studies investigating the perspective of caregivers should therefore be more extensive, by including for example a structured interview in a representative sample of parents and teachers. This generates opportunities to ask specific information in a wide range of topics, such as the impact of preterm birth on parents, not only right after birth, but also in the long-term.

Implications

In this section implications for policy, the educational system and future research will be further discussed.

Implications for policy

The current thesis shows that follow-up at two years of age on one hand is important to identify children who are already (severely) impaired in toddlerhood, since these children show little improvement in functioning over time. On the other hand, it is not a reliable assessment for later development in children who have a normal to mild abnormal outcome in toddlerhood. The rates of impairment start to rise during school-age, most likely due to the greater demands on abilities that are essential for learning at the start of primary school, such as attention regulation [27]. In the Netherlands, according to the guidelines of the national workgroup on neonatal follow-up (Landelijke Neonatale Follow-up; LNF) [28], follow-up assessments during primary school should be performed at age five and eight. However, in practice, this can unfortunately not always be achieved in all Dutch neonatal centers [29]. Currently, only children born below 30 weeks of gestation are included in long-term follow-up programs. In order to adequately monitor the development of all children affected by very preterm birth, investments should be made in for example staff trained to assess children born preterm, including pediatricians, neonatologist, physical therapists and child psychologists. This way, more preterm born children can be seen in outpatient departments by trained professionals, and hopefully, in the future, follow-up can be prolonged until at least adolescence. This will provide more information on long-term development of preterm born children.

When we aim to assess a child's day-to-day functioning, it should be considered to conduct a more extensive follow-up assessment during these time-points and include, aside from parental questionnaires, for example outcome measures regarding executive functioning (including working memory and cognitive flexibility) or school performance outcomes obtained in regular classrooms. Qualitative research highlights the importance of looking beyond the outcomes of behavioral questionnaires, since individual stories are unique and are hard to capture in quantitative research. So when truly grasping the influence of preterm birth on caregivers, asking them about their day-to-day experiences is important, in addition to standardized questionnaires classifying problem behavior.

The rate of impairment increased within our cohort from two to ten years of age, past the endpoint of the Dutch regular follow-up program. However, development continues and it is known that children born preterm are likely to experience difficulties in a range of areas during adolescence and adulthood, such as professional careers and forming romantic relationships [30].It should therefore be reconsidered to prolong follow-up into at least adolescence, since the quality of life can be greatly affected by difficulties within these areas. When it is not possible to include all preterm born children in the outpatient facilities of Dutch neonatal centers, investments should be made in facilities where parents can ask their questions to specialized professionals when they encounter difficulties. Knowledge on the functioning of preterm born children in this phase of life also creates possibilities for the development of targeted interventions, for example the enhancing of social skills or the support of a job coach.

Implications for the educational system

With the incidence of very preterm birth in the Netherlands affecting approximately 2500 infants each year, it is very likely for an elementary school teacher to have a preterm born child in the classroom. Teachers will not always be aware of their pupils' prematurity; parents may choose not to tell school to avoid stereotyping, or don't feel the need to inform their child's teacher. Knowing most impairments develop or become more visible during school age, it is important for school teachers to be familiar with the possible consequences of preterm birth and the effects on development and learning. For example, many children born preterm struggle with their working memory [31]. It might appear as though they are not paying attention, while in reality, their working memory is insufficient to cope with the demands of the task. Therefore, these children can be supported by allowing them to work in a quiet place or to give visual instruction in addition to verbal instructions.

A recent study showed that knowledge on long-term outcomes of premature birth is limited amongst teachers [27]. Information regarding preterm birth and how to support preterm born children should be accessible during their training. For teachers who already work at schools, additional trainings such as online modules (for example the in English available Preterm Birth Information for Educational Professionals [32]) can be provided. Primary school builds the foundation for future learning. Being able to attend and participate in primary school is therefore essential. Since the 1990s, there has been a political trend towards inclusive education in the Netherlands, indicating that children with special educational needs are included in mainstream primary schools with additional support [33]. Besides teachers, the support staff of mainstream primary schools should therefore also be taken into account when it comes to education on the effects of preterm birth, since they will most likely be the ones working with the children who are in need of additional support.

Implications for future research

The level of maternal education is an important predictor of functioning during school-age. A high level of maternal education is a protective factor in children with milder forms of brain injury, indicating that children of mothers with a low level of education are especially at risk. Future research should focus on the complex intertwine of multiple factors, including genes, perinatal, postnatal and sociodemographic factors, such as socioeconomic status and parenting style to understand the pathways of how parental education influences functioning. This may also provide guidance towards targeted interventions for specific groups of preterm born infants and their families.

Most of the children within our cohort had relatively mild forms of neonatal brain injury. It would be of interest to see whether the predictive value of neonatal MRI on long-term functioning differs in cohorts with extremely preterm born children (gestational age below 28 weeks) and in children with higher brain abnormality scores, since other studies suggest that moderate-severe brain injury is predictive of cognitive development and motor skills in toddlers and school-aged children [34, 35], whereas the predictive value seems limited in cohorts with less apparent brain injury [36].

Currently, neonatal MRI is not part of routine clinical care for preterm infants. With the results of this thesis in mind it is the question whether it should be, considering it is only beneficial for a select group of children. However, within a research setting, it might be useful to assess the effect of medical interventions and new daily practices at the NICU on brain development and brain injury to see whether the incidence of brain abnormalities changes over time in consecutive cohorts of preterm infants. Since long-term outcome can be very different compared to short-term outcome, it is important to consider outcome at multiple timepoints in order to adequately assess the effectiveness of, for example, neonatal interventions. Furthermore, additional, quantitative, MR imaging techniques (for example based on volumetric MRI and Diffusion Tensor Imaging) may be able to better predict future functioning, but currently these techniques are not commonly used in clinical practice.

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NEDERLANDSE SAMENVATTING

Vroeggeboorte kan zorgen voor (levenslange) uitdagingen in verschillende ontwikkeldomeinen. Het opvolgen van kinderen die te vroeg zijn geboren wordt echter vaak al na enkele jaren beëindigd. Dit is zorgelijk aangezien een deel van deze groep kinderen pas op latere leeftijd bepaalde moeilijkheden gaat ervaren. De volledige gevolgen van vroeggeboorte worden daardoor soms pas zichtbaar in de adolescentie, of bij volwassenheid.

De doelstelling van dit proefschrift was het in kaart brengen van een longitudinaal cohort van kinderen geboren voor de 32^e zwangerschapsweek, en het onderzoeken van associaties tussen neonatale risicofactoren en de uitkomsten in verschillende ontwikkelingsdomeinen op twee- en tienjarige leeftijd. Allereerst is er inzicht verkregen in het functioneren in verschillende ontwikkelingsdomeinen op twee- en tienjarige leeftijd. Hierbij is ook gekeken naar het beloop in ontwikkeling van individuele kinderen tussen deze twee tijdspunten. Het tweede doel was het onderzoeken van de relatie tussen de bevindingen op een MRI scan van de hersenen in de neonatale periode en zowel de vroege (peuterleeftijd) als de latere uitkomsten (basisschoolleeftijd). Om het functioneren van een kind in het dagelijks leven te beoordelen, wordt in onderzoek veelal gebruik gemaakt van standaard uitkomstmaten, waaronder intelligentiequotiënten. Omdat dit mogelijk geen goede maatstaf is voor de prestaties van een kind op school, was het derde doel het in kaart brengen hoe deze groep kinderen in de klas functioneert. Als vierde en laatste doel is inzicht verkregen in dagelijkse ervaringen van ouders en leerkrachten van te vroeg geboren kinderen, door ze te vragen naar hun belangrijkste zorg, en de beste eigenschap van hun kind in twee verschillende levensfasen (peuterleeftijd en basisschoolleeftijd).

Belangrijkste bevindingen

In Hoofdstuk 1 onderzochten we de mate en stabiliteit van beperkingen van te vroeg geboren kinderen in het neurologische, motorische, cognitieve en gedragsdomein op tweejarige leeftijd (gecorrigeerd voor prematuriteit) en tienjarige leeftijd. Elk kind werd per domein ingedeeld in één van de volgende categorieën: geen beperkingen, milde, of matig-ernstige beperkingen. Daarnaast werden de individuele uitkomsten op beide tijdspunten met elkaar vergeleken om te onderzoeken of en in welke mate de uitkomst voor een individueel kind tussen de leeftijd van twee en tien jaar verandert.

Wanneer een samengestelde score werd opgemaakt vanuit de uitkomsten binnen de vier domeinen, had op tienjarige leeftijd bijna een drievoud van de kinderen een matig-ernstige beperking ten opzichte van het aantal kinderen op tweejarige leeftijd. Daar stond een afname van het aantal kinderen met een milde beperking tegenover. Wanneer de domeinen echter apart van elkaar werden bekeken in plaats van tezamen, werden er door de jaren geen verschillen gezien in de verdeling van het aantal kinderen zonder beperking of met een milde of matig-ernstige beperking per domein. Hieruit zou geconcludeerd kunnen worden dat, op groepsniveau, de uitkomsten van kinderen binnen de verschillende domeinen relatief stabiel zijn. Maar, zoals te zien in de samengestelde score, zagen we aan het individuele beloop in ontwikkeling dat een groot aantal kinderen over de tijd heen veranderingen laat zien in hun functioneren binnen het neurologische, motorische en cognitieve domein (niet in het gedragsdomein). Wel was het zo dat binnen het motorische en cognitieve domein alle kinderen met een matig-ernstige beperking op tweejarige leeftijd ook een matig-ernstige beperking hadden op tienjarige leeftijd. Dit houdt in dat de individuele verschuivingen met name plaatsvonden bij kinderen zonder of met een milde beperking op tweejarige leeftijd. Dit benadrukt dat positieve uitkomsten in de peutertijd voorzichtig geïnterpreteerd moeten worden, en lange-termijn follow-up noodzakelijk is.

De individuele veranderingen in functioneren, zoals beschreven in Hoofdstuk 1, houden mogelijk ook in dat de voorspellende waarde van neonatale prognostische parameters met de jaren verandert. De afgelopen decennia heeft het gebruik van MRI scans van de neonatale hersenen veel aandacht gekregen als mogelijke prognostische marker. In Hoofdstuk 2 zijn daarom de associaties tussen neonatale hersenschade, zoals te zien op een neonatale MRI, en cognitieve, motorische en gedragsuitkomsten op twee- en tienjarige leeftijd onderzocht. Alle kinderen binnen het cohort ondergingen een neonatale MRI rondom hun uitgerekende datum. Met het Kidokoro scoringssysteem werd neonatale hersenschade, in de vorm van schade in de witte stof, corticale en diepe grijze stof en het cerebellum beoordeeld. De cognitieve, motorische en gedragsuitkomsten werden verkregen gedurende de follow-up bezoeken op tweejarige leeftijd (gecorrigeerd voor prematuriteit) en tienjarige leeftijd.

De globale score voor hersenafwijkingen, als algemene maat voor neonatale hersenschade, was geassocieerd met cognitie, motoriek en internaliserende gedragsproblemen op de leeftijd van twee jaar. Deze associaties bleven staan na correctie voor perinatale factoren en het opleidingsniveau van de moeder. De associaties met cognitie (zowel totaal, verbaal als performaal IQ) en gedrag verdwenen echter op tienjarige leeftijd. Op die leeftijd zagen we wel een veel groter effect van het opleidingsniveau van de moeder: kinderen van moeders met een laag opleidingsniveau presteerden als groep op zowel het verbaal als performaal IQ onder de gemiddelde scores van kinderen van moeders met een hoog opleidingsniveau (respectievelijk 18 en 11 punten). Het effect van het opleidingsniveau van de moeder op IQ was het sterkst bij kinderen met een milde vorm van hersenschade; voor kinderen met matig-ernstige hersenschade bleef neonatale MRI een onafhankelijke voorspeller voor cognitie op tienjarige leeftijd.

Het valt te betwijfelen of de gestandaardiseerde uitkomstmaten die gebruikt worden tijdens follow-up onderzoeken het dagelijks functioneren van een kind goed weergeven. Wanneer een kind ouder wordt, worden er op school bijvoorbeeld steeds meer eisen gesteld aan het kunnen reguleren van gedrag om mee te kunnen doen aan de leeractiviteiten. De schoolse vaardigheden van een kind worden voor wetenschappelijk onderzoek over het algemeen beoordeeld via gestandaardiseerde testen. Deze afnames worden vaak gedaan door een psycholoog, in een klinisch gecontroleerde één-op-één omgeving met weinig afleiding. Aangezien kinderen die te vroeg geboren zijn vaak cognitieve problemen hebben en ook kwetsbaarder zijn voor het ontwikkelen van gedragsproblemen, is in Hoofdstuk 3 onderzocht hoe de kinderen binnen het cohort op school functioneren, met alle afleiding die een klas van een basisschool biedt.

Allereerst zijn de gegevens met betrekking tot de speciale onderwijsbehoeften van de kinderen in het cohort vergeleken met het Nederlands gemiddelde. Hieruit bleek dat meer kinderen binnen het cohort een schooljaar doubleerden en dat ze vaker waren ingeschreven bij het speciaal basisonderwijs. Maar ook met deze vormen van onderwijsondersteuning presteerde deze groep in vergelijking met hun leeftijdsgenoten op een lager niveau op het gebied van begrijpend lezen, spelling en met name rekenen aan het eind van groep 4. Dit is zorgelijk, aangezien kinderen die te vroeg zijn geboren meestal geen inhaalslag meer maken op het gebied van schoolprestaties ten opzichte van hun op tijd geboren klasgenoten. Binnen de onderzoeksgroep zagen we vaker minder goede schoolprestaties bij jongens, kinderen met witte stof schade in de hersenen en kinderen waarvan de moeder een lager opleidingsniveau had.

Om te onderzoeken hoe ouders en leerkrachten de ontwikkeling van een te vroeg geboren kind over de jaren heen beleven, is in Hoofdstuk 4 gekeken naar hun dagelijkse ervaringen. Zowel de kwantitatieve als de kwalitatieve uitkomsten van een gedragsvragenlijst werden beoordeeld. Deze kwalitatieve uitkomsten werden gebaseerd op antwoorden van ouders en leerkrachten op twee open vragen die gericht waren op hun grootste zorg en dat waar zij het meest tevreden over zijn in de ontwikkeling van een te vroeg geboren kind.

De kwantitatieve uitkomsten van de gedragsvragenlijsten, ingevuld door ouders op tweejarige leeftijd (gecorrigeerd voor prematuriteit) en tienjarige leeftijd, lieten een grote toename zien van kinderen met klinische internaliserende gedragsproblemen tussen deze twee tijdspunten. Met betrekking tot externaliserend gedrag bleven de aantallen kinderen zonder gedragsproblemen en met gedragsproblemen in het grensgebied of in de klinische range tussen twee- en tienjarige leeftijd nagenoeg gelijk. In vergelijking met ouders rapporteerden leerkrachten veel minder vaak problemen in het grensgebied of in de klinische range, zowel voor internaliserend als externaliserend gedrag.

Kwalitatief was de grootste zorg van ouders gedurende de peutertijd gelijkelijk verdeeld over drie clusters: Ontwikkelingsmijlpalen (het leeftijdsadequaat kunnen behalen van mijlpalen), Ontwikkeling in Relatie tot Zichzelf en Anderen (voornamelijk peutergedrag) en Lichamelijke Ontwikkeling (waaronder de lichamelijke gezondheid van het kind). Op tienjarige leeftijd rapporteerde de meerderheid van de ouders zorgen in het cluster Ontwikkeling in Relatie tot Zichzelf en Anderen. Hieronder vallen onder andere de emotionele en sociale ontwikkeling van het kind, gedrag, temperament, persoonlijkheidsstijl en mindset. Vergelijkbaar met ouders rapporteerden ook leerkrachten met name zorgen binnen het cluster Ontwikkeling in Relatie tot Zichzelf en Anderen, al verschilden de onderliggende thema’s. Leerkrachten maakten zich bijvoorbeeld meer zorgen over de sociale ontwikkeling van hun leerling, terwijl ouders zich meer zorgen maakten om de emotionele ontwikkeling.

Met betrekking tot de positieve aspecten van de kinderen rapporteerden ouders het meeste binnen het cluster Ontwikkeling in Relatie tot Zichzelf en Anderen op beide tijdspunten. Zo rapporteerden zij onder meer dat hun kind vaak vrolijk en blij was op tweejarige leeftijd, terwijl ze meer complexe karaktereigenschappen omschreven op latere leeftijd, zoals het doorzettingsvermogen van hun kind en onafhankelijkheid en nieuwsgierigheid. Leerkrachten rapporteerden ook grotendeels in hetzelfde cluster, waarbij het merendeel de positieve karaktereigenschappen van de leerling noemden, waaronder hun leergierigheid en hulpvaardigheid.

Discussie en aanbevelingen

Op basis van de bevindingen in dit proefschrift kunnen er een aantal conclusies getrokken worden die implicaties hebben voor het follow-up onderzoek bij te vroeg geboren kinderen.

Positieve ontwikkelingsuitkomsten in de peutertijd bieden geen garantie

Allereerst is gebleken dat de gemeten ontwikkelingsuitkomsten op jonge leeftijd slechts in beperkte mate voorspellen hoe kinderen op tienjarige leeftijd functioneren. Vooral bij de kinderen waarbij op tweejarige leeftijd geen of slechts een milde beperking werd vastgesteld kunnen nog veranderingen optreden. Het is daarom belangrijk om alle kinderen langer te volgen in hun ontwikkeling, en niet uitsluitend de kinderen die op tweejarige leeftijd ernstige problemen vertonen.

De rol van voorspellende factoren

Dat er bij individuele kinderen verschuivingen optreden in de gemeten ontwikkelingsuitkomsten tussen twee en tien jaar kan er toe leiden dat bepaalde prognostische factoren een andere voorspellende waarde kunnen hebben op de verschillende tijdspunten in de ontwikkeling van een kind. Voor de bevindingen op de neonatale MRI scan gold dat deze geassocieerd waren met motorische, cognitieve en gedragsmatige uitkomsten op jonge leeftijd. Echter op de langere termijn hielden deze associaties (met name bij de kinderen met mildere MRI afwijkingen) geen stand. Gezien de beperkte voorspellende waarde moet neonatale MRI daarom terughoudend worden ingezet, bijvoorbeeld alleen bij kinderen met verwachte (ernstige) hersenschade.

Daar waar een neonatale MRI slechts een beperkte associatie laat zien met functioneren op latere leeftijd, is er wel een grote rol weggelegd voor het opleidingsniveau van moeder in zowel de cognitieve ontwikkeling als op het gebied van schoolresultaten van kinderen op basisschoolleeftijd. Als we later functioneren willen voorspellen, is het daarom van belang om omgevingsfactoren mee te nemen. Onderzoek laat echter tot nu toe zien dat de effecten van interventies op omgevingsfactoren, waaronder de sensitiviteit van ouders, beperkt zijn op de lange termijn.

IQ alleen is te beperkt als maatstaf voor cognitief functioneren

Een derde belangrijke bevinding is dat er tijdens follow-up onderzoeken breder gekeken moet worden dan enkel naar IQ als maatstaf voor cognitief functioneren. Binnen het cohort hadden de meeste kinderen een intelligentiescore in het gemiddelde gebied. Desondanks had deze groep kinderen vaker moeilijkheden op het gebied van begrijpend lezen, spelling en rekenen ten opzichte van hun leeftijdsgenoten. Dit houdt in dat een intelligentiescore alleen niet voorspellend is voor het wel of niet behalen van goede schoolresultaten.

Het voornaamste doel van follow-up onderzoek is het inzichtelijk maken van het dagelijks functioneren van een kind zodat waar nodig extra ondersteuning geboden kan worden. Aangezien kinderen veel tijd doorbrengen op school, kan het meenemen van hun schoolprestaties een belangrijke aanvulling zijn op de gestandaardiseerde testen die tijdens de follow-up worden afgenomen. Daarnaast is er de laatste decennia steeds meer aandacht gekomen voor de rol van executief functioneren. Executief functioneren is een complex systeem van neurocognitieve functies, waaronder werkgeheugen en impulsbeheersing. Kinderen die te vroeg zijn geboren ervaren vaker problemen op het gebied van executief functioneren. Dit kan weer gevolgen hebben voor het kunnen voldoen aan de eisen die in een klaslokaal worden gesteld, zowel op het gebied van gedragsregulatie, als bij specifieke vakken zoals rekenen. We moeten ons er daarom van bewust zijn dat intelligentie alleen onvoldoende is om een goed beeld te schetsen van het dagelijks functioneren van een kind.

Het belang van kwalitatief onderzoek

Naast dat kinderen die te vroeg zijn geboren vaker gediagnosticeerd worden met bijvoorbeeld ADHD of een autisme spectrum stoornis, is er ook een grote groep kinderen die niet voldoen aan de vereisten van een officiële diagnose, maar wel veel moeite hebben met onder meer hun concentratie of het opvolgen van instructies. Hoewel vragenlijsten op het gebied van gedrag inzicht geven in de gebieden waar te vroeg geboren kinderen mee worstelen, houden ze geen rekening met de dagelijkse persoonlijke ervaringen van de verzorgers van deze kinderen. Kwalitatief onderzoek geeft woorden aan deze ervaringen.

Aanbevelingen voor beleid

Investeer in het verlengen van de follow-up naar minimaal de adolescentie en in goed opgeleid personeel om deze groep kinderen in kaart te brengen.

Op dit moment wordt in de richtlijn Landelijke Neonatale Follow-up geadviseerd follow-up in ieder geval tot achtjarige leeftijd door te laten lopen. Aangezien kinderen ook op latere leeftijd tegen beperkingen aan kunnen lopen, is het van belang dat zij langer in hun ontwikkeling gevolgd worden door bijvoorbeeld artsen, fysiotherapeuten en psychologen. Enerzijds helpt dit de gevolgen van vroeggeboorte beter begrijpen, anderzijds geeft het aanknopingspunten om deze kinderen gerichter te begeleiden, zoals het vergroten van sociale vaardigheden of ondersteuning bieden bij het vinden van een baan. Daarnaast zou de follow-up uitgebreid moeten worden met aanvullende metingen en/of kwalitatief onderzoek, om een goed beeld te kunnen vormen van hun dagelijkse functioneren.

Aanbevelingen voor het onderwijs

Kennis over de langetermijngevolgen van prematuriteit onder onderwijspersoneel dient vergroot te worden.

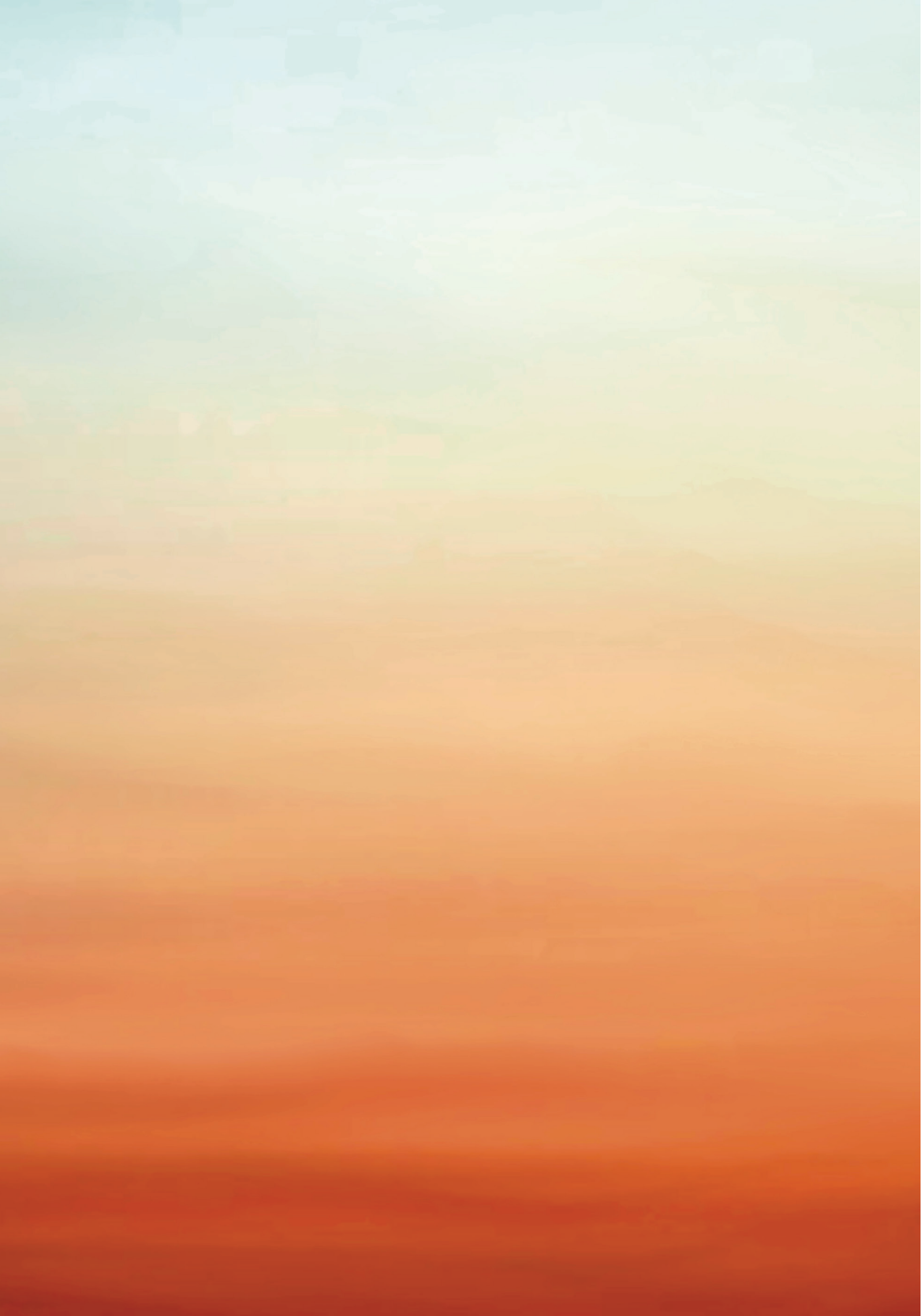
Aangezien er ieder jaar ongeveer 2500 kinderen te vroeg worden geboren, is het zeer waarschijnlijk dat leerkrachten in hun loopbaan met deze kinderen te maken krijgen in hun klas. Het is daarom belangrijk dat leerkrachten (en ondersteunend personeel op scholen) kennis hebben van de mogelijke gevolgen van vroeggeboorte en hoe ze deze in de klas kunnen herkennen. In de basisschoolperiode wordt de basis gelegd voor kinderen om te kunnen leren en hun vaardigheden steeds verder uit te breiden. Het goed kunnen begeleiden van kinderen die te vroeg zijn geboren in deze periode is daarom van groot belang.

Aanbeveling voor toekomstig onderzoek

Onderzoek naar de rol van omgevingsfactoren en hersenschade dient meer op de voorgrond te staan.

Gezien de complexe rol die het opleidingsniveau van moeder speelt bij het kunnen voorspellen van functioneren, dient toekomstig onderzoek zich te richten op het samenspel van verschillende factoren, waaronder perinatale, postnatale en sociaaldemografische factoren. Dit kan een basis vormen voor interventies gericht op specifieke groepen van te vroeg geboren kinderen en hun gezinnen.

Aangezien veel kinderen binnen dit cohort relatief milde vormen van hersenschade vertoonden, zou in toekomstig onderzoek vooral ook aandacht moeten zijn voor cohorten van kinderen met ernstigere vormen van hersenschade en de voorspellende waarde van de MRI op het functioneren van deze kinderen. Daarnaast zijn zouden additionele MRI technieken mogelijk beter in staat zijn om toekomstig functioneren te voorspellen. Deze worden in de klinische praktijk echter vaak (nog) niet gebruikt.



VIII

PART EIGHT

APPENDICES

Abbreviations
List of publications
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ABBREVIATIONS

ADHD: attention-deficit hyperactivity disorder
BPD: bronchopulmonary dysplasia
BSID-III: Bayley Scales of Infant and Toddler Development, third edition
BW: birth weight
CBCL: Child Behavior Checklist
CI: confidence interval
CP: cerebral palsy
FGR: fetal growth restriction
GA: gestational age
GBAS: global brain abnormality score
GMFCS: Gross Motor Function Classification Score
IQ: intelligence quotient
IQR: interquartile range
IVH: intraventricular hemorrhage
LUMC: Leiden University Medical Center
M-ABC-II: Movement Assessment Battery for Children, second edition
MND: minor neurological dysfunction
MRI: magnetic resonance imaging
NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
PIQ: performance intelligence quotient
PMA: postmenstrual Age
PROUD: PReterm brain injury, long-term OUtcome and brain Development study
SD: standard deviation
SGA: small for gestational age
TEA: term equivalent age
TRF: teacher report form
VIQ: verbal intelligence quotient
WISC: Wechsler Intelligence Scale for Children

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Pediatr Res. 2019 SEP;86:17-17.

CURRICULUM VITAE

Lisette Jansen werd in 1989 in Zoetermeer geboren. Na het behalen van haar eindexamen aan het Alfrink College in 2008, begon zij aan de bachelor rechtsgeleerdheid aan de Universiteit van Amsterdam. In 2011 startte zij daarnaast met de bachelor psychologie aan de Universiteit Leiden, waar zij ook aan het honours programma voor excellente studenten deelnam. Beide bacheloropleidingen rondde zij af in 2014, waarna Lisette startte met de master Child and Adolescent Psychology aan de Universiteit Leiden. In november 2015 studeerde zij af. Haar loopbaan als psycholoog begon in het angst- en stemmingsstoornissenteam van LUMC-Curium. Van mei 2016 tot september 2017 combineerde zij deze functie met een baan als psycholoog op de afdeling Medische Psychologie van het Willem-Alexander Kinderziekenhuis (LUMC). Daarna maakte zij de volledige overstap naar het LUMC. In mei 2018 begon zij hier aan haar promotietraject, onder begeleiding van prof. dr. Robert Vermeiren, dr. Cacha Peeters-Scholte en dr. Sylke Steggerda. Tot februari 2022 heeft zij het promotietraject gecombineerd met klinische uren op de afdeling Medische Psychologie. Sinds maart 2022 werkt Lisette als psycholoog in het Infant Mental Health team van Opvoedpoli Den Haag.

Lisette woont samen met Xander de Rond. Samen hebben zij twee kinderen, Bren (2018) en Loïs (2021).

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Na bijna vijf jaar (deeltijd) onderzoeker te zijn geweest, schrijf ik met dit dankwoord de laatste pagina's van 'mijn boekje'. Een boekje waarvan ik nog niet helemaal kan geloven dat het nu daadwerkelijk af is. En er niet geweest was zonder de inzet, ondersteuning en het geloof in het slagen van dit project door velen.

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Mijn twee paranimfen, Jeanine en Rianne.

Jeanine, als jij vijf jaar geleden niet aan mij had gevraagd ‘Goh, is het niets voor jou om eens een artikel te schrijven?’, was ik nooit aan deze reis begonnen. Je bent onmisbaar geweest bij het tot een goed einde brengen van dit traject. Ooit begonnen als collega's, inmiddels als vriendinnen; ik bewonder je humor, betrouwbaarheid en je enthousiasme. Het ontbreekt je nooit aan goede ideeën, je bent vrijwel overal voor in, en als ik weer eens twijfelde over wat dan ook, wist je deze twijfel vakkundig uit te wissen.

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