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# EXTREMELY PRETERM BIRTH: BRAIN IMAGING AND OUTCOME AT EARLY SCHOOL-AGE

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# EXTREMELY PRETERM BIRTH:
# BRAIN IMAGING AND OUTCOME AT EARLY SCHOOL AGE

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*To my beloved children Rasmus, Julia and Alexander*

# ABSTRACT

There has been a dramatic increase in the survival of extremely preterm children over the last decades, and the awareness of the consequences of extremely preterm birth on the developing brain is increasing. This thesis aimed at investigating the neurodevelopmental outcome of extremely preterm children at early school-age, focusing on visual-motor integration and motor impairments, and their relation to findings on early magnetic resonance imaging of the brain.

We used a population-based cohort study design, including all 6.5 year old children that had been born before 27 gestational weeks during three years in Stockholm for paper I and II, and in the whole of Sweden for Paper III and Paper IV- the EXPRESS (Extremely Preterm infants in Sweden Study) cohort.

In paper I we found that the preterm children with and without isolated subtle white matter changes, present on magnetic resonance imaging of the brain at term age in about half of extremely preterm children, was not related to visual-motor integration performance, motor function or other neurodevelopment at 6.5 years.

In paper II we found correlations between the extremely preterm children's neonatal brain volumes in the precentral gyrus, the cerebellum and the brainstem - areas known to be involved in visual-motor integration and fine motor skills – and visual-motor integration performance and/or fine motor skills at 6.5 years of age.

In paper III we found that 55% of the preterm children had poor visual-motor integration at 6.5 years compared to term-born controls, 78% among children born at 22-23 weeks, and that visual-motor integration scores were associated with cognitive function and fine motor skills.

In paper IV we found that motor impairments, defined as developmental coordination disorder, was common and present in 37.1% of apparently healthy extremely preterm children and in 5.5% of term-born controls (adjusted odds ratio 7.92, 99% confidence interval, 3.69-17.20) at 6.5 years. Developmental coordination disorder was associated with various behavioral problems and lower cognition. In half of the children the parents had not noticed the child´s motor problems.

In summary, this thesis demonstrated that the extremely preterm children had affected visual-motor integration and motor function, associated with several other problems, at 6.5 years. Also, extremely preterm children with and without isolated subtle white matter changes had similar neurodevelopment at 6.5 years of age, and neonatal brain volumes correlated with visual-motor integration and fine motor skills scores at 6.5 years, indicating that the brain growth is affected already at the time of expected birth. The thesis provides information that can be used when counselling parents about subtle findings on magnetic resonance imaging, and supports the importance of structured long-term follow-up of extremely preterm children.

# LIST OF SCIENTIFIC PAPERS

I. Lina Broström*, **Jenny Bolk***, Nelly Padilla, Beatrice Skiöld, Eva Eklöf, Gustaf Mårtensson, Brigitte Vollmer, Ulrika Ådén.
Clinical Implications of Diffuse Excessive High Signal Intensity (DEHSI) on Neonatal MRI in School Age Children Born Extremely Preterm.
*PlosOne* 2016 Feb 17, ISSN:1932-6203 Volume:11 Issue:2 Pages:e0149578

*These authors contributed equally to this work
.

II. **Jenny Bolk**, Nelly Padilla, Lea Forsman, Lina Broström, Kerstin Hellgren, Ulrika Åden.
Visual-motor integration and fine motor skills at 6.5 years of age and associations with neonatal brain volumes in children born extremely preterm in Sweden: population-based cohort study.
*BMJ Open* 2018 Feb 17;8(2):e020478. doi: 10.1136.

III. **Jenny Bolk**, Ylva Fredriksson Kaul, Lena Hellström-Westas, Karin Stjernqvist, Nelly Padilla, Fredrik Serenius, Kerstin Hellgren*, Ulrika Åden*
*These authors contributed equally to this work
National population-based cohort study found that visual-motor integration was commonly affected in extremely preterm born children at 6.5 years.
*Acta Paediatrica* 2018 May;107(5):831-837. doi: 10.1111/apa.14231. Epub 2018 Feb 8.

IV. **Jenny Bolk**, Aijaz Farooqi, Maria Hafström, Ulrika Åden, Fredrik Serenius.
Developmental Coordination Disorder at 6.5 years in apparently healthy children born extremely preterm.
*Manuscript.*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| Brown ADD | Brown Attention-Deficit Disorder Scales |
| DCD | Developmental Coordination Disorder |
| DEHSI | Diffuse Excessive High Signal Intensity |
| EXPRESS | Extremely Preterm infants in Sweden Study |
| FSIQ | Full-scale intelligence quotient |
| FTF | Five to Fifteen questionnaire |
| MABC-2 | Movement-Assessment Battery for Children -2 |
| MRI | Magnetic Resonance Imaging |
| SDQ | Strengths and Difficulties Questionnaire |
| VMI | Visual-Motor Integration |
| WISC-IV | Wechsler Intelligence Scale for Children-IV |

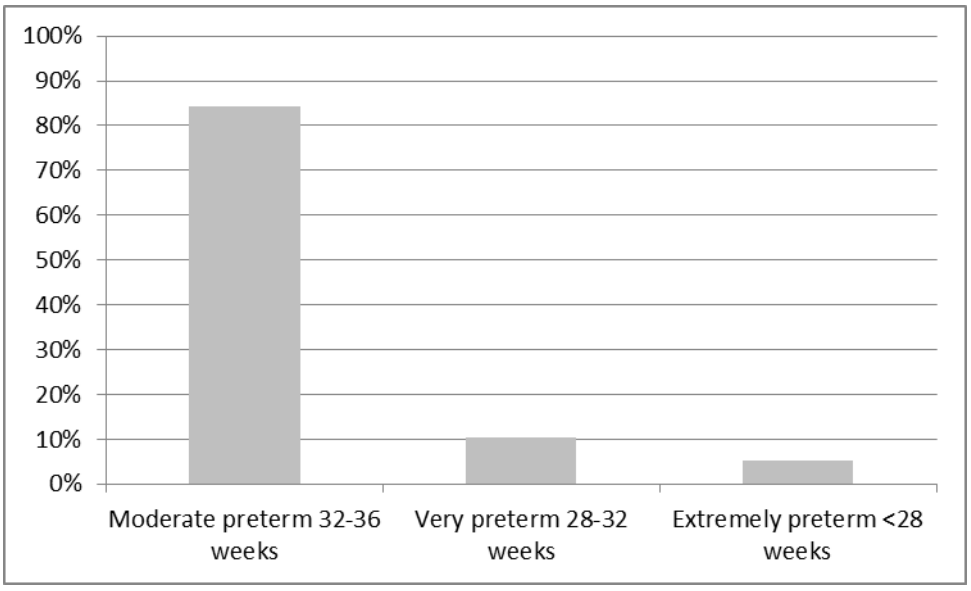
# 1 BACKGROUND

## 1.1 PRETERM BIRTH

### 1.1.1 Definition and prevalence

Preterm birth is a huge global problem with around 15 million babies being born preterm around the world each year [1]. It is also one of the most common causes of infant mortality in the world today [2]. Preterm birth is usually divided according to completed gestational weeks into [1]:

| | | |
|---|---|---|
| Moderate preterm birth | 32-36 | gestational weeks |
| Very preterm birth | 28-31 | gestational weeks |
| Extremely preterm birth | < 28 | gestational weeks |

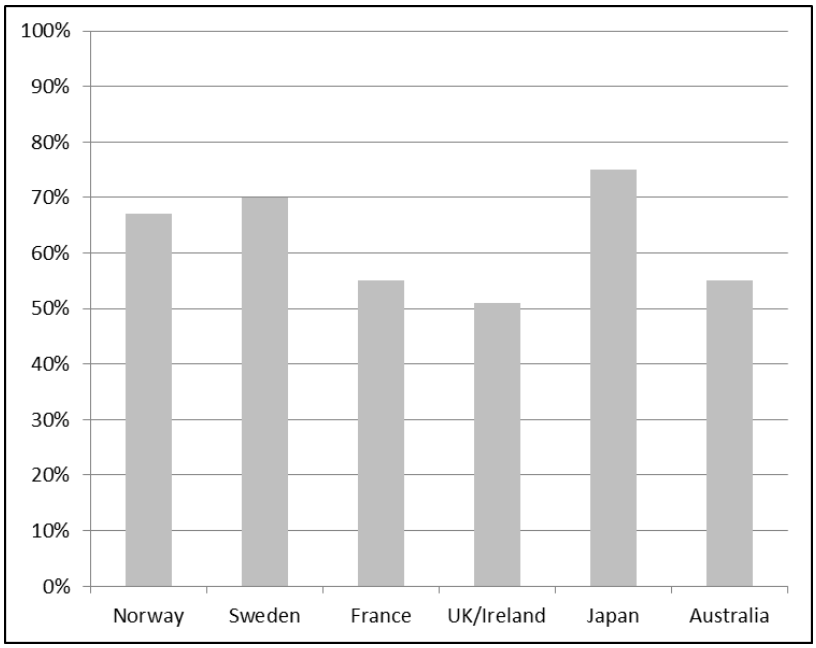



*Percentage of all preterm births* [1]
*- the majority of preterm births are moderate preterm births.*

This thesis focuses on extremely preterm children born before 27 gestational weeks. The prevalence of preterm birth before 27 gestational weeks has been reported to be 2.3 per 1000 live births in the Swedish Extremely Preterm Infants in Sweden study (EXPRESS) cohort [3] and in the Norwegian Extreme Prematurity Study-2 (NEPS-2) [4].

### 1.1.2 Survival rates

The survival rates of children born extremely preterm has increased dramatically in the developed world during the last decades [5,6], also of the most immature children born in week 22-24 [7]. The survival rate is depending on how proactive the initial care is [8,9].




*Survival rates of children born <27 gestational week in different countries [3,4,10-13]*
*(Japan represents children born <26 gestational weeks)*

In the Swedish EXPRESS cohort the one-year survival of live-born infants born before 27 weeks was 70% [3], and in the Norwegian NEPS-2 study the survival rate was 67% [4]. The French EPIPAGE-2, the UK/Irish EPICURE-2 and the Australian Victorian Infant Collaborative Study Group studies showed lower numbers with 55% [10] , 51% [6] and 55% [13], respectively, of children born before 27 weeks. In contrast, the Japanese Neonatal Research Network in Japan, including infants born before 26 weeks, reported a 75% survival to discharge [14]. The Japanese study also reported the highest proportion of survivors among the most immature children: 36% at 22 weeks and 63% at 23 weeks [14].

Comparisons of survival rates between different countries have shown that the largest variations in survival rates are among the most immature age groups [12].

### 1.1.3 Major neonatal morbidities

Major morbidities affect more than half of extremely preterm infants during their neonatal period [3,4], and contribute to the mortality and non-optimal development of these immature children. Examples of common and important neonatal morbidities are prolonged mechanical ventilation, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, septicemia, circulatory disturbances, patent ductus arteriosus and intraventricular hemorrhages.

Extremely preterm children often suffer from several of these morbidities during the neonatal period, and it is therefore often difficult to point out any specific morbidity as the main component affecting the brain. The children with the lowest gestational ages and birth weights are most at risk for these neonatal morbidities which makes it difficult to disentangle between specific neonatal morbidities and adverse outcomes [3,4].

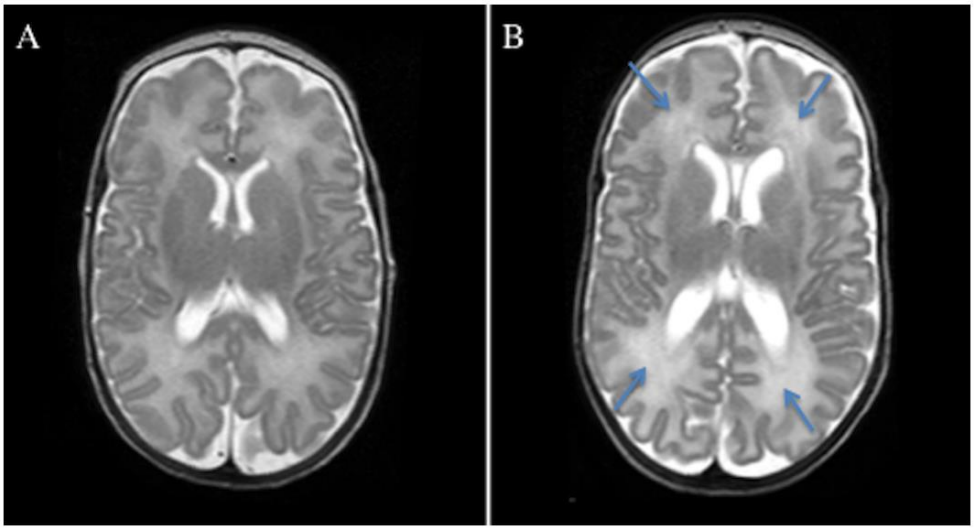
### 1.1.4 The vulnerable extremely preterm brain

The extremely preterm infant is born during a vulnerable phase of brain development [15] and is at risk for a suboptimal brain development, caused both by lesions that destroy the brain parenchyma and from disturbances of the normal maturation of the brain [16]. Ischemic injuries, systemic inflammation and infections all contribute to the altered brain development frequently reported in preterm infants [17].

Destruction of the brain parenchyma can be caused by a number of lesions, intraventricular hemorrhage being one of the more common. Severe intraventricular hemorrhage (grade 3-4), affecting around 10-15% of extremely preterm children [3,4,18], is associated with cerebral palsy and a poor neurodevelopmental outcome [19,20]. The germinal matrix, a structure surrounding the ventricles in the brain in newborn extremely preterm children, is a highly vasculated area with little support from surrounding support tissues and therefore prone to bleedings which can spill out into the brain parenchyma [16].
Another important cause for brain injury is cystic periventricular leukomalacia - an injury to the white matter which is highly associated with cerebral palsy; fortunately, the incidence of cystic periventricular leukomalacia has decreased substantially in the last decades [21]. Other destructive brain lesions include cerebellar hemorrhages.

Brain injuries can result in for example poor myelination of the brain or loss of important brain cells like pre-oligodendrocytes [17]. Since any injuries to the brain in the first days or weeks of a preterm baby´s life occur during a time of rapid brain growth and development, impact on the child´s future development can be the result also from minor lesions.

Apart from major brain lesions, there is also a high prevalence of more diffuse white and grey matter alterations in the brain of extremely preterm infants [22] . Diffuse excessive high signal intensity (DEHSI) [23] can be seen in the white matter around term equivalent age in a majority of extremely preterm infants, with a reported prevalence of up to 80% [24]. DEHSI can occur together with moderate/severe white matter abnormalities but can also be an isolated finding on MRI of the brain. There have been different speculations on what DEHSI might stand for. Some have argued that DEHSI indicates diffuse white matter injury [25,26]. Others argue that DEHSI is a sign of delayed maturation of the white matter, which is supported by histological findings pointing to DEHSI representing remnants of the subplate [27], a structure in the brain that disappears with increasing maturity of the brain.




*A=Normal MRI of the brain.*
*B= Diffuse Excessive Signal Intensity (DEHSI) (indicated by the arrows).*

Several studies have also demonstrated alterations in regional brain volumes, indicating an altered brain growth in children born extremely preterm, which has also been linked to a poor neurodevelopmental outcome [28-33]. Iatrogenic factors, such as the administration of postnatal steroids, have been shown to affect both brain growth [30] and outcome [34] adversely. Nutritional intake during the first neonatal period has also been reported to affect brain growth in extremely preterm children [35].

Many studies have shown that extremely preterm boys are more vulnerable both to brain lesions, smaller brain volumes [33,36], lower survival rates [37], more morbidities and a worse neurodevelopmental outcome [33,36,38], compared to extremely preterm girls. Therefore, studies on extremely preterm infants often have to be adjusted for sex.

## 1.2 OUTCOME AFTER EXTREMELY PRETERM BIRTH

### 1.2.1 Neurodevelopmental outcome

A large proportion of extremely preterm children risk adverse neurodevelopmental outcomes [39-44]. Comparisons of different cohorts and studies are not always straightforward, since there are differences in the definitions of disabilities, definitions of extremely preterm infants – for example, some studies include extremely low birthweight infants who are not necessarily born extremely preterm - and in the assessment tools used [45].

Since there are promising results from studies on early interventions to improve neurodevelopmental outcome in extremely preterm infants [46], early identification of children at high risk of neurodevelopmental impairments is important.

#### *1.2.1.1 Major disabilities*

There has been great concern that the rate of major disabilities would increase when the survival of extremely preterm infants rise, and early studies indicated that the dramatically increased survival of these infants in the 1990´s also came with a higher rate of major disabilities [47]. However, more recent studies have seen a decrease in major disabilities despite a continuously increased survival [7,21,48 43]. The major disabilities in the EXPRESS study are shown in the table below, and similar rates have been reported from other cohorts [41,43,49-51].

| | EXPRESS study |
|---|---|
| Cerebral palsy | 10.5 % |
| Blindness | 2.1 % |
| Hearing impairment not corrected with hearing aid | 2.1 % |
| Moderate-severe cognitive impairment | 30 % |

*The rate of major disabilities in the EXPRESS cohort [39,52]*

A meta-analysis of neurodevelopmental outcomes in extremely preterm children aged 4-8 years concluded that all extremely preterm children are at risk for adverse neurodevelopmental outcome and that the risk increases with decreasing gestational age at birth [50] . The moderate/severe disabilities in the EXPRESS study had increased compared to the prevalence at 2.5 years [39], emphasizing the need of long-term follow-up of extremely preterm born children.

#### *1.2.1.2 Cognitive function*

Many studies have investigated the cognitive outcome at toddler age. Different versions of tests administered make comparisons during different time periods difficult; for example, the sensitivity of the most commonly used test in toddler age, the Bayley scales, has decreased between the second and third edition [53,54]. Using local norms can thus be of value.

Meta-analyses of school-age children born preterm have shown 7.6-11.9 points lower mean full-scale (FS) IQ points, compared with term-born children [55,56 57]. Studies on exclusively extremely preterm children show even larger differences with 14 points lower FSIQ for children born before 27-28 weeks gestation [39,55] and 20 points lower FSIQ for children born before 26 weeks gestation [58]. A recent meta-analysis including 7752 extremely or very preterm children and 5155 controls, 5 years of age or older, reported a 0.86-SD lower full-scale IQ compared with controls [59]. The meta-analysis concluded that the included studies had heterogeneous results and that the cognitive outcome had not improved between 1990 and 2008 [59].

#### *1.2.1.3 Executive functions*

Executive functions involve a number of interrelated cognitive processes that support the ability to be flexible, and to enable adequate behavior in different situations. Abilities that are often included in executive functions are working memory, planning, cognitive flexibility, inhibition and verbal fluency. Meta-analyses have shown a 0.2 to 0.6 SD lower executive function in very preterm children [60,61], and an Australian study of adolescents born before 28 weeks gestation showed a 0.2-0.7 SD reduction [62]. Also, there are indications that the prevalence of executive function impairments is increasing [63].

#### *1.2.1.4 Behavior*

Extremely preterm children are consistently reported to have more behavioral problems compared to peers [64], including attentional problems [65,66], problems with peer relations [64], higher incidence of attention deficit/hyperactivity disorder (ADHD) [64,66-68], autism spectrum disorder [66,67,69,70] and emotional disorders [66]. In contrast, extremely preterm birth is not associated with a higher risk of criminality or drug abuse [67].

#### *1.2.1.5 Motor function and developmental coordination disorder*

Impaired motor function has been reported in several studies of extremely preterm children [71-73]. There are also reports showing that motor impairments are associated with other neurodevelopmental deficits [74].

Developmental coordination disorder (DCD) is one form of motor impairment that has been reported to be more prevalent in extremely preterm children [75,76]. Reported prevalence rates in preterm children have varied between less than 10% up to more than 50% [76-79] . The varying prevalence rates could possibly be explained by different definitions of DCD and heterogeneity of populations studied.

A clinical diagnosis of DCD includes motor impairment which affects daily life or academic achievements, and can be made according to the Diagnostic and Statistical Manual of mental disorders, fifth edition (DSM-V) (American Psychiatric Association 2013 Washington, DC), requiring four criteria:

1. Motor coordination performance is below than expected for age and intelligence of the child and the opportunities for skill learning, and are manifested as clumsiness and slowness/inaccuracy of performing motor tasks.
2. The motor difficulties interfere with daily living and academic performance.
3. The motor difficulties start in early childhood.
4. The motor difficulties cannot be explained by intellectual disability, visual impairment or a neurologic condition such as cerebral palsy.

In research settings DCD has often been defined as a significant motor impairment in the absence of cerebral palsy and intellectual disability. DCD is associated with several comorbidities such as inattention [80], learning difficulties and problems with psychosocial adjustment [81], lower cognitive function [82] and mental health problems [80,83].

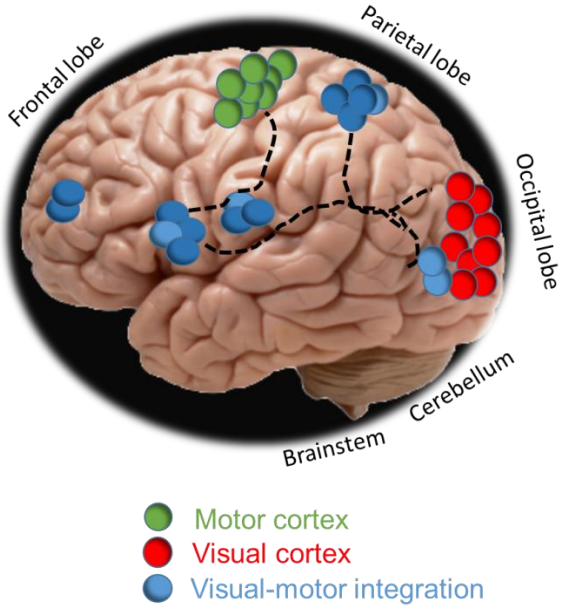
In the clinical setting of follow-up clinics for extremely preterm children, DCD is a highly relevant but clinically often neglected problem. It has been reported that DCD persists until adult age in the majority of children [84], may impact the development of the child´s self-esteem [85], and can lead to poor physical health [86, 87]. There is a lack of studies on the prevalence of DCD in large cohorts of extremely preterm children born in the 2000´s.

### *1.2.1.6 Visual-motor integration (VMI)*

Visual-motor integration (VMI) is important for the integration of visual function and fine motor skills, including eye-hand coordination. It has been consistently reported that VMI performance is lower in children born preterm [88], even though the prevalence of VMI impairment in large modern cohorts of extremely preterm children has been less studied.

An adequate VMI has been shown to be important for academic outcome [89-91]. It is well described that extremely preterm children are at risk for poor school performance [92], and VMI could be an important contributing factor. VMI is closely related to cognition, which is a major factor for school performance, but a meta-analysis of VMI in preterm born children concluded that a weaker IQ could not fully explain why VMI scores are lower in preterm children [88]. Fine motor skills are also an important part of mediating VMI in preterm children [93]. Naturally, visual function is important for VMI, but visual function in preterm children has also been reported to be connected to cognitive abilities [94].

VMI involves several regions and networks in the brain such as the cerebellum and the brainstem, the motor cortex, the visual, salience, sensory motor and default mode networks [95,96]. There are also reports on associations between VMI scores and brain volumes in the cerebellum and thalamus of adolescent subjects [97], the superior temporal gyrus, insula, occipital lobe, and temporal lobe [98] in preterm populations. Grey matter growth of the caudate and globus pallidus during the neonatal period has also been reported to be associated with VMI performance [99].




*Visual-motor integration involves several regions and networks. Some of these are indicated in this simplified figure [95,96]*

#### *1.2.1.7 Ophthalmological problems*

More than one third (38%) of children born before 27 gestational weeks in the EXPRESS cohort had major eye problems or visual problems at 6.5 years and almost 5% had visual impairment [100]. Similar rates are reported from the UK/Ireland EPICURE study [41]. Apart from visual impairment, strabismus and refractive errors are common ophthalmological problems in extremely preterm children, and the major risk factors for adverse ophthalmological outcome are low gestational age and severe retinopathy of prematurity [100]. Ophthalmological function is expected to be closely related to VMI.

#### *1.2.1.8 Academic outcome at early school age*

Children born extremely preterm are consistently reported to have worse academic performance than term-born peers [67,92,101], with around 50% of the children in need of special support in school [58,102].

A recent meta-analysis including 2390 children born preterm reported that, compared to term-born controls, they scored 0.71 SD lower on arithmetic, 0.44 lower on reading and 0.52 SD lower on spelling [92]. They were also almost three times more likely to have special education in school.

Visual-motor integration and motor function, the main focus of this thesis, are important components for a satisfactory academic performance.

### 1.2.2 Neuroimaging and outcome

#### *1.2.2.1 Neonatal MRI – findings in extremely preterm infants*

In the neonatal units cranial ultrasound is standard procedure for all extremely preterm born infants, in order to detect major brain lesions such as intraventricular hemorrhage and periventricular leukomalacia. Even though ultrasound is an excellent tool to detect major brain lesions, it is less sensitive for more subtle brain abnormalities.

MRI of the brain is superior to cranial ultrasound in detecting subtle white and grey matter abnormalities [22,103-105] and cerebellar injuries [106-108]. The most common findings in preterm children during the neonatal period in preterm children are white matter abnormalities [22,108], for example a thinner corpus callosum, signs of a delayed myelination, loss of white matter volume, punctate lesions and DEHSI [22,108]. Around 20% of extremely preterm children are reported to have moderate or severe abnormalities [22,109]. DEHSI, which is investigated in paper I, is reported to be present in 55-80% of extremely preterm infants [24,110].

More advanced MRI methodologies can give more detailed information on the development of the brain. Examples of such methods are diffusion tensor imaging to study the integrity and maturation of the white matter, resting-state fMRI to study the functional connectivity during resting, MR spectroscopy to study biochemical changes in the brain and three dimensional methodologies to study the structure of the brain in terms of volumes.

In this thesis, we used conventional MRI with T1 and T2 weighted images to determine if the presence of DEHSI affected the outcome, and three dimensional structural acquisitions to explore correlations between neonatal brain volumes and visual-motor integration and fine motor skills at 6.5 years.

# 2 AIMS

The main aim of this thesis was to further elucidate the neurodevelopment of extremely preterm children at early school-age, with special focus on their visual-motor integration and motor function, and if early neuroimaging with MRI can contribute to predicting the outcome of these functions.

The specific aims were

- To elucidate if the presence of diffuse excessive high signal intensity (DEHSI) on MRI of the brain at term equivalent age was related to neurodevelopmental outcome at 6.5 years of age (paper I).

- To explore the correlations between brain volumes at term equivalent age and visual-motor integration performance and fine motor skills at 6.5 years (paper II).

- To assess the prevalence of visual-motor integration impairment and associated perinatal factors and comorbidities at 6.5 years in extremely preterm children (paper III).

- To assess the prevalence of developmental coordination disorder and associated comorbidities at 6.5 years in extremely preterm children (paper IV).

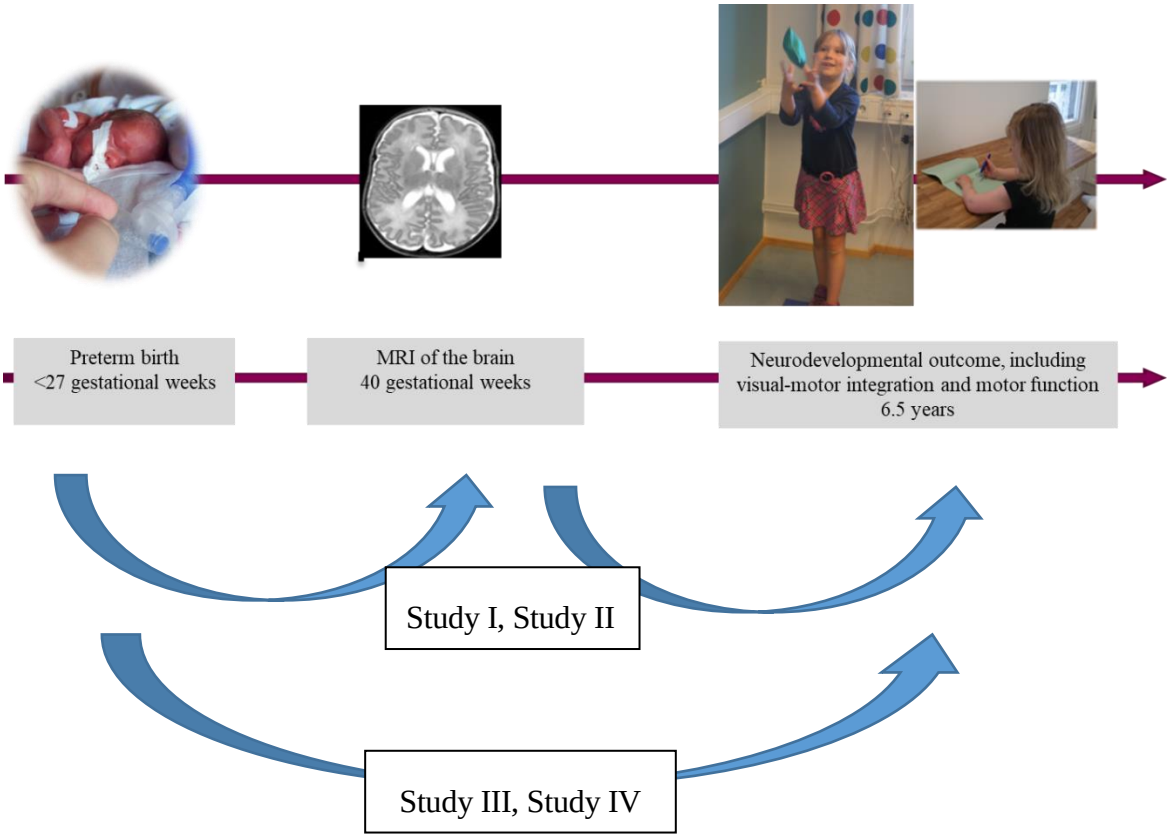
# 3 METHODS

## 3.1 STUDY DESIGN

This study is based on cohort study designs:

In study I and II we used a population-based prospective cohort study design.

In study III and IV we used a national population-based prospective cohort study design.




## 3.2 ETHICAL CONSIDERATION

The parents of all the children gave their written permission for the children to participate in the studies. The parents were informed of any clinically relevant findings on the MRI scan and of the results of the 6.5 year follow-up. When any potential clinically relevant problems were discovered, appropriate referrals were arranged for. The methods used in this thesis did not involve any painful or potentially harmful procedures for the participants.
All the studies in this thesis were approved by the ethical committees in Stockholm and Lund.

## 3.3 STUDY POPULATION

All the patients in this thesis were born extremely preterm and they were born before 27+0 gestational weeks.

### 3.3.1 Stockholm cohort (Study I and II)

Study I and II included all children born before 27 weeks, between January 1 2004 to March 31 2007, in Stockholm, Sweden.

Out of 192 children that were born during the time-period, 129 (69%) survived until term equivalent age [110] . All these children, except the ones born January 1 2004 to March 31 2004, were also part of the national EXPRESS cohort in paper III and IV.

Children without congenital infections, major malformations or chromosomal aberrations were invited to perform MRI of the brain at term equivalent age, and in total 108 children performed the MRI and were included in paper I.

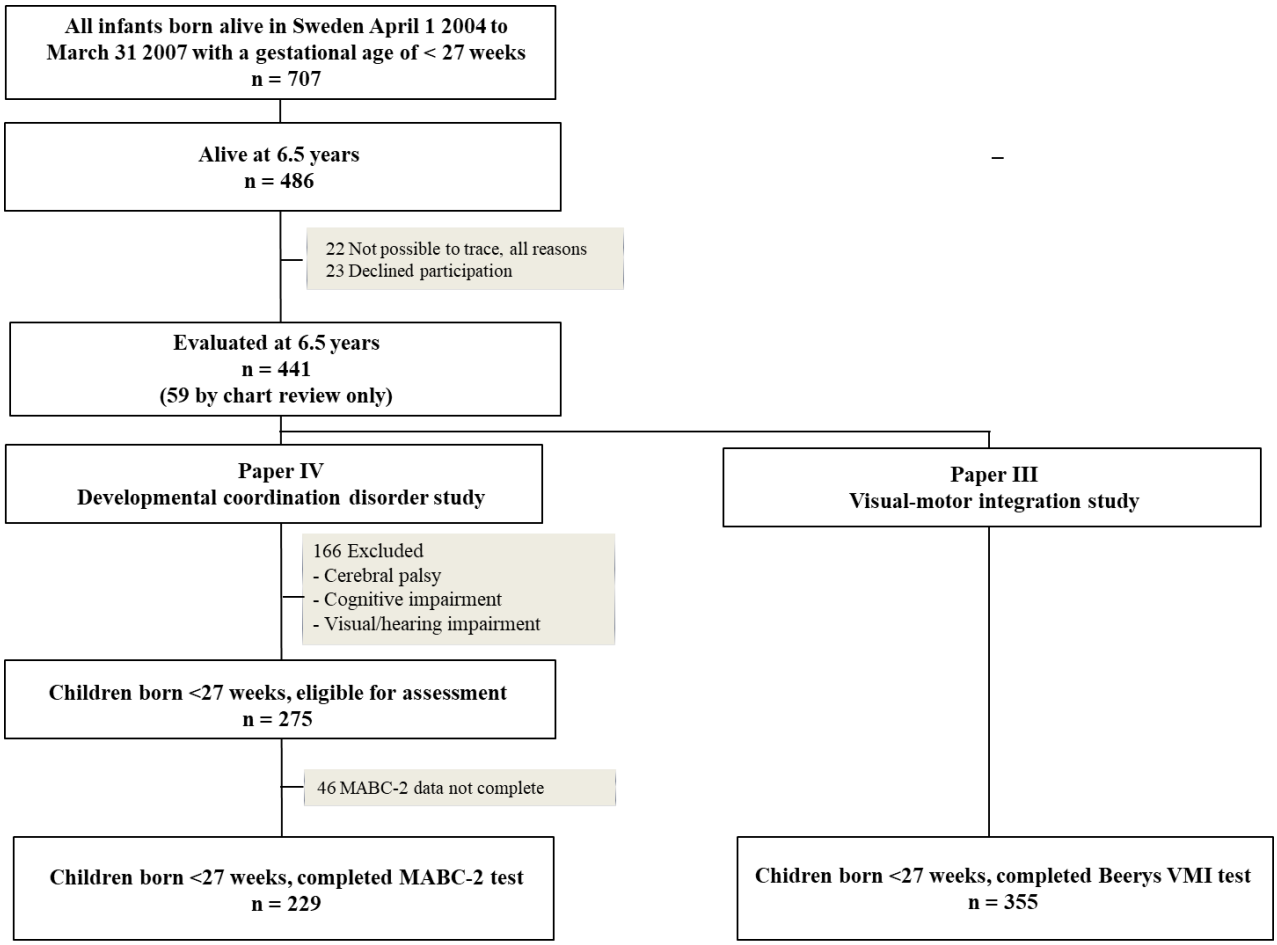
When working with paper II, it was discovered that one additional child had a major malformation, and therefore paper II was based on a total of 107 children born during this time period and without the above mentioned exclusion criteria.

Since we wanted to examine subtle brain abnormalities and regional brain volumes in paper I and II, we also excluded all children with major cerebral lesions and cerebral palsy, leaving a final study population of 66 children that fulfilled the inclusion criteria and had follow-up data at 6.5 years of age. A subsample of 34 children had high quality MRI suitable for assessment of brain volumes and 26/34 could have more detailed assessment of regional volumes. The children with and without high-quality MRI had similar background characteristics.

### 3.3.2 National cohort – EXPRESS (Study III and IV)

For study III and IV we included all children born before 27 gestational weeks between April 1 2004 to March 31 2007, in Sweden. This national cohort is the Extremely Preterm infants in Sweden Study (EXPRESS) [3] cohort.

During this time-period there were 1011 infants born before 27 gestational weeks in Sweden, and 707 of those were live-born [3]. At one year of age, 494/707 (70%) children were still alive. Eight children died between one and 6.5 years, leaving 486 children that were still alive at 6.5 years of age. We also included a similar number of children born at full term (gestational age 37+0-41+6 weeks), as controls, in both paper III and IV.




*Overview of the national EXPRESS study cohort (Paper III, IV)*

#### *3.3.2.1 Paper III*

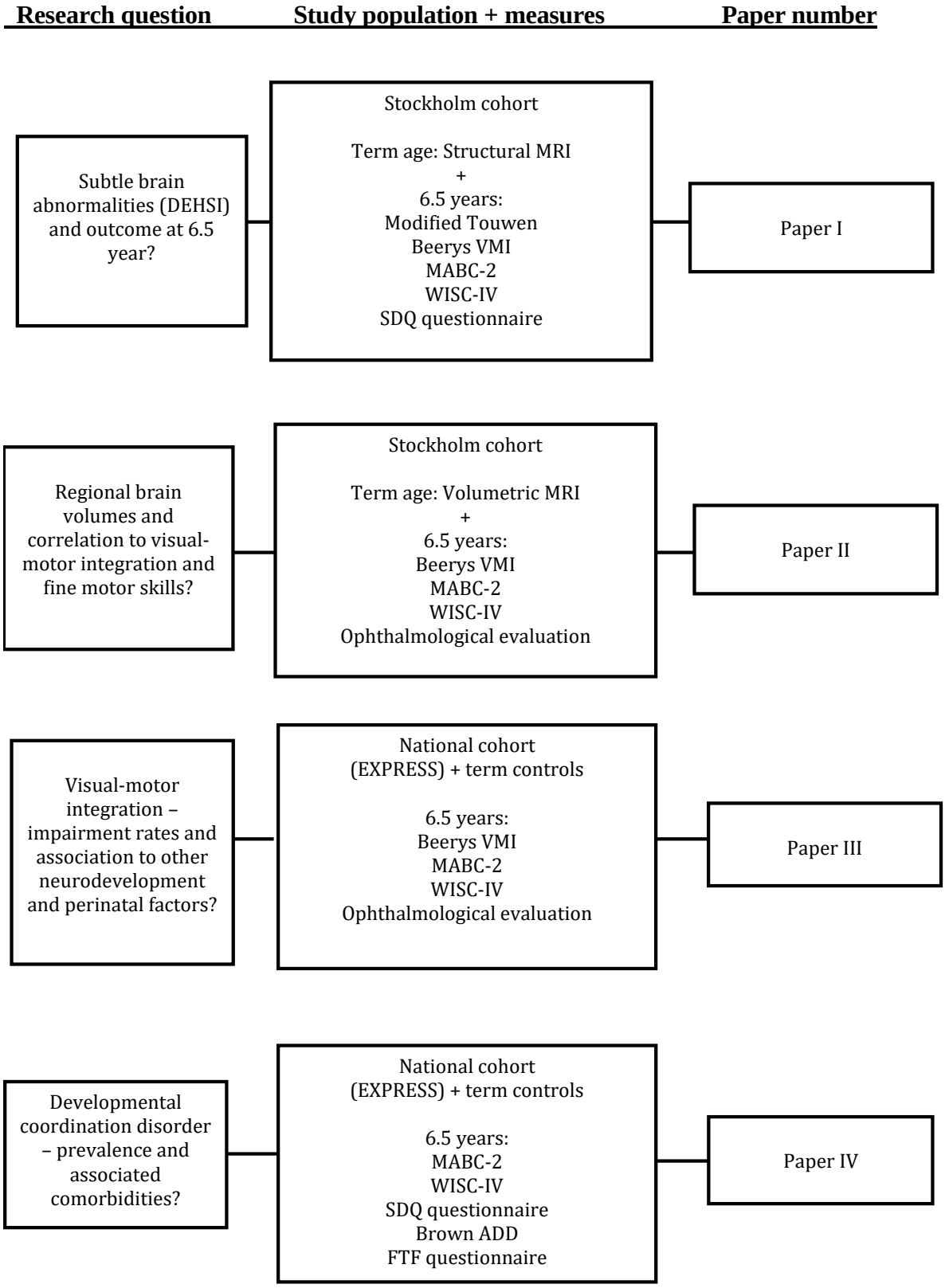
All 486 children in the national cohort fulfilled the inclusion criteria. Of those 355 had complete VMI data, together with 364 term-born controls, and the analyses were based on these children.

#### *3.3.2.2 Paper IV*

Since the research question here was to investigate the prevalence and comorbidities of developmental coordination disorder in apparently healthy extremely preterm children, we included the 275 children in the national cohort and the 359 term-born controls who did not have cerebral palsy, cognitive impairment, visual or hearing impairment. The analyses were based on the 229 extremely preterm children and the 344 term-born controls that had completed MABC-2 assessment.

## 3.4 MEASURES

### 3.4.1 Overview



### 3.4.2 Magnetic Resonance Imaging (MRI) (Study I and II).

All the children in Study I and II had undergone MRI of the brain at term equivalent age at Astrid Lindgren´s children´s hospital in Stockholm. The scanner used was a Philips Intera 1.5 Tesla (Philips International, Amsterdam, the Netherlands). The details of the MRI protocol have been published [110] – in brief, a sagittal T1-weighted turbo spin echo sequence, an axial recovery sequence and an axial T2-weighted sequence were used. The details of the acquisition of the three dimensional images used for brain volume measurements can be found in paper II, page 3.

All conventional MRI images were visually inspected for major brain lesions and white matter abnormalities using a previously described scoring system [22], and divided into four groups - no, mild, moderate or severe white matter abnormalities. Only children without moderate/severe white matter abnormalities or other major brain lesions (intraventricular hemorrhage grade III-IV, cystic periventricular leukomalacia, periventricular hemorrhagic infarction, cysts or hydrocephalus ) were included.. The 3D acquisitions were assessed for good quality assurance. Images with motion artifacts, incomplete coverage of the brain, and blurring of the grey matter and white matter interfaces were excluded.

#### *3.4.2.1 Study I – evaluating Diffuse Excessive High Signal Intensity (DEHSI)*

The presence of DEHSI was evaluated by visual inspection of the conventional MRI images by two independent observers, and thereafter the children were divided into two groups: one group with DEHSI and the other group without DEHSI. Only children without major brain lesions (intraventricular hemorrhage grade III-IV, cystic periventricular leukomalacia, periventricular hemorrhagic infarction, cysts, hydrocephalus or moderate/severe white matter abnormalities) were included.

#### *3.4.2.2 Study II – assessment of brain volumes*

Two different analyses were performed:

- Automatic segmentation to extract the mean volumes of the grey matter, the white matter, the cerebrospinal fluid, the basal ganglia, the brainstem and the cerebellum [111].

- Atlas-based segmentation to conduct regional segmentation of specific small regions of the brain [112].

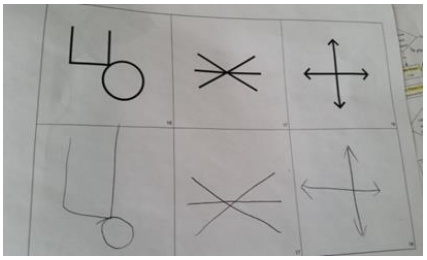
### 3.4.3 Neurodevelopmental follow-up at 6.5 years (study I-IV)

At 6.5 years of uncorrected age, all the included children underwent assessments during one day.
The assessments included:

#### 3.4.3.1 *Beery-Buktenica Developmental Test of Visual-Motor Integration - sixth edition (Beerys VMI)* [113]
*(Study I-III)*

This is a paper and pen test measuring the child´s visual-motor integration (VMI). It consists of 30 geometrical figures that the child is asked to copy, and it is terminated when three figures in a row are incorrectly copied. The raw score is transformed to an age-adjusted standard score, and the normative mean score is 100 points with one standard deviation of 15 points.

For paper III, mild impairment was defined as < - 1 SD and severe VMI impairment as < - 2 SD, compared to the mean of the term-born control group.



*Beery-Buktenica Developmental Test of Visual-Motor Integration – assessment of the ability to copy geometrical figures*

### 3.4.3.2 *Movement Assessment Battery for Children – Second Edition (MABC-2)* [114] *(Study I-IV)*

This test was used to assess the child´s motor function, and it gives information on both the gross and the fine motor function using different tasks assessing the balance, ball skills and manual dexterity. Better function is indicated by higher scores. Usually a total score <15$^{th}$ percentile is considered borderline abnormal and <5$^{th}$ percentile as definitely abnormal [114].

In paper I, the mean total scores of the subtests were used. In paper II, the scores from the manual dexterity subtest was used.

In paper IV, developmental coordination disorder was defined as <5$^{th}$ percentile on the total score, compared to the mean of the control group. This cut-off was equal to <15$^{th}$ percentile compared with the test norms.

*Movement Assessment Battery for Children*
*– assessment of ball skills, balance and manual dexterity/fine motor skills*

*3.4.3.3 Modified Touwen examination* [115]
*(Study I)*

All children were examined by a pediatrician, who assessed the neurological status of the child and according to the results of this examination each child could be classified as having
- normal neurology
- grade 1 minor neurological dysfunction
- grade 2 minor neurological dysfunction

3.4.3.4 *Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV)* [116]
*(Study I-IV)*

This test of the child´s general cognitive abilities have four different subtests (verbal comprehension, perceptual reasoning, working memory and processing speed) which together form the child´s Full Scale Intelligence Quotient (FSIQ). The normative mean FSIQ is 100 points with a standard deviation of 15 points.

*3.4.3.5 Strengths and Difficulties Questionnaire (SDQ)* [117]
*(Study I, IV)*

This parental questionnaire was filled in by the parents of the participating children. It contains 25 items about the behavior of the child. A score above the 90$^{th}$ percentile was considered as clinically significant behavioral problems [118], and in paper IV we used >90$^{th}$ percentile compared to the term-born control group as the cut-off.

3.4.3.6 *Brown Attention-Deficit Disorder Scales (Brown ADD)*[119]
*(Study IV)*

This test is a screening instrument for attentional problems and it was administered as a parental questionnaire. It consists of a number of questions that can be divided into six different clusters, five of which can be combined to a total inattention score and all six to get a combined inattention/hyperactivity score. A T-score ≥ 55 is considered clinically significant problems.

3.4.3.7 *Five to Fifteen questionnaire (FTF)* [120]
*(Study IV)*

This parental questionnaire was also filled in by the parents of the participating children. It comprises 181 statements about any difficulties the child might have compared to peers, in domains such as behavior, motor function, executive function, perceptual problems and social skills. A score >90$^{th}$ percentile compared to the term-born control group was considered as clinically significant problems.

### 3.4.4 Statistical analyses

All analyses were performed using the statistical software SPSS (IBM Corporation, Armonk, NY, USA). For paper I-III, SPSS version 22.0 was used and for paper IV SPSS version 25.0 was used.

For comparing two groups, the Student´s t-test was used for continuous normally distributed data, the Mann Whitney U test for continuous data with a skewed distribution and the Chi square test or the Fisher´s exact test for dichotomous data, as appropriate. For adjusted comparisons between two groups the analysis of covariance (ANCOVA) and logistic regression with odds ratios were used. For comparing more than two groups one-way analysis of variance (ANOVA), the Kruskal-Wallis test and the Chi square test for trend were used. To investigate associations and correlations partial correlation, linear regression and logistic regression were used. Effect sizes according to Cohen´s d and partial eta squared ($\eta 2$) were calculated. Interrater variability for assessment of DEHSI was assessed with Cohen´s kappa. To account for possible correlations due to multiple births, a complex sample analysis design [121] was applied to the logistic regressions and ANCOVAs in paper IV. The level of statistical significance was set at a two-sided p-value of $<0.05$ except in paper IV where the level of statistical significance was set at a two-sided p-value of $p<0.01$, to adjust for multiple comparisons.

# 4 RESULTS

## 4.1 NEUROIMAGING FINDINGS IN RELATION TO OUTCOME (PAPER I, II)

### 4.1.1 The presence of DEHSI in relation to outcome (Paper I)

DEHSI was seen in 39/66 (55%) of the extremely preterm infants that were without focal brain lesions. The children with DEHSI had a tendency to have a higher birth weight (p=0.056) but otherwise no differences in perinatal characteristics could be seen between children with and without DEHSI. There were no differences between boys and girls in the prevalence of DEHSI. Neither were there any differences in the neurodevelopment of the children with and without DEHSI, neither in neurological status, cognitive scores on the WISC-IV, motor scores on the MABC-2, visual-motor integration performance, or in the prevalence of behavior problems reported by the parents (all p>0.05).

### 4.1.2 Neonatal brain volumes and relation to outcome (Paper II)

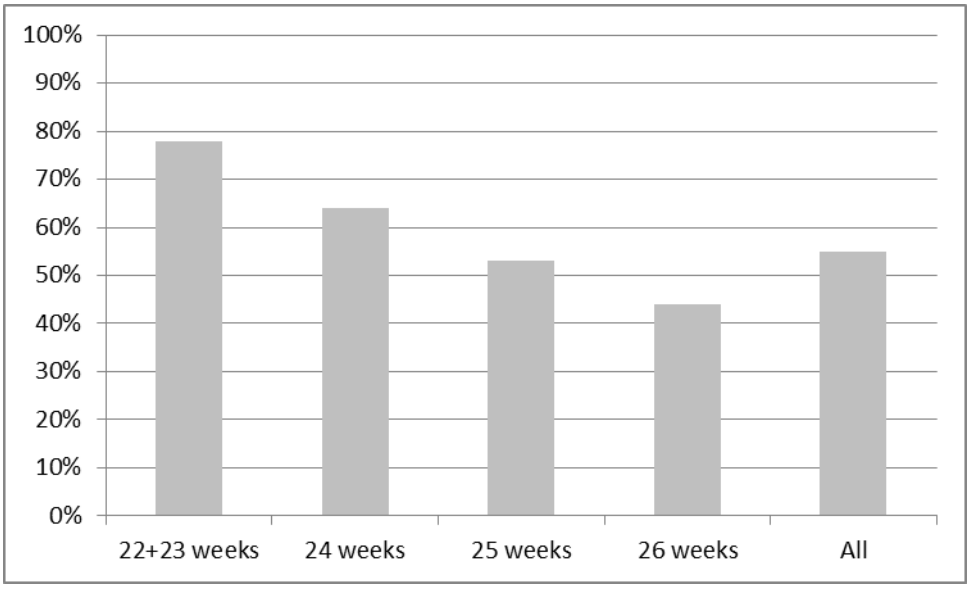
The extremely preterm children performed 7 points (0.5 SD) lower on the VMI test and 2 points (0.5 SD) lower on the manual dexterity subtest of the MABC-2 compared to the mean norms of the tests. Girls performed better on the VMI test (p=0.02), but there were no significant sex differences in the performance on the MABC-2 manual dexterity test (p=0.16).

The precentral gyrus showed a positive correlation with both VMI scores (partial r=0.54, p=0.007) and MABC-2 manual dexterity scores (partial r = 0.54, p=0.01) (Paper II, Figure 2). There were also correlations between MABC-2 manual dexterity scores and the cerebellum (partial r = 0.42, p=0.02) and the brainstem (partial r = 0.47 p=0.008) volumes, and a negative correlation with cortical grey matter volume (partial r = -0.38, p=0.04) (Paper II, Figure 2).

## 4.2 VMI AND DEVELOPMENTAL COORDINATION DISORDER AT 6.5 YEARS

### 4.2.1 Visual-motor integration (VMI) (Paper III)

Mild VMI impairment was common with 142/355 (40%) children born EPT performing <1 SD below the term-born control group. Also, there were 52/355 (15%) children born extremely preterm with severe VMI impairment with performance <2 SD below the term-born control group. The most immature children were more prone to VMI impairment.

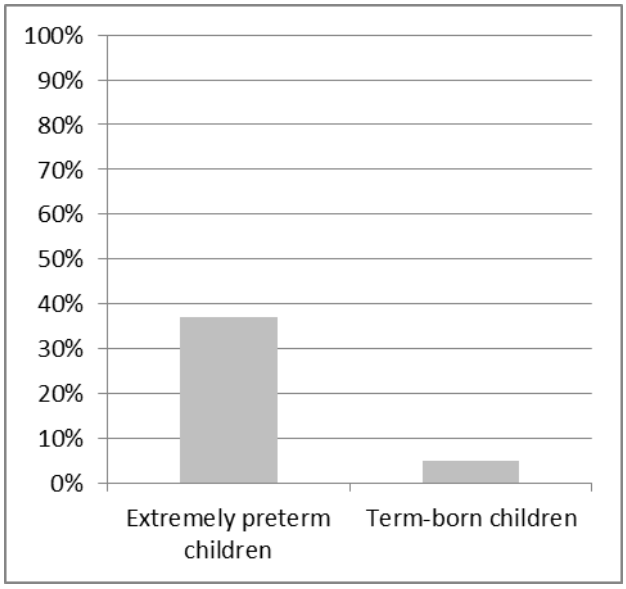



*Percentage of extremely preterm children with VMI impairment (less than one standard deviation compared to the control group), according to the gestational week the children were born in.*

Within the group of extremely preterm children the association between perinatal factors and VMI scores was weak. Male sex ($p=0.02$) and the administration of postnatal steroids ($p<0.001$) were significantly associated with VMI scores in multivariable analysis; however, the model only explained 13% of the variance in VMI scores. Instead, VMI scores showed a stronger association to manual dexterity scores ($p=0.004$) and FSIQ ($p<0.001$); adjusted $R^2=0.40$.

### 4.2.2 Developmental Coordination Disorder (DCD) (paper IV)

There were 85/229 (37.1%) of the children born extremely preterm that had DCD according to the study criteria, and 19/344 (5.5%) of the controls; adjusted odds ratio 7.92 (99% CI, 3.69-17.20).




*Percentage of children with DCD at 6.5 years of age among extremely preterm children compared to term-born children.*

Even though there were more preterm boys than preterm girls with DCD, the sex differences were not significant (p=0.08). Among the preterm born children, the parents of the children with DCD reported more behavioral problems compared to children without DCD. The adjusted odds ratios for behavioral problems were in the range from 2.71 (99% CI, 1.15-6.37) for total behavioral problems to 3.68 (99% CI, 1.47-9.16) for combined attention/hyperactivity problems. They also had a lower FSIQ.

Only half of the parents of the children with DCD had noticed that the children had significant motor problems.

Only a minority of the children with DCD had received any examination or support from a psychologist (14%) or a physiotherapist (12%) in the year preceding the study.

# 5 DISCUSSION

*General Discussion*

The overall aim of this thesis was to evaluate outcome at early school-age in children born before 27 gestational weeks, with special regard to their visual-motor integration and motor function, and to explore the impact of subtle findings on neonatal MRI of the brain on these outcomes.

The main findings were that both visual-motor integration impairment and motor impairments were common in the extremely preterm children - more than half of the children had impaired visual-motor integration and more than one third of the extremely preterm children had motor impairment/developmental coordination disorder. In half of the cases the parents had not noted that the child had motor problems. Subtle findings on neonatal MRI in the form of DEHSI did not affect the outcome of the children. In addition some regional brain volumes, known to be involved in visual-motor integration and fine motor skills, correlated to these functions.

In the following sections, the results from Paper I-IV will be discussed more in detail.

## 5.1 NEUROIMAGING FINDINGS IN RELATION TO OUTCOME (PAPER I, II)

***The presence of isolated DEHSI in relation to outcome (Paper I)***

In Paper I, we demonstrated that there were no differences in visual-motor integration, motor function, cognitive function, neurological status or behavioral problems at 6.5 years between children with and without isolated DEHSI on neonatal MRI. Our findings were in line with some previous studies in toddlers [122,123] [124,125] and one study in 9 year old children that only investigated cognitive function [126].

It could be argued that DEHSI is a sign of delayed maturation, which would also explain why it is only seen at term equivalent age and not later, and histological studies strengthen this hypothesis [27]. Others have argued that DEHSI is pathological and have found an association to outcome [24,127] ; however, in these studies the children were examined at toddler age and the sample size with isolated DEHSI was small.

The strengths of this study included the population-based study design, limiting the risk of selection bias. We covered several aspects of neurodevelopmental outcome since we compared children with and without DEHSI regarding visual-motor integration, motor function, cognitive, neurological, and behavioral outcomes in a long-term follow-up until early school-age. Possible limitations could be that the sample size was not large enough to detect more subtle differences in outcome. It would be interesting to evaluate the outcome of children with and without DEHSI at an older age. Also, we did not control for possible confounders, such as socio-economic background of the parents.

In summary, the results indicate that the presence of DEHSI does not affect outcome. Early prediction of future developmental problems is important since early interventions can improve the outcome of preterm children [46], but DEHSI does not seem to contribute with information in this matter.

***Neonatal brain volumes and relation to outcome (Paper II)***

In Paper II, we found correlations between regional neonatal brain volumes and visual-motor integration and fine motor skills.

Both visual-motor integration [88] and fine motor skills [128] are consistently reported to be lower in preterm children. Previous studies of preterm born adolescents have shown some correlations between the volumes of specific regions of the brain, and VMI scores [97,98]. Interestingly, one study also reported that the growth of the caudate and globus pallidus during the neonatal period could be related to VMI scores [99].
Our study did not find associations between VMI scores and the above mentioned regions, but with the precentral gyrus. This is a structure in the frontal lobe and from there the corticospinal tracts, which control fine motor function, emerge. Thomas et al reported, using diffusion tensor imaging MRI, that poor fine motor skills mediated poor visual-motor integration performance [93]. Their conclusion was that a probable explanation for the low VMI performance seen in preterm children is that preterm birth affects fine motor skills which in turn affect VMI.

Interestingly, caffeine therapy, which is commonly used in extremely preterm children to treat apnea of prematurity and which has a direct effect on the brain, has been shown to improve both VMI and fine motor coordination, but not cognition, at 11 years of age in the randomized multicenter CAP (Caffeine for Apnea of Prematurity) trial [129].

A strength of this study was the population-based study design. The majority of the infants in the cohort could be traced and drop-out analyses showed that the children with high-quality MRI were representative of the cohort. Possible limitations where that due to low quality of many MRI images, as is common in 3D imaging, we could only use half of the eligible study population, which left us with a small sample size. To explore several possible correlations in small sample sizes can pose a risk of type I errors – that is, false positive results. Another limitation is that we did not include a control group. The study explored correlations and nothing can be said about the causality, that is, whether smaller regional brain volumes actually causes adverse outcome in the functions studied.

In summary, even though assessing brain volumes is an interesting future option for evaluating care and speculatively could predict outcome, larger sample sizes, including also term-born controls, are needed to confirm our results.

## 5.2 VMI AND DEVELOPMENTAL COORDINATION DISORDER (PAPER III, IV)

***Visual-motor integration (VMI) (Paper III)***

In paper III we assessed the prevalence of poor VMI performance in the extremely preterm children in the EXPRESS group, compared with term-born controls. We also evaluated the associations between VMI scores, perinatal factors and cognitive and motor function at 6.5 years.
We found that impaired VMI performance (less than one standard deviation below the mean of the control group) was present in more than half of the children. The most immature children had the highest rates of VMI impairment. These findings are in line with previous reports on VMI performance in preterm populations [88,130,131].

There were only weak associations between VMI scores and perinatal factors. The reason could be that the lower VMI performance seen in extremely preterm children is an effect of the prematurity in itself due to the altered brain development often seen in these children. It is also possible that since VMI involves many regions and networks in the brain, several perinatal risk factors interact to cause the lower VMI performance.

It would be expected that an abnormal ophthalmological outcome would be associated with lower VMI scores, since VMI performance is depending on visual function. In univariate analysis, there was an association between abnormal ophthalmological outcome and VMI scores; however, when explored in a multivariable model together with FSIQ and fine motor scores, abnormal ophthalmological outcome was not significant. This could be explained by a stronger association between IQ, fine motor skills and VMI scores than between abnormal ophthalmological outcome and VMI scores.

In preterm children, the visual problems are not only caused by direct injury to the eye, such as retinopathy of prematurity, but often also by injuries to the brain affecting the visual functions. Cerebral visual impairment (CVI) is a term for visual defects caused by brain injury, and CVI has been shown to be common in preterm born children [132]. Even though CVI is interesting, it is not a defined diagnosis in International Statistical Classification of Diseases and Related Health Problems ( ICD-10), and it has not been further explored in this thesis.

Strengths of this study were the large population-based cohort with a high follow-up rate, the exploring of VMI performance in relation to both perinatal factors and outcome and the uses of a standardized test for assessing VMI. As opposed to many previous studies, our cohort also included a relatively high number of children born at the limit of viability, which was possible due to a relatively high survival rate among the youngest children. Possible limitations could be that we only investigated the results from the main VMI test, and not the supplementary tests of visual perception and motor function. Thus, we cannot tell which part of VMI that was most affected.

***Developmental coordination disorder (DCD) (paper IV)***

In paper IV we investigated the prevalence of DCD at 6.5 years in extremely preterm children without major disabilities, compared to a term-born control group. We also investigated if the extremely preterm children with DCD had associated behavioral or cognitive problems, had seen a physiotherapist or psychologist and if the parents had noted the children´s motor problems.

We found that more than one third of the extremely preterm children had DCD, many of those with DCD had behavioral problems, few had seen a physiotherapist or psychologist, and in about half of the preterm children with DCD the parents had not noticed the motor problems.

The findings were in line with previous studies reporting that motor impairments [71,73] and DCD [133,134,135] are more common in preterm children than in term-born children, and that they are associated with various behavioral problems [74]. A low sensitivity of parental questionnaires to detect DCD in preterm children has also been reported [75,133]. The previously reported prevalence of DCD in extremely preterm children has varied between studies - for example a study by Roberts et al found a prevalence of DCD of 16% [133] and a study by Goyen et al found a prevalence of DCD of 42% [135].

Strengths of this study included the national population-based study design with a high follow-up rate and a relatively large sample size. Standardized assessment tools were used. We defined the cut-off for the motor impairments compared to the term control group, which could be an advantage since the motor test used in this thesis, the MABC-2, is not validated in Sweden. There are also reports that the scores on the MABC-2 can vary between different countries [136]. Possible limitations could be that we defined developmental coordination disorder based on the motor assessment only. For a clinical diagnosis, an impact on daily life activities or academic performance must also be present. Since we did not compare behavioral or cognitive outcomes between preterm children and term children with developmental coordination disorder we cannot say if these associated comorbidities are specific for the preterm children. If the control group were to perform better than the general population of healthy children in Sweden, this could give a false high rate of motor impairment in our cohort of extremely preterm children.

The findings confirm that motor impairments are common in apparently healthy extremely preterm children. Motor impairments in the absence of cerebral palsy have also been reported to be increasing [137], making it even more important to acknowledge this common problem in extremely preterm children when planning and conducting follow-up clinics.

## 5.3 CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

*Clinical implications*

This thesis contributes with information on how to counsel the parents about subtle findings on MRI of the brain. Even though neonatal MRI of the brain in preterm children is used widely in research, its routine use in healthy preterm children at term age is debated [138]. Some claim that it may raise parental anxiety [139]. On the other hand, there are reports that the negative predictive value for major neurological disabilities is high [140], meaning that a normal MRI at term age makes it very likely that the child will not suffer from major neurological disabilities [140]. In our experience, parental anxiety could be minimized by cautious information about the results and interpreting the results in the child´s clinical context, especially when the MRI findings are subtle.

Concerning the measurement of neonatal brain volumes, our study (paper II) had limitations making the generalizability to the clinical setting limited. Assessing regional brain volumes could maybe in the future be an interesting tool to assess quality of care since, for example, a well-nourished infant without complications is expected to have a better brain growth than an undernourished or sick infant [35]. However, studies with a larger number of patients and inclusion of term-born controls are needed to evaluate if assessment of regional brain volumes is of value for the individual above that given by the routine measurement of the child´s height, weight and head circumference.

The thesis also contributes with information valuable for the planning of follow-up programs for children who were born extremely preterm. We could confirm that it is not enough only to focus on screening for major disabilities or to rely on parental questionnaires for identifying children with motor problems. Instead, the children need a structured assessment in combination with parental interviews and parental questionnaires. The fact that very few of the children with motor impairments (Paper IV) had seen a physiotherapist or psychologist at 6.5 years also supports the importance of a structured follow-up.

*Future directions*

We have explored subtle MRI findings and outcome at early school-age, but we do not know the outcome in later years of the children in the cohort. The children in the EXPRESS cohort are currently undergoing evaluation at 12 years of age, making it possible to evaluate any effects of extreme prematurity in the preteen years.

The Stockholm cohort in paper I and II has also undergone a new MRI of the brain at 10-12 years of age, and investigations of the development of their brain volumes in relation to neonatal brain volumes and 12 year outcome are underway. The evaluation of these later MRI examinations and the 12 year follow-up gives us exciting opportunities to increase our knowledge about the development of these extremely preterm born children.

The impact of the surrounding environment on the immature brain is also an area of great interest for future studies. Individualized care such as Newborn Individualized Developmental Care and Assessment Program (NIDCAP), skin to skin care, music therapy and other well adjusted sensory stimulations could theoretically improve the development of the brain. Further studies with randomized controlled trials are needed to evaluate the effect on long-term neurodevelopment of these and other environmental factors affecting the brain of the extremely preterm infant.

# 6 CONCLUSIONS

- Even though diffuse and isolated white matter abnormalities like DEHSI is a common finding on MRI of the brain at term age in extremely preterm infants, in our cohort we did not detect differences in neurodevelopmental outcome between children with or without DEHSI. One explanation for this could be that DEHSI indicates delayed maturation of the white matter of the brain or a transent process, but not persisting pathology.

- The finding of correlations between the volumes of four brain regions and visual-motor integration and/or fine motor skills at 6.5 years could indicate a non optimal neonatal growth in these regions with long-term effects on the child´s development.

- The lower visual-motor integration performance present in more than half of the extremely preterm children emphasize that assessment of visual-motor integration is an important part of cognitive and psychological long-term follow-up for these children.

- Developmental coordination disorder was common in extremely pretrm children without disabilities. These motor problems had not been noticed by many of the parents and very few of the children had received any referrals for this before the study, indicating that this is often a neglected problem in extremely preterm children. Screening with parental questionnaires is not enough to identify the children with problem, but structured assessment is necessary. Children with developmental coordination disorder should also be assessed for behavioral and cognitive comorbidities since these were common.

# 7 SVENSK SAMMANFATTNING

Under de senaste decennierna har överlevnaden för barn som är födda mer än tre månader för tidigt ökat dramatiskt. I takt med det så har också kunskapen om hur så tidig födsel kan påverka den omogna hjärnans utveckling ökat. Svår sjuklighet så som cerebral pares (CP), kraftigt nedsatt syn och intellektuell funktionsnedsättning har undersökts i många studier, men påverkan på andra delar av hjärnans funktioner har inte studerats lika mycket.

Den här avhandlingens mål var att kartlägga utvecklingen vid skolstart hos barn som fötts före graviditetsvecka 27, med fokus på barnens motoriska utveckling och utvecklingen av visuo-motorisk integration. Visuo-motorisk integration är förmågan att kunna koppla samman synintryck med att sedan kunna utföra en korrekt motorisk rörelse. De första två studierna i avhandlingen undersöker också samband mellan fynd på magnetkameraundersökning av hjärnan i nyföddhetsperioden och barnens utveckling vid skolstart.

I studie I och studie II ingick alla barn födda i Stockholm före graviditetsvecka 27 under en tre-års period (2004-2007). Dessa barn hade gjort magnetkameraundersökning i nyföddhetsperioden och genomgick kliniska undersökningar vid 6.5 års ålder.

I studie III och studie IV ingick alla barn födda i hela Sverige före graviditetsvecka 27 under samma tidsperiod – den så kallade EXPRESS studien (Extremely Preterm infants in Sweden Study). Här testades också ungefär lika många fullgångna barn på samma sätt som de för tidigt födda, och resultaten för de för tidigt födda barnen jämfördes med resultaten från de fullgångna barnen.

Studie I visade att subtila förändringar, så kallade DEHSI (Diffuse Excessive High Signal Intensity), som ofta ses i hjärnans ledningsbanor på magnetkameraundersökning i nyföddhetsperioden, inte hade något samband med utvecklingen vid 6.5 års ålder hos de för tidigt födda barnen. Det gällde både deras motorik, visuo-motoriska integration, nervsystemets funktion, kognitiva förmåga och beteende. Detta är viktig information eftersom DEHSI finns hos mer än hälften av barn som har fötts mer än tre månader för tidigt, men inte finns alls hos fullgångna barn. Resultaten ger vägledning om hur magnetkameraundersökningarna ska tolkas.

Studie II analyserade storlek, det vill säga volym, i vissa områden av hjärnan hos det för tidigt födda barnet i nyföddhetsperioden, och hur dessa volymer korrelerade till visuo-motorisk integration och finmotorik vid 6.5 års ålder. Studien visade att hjärnvolymer i några av dessa områden hade samband med de ovan nämnda funktionerna. Detta kan tyda på att hjärnans tillväxt i specifika regioner är påverkad redan under nyföddhetsperioden och att detta relaterar till senare funktioner. Om tillväxten av hjärnan kan optimeras tidigt, skulle funktionerna eventuellt kunna förbättras.

Studie III visade att mer än hälften av barnen födda mer än tre månader för tidigt hade försämrad visuo-motorisk integration jämfört med fullgångna barn, och hos barn födda i 22-23 graviditetsveckan hade tre fjärdedelar av barnen försämrad funktion. Försämrad visuo-

motorisk integration visade ett visst samband med syn- och ögonavvikelser och ett starkt samband med lägre IQ och sämre finmotorik.

Studie IV undersökte motoriska svårigheter hos barn födda mer än tre månader för tidigt och som var utan svår sjuklighet som CP, synnedsättning och intellektuell funktionsnedsättning. Studien fann att 37.1% av dessa till synes friska barn hade uttalade motoriska svårigheter, jämfört med 5.5% hos de fullgångna barnen som undersöktes på samma sätt. De motoriska svårigheterna var också associerade till olika typer av beteendeproblem. Hos hälften av barnen hade föräldrarna inte märkt deras barns motoriska svårigheter och få av barnen hade fått någon hjälp av sjukvården med motoriken.

Sammanfattningsvis visar den här avhandlingen att svårigheter med visuo-motorisk integration och motorik är mycket vanliga vid skolstart hos barn som har fötts mer än tre månader för tidigt, och att dessa svårigheter hänger samman med ett flertal andra problem. Detta innebär att strukturerad långtids-uppföljning av dessa barn är viktig, eftersom det är väl känt att dessa typer av svårigheter påverkar möjligheten till adekvata prestationer i skolan och även socialt samspel med jämnåriga.
Små avvikelser i hjärnans ledningsbanor som nyfödd bör tolkas med försiktighet, då dessa inte verkar påverka barnets framtida utveckling, åtminstone inte fram tills 6.5 års ålder. Mätning av hjärnvolymer på magnetkameraundersökning i nyföddhetsperioden indikerar att tillväxt i vissa regioner av hjärnan är påverkad redan tidigt. Då denna påverkade tillväxt var associerad med en sämre visuomotorisk integration och finmotorik är det viktigt att optimera hjärnans tidiga tillväxt, till exempel genom optimal näringstillförsel till barnet.

# 8 ACKNOWLEDGEMENTS

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