

**A randomised clinical trial on the impact of early intervention on parental  
child-rearing attitudes and cognitive, motor and behavioural outcomes in  
preterm infants.**



**Thesis by**

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## List of contents

Acknowledgement.....	4
List of papers.....	7
Definitions and abbreviations.....	8
Introduction.....	12
1. Neurodevelopmental outcomes in childhood, adolescence and young adulthood .....	12
1.1. Cognition and intelligence tests.....	13
1.2. Cognitive outcomes.....	13
1.3. Mental retardation.....	14
1.4. Academic achievement and executive function.....	15
1.5. Methodological considerations in outcome studies.....	16
1.6. Behaviour problems.....	17
1.7. ADHD and other psychiatric diagnoses.....	18
2. Factors affecting neonatal outcomes.....	19
2.1. Neonatal complications of prematurity.....	20
2.2. Visual and hearing impairments.....	20
2.3. Minor motor impairments.....	21
2.4. Other factors influencing neonatal outcomes.....	21
3. Preterm birth; impact on parents.....	22
3.1. Sensitive parenting.....	22
3.2. Contingent response.....	23
3.3. Parent-infant interactions.....	24
3.4. Parental child-rearing attitudes.....	25
4. Preterm birth; impact on economy.....	26
5. Early intervention.....	27
5.1. The theoretical framework of early intervention.....	28
5.2. The transactional model of development and contingent responsiveness.....	29
5.3. The transactional model of intervention.....	30
5.3.1. The remediation strategy.....	31

5.3.2. The re-education strategy.....	32
5.3.3. The redefinition strategy.....	32
5.4. Post-discharge intervention programs.....	34
5.5. NIDCAP.....	35
Aims of the study.....	36
Material and methods.....	38
Summary of main results.....	52
Discussion.....	54
Main conclusions.....	68
Clinical implications and future aspects .....	69
References.....	71

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## **List of papers**

### **Paper I**

Nordhov SM, Kaaresen PI, Rønning JA, Ulvund SE, Dahl LB. A randomized study of the impact of a sensitizing intervention on the child-rearing attitudes of parents of low birth weight preterm infants. *Scand J Psychol.* 2010;51(5):385-391.

### **Paper II**

Nordhov SM, Rønning JA, Dahl LB, Ulvund SE, Tunby J, Kaaresen PI. Early intervention improves cognitive outcomes for preterm infants: Randomized controlled trial. *Pediatrics* 2010;126:e1088-e1094.

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## Definitions and abbreviations

ADD	Attention deficit disorder
ADHD	Attention deficit/hyperactivity disorder
APIP	Avon Premature Infant Project
BPD	Bronchopulmonary dysplasia; various definitions. Today usually need for supplemental oxygen at 36 weeks of gestation
BSID	Bayley Scales of Infant Development
BW	Birth weight
CBCL	Child Behaviour Check List
CI	Confidence interval
CNS	Central nervous system
CP	Cerebral palsy
CRPR	Child Rearing Practises Report
DI	Developmental index
DNA	Deoxyribonucleic acid
DQ	Developmental quotient
ED	Executive dysfunctions
EF	Executive functions
ELBW	Extremely low birth weight; < 1000 gram

EPT	Extremely preterm; usually < 28 weeks of gestation
ES	Effect size
FIQ	Full scale intelligence
GC	Glucocorticoid
GA	Gestational age
HPA	Hypothalamic-pituitary axis
IBAIP	Infant Behavioural Assessment and Intervention Program
ICC	Intra correlations coefficient
IHDP	Infant Health and Developmental Program
IQ	Intelligence quotient
IVH	Intraventricular haemorrhage
LBW	Low birth weight; < 2500 gram
LMM	Linear mixed models
LPT	Late preterm
MDI	Mental developmental index
MITP	Mother Infant Transaction Program
MRI	Magnetic resonance imaging
NBW	Normal birth weight; variously defined (>2800 – 3000 gram)

ND	Neurodevelopmental
NDT	Neurodevelopmental therapy
NICU	Neonatal intensive care unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Program
OR	Odds ratio
PDA	Persistent ductus arteriosus
PDI	Psychomotor developmental index
PIQ	Performance IQ
PMA	Postmenstrual age
PVL	Periventricular leucomalacia
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity
RR	Relative risk
SES	Socioeconomic status
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SGA	Small for gestational age: various definitions; often BW > 2 SD below mean BW according to gender, and gestation or below the 10 <sup>th</sup> percentile
SNAP	Score for Acute Physiology

TR	Term reference
UNN	University Hospital of North Norway
VIBeS	Victorian Infant Brain Studies
VIQ	Verbal IQ
VLBW	Very low birth weight; <1500 grams
VP	Very preterm; usually defined as GA < 32 weeks of gestation (sometimes <33 weeks)
w	Weeks
WMD	Weighted mean difference
WMI	White matter injury
WPPSI-R	Wechsler Preschool and Primary Scale Intelligence-Revised
y	Years

## **Introduction**

The introduction of antenatal steroids, postnatal surfactant therapy<sup>1</sup> and improved standard of neonatal care has contributed to increased survival of preterm infants over the past decades.<sup>2</sup> The incidence of preterm birth in Norway is 7.5% and this equals approximately 4400 infants per year.<sup>3</sup> Almost 70% of the preterm infants are born at gestational ages (GAs) of 34 – 36 weeks (w), so-called late preterm (LPT),<sup>2</sup> and the incidence of this subgroup has increased with 25% since 1990.<sup>4</sup> Furthermore, 5% of preterm births occur at <28 w (extreme prematurity; EPT), 15% at 28 – 31 w (severe prematurity) and 20% at 32-33 w (moderate prematurity).<sup>2</sup> During the 90ties the increased survival of EPT appeared to be at the expense of increased morbidity.<sup>5</sup> However, there was a reduction in the cerebral palsy (CP) rates from 60.9/1000 live births in 1980 to 39.5/1000 in 1996<sup>6</sup> and outcome data on a Norwegian cohort of extreme low birth weight (ELBW; BW < 1000g) infants<sup>7</sup> revealed favourable morbidity and mortality rates compared to other countries.<sup>8,9</sup> In addition to the biological risk of prematurity, there is growing evidence that environmental factors such as parental adjustment to the preterm birth and specific parenting behaviours are important for the neuro-behavioural development of the infants.<sup>10,11</sup> Various intervention strategies have been developed to improve long-term outcomes,<sup>12-15</sup> but the long-term effects are sparse and conflicting.<sup>16,17</sup>

### **1. Neurodevelopmental outcomes in childhood, adolescence and young adulthood**

A substantial amount of research has shown that very preterm (VPT) and/or ELBW infants are at increased risk for neuro-behavioural impairments, including major neuro-sensory impairments (CP, blindness and deafness),<sup>18</sup> lower general intelligence,<sup>19</sup> specific cognitive deficits,<sup>20,21</sup> more learning disabilities,<sup>22,23</sup> behavioural and emotional problems compared to term peers.<sup>24,25</sup> Follow-up studies have shown that these problems persist through childhood until adolescent and early adult life.<sup>26-30</sup>

## 1.1 Cognition and intelligence tests

The term “cognition” refers to multiple processes including visual and auditory memory, abstract reasoning, complex language processing, understanding of syntax, visual perception, visual motor integration and visual spatial processing.<sup>31</sup> Cognitive outcomes in children however, are measured by the use of standardized tests (often referred to as intelligence tests) where scores across several cognitive tasks are summed to form an intelligence quotient (IQ) score for older children and a developmental quotient (DQ) for younger children.<sup>32,33</sup> The tests include assessment of visual-motor and perceptual abilities, and the predictive ability increase with increasing age.<sup>34</sup> The IQ tests yield scores on a normalized distribution (mean=100, standard deviation (SD) =15) which makes them statistically comparable.<sup>32</sup> Throughout the years the tests have developed from measuring global functions, to be more domain-specific, which increases the ability to differentiate among more subtle neuropsychological disabilities.<sup>32</sup> A commonly used test in pre-school age is the Bayley Scales of Infant Development (BSID),<sup>35</sup> yielding a mental developmental index (MDI) score and a psychomotor developmental index (PDI) score. In school age the Wechsler Preschool and Primary Scale of Intelligence Revised (WPPSI-R),<sup>36</sup> yielding a full scale IQ (FIQ), a verbal IQ (VIQ) and a performance IQ (PIQ), is commonly used. The IQ score does not necessarily reflect the full range of cognitive deficits and is not recommended used for children younger than 3 y.<sup>34</sup>

## 1.2 Cognitive outcomes

Considerable research has shown that VPT/ELBW children without severe disabilities are at increased risk for subnormal IQ scores,<sup>19,22,37,38</sup> specific cognitive deficits<sup>22,39</sup> and learning disabilities in school age.<sup>23</sup> A meta-analysis revealed that VPT school-aged children, regardless of country, age at assessment and regional versus hospital-based cohorts, scored 10.9 IQ points (95% confidence interval (CI); 9.2 to 12.5) lower than term born controls.<sup>19</sup> In comparison, a Norwegian cohort of ELBW 5-year old children<sup>40</sup> revealed a FIQ score of  $94 \pm 15$ , and with significantly lower mean PIQ compared to VIQ scores.<sup>40</sup> There were no significant gender difference for FIQ or VIQ, but the boys scored lower on the PIQ.<sup>40</sup> These

scores are in line with one other Norwegian study<sup>41</sup> and reports from Australia and Finland,<sup>22,42</sup> but higher than scores reported from studies in the US and France.<sup>43,44</sup> However, a recent publication found no difference in FIQ scores between VLBW-born 5-year old children born in the 2000s and term born controls, which is an improvement compared with earlier publications.<sup>37</sup> Low VIQ and motor problems at 5 y have been shown to predict need for extra support in school.<sup>45</sup> Some studies have demonstrated that preterm girls do better in cognitive tests than preterm boys,<sup>40,46,47</sup> but the literature is not consistent.<sup>48</sup>

However, a number of studies have shown a linearly decrease in mean IQ scores with an average of 1.5 – 2.5 points per week below 32 w of GA.<sup>19,49,50</sup> Hack and collaborators found that ELBW born children scored 13 points lower than term born controls, and 6 points lower than LBW controls matched for age, sex and ethnic group.<sup>50</sup> Some studies have found a deterioration in IQ with increasing age<sup>45,51</sup> whereas other studies have found the opposite.<sup>52</sup> A longitudinal study<sup>50</sup> which investigated cognitive, educational and behavioural development in a sample of children with BWs < 750g and two matching comparison samples (children with BWs 750 – 1499g and full term children) revealed an estimated IQ score of 1 SD below matched term in the <750g group. At 11 y this difference had increased to 1.5 SD.<sup>50</sup> At 16 y, however, the mean IQ for the <750g group had improved slightly, while the IQ scores for the two other groups remained unchanged.<sup>53</sup> The cognitive disadvantages of prematurely born children have been found to persist until adolescence and young adulthood.<sup>29,54-57</sup>

### **1.3 Mental retardation**

Mental retardation is characterised by several limitations in both intellectual functioning and adaptive behaviour expressed as conceptual, social and practical adaptive skills.<sup>58</sup> Intellectual function is considered to be significantly limited with an IQ score is <2 SDs below the mean of on a standardised intelligence test (generally IQ scores less than 70 or 75 depending on the test).<sup>19</sup> A borderline intelligence is defined as an IQ score between 1 and 2 SDs below the mean (generally IQs of 70 – 80 or 85).<sup>59</sup> An UK study from 1995 of infants born at  $\leq 26$  w of GA revealed that 21% fulfilled the criteria for mental retardation, and 25% had borderline intelligence, compared to 0 – 2% for controls born at term.<sup>18</sup> In comparison, a Norwegian

study of 5 year old ELBW children revealed that 5% had FIQ scores of 55-70 and 14% scored in the borderline intelligence range.<sup>40</sup>

#### **1.4 Academic achievement and executive function**

More than 50% of former VLBW and 60 - 70% of ELBW children require special assistance in school,<sup>60,61</sup> and despite normal intelligence ELBW born children have a 3-10 times increased risk of reading, arithmetic, writing or spelling problems compared with term born classmates.<sup>62</sup> Furthermore, language delay is commonly found in preterm infants.<sup>63,64</sup> Language development is closely related to executive function (EF), cognitive or hearing impairments<sup>65</sup> and is susceptible to influences such as low maternal education<sup>66</sup> and heredity.<sup>67</sup> A meta-analysis revealed that VPT and VLBW children scored 0.60 SD lower on mathematics tests, 0.48 SD lower on reading tests and 0.76 SD lower on spelling tests compared to term born peers.<sup>62</sup>

Impairments in cognitive skills are related to disturbances in the EFs.<sup>61,68-71</sup> The term EF refers to the coordination of interrelated processes in the brain and involves purposeful, goal-directed behaviour which is instrumental in cognitive, behavioural, emotional and social functions.<sup>65</sup> EF is critical in the integration of information and involves strategy use, cognitive flexibility and inhibitory control.<sup>65,72,73</sup> In contrast, executive dysfunction (EDs) reflect dysfunctions in a range of phenotypes such as conceptual reasoning, verbal working memory, spatial conceptualisation, planning and inhibition.<sup>65</sup> EDs are commonly found VPT and are associated with cognitive deficits and behavioural problems, but the exact relationships remain unclear.<sup>20,56,57,61,72,73</sup> ELBW children are two to three times more likely to have problems with initiating activities, flexibility, make strategies for problems solving, working memory, planning a sequence of actions in advance and organising information.<sup>20</sup>

The EDs have been shown to persist until adolescent and young adult life.<sup>56,57,74-77</sup> Lower IQ scores and many of the same EDs exhibited in childhood are commonly found in children born VLBW/ELBW adults compared to term born controls.<sup>57,78</sup> The pathogenesis has been suggested to be structural alterations in the brain with disturbances of the integrity of the

neural network connecting the prefrontal cortex to the brainstem, the cerebral lobes and the limbic and sub-cortical regions.<sup>79,80</sup> This is supported by neuro-imaging studies which have revealed reduced cortical and hippocampal volumes and increased size of the lateral ventricles in VPT adolescents compared to controls.<sup>81-84</sup>

### 1.5 Methodological considerations in outcome studies

The methodological problems related to outcome studies of preterm infants are extensively reviewed,<sup>34,85</sup> and some important points are summarised in Text box 1.

1. Assessment instruments should be used as references, not gold standards.
2. The content of the tests should always be carefully considered after revision.
3. When to decide if a child has a developmental delay, SD cut-offs are recommended prior to percentage delays.
4. Developmental quotient does not necessarily equal intelligence quotient, and it is important to emphasize which abilities are being assessed at different ages.
5. It is very important that developmental tests are administered by clinicians who possess a good understanding of normal development in children.
6. The use of prediction should be used with great care due to rapid developmental changes.

**Textbox 1.** Summarised according to Aylward.<sup>34</sup>

Correction for prematurity is generally recommended until 2 y of age.<sup>86</sup> When preterm children's performances on IQ tests are compared against published test norms, their cognitive disadvantages may be underestimated.<sup>34</sup> Although the tests are standardised on the basis of a mean IQ of 100 for normal populations, there is a tendency for an increase of the mean IQ score over time often referred to as "the Flynn effect".<sup>18,34</sup> The Flynn effect is an expression of an upward drift of the mean IQ scores by 0.3 – 0.5 per year as a function of increased time from standardisation of the test.<sup>87</sup> The explanation for this phenomenon is not clearly

understood, but more years in school and a constant increase of stimulation from the media and the internet may contribute to improved abilities in solving abstract problems among children and adolescents.<sup>88</sup> In the EPICure study, Marlow et al.<sup>18</sup> noted that the mean cognitive IQ score of the term born control group was 106 rather than 100. When this was entered into the analysis to re-standardise the mean, the percentage of children born < 26 w of GA who had cognitive scores < 2 SD below the mean increased from 21 to 49%. This underlines the importance of a concurrent comparing group in clinical trials.<sup>86</sup>

## 1.6 Behaviour problems

Prematurely born children have an increased prevalence of attention<sup>89,90</sup> and emotional problems.<sup>91</sup> The prevalence of internalising (e.g. withdrawn, anxious/depressed behaviour) and externalising (e.g. aggressive and delinquent behaviour) problems are less consistent.<sup>19,62</sup> However, shyness, conduct disorders, unassertiveness, withdrawn behaviour and social skill deficits occurs more frequently in LBW children compared to normal birth weight (NBW) children.<sup>24,90-92</sup> A meta-analysis by Bhutta et al.<sup>19</sup> found significant excess of total behaviour problems in preterm children in 81% of the studies included in the analysis, and more than twice the relative risk (RR) for developing ADHD (pooled RR: 2.64;95% CI: 1.85 to 3.78) compared to term born controls. The sub-scale analysis revealed an increased prevalence of internalising symptoms in 69% and a higher prevalence of externalising symptoms in 75% of the included studies.<sup>19</sup> Externalising problems are more frequently reported in boys, whereas internalising problems are more common in girls.<sup>93</sup> The incidence of behavioural problems has been shown to be independent of cultural factors.<sup>94</sup> A population based study from Norway showed that 40% of prematurely born 11 year old boys had behaviour problems compared to 7% of their term peers.<sup>24</sup> Almost 1/3 was diagnosed with a specific psychiatric diagnosis, and these children were described as more inattentive with lower self-esteem and more social problems.

Long-term follow-up studies have shown that behavioural problems persist into adolescence and young adulthood.<sup>26,29</sup> There are, however, a discrepancy among parental and the adolescent reports.<sup>29,95</sup> In a study by Hack et al.<sup>29</sup> parents of VLBW men reported more

thought problems compared with the parents of NBW controls. In contrast to this, the VLBW men reported less delinquent behaviour, but besides this, no significant differences in internalising, externalising or total problems compared with NBW peers. The prematurely born adolescent girls reported more withdrawn and less delinquent behaviour, and twice as many (30%) rated internalising behaviour above the clinical cut-off compared to controls (16%). Their reports were partly consistent with their parents, who reported significantly higher scores on the anxious/depressed, withdrawn and attention problems subscales compared with parents of the control group.<sup>29</sup> In a Norwegian study, parents of VLBW male adolescents reported more behaviour and emotional problems, and less social competence compared to classmate controls.<sup>26</sup> The adolescent boys however, reported less behaviour problems and similar or even higher competence, than their normative peers. The teenage adolescent girls reported increased emotional and behavioural problems. The self-reported behaviour problems among the girls were in contrast to parental reports, reflecting the difficulties for parents to recognise emotional problems among teenagers.<sup>26</sup>

### **1.7 ADHD and other psychiatric diagnoses**

The increased prevalence of attention problems and ADHD among prematurely born children is a robust finding.<sup>19,62,89,93,96,97</sup> Symptoms suggestive of ADHD occur 2.6 to 4 times more frequently in VLBW/ELBW compared to controls, and almost 50% of LBW children display symptoms of ADHD in childhood and adolescence.<sup>19,65,98,99</sup> Children with ADHD often display externalising symptoms such as aggression and disruptive behaviour, and this combined with attention problems may contribute significantly to problems in school, social settings and establishing of friendships.<sup>27,100</sup> However, the hyperactivity component and other co-morbid disruptive behaviour are less common in LBW children with ADHD compared to term born children with the same diagnosis.<sup>32,24,26,93,96,101-103</sup> The reasons for this have been suggested to be that prematurely born children exhibit a more “pure” form of ADHD, or the symptoms are sub-clinical.<sup>32</sup> Studies have shown that preterm birth, medical and genetic factors are more strongly associated with ADHD than social factors.<sup>104</sup> The exact pathogenesis is not clearly understood, but disruptions in cortical and brain connectivity (including cortical

/sub-cortical circuits connecting the frontal, striatal and thalamic regions) leading to deficits in inhibition and working memory have been suggested.<sup>62,105</sup> ADHD is commonly associated with the complex version of Developmental Coordination Disorder (DCD)<sup>106</sup> characterised by poor motor coordination and adaptation.<sup>107,108</sup>

The prevalence of other psychiatric disorders in preterm children has been estimated to 25 – 28%.<sup>32</sup> One study revealed that 27% of LBW 11 year old children had a psychiatric diagnosis compared to 9% of NBW controls.<sup>24</sup> Besides ADHD, which was the most common diagnose, depression, separation anxiety, phobia, and conduct disorders were other common morbidities.<sup>24</sup> These findings are supported by other studies.<sup>27,84,103</sup> Long-term follow-up studies have revealed an increased incidence of depression and anxiety in adolescence,<sup>96,99,109</sup> but less evidence for major psychiatric disorders.<sup>110</sup> In a Swedish study however, there was a stepwise increase in psychiatric hospital admissions and suicidal behaviour with decreasing GA and SES.<sup>111</sup>

## **2. Factors affecting neonatal outcomes**

The variability in outcomes are likely to be a result of complex interactions involving genetic, perinatal and social-environmental factors,<sup>21</sup> and research has revealed that BW, GA and the severity of medical complications only partly explain the variance for cognitive outcomes.<sup>8,18,40,68,112,113</sup> The risk of neonatal complications increase with decreasing birth weight (BW) and GA.<sup>7,18,32,42,114</sup> Intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL), bronchopulmonary dysplasia (BPD) in addition to frequent apnoeas and bradycardias, serious infections, hyperbilirubinemia and persistent ductus arteriosus in the neonatal period are all factors known to have an impact on CNS integrity.<sup>115-117</sup> However, a number of other factors such as parental factors and SES may affect outcomes directly or indirectly.

## 2.1 Neonatal complications of prematurity

Although all organs are immature, the brain<sup>118</sup> and the lung<sup>119</sup> are particularly vulnerable to the consequences of preterm birth. A meta-analysis revealed that the presence of three common morbidities, BPD, PVL or ventricular enlargement, and severe retinopathy of prematurity (ROP) were associated with a significant increase of poor long-term outcomes in ELBW infants.<sup>120</sup> BPD is associated with lower intelligence scores,<sup>121,122,123</sup> more behavioural problems<sup>122,124,125</sup> and ADHD.<sup>121</sup> Furthermore, prematurely born children with BPD are at increased risk of speech and language disorders,<sup>126,127</sup> visual-spatial perception deficits,<sup>128</sup> auditory impairments,<sup>129</sup> EDs,<sup>53</sup> minor motor disorders and CP.<sup>122,127</sup> PVL, severe IVH, and white matter injury (WMI) are precursors of neurosensory, cognitive and motor impairments.<sup>31,130-134</sup> Magnetic resonance imaging (MRI) studies of prematurely born children and adolescents have shown delayed myelination<sup>135</sup> and reduced volumes in specific cortical areas<sup>80,136-141</sup> which are significantly associated to EDs and psychiatric symptoms.<sup>80,84,142</sup> CP is often accompanied by various disturbances of cognition and other neurological difficulties, and a significant proportion of the children have psychological symptoms or social impairments sufficiently severe to warrant referral to specialist services.<sup>143</sup> This increased risk may be explained by the direct link between brain and behaviour<sup>144</sup> or that negative social experiences (i.e. being bullied or feeling excluded) contribute to emotional or behavioural maladjustment.<sup>145,146</sup>

## 2.2 Visual and hearing impairments

Intact hearing and vision is fundamental for normal cognitive and behavioural development.<sup>61,147,148</sup> However, preterm infants are at increased risk of severe ROP,<sup>9,149</sup> which is an important cause of visual impairments or blindness.<sup>150</sup> The severity of ROP is closely related to the degree of ND impairments,<sup>148,151,152</sup> and the most severe forms are associated with lower PIQ scores and problems with fine and gross motor function.<sup>40,152</sup> Despite normal vision, VLBW born children and adolescents display more difficulties in processing and analysing visual information compared to controls<sup>83,141,153</sup> which affects both daily life and learning abilities in school.<sup>154,155</sup> Recent follow-up studies report the prevalence of

neurological hearing deficits to be in the range from 0.8 – 6%.<sup>1</sup> The majority of hearing impairments are sensorineural, and prematurely born children also exhibit problems with auditory processing and discrimination.<sup>31,156</sup>

### **2.3 Minor motor impairments**

Dystonia without CP is a common minor motor impairment characterised by excess extensor tone in the trunk and the legs, increased hip adductor tone and delayed supporting reactions.<sup>157,158</sup> The peak incidence is 7 months and most resolves during the 2<sup>nd</sup> year of life.<sup>159</sup> Dystonia is associated with increased risk of later cognitive and motor problems including CP, minor neurological dysfunctions (MND), ADHD and aggressive behaviour.<sup>158,159</sup> DCD and MND are other common minor motor impairments described in prematurely born children.<sup>1,160</sup> These morbidities include a wide variety of deficits of gross and fine motor performance which persist during childhood and into adolescence, and are often associated with subtle or “soft” neurological signs and reduced neuropsychological function.<sup>160,161</sup> Children with DCD have worse outcomes on cognitive and academic test scores (up to 1 SD below children without DCD), and more adaptive and externalising behaviour problems.<sup>160</sup> MND occur in a simple and a complex form and the latter is strongly associated with perceptomotor and sensory integration.<sup>161</sup> However, children with poor cognitive outcomes may have problems to understand and perform the test, and thus bias the results.<sup>42,61</sup>

### **2.3 Other factors influencing outcome after preterm birth**

Socioeconomic status (SES), typically measured by maternal education and/or income, and other social risk factors<sup>40,52,55,162</sup> become increasingly important for child development in the pre-school (2-5 y) and school (>5 y) age.<sup>32,86,163</sup> High maternal education is a strong predictor of later IQ which probably reflects both social, educational and genetic influences<sup>52,55,164,165</sup> and low maternal education has been shown to predict the need for ADHD-medication in school-age.<sup>166</sup> Maternal education is associated with verbal, academic and intelligence

outcomes, whereas medical/biological factors are more related to neuropsychological, motor and perceptual-performance outcomes.<sup>111,167-169</sup> There has been less focus on the paternal education and infant development, but one study revealed that more educated father's spent more time with their preterm infants, and this improved cognitive outcomes at 3 y.<sup>170</sup>

Genetic factors have been found to account for up to 72% of the variance in intelligence.<sup>171</sup> However, in children with high biological risk, the genetic factors may be shadowed by environmental factors<sup>172</sup> and an optimal environment may stimulate to a cognitive “catch-up”.<sup>173,174</sup> In a Norwegian study, SES was a stronger predictor of child IQ at 5 and 11 y than BW,<sup>41,175</sup> although the literature is not consistent.<sup>49</sup> Preterm infants are frequently born into families of lower SES,<sup>176,177</sup> and combined with the biological risk factors, this is commonly described as a “double jeopardy”.<sup>178-180</sup> This term is an expression for when non-optimal biological and environmental risks work synergistically and constitute negative effects on the development and later functioning of the child.<sup>180,181</sup>

### **3. Preterm birth; impact on parents**

Most parents experience preterm birth highly stressing and difficult<sup>182-185</sup> and frequently report more early bonding difficulties,<sup>186</sup> grief,<sup>187</sup> lower self-confidence<sup>188</sup> and care-giving burdens<sup>189</sup> compared with parents of term infants. Furthermore, both parents are at increased risk for developing depression, anxiety and post-traumatic stress symptoms after discharge from hospital.<sup>190-194</sup> Parenting stress and maternal anxiety have been shown to predict later cognitive impairments and internalising behaviour problems in the pre-school age.<sup>193</sup> The increased emotional burdens for parents have been shown to persist through childhood and adolescence,<sup>195</sup> with the highest impacts if the teenager suffers from psychiatric disease and/or CP.<sup>196</sup> However, families also experience positive effects of preterm birth such as a closer relationship within the family and with friends.<sup>197</sup>

### **3.1 Sensitive parenting**

A good quality of the parent-child interaction is protective and is an important fundament for the infants' later development and competence.<sup>198,199</sup> Already in 1969, Lewis and Goldberg found a positive correlation between maternal responsiveness to the infants' behaviour and short-term cognitive development.<sup>200</sup> One definition of sensitive parenting is "the parental ability to behave in a manner that gives the children an opportunity to act autonomously and express their experiences and emotions in an authentic way".<sup>201</sup> The role of the sensitive caregiver is to modulate the infant's level of arousal especially in stressing situations by calming and restore the infant to a tolerable emotional state free of anxiety.<sup>202</sup> The early mother-infant interaction can be viewed as a bio-behavioural system; when an infant sees a responsive mothers face, endorphins responsible for the pleasurable aspects of social interaction and attachment are released.<sup>203</sup>

### **3.2 Contingent response**

Closely related to sensitive parenting is the parental ability to respond in a contingent way.<sup>204</sup> A contingent response is an expression of how quick and consistent parents respond to their infant's behaviour such as crying, wakefulness and other behavioural states.<sup>200,204,205</sup> The optimal infant is awake and attentive, but some infants are drowsy and inattentive, or distressing and overactive. The sensitive and contingent caregiver in the drowsy, inattentive infant would use behaviours designed to arouse and focus the child, whereas in the distressing, overactive infant the strategies selected would be to soothe and calm the child. Good dyadic attachment relationships increase the infants' ability to soothe and calm themselves, and this ability is crucial for later development of advanced social, emotional and cognitive functions.<sup>206</sup> Prolonged experience of contingent stimulation generates an expectation of control or a sense of the "self" as an effective agent in the infant which forms effective pathways for attraction of others attention.<sup>207</sup> Through these experiences the infant learn that their responses have an effect on the social environment,<sup>208</sup> and the more consistently these experiences are, the more likely he or she will approach a new object or situation with the expectation that they can control the effects.<sup>200,207</sup>

### 3.3 Parent-infant interactions

Secure parent-infant interactions are important modulators of biological stress responses,<sup>209</sup> and animal studies have revealed that sensitive, contingent maternal behaviour may change the gene-controlled patterns of stress responsivity in the infant.<sup>209</sup> Rodent models showed that sensitive maternal behaviour promoted less reactive and more resilient stress responses through permanent modifications of the deoxyribonucleic acid (DNA) which controls the expressions of glucocorticoid (GC) receptors in the brain.<sup>209</sup> However, parental responses or abilities to respond contingently are influenced by the infants' temperament and responsiveness.<sup>210,211</sup> Preterm infants are more fussy and irritable, show more negative emotions, are less focused and give less eye-contact compared with NBW infants.<sup>212-215</sup> These behaviours may be interpreted as negative by the parents and contribute to increased stress, anxiety and consequently reduce the parental abilities to be a responsive and contingent caregiver.<sup>211</sup>

Mothers of preterm infants are described to be more intrusive, active, stimulating and at the same time more distant in the interaction.<sup>216,217</sup> These behaviours have been related to increased level of distress and discomfort in the parental role.<sup>215,216,218</sup> In the literature two patterns of mother-infant dyads have been described; (1) a cooperative pattern which describes a sensitive mother and a cooperative-responsive infant, and (2) a controlling pattern which describes a controlling mother and a compulsive-compliant infant.<sup>11</sup> The mother-preterm dyad is most likely to follow the controlling pattern which increases the risk for behavioural and eating-problems in the long-term.<sup>11</sup> Furthermore, sensitive and responsive father-infant interactions are related to a more optimal child development.<sup>210,219</sup> In particular, fathers' sensitivity to infant behaviour and his ability to engage the infant in interactions is associated with emotion regulation in 12-month-old infants<sup>220</sup> and language development at 18 months.<sup>205</sup> Additionally, low-income fathers who are more responsive in free play with their children are almost 5 times more likely to have children within the normal range in cognitive development at 24 months compared to controls.<sup>219</sup>

Disturbed parent-child synchrony has been shown to predict cognitive development in preterm infants.<sup>10</sup> Parents who displayed more negative affects with their preterm infants were

more likely to rate their children as withdrawn, anxious and inhibited. On the contrary a good parent-infant synchrony lead to better social-emotional competence in the children and their mothers were more positive, warm and sensitive. <sup>10</sup>

### **3.4 Parental child-rearing attitudes**

Parental child-rearing attitudes are important factors for infant development. <sup>221</sup> The “typological model of parenting styles” is one of the most widely employed models within the field of child-rearing research. <sup>222</sup> Within this model there are two orthogonal factors (1) responsiveness (i.e. if parents foster individuality and self-assertion) and (2) demandingness (i.e. the claims parents make on children to become more integrated into society by behaviour regulation, direct confrontation and maturity demands). <sup>222</sup> From these dimensions four parenting styles have been created; (1) authoritarian (high control, low warmth), (2) authoritative (high control, high warmth), (3) permissive (low control, high warmth) and (4) rejecting-neglecting (low control, low warmth). <sup>223</sup> Furthermore, Dekovic<sup>224</sup> has described two theoretical categories regarding parental child-rearing principles called “nurturance” and “restrictive”. Nurturant child-rearing attitudes describe rational guidance, inductive reasoning, encouragement of child independence and parent-child communication, whereas restrictive child-rearing attitudes describe use of physical punishment, verbal reprimands, power-assertive strategies and discouragement of the child’s emotional feelings. <sup>224</sup> Generally, research has documented that in western culture nurturant child-rearing attitudes are associated with positive development of the child, <sup>225-227</sup> whereas more adverse outcomes are related to restrictive child-rearing attitudes. <sup>225,228,229</sup>

Parents of VLBW infants have been described to be less likely to use guilt as a control strategy and less child-centred in their child-rearing attitudes. <sup>221</sup> In a Norwegian cohort of small for gestational age (SGA) born children Andersson and collaborators<sup>225</sup> studied the impact of maternal child-rearing attitudes on VIQ and PIQ at the age of 5 y. They found that restrictive child-rearing attitudes were negatively correlated with cognitive outcomes. However, this significant negative correlation disappeared when the effects of maternal IQ and SES were controlled for. Furthermore, maternal nurturant child-rearing attitudes were

significantly related to VIQ and PIQ in boys, also after adjustment for maternal IQ and SES. They speculate that maternal child-rearing attitudes have stronger impact on cognitive development in boys compared to girls.<sup>225</sup> Parents of VLBW adolescents have also been found to be more protective compared to parents of term born controls.<sup>195</sup>

#### **4. Preterm birth; impact on economy\***

Despite the large body of work on the clinical sequelae of preterm birth, relatively little is known about the economical consequences for the health services, public sectors of economy, the families and the society. The majority of the total societal costs are associated with infants born >28 w of GA since they account for the vast majority of preterm births and 1/3 of total medical costs are accounted for by the ELBW infants.<sup>230</sup> In the United States, the societal economic burden associated with preterm birth has been estimated to be €35,000 per infant.<sup>230</sup> Nearly 2/3 of the societal costs were accounted for by medical care services, with > 85% delivered in infancy.<sup>230-232</sup> The cost per infant after preterm birth has been estimated to €22,300, whereas €2,550 was attributed to maternal delivery, €800 to early intervention services, €1,500 to special education services, and €7,500 for lost household market and labour market productivity associated with major disabilities.<sup>230</sup> Non-healthcare costs such as travel expenses, lost earning and family accommodation have been estimated to 4% of total costs.<sup>233</sup> Healthcare costs following the initial hospital discharge are inversely related to GA and BW,<sup>231</sup> and the mean cost of special education services in school age have been estimated to approximately €12,500.<sup>234</sup> Few studies have considered broader societal costs attributed to preterm birth. However, Tommiska et al.<sup>233</sup> estimated wage losses by parents during the first year at €5990 for ELBW compared to €880 for the NBW group. In a more recent Finnish study by Korvenranta and collaborators<sup>235</sup> found a small difference in average health costs during the 5<sup>th</sup> year of life of approximately €300 between term born children (€749) and

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\* For a more uniform presentation in this section, estimated costs have been converted to Euro and rounded to the nearest 1000.

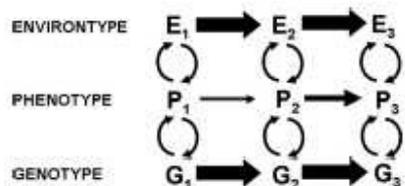
VLBW born children (€1,023) without morbidity. In VLBW 5-year olds with morbidities though, the average health costs were tripled (€3,265).<sup>235</sup> The yearly hospitalisation costs decreased with age, but in contrast, cost related to other health-care services increased.<sup>235</sup> Despite this, the total costs during the fifth year of life were still low compared with the initial hospitalisation costs which were estimated to €54000 per VPT infant.<sup>235</sup> A Swedish study of prematurely born young adults revealed that 13,2% of children born at 24 to 28 w of GA and 5,6% born at 29 to 32 w of GA received economic assistance from the society because of handicap or persistent illness, which equals four times more than those born to term.<sup>236</sup> The total economic gain for the society in terms of taxes and decreased costs from benefits, if all long-term effects could have been prevented, were estimated to 65 million Euros in one year.<sup>236</sup> These numbers underlines the importance of developing intervention strategies which lead to persistent improvements of long-term outcomes in preterm infants.

## **5. Early intervention**

The medical, societal and economical consequences of preterm birth have resulted in increased focus on early intervention programmes to prevent long-term impairments. The term “early intervention” (EI) is commonly used to describe programmes directed to infants and pre-school children at-risk for developmental problems,<sup>237</sup> and refers to; “..an experimental, educational or therapeutic treatments designed either to prevent or ameliorate an anticipating or existing deficiency among a target population of children (p. 155 – 156)”<sup>238</sup> There is a widespread agreement on the value of starting early in infancy, when plasticity of the brain is maximal rather than addressing problems at a later age.<sup>239</sup> Due to the complexity in infant development, different EIs may composite different components and the services may be provided by a variety of disciplines.<sup>240</sup>

## 5.1 The theoretical framework of early intervention

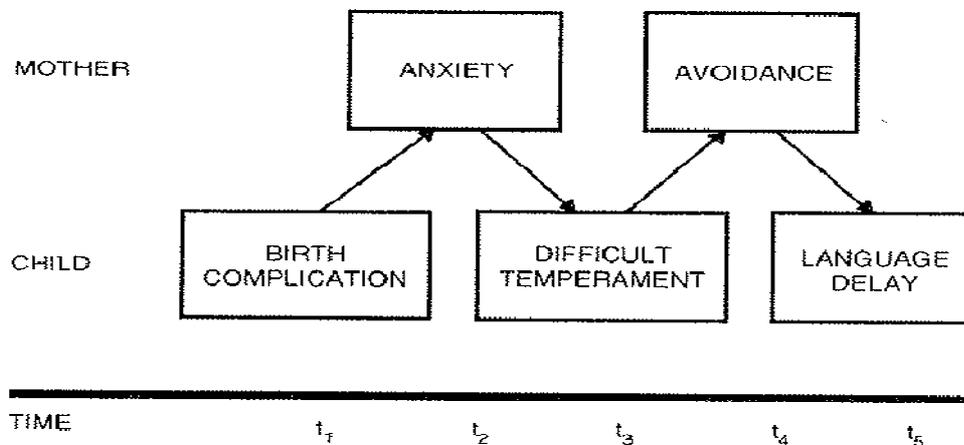
An important issue before designing an EI programme is to identify the crucial factors of infant development regulation, and then try to change the development through EI. However, it is often difficult to determine the correct factors. One alternative is to understand determinants of development in sufficient degree to choose the appropriate level for the intervention based on the developmental stages of the child, the family and other available supports.<sup>241</sup> Physical outcomes in each individual is regulated by a biological organisation, whereas a social organisation regulates the way human beings fit into the society. According to Sameroff<sup>242</sup> this organisation operates through family and cultural socialisation patterns, and has been described as the “enviromtype” analogues to the biological “genotype”. An intervention can be understood in terms of a completion of transactions within the enviromtype, and the development of a child’s behaviour as a product of transactions between the phenotype (i.e. the child), the enviromtype (i.e. the source of external experience) and the genotype (i.e. the source of biological organisation).<sup>241</sup> The regulatory system is reciprocally determined at each point in the development. This is illustrated in figure 2.



**Figure 2.** Regulation model of development with transactions among genotype, phenotype and enviromtype. Reprinted from<sup>241</sup> (p.143) with permission from Cambridge University Press.

## **5.2 The transactional model of development and contingent responsiveness**

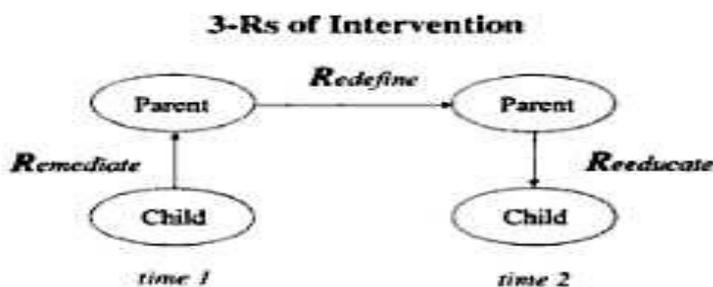
The transactional model of development is the most frequently applied models on child development.<sup>243</sup> Transactions occur when the activity of one element changes the usual activity of another, either quantitatively or qualitatively.<sup>244</sup> Transactions should not be mixed up with “interactions” which occurs when the activity of one element is correlated with the activity of another, e.g. a smile is reciprocated by a smile which elicits further smiling and so forth.<sup>244</sup> Within the transactional model of development, child development is seen as a product of the continuous dynamic interactions of the child and the experience provided by his or her family and the social context.<sup>244</sup> What is innovative within this model is the equal emphasis placed on the bidirectional effects on the infant and the environment.<sup>244</sup> Thomas, Chess and Birch demonstrated already in 1968 that children with difficult temperament stimulated to maladaptive parenting and later developed behavioural disturbances.<sup>245</sup> The behavioural deviance was found only in those parent-infant dyads where the parents reacted negatively to the temperament of their children. Transferred to preterm infants the transactional model of development may be illustrated in the following way; a complicated preterm birth may turn a calm mother into an anxious mother. Due to prematurity, the infant may develop irregularities in self-regulation which give the appearance of a difficult temperament. This makes the infant less pleasant to be with and the maternal response will be to spend less time with the child. The final result is less maternal interaction and stimulation of the child, and a consequence for the child can be development of language delays in the pre-school and school age.<sup>243</sup> This is illustrated in figure 3.



**Figure 3.** Example of transactional process leading to a developmental problem. Reprinted from <sup>241</sup> (p.142) with permission from Cambridge University Press.

### 5.3 The transactional model of intervention<sup>241</sup>

The transactional model of development has implications for EI in preterm infants. Changes in behaviour are a result of a number of interchanges among individuals within a shared system following specifiable regulatory principles described in the literature as “*remediation*”, “*redefinition*” and “*re-education*” (often referred to as “three R’s of intervention”).<sup>241,246</sup> This is illustrated in figure 4.



**Figure 4.** “The three R’s of intervention.” Reprinted from <sup>241</sup> (p. 150) with permission from Cambridge University Press.

### *5.3.1 The remediation strategy*

The remediation strategy is implemented outside the family by a professional interventionist whose goal is to change an identifiable condition in the infant. These interventions are often based upon neuro-developmental therapy (NDT) which aims to modify sensory inputs and/or abnormal movement patterns to improve motor outcome.<sup>247</sup> Whereas it previously was thought that preterm infants needed extra stimulation to catch up with term infants it is now known that sensory stimulation needs to be decreased to optimise infant development. Field et al.<sup>248</sup> demonstrated that preterm infants who received gentle stroking in the prone position and passive movements of the limbs in supine position showed more weight gain, mature habituation, better orientation, more awake periods and better scores at the BSID test one year after the intervention compared to controls.<sup>248</sup> The author suggested that the intervention led to a more responsive, active and alert infant which improved the parent-infant interaction.<sup>248</sup> The remediation strategy is most effective when the intervention is time-limited and within a family where the parents can take over routine care-giving activities once the intervention is complete.<sup>241</sup> If the family cannot co-operate successfully the redefinition strategy needs to be implemented.

### *5.3.2 The re-education strategy*

The re-education strategy is a teaching intervention strategy directed toward adults who lack the knowledge base in raising children (e.g. alcoholic or teenage parents).<sup>241</sup> The “Infant Health and Developmental Program” (IHDP) is an extensive EI study which aimed to enhance development of LBW infants.<sup>249</sup> The IHDP employed a variety of EI strategies to enhance infant development, including a home based component (weekly home visits) which helped the mother to improve her interaction and teaching skills with the child, and the mothers were taught about problem solving and provided social support.<sup>250</sup>

### 5.3.3 *The redefinition strategy*

The redefinition strategy may be selected if there is a mismatch between the family codes and the child's behaviour.<sup>241</sup> In this model, redefinition is directed toward a facilitation of more optimal parenting interactions through an alteration of parental beliefs and expectations when parents have defined the child as abnormal or are unwilling to provide normal care-giving. Intervention strategies may be directed (1) toward parents who disqualify themselves as good caregivers by automatically translating the child's physical or mental handicap into a condition which only can be treated by professionals<sup>251</sup> or (2) toward parents who become disenchanting in child-rearing because their child's performance does not fit with their own expectations or (3) toward parents who are prevented by own childhood experiences to provide current care-giving demands.<sup>241</sup> Preterm infants are often sent home in a biologically vulnerable state which may overwhelm their parents. Additionally, the parents often have attributions of their child's behaviour which may prevent them from sensitive parenting. In this case, redefinition intervention strategies aims at normalising the care and decrease the emphasis on the "special care" demand among the parents by teaching them about what is normal behaviour for preterm infants, and then hopefully make them more able to proceed with their intuitive parenting.<sup>241,252</sup>

"The Vermont Intervention program for Low Birth Weight Infants", often referred to as "the Vermont study" is a well-known EI study which used the re-definition strategy.<sup>253</sup> The intervention programme used in this study was "The Mother Infant Transaction program" (MITP) which aimed to redefine the maternal expectations of the infant's behaviour and through this make parents more able to interact with their preterm infant in a more dynamic and sensitive way.<sup>254</sup> This is one of the few EI programmes/studies which have demonstrated persistent beneficial long-term effects in prematurely born children.<sup>255,256</sup> The MITP was based on the Bromwich's concept of a stepwise progression in parental nurturing skills after childbirth, implemented in the hospital-home transition and provided by nurse specialists.<sup>257</sup> When the MITP was designed, the following facts about preterm infants and their parents were emphasised:<sup>15</sup>

1. Preterm infants are poorly regulated, unpredictable in their autonomic responses and inaccessible for parents because of the incubator which in total contributes significantly for less alertness and capacity for social interaction.
2. Parents worry about survival of their preterm infant, and often find them aversive in skin colour and size.
3. Mothers often feel guilt about the preterm delivery and not for carrying the foetus to term, they suffer from a lack of self – confidence in caring for the tiny infant and find the NICU environment strange and scary.

The researchers anticipated that all these factors would contribute to a downward spiral of unfavourable mother-infant interactions, and saw a possibility to intervene before an adverse pattern of interaction had been initiated.<sup>15</sup> More detailed description of the content of the intervention programme will follow in section 7.2.1. The programme was tested in a randomised clinical trial (RCT) including preterm infants with BW <2250g, and four reports have been published on developmental outcomes from 6 months until 9 y.<sup>15,253,254,258</sup> In summary, no significant differences were found between the two preterm groups at 6 and 12 months, and both groups lagged significantly behind the NBW group. At 2 y, the intervention group scored higher on the BSID-MDI, but the difference did not reach significance. Thereafter, the divergence between the intervention and control group increased, with children in the intervention group scoring higher on cognitive outcomes at the ages of three and four y. This divergence continued to increase at 7 and 9 y, where the children in the intervention had similar (7 y) and higher (9 y) scores than the NBW group. Compared to the preterm control group, the difference on the cognitive scores at 7 y was estimated to 0.96 SD, which was considered to be of practical importance for the children's academic and adaption progress.<sup>258</sup> At 9 y, children in the preterm intervention group were not inferior to the NBW children on any measure.<sup>258</sup> The authors suggested that the MITP facilitates development of the infant indirectly through more favourable mother-infant transaction patterns, the “sleeper effect” or a combination of both.<sup>258</sup> The “sleeper effect” describes a phenomenon in which transactions cause change over time.<sup>259</sup> However, there were several limitations of this study, such as few,

rather mature infants who were born in the pre-surfactant era and before antenatal steroids were widely used.<sup>258</sup> No other follow-up reports after 9 y are published.

#### **5.4 Post-discharge EI programmes**

Various types of post-discharge EI programmes have been developed, but no consensus exists on the best approach to achieve optimal development for preterm infants. The different programmes focus on different aspects of development dependent on the outcomes being targeted, and there is some evidence that EI programmes focusing both on the parent-infant interaction and infant development are more effective.<sup>16</sup> A Cochrane review on post-hospital EI programmes revealed an improved DQ with 0.46 SD at infant age, and 0.46 SD higher IQ score in pre-school age.<sup>16</sup> The effects did not sustain until school age and the EI programmes which focused on the parent-infant relationship were most effective.<sup>16</sup> These results were confirmed in another meta-analysis by Vanderveen and colleagues.<sup>17</sup> In this meta-analysis, 25 trials with different interventions such as parent education, infant stimulation, home visits or individualised care, were included. This study found significantly higher mental and physical performance scores in favour of the intervention groups at corrected age of 12 months. There were still favourable mental outcomes at 24 months corrected age, but no longer on motor outcomes. At 5 y, however, there were no longer significant effects in favour of the intervention groups on neither mental nor motor outcomes.<sup>17</sup> Limitations of these studies are the heterogeneity of the patient populations in terms of BW and GA and many of the studies were performed before the modern era of neonatology (pre-surfactant and administration of maternal steroids). The authors of both meta-analyses call for more RCTs to address the effectiveness of early developmental intervention programmes on both motor and cognitive outcomes in preterm infants.<sup>16,17</sup>

NDT aims to improve motor outcomes through modifications of sensory inputs or abnormal movement patterns through active or passive techniques.<sup>247</sup> The benefits of NDT are inconclusive. One study revealed short term benefits on motor outcomes at 18 months of age,<sup>260</sup> but a Cochrane review concluded with little or no effects of NDT on motor outcomes in the infant and pre-school age.<sup>16</sup>

## **5.5 Newborn Neonatal Individualised Developmental Care and Assessment Program (NIDCAP)**

“Developmental care” is newborn care which aims to minimise the impact of the NICU environment, invasive care practises and encourage to more parental participation in the care of the newborn preterm infant. NIDCAP is an interventional approach which has been implemented in an increasing number of NICUs during the last 10 years. Through careful observations of the infants behaviour (e.g. colour, visceral responses, motor state, facial expressions and attention),<sup>261</sup> NIDCAP aims to control external stimuli (vestibular, auditory, visual, tactile), optimise the positioning of the infant to provide a sense similar to the intrauterine experience, and cluster the nurse activities.<sup>262</sup> The observations are used to evaluate the infant’s tolerance and capacity to the environment and care-giving activities, and use them as a fundament for optimising the care and decrease possible detrimental effects of the NICU environment. Trained NIDCAP observers are educated on certain NIDCAP centres, and the training cost is approximately U.S. \$ 6,000 per observer.<sup>263</sup>

Although some trials have demonstrated beneficial effects of NIDCAP on short term outcomes such as duration of ventilation and BPD<sup>262,264</sup> many of these studies are of a small sample size and lack masked outcome evaluators.<sup>262</sup> Other positive effects reported after NIDCAP use includes higher Bayley scores at 9<sup>261,265</sup> and 12 months.<sup>266,267</sup> A few studies have reported developmental outcomes after 18 months with marginal effects on behaviour.<sup>268,269</sup> The Edmonton NIDCAP trial<sup>264</sup> found that NIDCAP infants had less disability, and mental delay in particular, at corrected age of 18 months, but they found no significant favourable effects measured with Bayley MDI. The results are in line with a study from the Netherlands which found no difference between the groups on Bayley at corrected age of 24 months.<sup>270</sup> To conclude, the long-term beneficial effects of the NIDCAP are conflicting, and further high-quality RCT studies are warranted.

## **Aims of the study**

To examine the effects of a modified MITP in preterm infants with a BW < 2000g on:

1. Parental child-rearing attitudes:
  - a. Do the modified version of the MITP:
    - i. Enhance more nurturant and less restrictive child-rearing attitudes at corrected ages of 12 months (mothers only), 24 and 36 months among parents in the preterm intervention group?
    - ii. Facilitate stronger agreement between parents in the preterm intervention group on child-rearing attitudes at corrected ages of 24 and 36 months?
  - b. Do nurturant and restrictive child-rearing attitudes among parents of preterm infants and term infants change during the study period of corrected ages of 12 – 36 months?
2. Cognitive and motor outcomes at corrected ages of 3 and 5 y:
  - a. Do the modified version of the MITP:
    - i. Improve cognitive outcomes in the preterm intervention group at corrected ages of 3 and 5 y?
    - ii. Improve motor outcomes in the preterm intervention group at corrected ages of 3 and 5 y?
3. Behavioural outcomes at corrected age of 5 y:
  - a. Do the modified version of the MITP:

- i. Lead to less parent reported behavioural problems in the preterm intervention group at corrected age of 5 y?
- ii. Lead to less behaviour problems among children in the preterm intervention group reported by pre-school teachers at corrected age of 5 y?

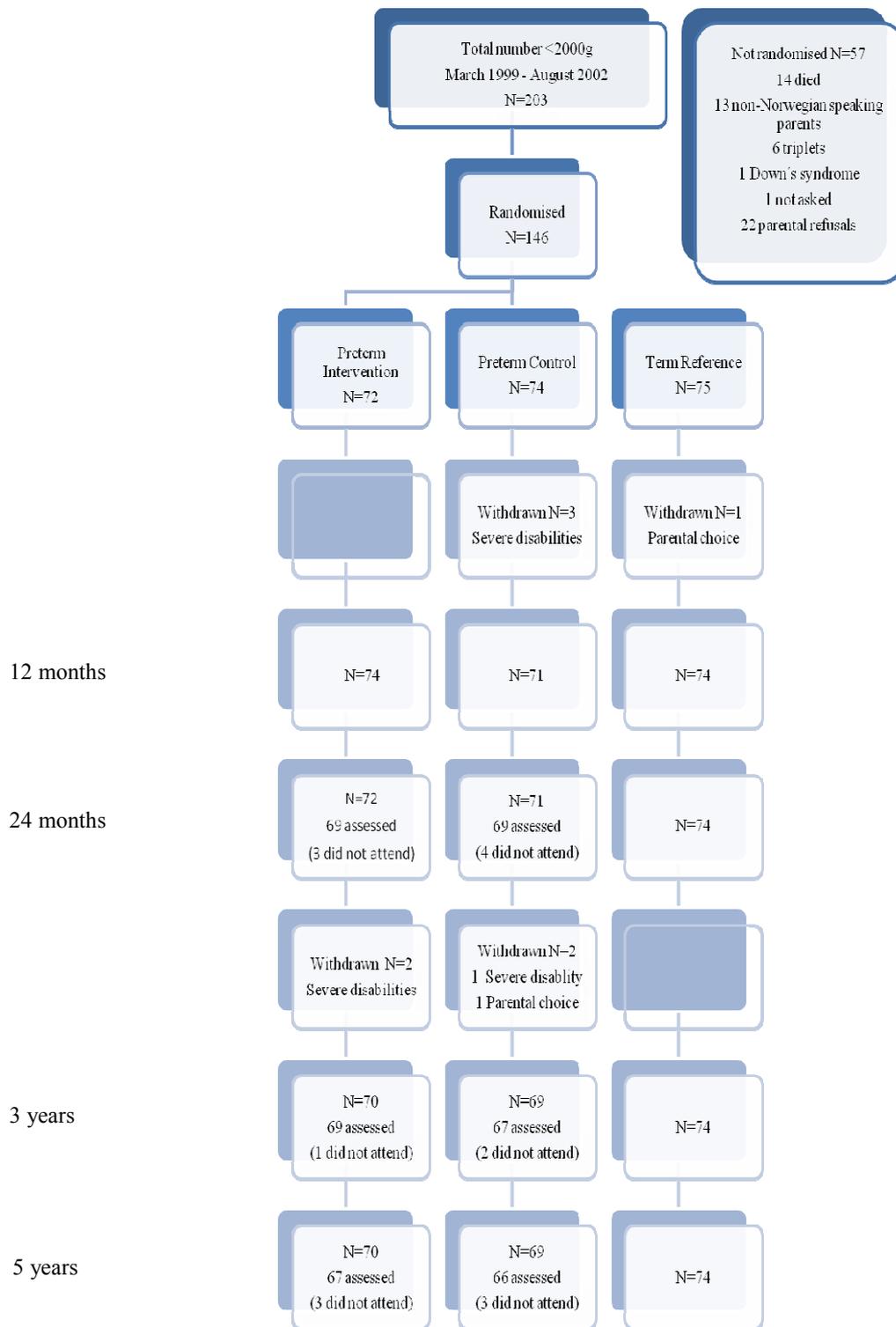
The papers included in this thesis are based on results from a more extensive study called “Project Early Intervention 2000” performed at the University Hospital North Norway (UNN) and Institute for Clinical Medicine at the University of Tromsø.

## **Materials and methods**

### **Patients and methods**

Preterm infants with a BW < 2000g treated at the University Hospital of North Norway (UNN) between March 1999 and September 2002, with no major congenital abnormalities and where the mothers' first language was Norwegian were eligible for the study. The parents were informed about the study about two weeks before planned discharge by the study coordinating nurse (Mrs. Tunby), and written informed consent was obtained if they agreed to participate. Within GA strata (<28 and  $\geq$ 28 w), infants were randomised into a preterm intervention (PI) or a preterm control (PC) group. The randomisation was arranged in random blocks of 4 and 6, using computer-generated random numbers. Allocation was by sealed opaque envelopes, identified by stratification group and consecutively numbered, which were opened by the coordinating study nurse after the parents had completed various questionnaires.

During the recruitment period 212 infants with BWs <2000g were born alive in Troms and Finnmark counties, and 203 (96%) were treated at UNN and eligible for this study. Of these 146 were randomised to the PI or the PC group. Because of the nature of the intervention, twin pairs were allocated to the same group and triplets were excluded. A term reference (TR) group of term born infants with at GA of  $\geq$ 37 w and BW >2800g without congenital anomalies and with an uncomplicated pregnancy and birth were recruited from the well-baby nursery. By using the hospital's birth registry, the parents of the first term baby born after a preterm infant allocated to the PI group, were asked to participate. If they declined the next parents of the next born infant was approach and so on. The patient flow until corrected age of 5 y is showed in Figure 5.



**Figure 5.** Patient flow until 5 y.

### **Schedule of the intervention**

The intervention programme used in this RCT study was a modified version of the MITP.<sup>15</sup> The modification was to add an initial debriefing session where the parents could talk about their experience of the hospital stay, and express feelings such as grief, disappointment or anger. Furthermore, both parents were encouraged to participate in the intervention sessions. After the initial session, the intervention consisted of one-hour daily sessions with both parents and their infant on 7 consecutive days, starting one week prior to planned discharge at a postmenstrual age of  $\geq 34$  w. These sessions were followed by four home-visits at 3, 14, 30 and 90 days after discharge. The EI programme was implemented by 8 neonatal nurse specialists trained especially for this intervention, and four were trained and certificated in the use of “Neonatal Behavioural Assessment Scale” (NBAS).<sup>271</sup> In our hospital, three nurses per 1000 live births were specially trained to deliver the intervention.

The timing of the intervention to the hospital-home transition was chosen in an effort to reduce the risk of spill-over effects in small NICU like ours. To maintain the consistency of the intervention, a detailed log of every intervention session was regularly reviewed and supervised by the coordinating nurse and a clinical child psychologist (Prof. Rønning). The participants in the PI group did not have access to the intervention nurses outside the scheduled intervention dates.

### **Summary of the intervention programme**

The intervention programme is summarised according to the Norwegian study protocol<sup>272</sup> and the publication by Rauh et al.<sup>15</sup> In this section, the primary caregiver will be referred to as the mother or “her” even though both parents were present.

*Session 1: Become acquainted.* In the first session, the nurse became acquainted to the mother, explained the intervention and demonstrated the infant’s unique potential for self-regulation and interaction by using the NBAS.<sup>271</sup>

*Session 2: Homeostasis.* The nurse introduced the mother to the behavioural indices of the homeostatic reflex system. By verbal explanation, handling of the baby and demonstration the nurse taught the mother to recognise the infants' cues and signs of stress through observations of the infants skin colour, respiration, visceral movements and activities. Furthermore, she learned how to analyse and reduce environmental stress and how to support the infants' homeostatic control through providing warmth, pauses, soothing sound and reduced lightening.

*Session 3: Motor system.* The mother was introduced to the concept of the motor system such as the tone, posture and movement of the infant. She learned how to distinguish different movements, muscle tones and immature movements from more well-modulated and organised movements. Additionally the nurse demonstrated how to inhibit twitches and tremor. The mother was taught different levels of behavioural organisation and guided in how to respond to the baby's cues in an effort to reduce stress and promote organisation.

*Session 4: State regulation.* The mother learned about the infant's different levels of sleep, drowsiness and alertness and how this could be recognised according to autonomic and motor characteristics. In addition, she learned how the infant responds to the different levels of consciousness and how they often show undistinguished, diffuse and poorly defined states of alertness. Together they noted the different predominant states and talked through how to recognise and take advantage of the quiet, alert state. Finally the nurse showed to the mother how the infant could regulate itself by for example sucking their own hands. The mother was encouraged to experiment with vocalisation and sounds, and to help the infant organise itself when distressed.

*Session 5: Social Interaction.* The nurse demonstrated how the infant could be roused to alertness, how long it could stay awake and how the awareness could be prolonged by external stimulation without inducing stress. Furthermore, she learned how the baby could imitate inanimate stimuli such as imitating the baby's facial expression or stimulation with a coloured red ball. In the same session she learned about signals of over-stimulation, hyper-alertness, exhaustion or inaccessibility.

*Session 6: Daily Care.* In this session, the mother learned how to imbed her increased sensitivity and responsiveness into daily routines and caretaking of the infant. In addition, the nurse helped to suggest how these situations could be an opportunity to learn more about her infant's cues, reduce stress, enhance organisation and enjoy the special characteristics and potential of the baby.

*Session 7: Preparing for home.* The mother and the nurse reviewed the intervention programme so far. Furthermore, the nurse encouraged the mother to trust her own assessments, take use of the new knowledge and try to implement it into daily routines. Finally, they scheduled the first home visit.

*Home visit 1 (three days): Consolidation.* The nurse and the mother reviewed the mutual attunement in the mother-infant dyad and talked through the adjustment to the home environment. The nurse evaluated if the maternal sensitivity and responsiveness to the infant's cues had deteriorated, and if so, the mother was invited to discuss possible problems. Furthermore, the nurse helped the mother to adjust her style and discuss activities (least and most enjoyable) for the infant. Through the whole visit, the nurse noted the mother's strengths which she supported and reinforced.

*Home visit 2 (two weeks): Mutual enjoyment through play.* In this home visit the nurse and the mother explored new play ideas and noted which activities the infant found most rewarding and enjoyable. The nurse suggested various techniques to help the parents to expand their play repertoire through tactile, visual and auditory methods.

*Home visit 3 (one month): Temperamental patterns.* The mother was introduced to different temperamental patterns, and taught how she could enhance the "fit" between the infant and herself by take into consideration her baby's likes and dislikes. Together they analysed the infants' temperamental patterns and she was guided how to adjust her interaction behaviour with the behaviour of the infant.

*Home visit 4 (three months): Review and termination.* In this final session the nurse and the mother reviewed the content of the intervention programme. The nurses reviewed the results

of the intervention and the mother was provided with the logbook of their baby's development perceived by the nurse through the programme.

### **The preterm control group**

The PC group followed the department's standard protocol for discharge which included a physical examination and an offer of training in baby massage from the unit's physiotherapist, a clinical examination including visual and auditory screening and a discharge consultation with one of the paediatricians from the ward. The group had access to standard follow-up care after discharge, and was referred to physiotherapy etc on indication.

### **The term reference group**

Infants in the TR group underwent a clinical examination on the 3<sup>rd</sup> day of life. No other intervention or follow-up were offered.

### **Follow-up**

For the purpose of the study, all participants received the same medical, developmental and psycho-social assessments (corrected ages of 6, 12, 24, 36 and 60 months) by blinded assessors, with referrals to other services if needed.

## Measures

### *Bayley Scales of Infant Development II (BSID-II)*<sup>35</sup>

Cognitive and motor outcomes at 3 y were assessed using the Norwegian version of the BSID-II. MDI and PDI are standardised to give a mean score of 100 and SD=15. Subnormal (mildly delayed) and abnormal (significantly delayed) developments were defined as being present when the total score is <85 (- 1 SD) or <70 (-2 SD), respectively.<sup>35</sup> If the infant scored < 50, a nominal score of 40 was assigned as suggested by others.<sup>273</sup> The assessors were blinded to the child's group allocation, all examinations were video recorded and reviewed regularly to maintain consistent scoring.

### *Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R)*<sup>36</sup>

The Norwegian version of WPPSI-R<sup>36</sup> was used to measure cognitive outcomes at corrected age of 5 y. This test consists of 11 subtests which yields a FIQ summed up by the scores from the VIQ and the PIQ. The VIQ express reasoning and conceptual ability with language, and PIQ express non-verbal reasoning, spatial-mechanical and perceptual tasks.<sup>274</sup> Reference means for the IQ scores are 100 and SD = 15.<sup>36</sup> All assessors were blinded to the child's group allocation, all examinations were video recorded and reviewed regularly to maintain consistent scoring.

### *McCarthy Scales (part 9 and 11) of Children's abilities*<sup>275</sup>

Motor outcomes were measured by McCarthy Scales (part 9 and 11) of Children's abilities<sup>275</sup> which consists of 5 subtests of gross coordination and imitating. Part 9 of the test includes walking backwards, on the toes, on a straight line, stand on one foot, stand on the opposite foot and jump on one foot. The performance is scored on a Likert scale from 0 – 2 and higher scores indicates better performance. Part 11 of the test includes imitation including crossing the feet, folding the hands, twinning the thumbs and look through a tube. Maximum score is 4 and higher scores indicate better performance. To measure fine motor function, Grooved

Pegboard Test<sup>276</sup> was used. All assessors were blinded to the child's group allocation, all examinations were video recorded and reviewed regularly to maintain consistent scoring.

#### *Child Behaviour Checklist/4-18 (CBCL/4-18)*<sup>277</sup>

Behavioural outcomes were assessed by using the Norwegian version of the CBCL /4-18.<sup>277</sup> The problem items of the CBCL are scored on a Likert scale from 0 – 2 and yield nine narrow-banded syndrome scales; Withdrawn, Somatic complaints, Anxious/Depressed, Delinquent and Aggressive behaviour, Social, Thought, Attention and Sex problems. The three syndrome scales Withdrawn, Somatic complaints and Anxious/Depressed yields the Internalising broadband syndrome, while Aggressive and Delinquent behaviour yields the Externalising broadband syndrome. A total score is calculated and higher score indicates more problems.<sup>277</sup> The TR group served as the norm due to low response rate in the Norwegian normative dates of the CBCL.<sup>278</sup> On the main scales scores  $\geq 82^{\text{nd}}$  and  $\geq 90^{\text{th}}$  percentiles were used as a cut-off for borderline and clinical ranges respectively, and for the subscales at the  $\geq 95^{\text{th}}$  and  $\geq 98^{\text{th}}$  percentiles, respectively.

#### *Strengths and Difficulties Questionnaire (SDQ)*<sup>279</sup>

The extended SDQ consists of a 25-item informant rated questionnaire and an impact supplement. The 25 items are divided by 5 generating 5 subscales for emotional symptoms, conduct problems, hyperactivity-inattention, peer problems and pro-social behaviour; all but the last one are summed to form a total difficulties score.<sup>280</sup> Higher scores indicate more problems, and scores  $\geq 90^{\text{th}}$  percentile was considered to be in the clinical range.<sup>281</sup> The first question (perceived difficulties) of the impact supplement asks if the respondent thinks the child has a problem in one or more of the following areas: emotions, concentration, behaviour or being able to get along with others Perceived difficulties were dichotomised into low (0-1) and high (2-3).<sup>280</sup> The scores in the TR group were used to derive cut-offs for the SDQ.

### *Child-rearing Practices Report (CRPR)*<sup>224</sup>

Parental child-rearing attitudes were assessed using a 65 item Norwegian version of the CRPR.<sup>282</sup> CRPR is a widely used instrument designed to assess parental attitudes toward child-rearing, and it has been modified from the original instrument.<sup>224</sup> CRPR has been used to establish reliable scales for assessing the child-rearing factors nurturance and restrictiveness<sup>92,224,225</sup> which were used in this study. These factors have proved reliable and stable across different samples and cultures.<sup>224,225</sup> The scale construct is formed by 17 inventory items with high loadings of the nurturance factor, and 15 items with high loadings on restrictive factor.<sup>41</sup> Both the nurturance and restrictive factors had satisfactory internal consistency in our sample. Cronbach's alpha for the nurturance factor in mothers varied from 0.83 to 0.87 and from 0.84 to 0.86 in the fathers. For the restrictive category Cronbach's alpha ranged from 0.73 to 0.79, and 0.78 to 0.80 in mothers and fathers, respectively. Furthermore, CRPR has been used to obtain an index on parental agreement,<sup>283</sup> to assess stability of childrearing attitudes over time<sup>284</sup> and corresponds well with the actual parental child-rearing practice.<sup>224</sup> The questionnaire utilises a 6 point Likert point scale ranging from 1 = strongly disagree, to 6 = strongly agree and was filled in at 12 (mothers only), 24 and 36 months. Higher scores indicate more nurturant child-rearing attitudes and more restrictive child-rearing attitudes. Despite the age of CRPR, we considered it to be the best available instrument since it has both been validated in Norwegian parents of preterm infants, and used in a similar Norwegian cohort.<sup>41</sup>

### *Clinical examination*

All children were examined clinically by an experienced paediatrician (Prof. Dahl) at the corrected ages of 6, 12, 24 months for possible neurological impairment. Clinical examinations at the corrected ages of 36 and 54 months were on clinical indication only. Severe disability was defined as non-ambulant CP, a MDI scores more than 3 SD below the mean (<55), profound sensorineural hearing loss or blindness. Neurodevelopmental impairment (NDI) was defined as the presence of CP, MDI/PDI <70, blindness or deafness (Paper II and III).

## **Baseline Data**

Perinatal variables were collected from medical records. GA was based on ultrasound examination at 16 – 18 w of gestation. The Score of Neonatal Acute Physiology (SNAP-II)<sup>285</sup> and Clinical Risk Index for Babies (CRIB)<sup>286</sup> were calculated as a measure of the initial illness severity. SGA was defined as BW <2 SD below the mean for GA. Norwegian BW data were used.<sup>287</sup> IVH was graded according to Papile<sup>288</sup> and PVL was defined by the presence of echolucencies by cerebral ultrasound. BPD was defined as need of supplemental oxygen at 36 w postmenstrual (PMA) age. Social variables used in the analyses were collected from parents at discharge in a separate questionnaire. Baseline characteristics at the time of randomisation are shown in table 1.

**Table 1.** Infant Characteristics and Social Factors at Randomisation

	Preterm intervention N=72	Preterm control N=74	Term reference (N = 75)
<b>Infant characteristics</b>			
Birth weight, g, mean (SD)	1396 (429)	1381 (436)	3619± 490
400 – 1000 g	20 (28)	20 (27)	
1001 – 1500 g	15 (21)	20 (27)	
1501 – 2000 g	37 (51)	34 (46)	
Gestational age, mean (SD)	30.2 (3.1)	29.9 (3.5)	39.3 ± 1.3
< 28 w	17 (24)	19 (27)	
28 – 32 w	36 (50)	37 (50)	
≥ 33 w	19 (26)	18 (24)	
Males	38 (53)	39 (53)	40 (54)
Twin pairs	16 children (22)	14 children (19)	0
Prenatal steroids	53 (74)	57 (77)	
SNAP II, mean (SD) <sup>1</sup>	8.3 (10.9)	10.4 (11.3)	
CRIB score mean (SD) <sup>2</sup> n = 85	3.2 (2.8)	2.7 (2.9)	
Number ventilated	29 (40)	37 (50)	
Duration of ventilation Mean (SD) n=62	7.0 (18.6)	7.1 (17.3)	
Postnatal steroids	9 (13)	10 (14)	
Oxygen therapy at 36 weeks gestation	11 (15)	14 (19)	
Abnormal cerebral ultrasound			
IVH <sup>3</sup> gr. 1-2	7 (10)	8 (11)	
IVH gr. 3-4	3 (4)	5 (7)	
Periventricular leukomalacia	4 (6)	8 (11)	
<b>Maternal and social characteristics</b>			
Mother's age, y, mean (SD)	30.8 (6.1)	29.1 (6.4)	29.7 (6.1)
Firstborn child	40 (56)	37 (54)	27 (37)
Mother's education (years) <sup>4</sup>	14.6 (2.8)	13.5 (3.2)	14.9 (2.8)
Father's education (years) <sup>4</sup>	13.8 (3.1)	13.5 (3.2)	14.4 (3.2)
Mother's income <sup>4,5</sup>	15.8 (7.7)	14.6 (6.7)	15.9 (8.0)
Father's income <sup>4,5</sup>	21.1 (8.7)	19.9 (8.1)	21.9 (9.8)

*Notes.* Numbers are given as number of infants (%) unless otherwise stated.<sup>1</sup> Score for Neonatal Acute Physiology-II (mean blood pressure, lowest temperature, PO<sub>2</sub>/FiO<sub>2</sub> ratio, Serum pH, multiple seizures, urine output)<sup>2</sup> Clinical Risk Index for Babies (birth weight, gestation, congenital malformation, maximum base deficit first 12 h, minimum appropriate FiO<sub>2</sub> in first 12 h, maximum appropriate FiO<sub>2</sub> first 12 h)<sup>3</sup> IVH Intraventricular haemorrhage<sup>4</sup> n = 199<sup>5</sup> Average monthly income (SD) in 1000 Norwegian kroner (NOK)

## **Statistical Analyses**

Differences in continuous variables between the preterm groups were tested using linear mixed models (LMM), which make it possible to account for the potential clustering effects by including twin pairs when family is included as a random effect. LMM was also used to analyse possible changes in child-rearing attitudes over time (Paper I). A random intercept for family and random time coefficient was used. Intraclass correlation coefficients (ICCs) were used to test for agreement between the parents (Paper 1), and the ICCs were compared using the method outlined by Alsawalmeh and Feldt.<sup>289</sup> Differences in continuous variables are given as mean difference with 95% confidence intervals (CIs). Binary outcomes were analysed by logistic regression with robust SEs and differences given as odds ratios (ORs) with 95% CIs (Paper II and III). Cohen's *d* was used as an estimate of effect sizes (ESs) and is the ratio between the mean difference and the pooled SDs for the sample. An ES of 0.20 was considered small, 0.50 moderate and 0.80 large.<sup>290</sup> *P* values of < .05 were considered significant. All tests were 2-sided. All results are reported on the basis of intention to treat. Stata 10 (Stata Corp, College Station, TX) was used for the analyses.

## **Power calculations**

The study size was originally calculated to detect a difference in Bayley Scales of Infant Development II, Mental Development Index at 2 y corrected age of about 0.5 SD ( $\alpha=0.05$ ,  $\beta=0.80$ ). This analysis indicated that 63 infants were needed in each preterm group. Allowing for withdrawals the target size was set to 70 infants in each group.

## **Lost to follow-up**

Two children in the intervention group and four children in the control group were withdrawn at corrected age of two years due to severe disabilities. Furthermore, one child in the preterm control group and one child in the term reference group were withdrawn at corrected age of two years due to parental choice.

**Ethical considerations**

The study was approved by the Regional committee for medical research ethics and The Norwegian Data Inspectorate. Informed consent was obtained from all parents before inclusion in the RCT. The study is registered in the National Clinical Trial register; NCT00222456.

## Summary of main results

### Main results Paper I

Nordhov SM, Kaaresen PI, Rønning JA, Ulvund SE, Dahl LB. A randomized study of the impact of a sensitising intervention on the child-rearing attitudes of parents of low birth weight preterm infants. *Scand J Psychol.* 2010;51(5):385-391.

- Mothers in the PI group reported significantly more nurturant child-rearing attitudes than mothers in the PC group at corrected ages of 12 and 24 months.
- There were no significant differences reported by fathers in the two preterm groups in nurturant child-rearing attitudes.
- Mothers in the PC group reported significantly lower scores on nurturant child-rearing attitudes at corrected ages of 12, 24 and 36 months compared to mothers in the TR group.
- There were no significant differences between parents in the PI and PC group in restrictive child-rearing attitudes.
- Mothers and fathers in both preterm groups agreed significantly on nurturant and restrictive child-rearing attitudes at corrected ages of 24 and 36 months.
- When comparing the level of agreement in the preterm group (as a combined group), there was significantly higher parental agreement in nurturant child-rearing attitudes at corrected age of 36 months.
- There was significant change over time in nurturant and restrictive child-rearing attitudes among mothers in both preterm groups.

## Main results Paper II

Nordhov SM, Rønning JA, Dahl LB, Ulvund SE, Tunby J, Kaaresen PI. EI improves cognitive outcomes for preterm infants: Randomized controlled trial. *Pediatrics* 2010;126:e1088-e1094.

- Children in the PI group had significantly higher MDI score of 5.7 points at corrected age of 3 y. When adjusting for maternal education the difference was no longer significant.
- There was no significant group difference in PDI scores at corrected age of 3 y.
- There were significant differences in FIQ (7.2. points), VIQ (6.2 points) and PIQ (6.3 points) in favour of the PI group at corrected age of 5 y. When adjusting for maternal education the difference in VIQ was no longer significant.
- 26 % of the children in the control group had FIQ scores of <85 compared to 5 % of children in the PI group.
- There were no significant differences between the PI and the PC group in motor skills at corrected age of 5 y. In subscale analyses, children in the PI group was significantly more skilled in standing on one foot and place the right keys in a bow with the non-dominant hand.

### **Main results Paper III**

Nordhov SM, Rønning JA, Ulvund SE, Dahl LB, Kaaresen PI. Early Intervention Improves Behavioural Outcomes for Preterm Infants: Randomized Controlled Trial. *Pediatrics*, submitted for publication.

- Mothers in the PI group reported significantly lower scores on total behaviour problems measured with the CBCL, and lower scores on the syndrome scales withdrawn, social, thought, attention and aggressive at corrected age of 5 y.
- The fathers in the PI group reported significantly lower scores on the CBCL subscales attention and aggressive behaviours.
- Forty-eight percent of the children in the PC group scored  $\geq 82^{\text{nd}}$  percentile on total problems compared to 19 % in the PI group. On the CBCL subscale attention, mothers in the PI group reported significant fewer children with scores  $\geq 95^{\text{th}}$  percentile.
- Measured with SDQ, there were significant differences in favour of children in the PI group on total problems and the subscale hyperactivity reported by both parents.
- Significantly fewer mothers in the PI group reported SDQ scores within the clinical range on the subscale hyperactivity compared to the mothers in the PC group.
- There were no significant differences between the preterm groups in behaviour problems reported by pre-school teachers.
- Significant more parents in the PC group scored positively on the “perceived difficulties” compared to the PI group.

## **Discussion**

In this RCT we have documented that this modified version of the MITP has a significant impact on maternal child-rearing attitudes at corrected ages of 12 and 24 months (Paper I), IQ scores at corrected ages of 3 and 5 y (Paper II), and behavioural problems (Paper III) at 5 y in prematurely born children with a BW < 2000 grams. The specific findings on parental child-rearing attitudes, cognitive and behavioural development in prematurely born infants are thoroughly discussed in each paper and will not be restated here. In this section, the results are discussed in relation to each other, the previous finding from “Project Early Intervention 2000” on parenting stress and in the light of other intervention programmes.

### **The impact of the modified version of the MITP on parental child-rearing attitudes**

To our knowledge, except for the Vermont study, this is the only RCT which has evaluated the effects of an EI programme on child-rearing attitudes in the parents of preterm infants. In the first paper we hypothesised that this intervention programme would contribute to more nurturant child-rearing attitudes among parents who had received the revised MITP compared to those who received standard follow-up care. This was confirmed among mothers in the PI group, who reported scores close to the TR group, and significantly more nurturant child-rearing attitudes at corrected ages of 12 and 24 months compared to mothers in the PC group. Our results are in line with published results from the Vermont study at corrected age of 6 months,<sup>254,255</sup> but unfortunately no other results on child-rearing attitudes from this study are published. The sustained effect of this EI programme until corrected age of 24 months is surprising since no elements in the modified version of the MITP focus on child-rearing attitudes in particular. The authors of the Vermont study speculated that the effects were due to a “Hawthorne effect”, i.e. that the subjects modify their behaviour in response to the fact that they are being studied, and not in response to any particular experimental manipulation.

<sup>254</sup> However, “the Hawthorne effect” is less likely in our study since the effect lasted until 3 y, even though it did not reach statistical significance (P= .07).

Parental child-rearing attitudes play a salient role in infant development. Due to the “double jeopardy” of preterm infants<sup>180</sup> an optimal child-rearing environment is of particular importance.<sup>291</sup> Parental personality traits and child-rearing attitudes may influence on cognitive development and outcomes in infants positively or negatively.<sup>225,226</sup> In a study by Butcher and collaborators,<sup>226</sup> they found that less rigid maternal attitudes (both as a personal trait and toward child-rearing) were positively associated with FIQ and PIQ scores in school aged children. The authors suggested that children of flexible mothers were positively influenced by them and thereby became more flexible their approach to problem solving in the IQ test situation.<sup>226</sup> However, the behavioural characteristics of preterm infants may also change parenting behaviour into a more compensatory style. This may influence the child development negatively, and has been shown to be associated with hyperactivity in the long term.<sup>292</sup>

Our study revealed that parents of preterm infants, independent of the intervention programme, reported low scores on restrictive child-rearing attitudes and a high level of agreement on child-rearing issues. Low prevalence of the restrictive child-rearing attitudes among parents of preterm infants have been found in another Norwegian study.<sup>41</sup> But, one may question if self-reported child-rearing attitudes correspond with daily-life practices. However, a study by Kochanska et al.<sup>293</sup> demonstrated that child-rearing attitudes endorsed by the mothers corresponded well with their performed child-management strategies when assessed naturalistically. We anticipate that the modified version of the MITP has contributed to more nurturant child-rearing *practises*, not only to nurturant child-rearing attitudes, among mothers in the PI group. The ideal study design would be to evaluate the effects of MITP on child-rearing practices with direct observations in the home, or present parents with several child-rearing relevant tasks followed by direct observations in an experimental setting.

Restrictive child-rearing attitudes may put parents at risk to implement harsh and abusive parenting. The risk of child abuse and neglect increases with the increasing number of risk factors.<sup>294,295</sup> The fuzzy behaviour of preterm infants, and the fact that they are more

often difficult to comfort, may put them at increased risk for abuse and maltreatment. In addition, low involvement and disturbed attachment due to separation in the newborn period are maternal factors which may utterly increase their risk for maltreatment.<sup>291,294,296</sup> Brown et al.<sup>294</sup> found that low maternal education and dissatisfaction with the child increased the risk for physical abuse and neglect. We do have a concern about one subgroup analysis in our study which revealed that mothers with fewer years of education displayed more restrictive child-rearing attitudes compared to mothers with more years of education. It is important to identify families at risk for child abuse as soon as possible after birth, and the EI used in our study may be a useful tool in supervision and supporting of these parents. Even though we found no significant differences reported between parents of the preterm groups in restrictive child-rearing attitudes, we speculate that the modified version of the MITP may indirectly protect preterm infants from child abuse and neglect by increasing the prevalence of more nurturant parental child-rearing attitudes among parents of preterm infants.

We found that maternal child-rearing attitudes changed significantly over time, and the outlines in both nurturant and restrictive child-rearing attitudes were similar in all three groups independent of the EI programme. There were two different patterns in the two dimensions; a V-shaped pattern in maternal reported nurturant child-rearing attitudes and a linear increase in maternal reported restrictive child-rearing attitudes during the study period. As discussed in Paper I we suggest that the “dip” in nurturant child-rearing attitudes at corrected age of 24 months is partly explained by the terrible twos. Furthermore, we suggest that the linear increase of restrictive child-rearing attitudes from 12 to 36 months may be explained by the conflict between the caregiver’s concerns for safety and the infant’s desire for mobility and exploration. Moreover, the infant’s new independence prompts parents’ tendencies to restrict their infant’s actions in later infancy.<sup>297</sup> Parental child-rearing attitudes are closely related to parenting stress and the behavioural characteristics of the infant, and one study revealed that mothers with medium and high levels of restrictive child-rearing attitudes experienced more parenting stress when exposed to infant distress, compared to less restrictive mothers.<sup>297</sup>

To summarise, the modified version of the MITP leads to more nurturant child-rearing attitudes and higher agreement on child-rearing issues among parents of preterm infants. Our study group has previously published reduced parenting stress in favour of parents in the

intervention group (to be discussed later).<sup>298</sup> These are both important factors which may contribute to better dynamics within the family, and indirectly contribute to enhanced infant development.

### **The impact of the modified version of the MITP on cognitive outcomes at corrected ages of 3 and 5 y**

One of the main hypotheses in Paper II was to evaluate the impact of the modified version of the MITP on cognitive outcomes at corrected ages of 3 and 5 y. Previously, our research group has reported a non-significant difference favour of the PI group at corrected age of 2 y.<sup>299</sup> At corrected age of three years children in favour PI group scored significantly higher on BSID-II MDI compared to children in the PC group. However, after adjusting for maternal education the difference did no longer reach significance. Nevertheless, significant more children in the PC group scored below the normal range compared to the children in the PI group. At corrected age of 5 y, children in the PI group scored significantly higher on FIQ, VIQ and PIQ, and significantly more children in the PC group had FIQ scores below the normal range. The differences in IQ scores at both 3 and 5 y were within the clinically significant range, which is considered to be  $\geq 5$  points.<sup>300</sup>

Our results are in line with the results of the Vermont study reported by Achenbach<sup>253</sup> and a small case-control study from Finland,<sup>301</sup> but in contrast to three meta-analyses on post-discharge interventions.<sup>16,17,302</sup> However, the cognitive improvements found in the meta-analyses were based on the results of heterogeneous programmes. Moreover, the cognitive outcomes were predominantly determined by the large sample size (985 infants) of the IHDP.<sup>12</sup> The IHDP reported significant differences in cognitive outcomes in favour of the intervention group at corrected ages of 2 and 3 y, but the effects were no longer detectable at 5 y.<sup>16</sup> However, there was a preservation of cognitive differences in the subgroup of infants with BW >2000g, and although an attenuation of IQ occurred from 14 points at 3 y to only 4 points at 18 y, certain measures including Peabody Picture Vocabulary were stable until 18 years.<sup>303</sup> Another large high-quality intervention study is the “Avon Premature Infant Project”

(APIP).<sup>304</sup> In this trial they had two intervention groups. One intervention group received “Portage”, which is a programme focusing on the developmental progress of the infant in addition to parental support. In an attempt to control for the parent support component of developmental programme, the other intervention group received parental support only in terms of seminars, individual and group work. Additionally, a term reference population was recruited. Similar to our study, the intervention was given by specially trained nurses. The families were visited weekly the first two months, then every 2 – 4 weeks for the next year and monthly until two years (or earlier if requested by the parent).<sup>13</sup> This study demonstrated a small advantage in cognitive outcomes at corrected age of two years.<sup>13</sup> At 5 years, the preterm infants scored 0.5 SD below the term reference group, but there were no significant differences between the preterm groups in mean cognitive scores. To summarise, this RCT demonstrated that developmental education was no more effective than parental support alone, and the authors suggested that future intervention programmes should combine elements of both. Furthermore, they recommended that intervention programmes should be implemented as soon as possible after birth while the baby still is in the NICU and before adverse parent-infant interactions are established.<sup>304</sup>

In the APIP study cognitive outcomes were measured by the British Ability Scales 2<sup>nd</sup> Edition (BAS-II),<sup>305</sup> while WPSSI-R was used in the IHDP and our study. Both instruments are comparable with a mean of 100 and SD=15. Both the APIP and our study demonstrated that prematurely born children had mean scores approximately 1 SD lower than term controls. Furthermore, the prematurely born children in these two studies scored almost  $\frac{3}{4}$  SD higher than children in the IHDP study. This may be explained by that children in the IHPD were born before the modern era of neonatology and/or the Flynn effect.<sup>87</sup>

Recent trials on post-discharge intervention,<sup>306-309</sup> among them two programmes not included in the meta-analyses, are less diverse and more similar to the modified version of the MITP. In 2010 an Australian group reported the impact of a MITP-based intervention (“PremieStart”) on brain structure and development in infants with GA <30 weeks.<sup>308</sup> In addition to the original MITP programme, a massage, a bath session and kangaroo care was added. Post-intervention, at 40 weeks PMA, MRI revealed enhanced maturation and connectivity in all brain regions, with the strongest effects in the superior regions, in favour of

the intervention group.<sup>308</sup> The authors speculate that “PremieStart”, like NIDCAP care, promotes stress –sensitive care for the infants, which in turn improve the microstructure of the white matter through beneficial alterations in the hypothalamic-pituitary-adrenal (HPA) axis.<sup>308</sup> This hypothesis is supported by other studies, which have demonstrated that mild or chronic stress may worsen brain injury through alterations in the HPA-axis.<sup>310,311</sup> Two year follow-up data on cognitive outcomes after “PremieStart” revealed that children in the intervention group had higher scores in the “communication” dimension of Ages and Stages at corrected age of 2 y.<sup>309</sup> This is encouraging and it will be interesting to see if this effect sustains over time.

Another EI programme is the “Parent Baby Interaction program” (PBIP),<sup>306</sup> which is a modified version of the APIP. Similar to APIP, this intervention was delivered by specially trained nurses and aimed to promote contingent sensitivity to infant cues and enhance the confidence in the parental role.<sup>306</sup> In contrast to APIP, however, the programme started few weeks after birth and continued until post-discharge. The families received a median of 8 in-hospital and two at-home intervention sessions. Unfortunately, neither this programme demonstrated beneficial effects on MDI or PDI scores at corrected age of 24 months.<sup>307</sup> Furthermore, there were no significant differences in MDI or PDI scores for subgroups dichotomized by GA (<28 w /≥28 w), parity (1<sup>st</sup>/other child) or maternal cohabiting status (supported/unsupported). The authors concluded that the lack of effect may be attributed to a low intervention load, wrong target population or that parenting interventions may better be delivered after discharge.<sup>307</sup>

The meta-analysis by Vanderveen et al.,<sup>17</sup> pooling studies at 36 months revealed a weighted mean difference (WMD) in a population of 961 infants of 9.66 (95% CI; 5.01 to 14.31) in favour of the intervention group. In our study we found a mean difference on BSID-II MDI of 5.7 point (95% CI; 0.9 to 10.5). However, different scales on neurodevelopment were pooled in this meta-analysis, and these scales measure slightly different aspects of neurodevelopmental disabilities. The most common used neurodevelopmental test is the BSID, but there are some concerns about the long-term predictive ability of this tool.<sup>164</sup> A study by Hack and colleagues<sup>164</sup> demonstrated a 12 point increase in mean BSID scores from 20 months until 8 y in ELBW born children.<sup>164</sup> During the same time period, the proportion of

children with IQ scores <2 SDs below the mean (in the total population) decreased from 39 to 16 per cent.<sup>164</sup> In a Finnish study, however, they found that Bayley MDI score at two y was a good predictor in identifying an increased risk for language impairment at 4 y.<sup>312</sup>

To our knowledge, the modified version of the MITP is the only recent trial showing improvements in VIQ, PIQ and VIQ in preterm infants at 5 y. However, few studies have reported results after 2 y. Even though all the EI studies mentioned above aim to stimulate infant development, the programmes differ considerably in content, time delivered, intervention load and profession of the interventionist. In addition, most programmes target the mothers. The APIP and IHDP are extensive intervention programmes with a high intervention load delivered post-discharge. In contrast to this, the modified version of the MITP used in our study and “PremieStart” is brief and delivered in the hospital-home transition. Less extensive programmes may be less overwhelming and easier for parents to follow and complete, and one review on sensitising interventions concluded that “less is more”.<sup>313</sup> However, in a review of prevention programmes with mothers, Beckwith<sup>314</sup> noted that short, behaviourally focused interventions are effective in promoting child attachment and development in relatively well-functioned families, and longer, more intensive interventions are sometimes more effective in families with multiple social and health risks.

The timing of the intervention is another important issue when designing early intervention programmes. In the APIP-study feedback provided from both research nurses and parents expressed that the intervention sessions were provided too late for real benefits to ensue.<sup>304</sup> As a result of this, PBIP introduced their intervention as soon as possible after birth, but still the programme failed to have a short-time effect on parenting stress or infant outcomes.<sup>306</sup> One reason may be that the effects were evaluated too soon after the intervention was implemented. However, one should expect some immediate effects on at least parenting stress at that time. Another explanation may be that the parents were in shock after the preterm birth of their infant, and thereby not susceptible to an educational early intervention programme. In the hospital-home transition however, they may be more mentally ready and motivated as they are soon to leave the hospital. The first home visit in the MITP is after three days, and it is likely that parents find security in knowing that an experienced nurse, who they already know and trust, will come to their home shortly after discharge from the hospital.

Most intervention studies target mothers in the assumption that mothers provide the majority of care, and less is known about the effectiveness of early interventions with fathers. A review by Magill-Evans et al.<sup>315</sup> concluded that interventions are effective in fathers, and especially if the fathers have multiple exposures to the intervention. Fathers in our study participated in 50% of the sessions. There may be several reasons for this modest participation rate, but the most possible explanation may be that they were at work or at home taking care of other siblings. One study showed that fathers with several exposures had the greatest positive change in direct interaction with their child,<sup>316</sup> but others found improved interactions after only one session.<sup>317</sup> However, more research is needed to determine the appropriate dose over time and the differential impact of interventions with mothers and fathers.<sup>315</sup>

To summarise, in this paper we have documented that the modified version of the MITP do have an impact on cognitive outcomes on corrected ages of 3 and 5 y in preterm infants. We suggest that the content, the timing and the intervention load of this EI programme are important contributing factors.

### **The impact of the modified version of the MITP on motor outcomes**

The other main hypothesis in Paper II was to study the impact of the modified version of the MITP on motor development. In line with other literature<sup>16,260</sup> we did not find an effect of the MITP on motor outcomes at neither 3 nor 5 y except in two subscale analyses. However, the differences in subscales should be interpreted with great care due to multiple comparisons. Furthermore, the motor outcome measures used in our study are fairly crude and may not be able to detect subtle motor changes. It is important though, that the aim of this EI programme was to enhance early parent-infant relationship, and not improve motor skills in particular.

An on-going intervention study with a comparable intervention programme is the Infant Behavioural Assessment and Intervention Program (IBAIP).<sup>14</sup> IBAIP is a post-hospital intervention programme delivered until the corrected ages of 6-8 months which aims to enhance the infants' social interaction without distress, reinforce the infant's motivation and autonomy to explore, and learn from social interactions. The interventionists were specially

IBAIP trained child physiotherapists. Among the recent intervention trials IBAIP is the only programme which has demonstrated improvements in motor development at two years.<sup>318</sup> Furthermore, mothers in the IBAIP intervention group reported less parenting stress and conceptualized their infants to be happier and less distractible/hyperactive compared to controls.<sup>319</sup> The authors hypothesised that the IBAIP contributed to improved motor development through improved self-regulatory competencies in the infants and thereby increased ability to explore and learn.<sup>318</sup>

Despite the lack of effects on motor outcomes, it is of major importance to design EI programmes which target both motor and developmental outcomes as the ability to explore is an important stimulus to process information for developing infants.<sup>100,318</sup>

### **The impact of the modified version of the MITP on behavioural outcomes**

The main purpose of the third paper was to evaluate the effects of the MITP on behavioural and emotional outcomes reported by both parents and pre-school teachers at corrected age of 5 y. At corrected age of 5 y, mothers in the PI group reported significantly less total behaviour problems measured by two questionnaires, and less attention/aggressive problems in particular. More children in the PC group scored within the clinical range on both total and attention problems. Furthermore, children in the PI group had an OR of 0.32 for a high score on the “perceived difficulty” on the SDQ which is associated with an increased risk of later psychiatric illness.<sup>280</sup>

Few EI studies have actively involved fathers and to our knowledge this is the first study to report father-reported behavioral outcomes in preterm children. Unfortunately, there was an attrition of fathers in the intervention group which may have influenced the results. An interesting finding was that fathers scored their children consistently lower in all subgroups regardless of group affiliation in contrast to the mothers. This is in contradiction of other studies<sup>320,321</sup> which found no impact of the parents gender on agreement of childrens behaviour. However, a similar pattern in this cohort was found in some subscales of the on

parenting stress.<sup>298</sup> This can be an illustration of that fathers perceive behavior based on a cultural or societal context and not prematurity per se.

The only EI study which has shown long-term beneficial effects on behavioural outcomes in the long-term (9 y) is the Vermont study.<sup>253</sup> Unfortunately, no subscales were reported which makes it difficult to compare the results of this study with ours. In addition to the Vermont study, Westrup et al.<sup>269</sup> found marginal effects on attention at 5.5 y after NIDCAP care. Few other EI studies have published long-term follow-up results on behaviour outcomes. The APIP<sup>13</sup> and the IHDP<sup>12</sup> found beneficial effects on behavioural outcomes at 2 and 3 y, but no-longer at 5 years.<sup>16</sup> This is in contrast to our study which found no statistical difference in favour of the PI group in behavioural outcomes at corrected age of 2 years.<sup>299</sup> A recent publication from the Victorian Infant Brain Studies<sup>322</sup> (VIBeS) in Australia reported less externalising problems in favour of the intervention group at corrected age of 24 months, but no difference on internalising problems. The intervention programme used in this study (referred to as “VIBeS Plus”) is similar to the MITP and teach the parents about infant-regulation, techniques for improving postural stability, coordination and support. Furthermore, the intervention aimed to support parental mental health and improve the parent-infant relationship throughout the first year. This EI programme consisted of 9 home visits each lasting ~1.5 to 2.0 hours in the first year of life, and the interventionists were a team comprising a psychologist and a physiotherapist. No results beyond two years are published.

SDQ filled in by pre-school teachers revealed no significant differences between the two preterm groups. The reason why SDQ was selected rather than both SDQ and CBCL was that it is less extensive and thereby easier to fill-in for busy preschool teachers. Our results are in contrast to the Vermont study, where teachers reported significantly fewer behaviour problems for the children in the intervention group on the attention problem syndrome and on the total problems scale.<sup>258</sup> Furthermore, on the adaptive and problem scores, children in the intervention group were superior to the children in the control group on all comparisons.<sup>258</sup>

Reports from different informants may contribute to obtain a better picture of behavioural problems in children.<sup>280</sup> However, a meta-analysis<sup>323</sup> demonstrated low correlations between different informants due to the fact that children behave differently in

different situations, the informants perceive behavior differently or are influenced by the relationship with the child. Pre-school teachers assess children in special learning tasks, whereas the parental assessment often is based on diverse tasks in the daily life and less dependent on specific functions.<sup>324</sup> One old study revealed that parents perceived more problems than teachers,<sup>321</sup> but other studies did not confirm this.<sup>320</sup> The degree of agreement between parents and teachers ratings vary depending on gender, age and dimension studied.<sup>320,323</sup> A study by Kumpulainen et al.<sup>320</sup> revealed better agreement between parents and teachers on externalizing and hyperactive behavior in elementary school-aged children, and the correlation of factors were clearly higher for deviant boys than deviant girls.

One of the major findings in our study is that both parents in the PI group reported significantly less attention and aggressive behaviour at corrected age of 5 y, and significant fewer children in the PI group scored within the clinical range. These are important findings due to the fact that ADHD is the most common child neuropsychiatric disorder in prematurely born children<sup>62,91</sup> with a great impact on the affected individuals, their families, and the school environment.<sup>27,102</sup> Behavioural problems and ADHD have been suggested to be closely related to intelligence,<sup>68,324-326</sup> and hyperactivity in the pre-school age has been shown to be a predictor of global IQ in school age.<sup>324,327</sup> Inattentive problems have been explained by deficits in working memory.<sup>324</sup> It has been speculated that prematurity leads to specific deficits in cognitive and neuro-motor functions which in turn result in behavioural problems and conditions such as ADHD.<sup>325</sup> This is supported by MRI studies of prematurely born adolescents which have demonstrated alterations in the left and right fasciculus fronto-occipitalis, cingulum (a part of the limbic system) and the fasciculus longitudinalis inferior, all strongly associated with ADHD.<sup>80,328</sup>

Parenting stress is a risk factor for later behavioural problems in prematurely born children.<sup>329,330</sup> It is assumed that parenting stress interferes negatively in the parent-infant relationship and thereby contributes negatively to the development of the child. Our research group have previously reported a sustained effect of the MITP on parenting stress in LBW children, with an increasing effect from 6 – 36 months.<sup>184</sup> In the PC group, the stress level increased over time whereas it decreased in the PI group, and repeated measurements revealed a significant group by time interaction. Throughout the study period, the total stress scores

among both parents in the PI group were equivalent to scores reported by mothers in the TR group. Other intervention programmes have been targeting parenting stress among parents of preterm infants, but the results are conflicting.<sup>306,319,331</sup> An RCT from the United States including three centres demonstrated a reduction in parenting stress in favour of NIDCAP.<sup>331</sup> In contrast to this, the PBIP found no effects on parenting stress at corrected age of 3 months.<sup>306</sup> However, both the Vermont study,<sup>253,258</sup> and our study,<sup>332</sup> documented that neuro-behavioural effects of intervention programmes become evident after several years. This is a strong argument for a long-term follow-up period before a conclusion about the impact of an intervention is reached.<sup>258</sup>

To summarise, in this paper we have documented that the modified version of the MITP do have an impact on behavioural problems reported by parents in preterm infants. Combined with the cognitive outcomes these results may have a substantial impact on the children's later function in school and social life.

### **Strengths and limitations**

A major strength of this study is that this is a population-based RCT recruited from a well-defined geographical area with an overall follow-up rate of 91%. Furthermore, both parents were included both in the intervention and the follow-up. Few studies have actively involved fathers in the intervention programme, and to our knowledge we are the first research group to report father-reported behavioural outcomes and child-rearing attitudes. A review from 2006<sup>315</sup> revealed evidence that the effectiveness of an intervention increase through enhanced paternal interactions and a more positive perception of the child, if the program involve active participation with, or observation of the father's own child. An additional strength is the use of two different questionnaires and three informants when evaluating behavioural outcomes. The SDQ and CBCL are both well validated questionnaires, the correlations between them are high and equal to discriminate psychiatric from dental cases.<sup>333,334</sup> Due to the sparse long-term effects of EI programmes, critics will argue that they are highly expensive and not cost effective.<sup>335</sup> However, the results of this study may argue

for that the overall cost effectiveness is beneficial. The modified version of the MITP is cheap compared to other EI programmes<sup>16</sup> or NIDCAP.<sup>263</sup> The intervention costs per child have been estimated to €430 and the average travel expenditure per family was €1,150. Additionally, the estimated training cost per intervention nurse was approximately €670. However, a more extensive cost-beneficial analysis of this intervention programme is urgently needed.

A possible weakness of our study is that BW, rather than GA, was used as an inclusion criterion. This has resulted in inclusion of growth restricted infants, which can make the interpretation of the results in more difficult. However, the SGA children were evenly distributed between the two preterm groups and should therefore not influence on the results. Additionally, lack of baseline assessment data on child-rearing attitudes is a problem, which makes it difficult to be certain that there were no differences between the groups from the beginning. However, this is a randomised study and there were no significant differences between the parents in the preterm groups in terms of social demographic or medical factors. From this we may presume that the groups were quite similar in child-rearing attitudes as well. Another limitation is the use of parent-reported questionnaires and CRPR in particular (Paper I). The CRPR is an old questionnaire and may not fully reflect parental child-rearing attitudes in 2011. However this should not influence on the group differences and CRPR is a validated and still a widely-used questionnaire in the field of research on child-rearing attitudes. In addition, using this tool allowed us to make valid comparisons with data from another Norwegian observation study,<sup>41</sup> which was helpful in the interpretation of our results. We used a multi-informant approach to get a better view on observed behaviour problems in this cohort. It is a problem though, that parents and teachers report different problem behaviours pertaining to the same children,<sup>336</sup> and the correlations among different informants are low to moderate dependent on the dimension studied.<sup>320</sup> Unfortunately we did not perform a correlation analysis on these data. At corrected age of two years there were no differences in maternal education, income, BW or GA between maternal responders versus non-responders. At 5 years, there was a substantial attrition of the fathers in the CBCL (26%) and SDQ (23%) and the non-responding fathers were less educated and had lower incomes compared to the responders. This may have biased the results. Finally, we still do not know if the positive

effects in the intervention group were due to the content of the intervention programme or the interaction with the intervention nurses per se. To answer this, a RCT with a dummy-treated control group must be performed.

### **Possible explanations for the effects of the MITP**

We speculate that MITP leads to improved parent-infant interactions according to the transactional model of development<sup>243</sup> and the theoretical redefinition strategy described previously. Our research group has reported earlier on reduced parenting stress<sup>184</sup> and increased joint attention in the infants<sup>337</sup> in favour of the PI group. In an attempt to analyse all the results together, we suggest that the MITP empowers the parents through support that leads to increased self-confidence in understanding the communication of their preterm infant. This in turn contributes to more sensitive,<sup>338</sup> contingent parent-infant interactions, and a positive feedback-loop is created according to the transactional model of development.<sup>243</sup> The increased competence among parents in the PI group leads to less parenting stress<sup>184,298</sup> and more nurturant child-rearing attitudes (Paper I). The result of these transactions becomes measurable by increased intelligence (Paper II) and less behavioural problems at 5 years (Paper III). The increasing intervention effect over time found on cognitive outcomes and parent-reported behaviour might be an expression of a “The Matthew effect”.<sup>244</sup> This is characterised by a deviation amplifying process which means using e.g. positive feedback to enhance infant development away from a given set-point. An example of this phenomenon is when small differences in early development diverge through positive feedback mechanisms into later larger differences over time.<sup>339</sup> This model was first applied to child development by Stanovich<sup>340</sup> who discovered that already in kindergarten those children with high letter recognition became increasingly more advanced, and those who were behind became increasingly behind. “The Matthew effect” may be transferred to parents in the PI group compared to parents in the PC group. We also raise the question of if the fact that the families knew the intervention nurse before randomisation may have contributed to an extra feeling of security and confidence among the parents in the intervention group.

## **Main conclusions**

1. The modified version of MITP has an impact on nurturant child-rearing attitudes in mothers of preterm infants in the pre-school years, which may contribute to enhanced child development.
2. The modified version of the MITP improved cognitive scores at both 3 and 5 y and the differences were of a magnitude considered being of clinical importance.
3. The modified version of the MITP had no effect on motor outcomes.
4. The modified version of the MITP had an impact on parent reported behavioural problems at corrected age of 5 y, with attention and aggressive behaviour in particular, and fewer children in the PI group had scores in the clinical range.

## Clinical implications and future aspects

Norwegian national follow-up guidelines for preterm infants after discharge from hospital were published in 2007.<sup>3</sup> However, a structured sensitising parental programme is not a part of this guideline.<sup>3</sup> Given the results of this RCT on the impact of the MITP on parental, cognitive and behavioural results in prematurely born children, we suggest that this programme, or at least elements from it, will be considered included as standard follow-up care for preterm infants. Several NICUs in Norway provide NIDCAP and family developmental care, and we advocate for that the modified version of the MITP becomes a supplement to these practises.

However, there are still questions to be asked. Even though we have demonstrated effects of this intervention, we still do not know *which* elements in the modified version of the MITP that are more effective; the initial debriefing session, the hospital sessions or the home sessions. Is it necessary to provide all these components, or is it possible to reduce/compress the sessions? As already mention in the discussion, only a future RCT with a dummy-treated control group can provide answers to some of these questions.

Another important question is the target population. The literature provides no evidence for offering intervention to all families with preterm infants. The IHDP reported more effect of the intervention in the “heavier” preterm infants (>2000g),<sup>341</sup> but we did not detect differences in intervention effect according to BW or GA (data not shown). However, the largest subgroups of preterm infants are the LPTs, and moderate prematurity is associated with long-term neurodevelopmental consequences.<sup>342</sup> One ongoing Norwegian trial is studying the effects of the MITP on moderately mature preterm and LPT infants, and they recently reported beneficial effects on maternal sensitivity and infant mood at the corrected age of 12 months.<sup>338</sup> Hopefully, follow-up will contribute to increased knowledge about the effects of the MITP on moderately and LPT infants.

Another important issue is the economical aspects of implementing this intervention programme. Even though this programme is cheap compared to other EI programmes, there

are always financial challenges associated with introducing new cost-intensive measures in the public health service. To reduce the expenses of the intervention further, the use of telemedicine to reduce the nurse travel costs should be considered. This is of special interest in Norway and other countries with remote areas, and long, expensive travel distances. An argument against the use of this new technology is that it may be more difficult for mothers to bring up e.g. problems due to the “distance” between her and the nurse.

Another discussion is; which profession should implement the intervention? Besides specially trained nurses, physiotherapists, psychologists and other health-care providers are reported to perform interventions of preterm infants. Some know the families from the NICU, others are “professional” interventionists who have not met the parents before the actual intervention session. There is no consensus on who is better.<sup>16</sup> One question that has been raised is; can a specially trained district nurse/health visitor provide this intervention programme? In Norway, district-nurses provide at least one home visit to all newborns regardless of GA or BW after discharge from the hospital. In addition, they often know the families due to previous health-care checks of older siblings. However, the nurse specialists know the parents (or at least the mothers) from their NICU stay, they often know the medical history of the preterm infant, and, last but not least, they possess a special knowledge and competence about several aspects of preterm infants. We think this is crucial and an important contributing factor to the successful results of this intervention study.

Finally, further follow-up studies until adolescence and young adult age are needed to evaluate if the effects of the MITP persist. It is of major importance to perform MRI of all the participants in this RCT to help us understand the relationships between early intervention and long-term child development in prematurely born infants.

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