Chapter 7

General discussion
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The main aims of this thesis were 1) to describe the development of very preterm born children at the age of 5 on multiple domains in comparison with term born controls, and 2) to identify risk factors for developmental problems. The theoretical model that was used for this study was based upon the model described by Deater-Deckard and Bulkley\(^1\) (see Figure 1).

**Figure 1** Theoretical model based on Deater-Deckard and Bulkley\(^1\)

On the basis of these aims and the theoretical model, three research questions were formulated: 1) What is the prevalence of disabilities on the areas of neurology, motor functioning, behaviour, intelligence and broader neurocognitive functioning in 5 year old very preterm born children compared with term born children?, 2) Which biological and environmental risk factors for disabilities in developmental functioning of very preterm born children at the age of 5 can be identified, and how do these risk factors interact?, and 3) How does the parental environment of very preterm born at the age of 5 compare with the parental environment of term born children and which risk factors for problems in the parental environment can be identified? In **Chapter 2 to 6** different aspects of these questions were investigated. Main findings of these chapters are presented in Table 1. In this chapter the three research questions will be answered based on our findings and related to findings from previous research. Also the three questions which concern the adjustment of clinical practices of follow-up and intervention on the basis of the results of this study are discussed. This chapter will finish with a discussion of the study limitations and some future directions.
1) What is the prevalence of disabilities on the areas of neurology, motor functioning, behaviour, intelligence and broader neurocognitive functioning in 5 year old very preterm born children compared with term born children?

Figure 2 Part of the theoretical model that is investigated in research question 1.

This first research question was addressed in Chapters 2 and 3. In Chapter 2, the occurrence of disabilities on the areas of neurology, motor functioning, behaviour and intelligence is described. Results were that 75% of very preterm children had disabilities and 50% had more than one disability, compared to 27% and 8% of the term controls, respectively. Although other studies have also shown that more than half of very preterm children have disabilities,1-5 the percentage of children with disabilities was higher in our study. An explanation for the higher incidence of disabilities is the more inclusive definition of disability that was used, and the use of multiple informants. Besides neurologic functioning, we assessed motor functioning separately, resulting in more children with minor to major motor disabilities besides cerebral paresis. Motor functioning is often a problem in preterm born children,6 even if no detectable neurologic dysfunction is present. Furthermore, multiple informants were used to assess behaviour problems; not only parents, but also teachers rated the children's behaviour. It is important to use more than one informant when behaviour is assessed, because parents and teachers usually do not agree on the identification of children with clinically significant behaviour problems.7 Differences between parent and teacher ratings can be explained by the different characteristics of the situation in which the behaviour is observed, by different perceptions of the informants7 and by a better recognition of externalising disorders by teachers and a better recognition of internalising disorders by parents.8,9 Therefore, the use of multiple informants for the rating of behaviour seems justified. Following the suggestions of Aylward10 in his paper ‘Cognitive and neuropsychological outcomes: more than IQ-scores,’ we did not use a full scale intelligence score only as a measure for neurocognitive functioning, but took into account different aspects of intelligence.
### Table 1: Main findings of Chapter 2 to Chapter 6.

<table>
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<tr>
<th>Chapter</th>
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| Chapter 2 | High incidence of multi-domain disabilities in very preterm (VPT) children at five years of age. | VPT children: N = 104
Term controls: N = 95 | Disabilities on the domains of:
- Neurology (Touwen neurological examination)
- Motor functioning (M-ABC-2)
- Behaviour (SDQ for parents and teachers)
- Intelligence (WPPSI-III) |
| Chapter 3 | Perinatal risk factors for neurocognitive impairments in preschool very preterm children. | VPT children: N = 102
Term controls: N = 95 | Neurocognitive functioning:
- Processing speed (Baseline speed, ANT)
- Working memory (Digit span, WISC-III)
- Inhibition and sustained attention (Stop signal task)
- Focused attention (Focused attention, ANT)
- Visual-motor coordination (Tracking and Pursuit, ANT)
- Face recognition (Face recognition, ANT)
- Emotion recognition (Identification of facial expressions, ANT) |
| Chapter 4 | Prediction of cognitive abilities at the age of 5 using developmental follow-up assessments at the age of 2 and 3 in very preterm children. | VPT children: N = 102
Term controls: N = 95 | Intelligence (WPPSI-III)
- Full scale intelligence
- Verbal intelligence
- Performance intelligence
- Processing speed |
| Chapter 5 | Behaviour problems in very preterm born children: association with maternal and paternal perception of child vulnerability. | VPT children: N = 104
Term controls: N = 95 | Behaviour (SDQ), rated by:
- Parents
- Teachers |
| Chapter 6 | Difference in mother-child interaction between preterm and term born preschoolers with and without disabilities. | VPT children: N = 94
Term controls: N = 85 | Mother-child interaction observations (Three boxes procedure), scored using the NICHD Early Child Care Research Network coding system:
- Maternal supportive presence
- Maternal respect for autonomy
- Child positive engagement
- Child task orientation
- Affective mutuality |
Main findings
- VPT children have more disabilities on the domains of neurology, motor functioning, behaviour and intelligence
- Of the VPT, 75% had at least one disability and 50% more than one, compared to 27% and 8% respectively of term controls
- Socioeconomic status is associated with behaviour and intelligence but not with neurology and motor functioning
- The difference in intelligence and behaviour between VPT and term born children increases as socioeconomic status (SES) decreases

- VPT children scored worse than term born controls on the domains of processing speed, working memory, focused attention, visual-motor coordination, face- and emotion recognition, with effect sizes varying between 32 and 70
- Results concerning inhibition and sustained attention were inconclusive
- Bronchopulmonary dysplasia is an independent risk factor for neurocognitive disabilities on the areas of processing speed, attention, face and emotion recognition and visual-motor coordination
- SES is not a risk factor for functioning on aforementioned cognitive domains

- Cognitive development at the age of 2 and 3 is predictive for verbal and full scale intelligence at the age of 5 in VPT children; approximately half of the variance of verbal intelligence is explained by cognitive development at age 2 and 3
- Performance intelligence and processing speed are predicted less well by cognitive development at the age of 2 and 3
- When cognitive development at the age of 2 and 3 is taken into account, other developmental assessments at the age of 2 or 3 only marginally improve the prediction of intelligence at the age of 5
- Neonatal infections and low socioeconomic status are risk factors for lower intelligence at the age of 5, when development at the age of 2 and 3 is already taken into account

- Risk factors for parent rated behaviour problems are: socioeconomic status, preterm birth and very small for gestational age-status at birth, maternal and paternal level of distress, and maternal perception of child vulnerability.
- Maternal perception of child vulnerability was especially a risk factor for preterm born children (both with and without developmental and physical vulnerabilities)
- Risk factors for teacher rated child behaviour problems are: SES and parental foreign country of birth, very small for gestational age-status at birth, and developmental and physical child vulnerabilities

- Mothers of very preterm born children are less supportive of their child's autonomy than term born children.
- A combination of environmental risk (low SES) and child risk factors (preterm birth and the occurrence of disabilities) is associated with a lower level of maternal respect for the child's autonomy.
In Chapter 3, a broad array of other aspects of neurocognitive functioning, namely processing speed, focused and sustained attention, inhibition, working memory, visual-motor coordination and face and emotion recognition was examined. In concordance with other studies^{11-15}, it was found that very preterm children scored had more difficulties than term controls in performing tasks measuring processing speed, working memory, focused attention and visual-motor coordination. Very preterm children also showed more difficulties on face- and emotion recognition tasks than term born children. Problems in facial recognition have been demonstrated in a group of children with periventricular leukomalacia. As in our study cohort, only 5% of the children had periventricular leukomalacia, the results of our study suggest that this problem is not limited to preterm born children with periventricular leukomalacia. Results concerning inhibition and sustained attention are inconclusive. Previous studies show mixed results concerning inhibition and sustained attention. Mixed results from previous studies could be due to differences in age of measurements or differences in gestational age of the study participants. In the case of inhibition, outcomes are likely to depend on the type of inhibition that is being measured. Besides from these two domains that yielded inconclusive results, our study findings show general problems in neurodevelopment (without a specific profile of deficiencies and unaffected domains of functioning). This suggests that disabilities in very preterm children are not due to damage in specific brain areas, but to a generalized reduction in white matter. As focus of research on developmental outcomes has shifted from major disabilities to milder forms of dysfunction, research on cerebral abnormalities has also moved from a focus on major lesions to more global and diffuse forms of abnormalities in the brain. Seventy percent of very preterm children were shown to have mild to severe white matter abnormalities and 27% to have gray matter abnormalities on MRI.^{16} This percentage is similar to the percentage of children with disabilities we found in our study. We were not able to investigate whether children with MRI abnormalities are also the children with clinical disabilities, as we did not have MRI-data available. We did investigate whether risk factors for disabilities could be isolated. This will be discussed in the next paragraph.

It can be concluded that very preterm children have a very high risk for developmental disabilities. In this study 75% had at least one disability on the area of neurology, motor functioning, behaviour or intelligence. Also the co-occurrence of disabilities was high: 50% of very preterm children had disabilities on at least two of aforementioned developmental areas (Chapter 2). Very preterm children were also shown to have a higher risk of dysfunction on a broad range of neurocognitive abilities (Chapter 3).
2) Which biological and environmental risk factors for disabilities in developmental functioning of very preterm born children at the age of 5 can be identified?

As was discussed above, preterm birth is a risk factor for a wide range of developmental disabilities. More specific biological risk factors have also been identified in this study. In this study, specific biological risk factors for intelligence, broader neurocognitive functioning and behaviour were investigated.

In Chapter 4, it was investigated whether biological risk factors would improve the prediction of aspects of intelligence at the age of 5 when developmental assessments at the age of 2 and 3 were already taken into account. In this way we investigated whether biological risk factors continued to have an impact on cognitive development between the ages of 2/3 and the age of 5. We found that, in the prediction of full scale and verbal intelligence, this was the case for sepsis and/or meningitis. An association between neonatal infections and cognitive development has been found in earlier research, but this study adds that the consequences still manifest themselves after the age of 2 and 3. We did not do analyses in which risk factors for low intelligence, independently of cognitive functioning at age 2/3 were investigated. Earlier research did identify independent risk factors for lower cognitive scores: Antenatal steroids, prolonged rupture of membranes, chronic lung disease, small for gestational age-status at birth, abnormal cranial ultrasound and a gestational age of less than 25 weeks.

In Chapter 3, it was investigated whether biological risk factors could be identified for broader neurocognitive functioning. Bronchopulmonary dysplasia (BPD) was shown to be a risk factor for the neurocognitive functions of attention (reaction time and accuracy), visual-motor coordination and emotion- and face recognition. Associations with problems in the recognition of faces and
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emotions have not been found before, but earlier research did show that BPD is, just as preterm birth itself, a risk factor for a broad range of developmental problems, including attention and visual-motor coordination.\textsuperscript{21,22} Aarnoudse-Moens et al.\textsuperscript{23} did not find BPD or other biological risk factors for neurocognitive and specifically executive functioning in their study. However, the domains of neurocognitive functioning investigated in the study by Aarnoudse-Moens et al.\textsuperscript{23} (working memory, verbal fluency, planning, inhibitory control) differed from the abilities that were shown to be related to BPD in the current study.

Chapter 3 showed that very small for gestational age (VSGA)-status at birth, i.e. intrauterine growth restriction (IUGR) and gestational age were biological risk factors for visual-motor coordination as well, but not for attention and emotion- and face recognition. This is in line with earlier research showing that children with IUGR exhibited poorer on motor tasks, including a visual-motor coordination task, but not on other neurocognitive measures.\textsuperscript{24} A borderline effect of gestational age on visual-motor integration performance was shown in a meta-analysis.\textsuperscript{15}

In Chapter 5, risk factors for behaviour problems were investigated. Also for behaviour problems, VSGA-status at birth (IUGR) turned out to be the only biological risk factor, when a lot of other risk factors were taken into account. In other studies, results regarding IUGR and subsequent behaviour problems in preterm born children were equivocal.\textsuperscript{25,26} In those studies, a milder form of IUGR was investigated. The effect of IUGR on behaviour might depend on its severity. According to Guillec,\textsuperscript{26} the severity of prematurity could possibly moderate the effect of IUGR. They did find an effect of IUGR on behaviour for children born between 29 and 32 weeks of gestation, but not for children born between 24 and 28 weeks of gestation. Possibly, the effects of the extreme premature birth overshadow those of IUGR. It is interesting that distinct perinatal risk factors have been found for different neurodevelopmental outcomes. Possibly, the timing of the perinatal event is associated with the neurodevelopmental domain that is affected. BPD and neonatal infections have their impact on the developing brain at 26-40 weeks postmenstrual age, while IUGR impacts in an even earlier stage.

Concerning environmental risk, in this study two types were investigated, namely 1) sociodemographic characteristics (SES [measured by level of parental education] and parental foreign country of birth), and 2) characteristics of the parental environment (parental stress, parental perception of child vulnerability and mother-child interaction). In Chapter 2, we showed that SES is not associated with motor and neurologic functioning. This result converges met results of earlier studies examining risk factors for motor\textsuperscript{27} and neurologic functioning\textsuperscript{28} at the age of 5. In contrast, we did show an association between SES and behaviour and intelligence. Not only was low SES a risk factor for lower intelligence, SES also seemed to modify the effect
of preterm birth on intelligence. The difference between preterm and term born children increased as level of SES decreased. We hypothesized that a rich social environment is a basis for resilience. Parental foreign country of birth was not included in this part of the study, but Chapter 4 showed that when cognitive outcome at ages 2 and 3 was accounted for, both SES and parental foreign country of birth were associated with lower intelligence at the age of 5. This means that sociodemographic characteristic influence cognitive development between the ages of 2/3 and the age of 5. Interestingly enough, Chapter 3 showed that SES was not associated with neurocognitive functions other than intelligence, namely attention (processing speed and accuracy), visual-motor coordination and face- and emotion recognition. The results of this chapter suggest that these domains of neurocognitive development may be more particularly determined by biological factors. However, other studies in this field did show associations between SES and other domains of neurocognitive functioning, like verbal fluency, inhibition, cognitive flexibility, verbal, visuospatial and working memory, adaptive functioning and academic achievement. Possibly, the extent to which SES influences neurocognition depends on the domain of neurocognitive functioning.

In Chapter 2, an association between SES and child behaviour was shown. For parent-rated behaviour problems, the same moderation of the variable preterm birth by level of SES was observed as was the case for intelligence. In Chapter 5, risk factors for child behaviour problems were investigated in more detail. For teacher-rated behaviour problems, not only SES but also foreign parental country of birth was a risk factor. These sociodemographic characteristics were still significant predictors of child behaviour when all other risk factors were taken into account.

Chapter 5 also showed that characteristics of the parental environment were significant risk factors for parent-rated behaviour (but not for teacher-rated behaviour). Stress levels of both parents were associated with child behaviour problems. Previous research reported on an association between maternal stress and behaviour problems in preterm born children. An association between paternal stress and child behaviour problems had only been shown in groups of term born children. The current study made clear that paternal stress is an equally important risk factor for behaviour problems in preterm born children as maternal stress. In this study, also both maternal and paternal perceptions of child vulnerability were investigated. Previous research had not investigated perception of child vulnerability of both father and mother as risk factors for child behaviour problems, nor did previous research take into account the broad range of risk factors that were investigated in this study. Even when maternal and paternal stress, sociodemographic characteristics, perinatal risk factors and true (developmental or physical) child vulnerability is taken into account, maternal perception of child vulnerability is a risk factor for parent-rated behaviour problems. Previous research showed that a heightened maternal perception of child vulnerability
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is associated with a diminished sense of parental efficacy. Parental sense of insecurity and/or lacking parenting skills could mediate the relationship between perception of child vulnerability and behaviour problems in preterm born children, but this requires further study.

It can be concluded that certain developmental domains, namely neurologic and motor development (Chapter 2) and some aspects of neurocognitive development (Chapter 3) seem to be predominantly biologically determined. This study showed that other domains, namely behaviour and other aspects of cognition (intelligence), are associated with a combination of biological and environmental factors. Environmental risk appears to modify biological risk, or more specifically, environmental risk seems to have more impact when the biological risk of preterm birth is present (Chapter 2 and 5).

3) How does the parental environment of very preterm born at the age of 5 compare with the parental environment of term born children and which risk factors for problems in the parental environment can be identified?

Figure 4 Part of the theoretical model that is investigated in research question 3.

As was pointed out above, the parental environment is important for children’s development, and environment might be even more important for preterm children, who are born with biological vulnerability. This underscores the importance of including assessments of the quality of the parental in studies examining development of preterm born children. Aspects of the parental environment that were investigated in this study were parental stress, parental perception of child vulnerability and mother-child interaction.

In Chapter 5, parents of 5 year old preterm born children did not report elevated stress levels as compared to parents of term born controls. This was the case for parental psychological distress.
as well as for parenting stress. Previous research concerning parenting stress and psychological
distress yielded mixed results.\textsuperscript{35-37} Although results seem to indicate a decrease in stress over the
years, this might not be the case for parents in families who experience multiple risks.\textsuperscript{4}
In concordance with another study,\textsuperscript{38} we found that perception of child vulnerability was higher
in parents of preterm born children as compared to parents of term born children. Another study
did not find elevated perception of child vulnerability in parents of children who were born late
preterm and without a history of high medical risk.\textsuperscript{39} The difference in outcomes between this
study, focusing on late, low-risk preterm children and the current study could be explained by the
difference in the degree of prematurity of the children, and the thus to the degree of uncertainty
for parents about the survival of their child. Green and Solnit,\textsuperscript{40} who introduced the notion of
the ‘vulnerable child syndrome’ concluded that parents are at risk for perceiving their child as
vulnerable if they went through a period in which they were uncertain whether the child would
survive.

Specific risk factors for elevated parental perception of child vulnerability were not investigated
in the current study. Previous research reported that within a group of NICU graduates, no
relationship was found between severity of neonatal problems or child cognitive functioning and
parental perception of child vulnerability.\textsuperscript{41} Another study did find risk factors for high parental
perception of child vulnerability, namely preterm birth, low SES, low maternal perception of
marital satisfaction and high psychological distress of the mother were independent risk factors of
maternal perception of child vulnerability.\textsuperscript{18} The results of aforementioned studies might implicate
that a very preterm birth (irrespective of severity of neonatal problems and current child cognitive
functioning) in combination with environmental risk factors is predictive of high perception of
child vulnerability.

\textbf{Chapter 6} describes the quality of mother-child interaction in very preterm and term born
children and their mothers. Very preterm children received less respect for their autonomy and
more interference from their mothers than term children at the age of 5. This difference was
only partly explained by sociodemographic factors. Previous studies reported similar findings
for younger children.\textsuperscript{42-44} Quality of mother-child interaction is associated with later cognitive
development, reminiscing skills, academic competence, emotional development, social skills
and relationships with teachers and peers, and brain morphology in adolescence.\textsuperscript{45-48} Consistent
maternal responsiveness until the fifth year of life predicts faster cognitive and social growth than
inconsistent responsiveness or responsiveness in the first two years of life, especially in preterm
born children.\textsuperscript{49,50} Presumably, the association between quality of mother-child interaction and
child functioning is bidirectional.\textsuperscript{44,51}
In Chapter 6, it was shown that preterm birth is a risk factor for low respect for autonomy especially when maternal level of education was low. Also the combination of a mother with low level of education and a child with a severe disability predicted lower respect for autonomy. Low SES and child disability were also risk factors for other aspects of mother-child interaction, namely maternal supportive presence, child interactive behaviour and affective mutuality between mother and child. This is in line with earlier research, in which both SES and child disability were identified as risk factors for problems in mother-child interaction.

Regarding the parental environment of very preterm children at the age of 5, it can be concluded that parental perception of child vulnerability seems to be elevated as compared to term born children. Parental stress on the other hand appears to be comparable in parents of preterm and term born children. This study also showed that very preterm children (especially those with severe disabilities) received less respect for their autonomy from their mothers (particularly when they had a low level of education) than term children. Because the association between child functioning and the parental environment seems to be directional, there might be a risk for a vicious circle when child disabilities and problems in the parental environment are both present.

**Key messages**

- Seventy-five percent of preterm born children have one or more disabilities in the area of neurological functioning, motor development, behaviour or intelligence.
- The biological risk factor of very preterm birth in itself is the most important risk factor for developmental problems.
- Our findings also suggest that bronchopulmonary disease is a risk factor for neurocognitive functioning, lower gestational age and intrauterine growth retardation are risk factors for visual-motor coordination, and intrauterine growth retardation led to more behaviour problems. Also neonatal infections seem to be related to slower cognitive development between toddler age and the age of 5.
- Low socioeconomic status is a risk factor for behaviour problems and reduced intelligence, but not for other neurocognitive functions (attention, visual-motor coordination and face- and emotion recognition), neurologic and motor functioning.
- (Parental) environmental factors can alleviate or aggravate the consequences of preterm birth. However, the environment is not static; child characteristics can be risk factors for problems in the parental environment as well. This might imply a risk for a vicious circle when child disabilities and problems in the parental environment are both present.
Clinical implications

Our study was designed, and our main objectives and research questions were formulated on the basis of our ultimate goal, which is to contribute to the improvement of care for very premature children and their parents. We hoped to provide answers to the following questions, and through these answers to contribute to the improvement of the follow-up and treatment of such children: 1) Which ages are optimal for follow-up assessment of very preterm children?, 2) Which developmental domains should be included in the follow-up of very preterm children?, and 3) What are possibilities for intervention aimed at improving developmental outcome in very preterm children?

1) Which ages are optimal for follow-up assessment of very preterm children?

Chapter 2 showed that three quarters of our study group showed at least one disability and half of them showed disabilities on at least two domains at the age of 5. These high percentages underscore the importance of standard long-term follow-up of all very preterm children (with a gestational age of <30 weeks and/or a birth weight of <1000 gram). The question is whether it is possible to detect these disabilities at a younger age, so that interventions can be started as soon as possible in order to yield optimal results.
In Chapter 4, this question is addressed specifically for the follow-up assessment of cognitive development. For this chapter, the study group of very preterm children was assessed at the ages of 2, 3 and 5 years. Cognitive development scores at the age of 2 and 3 predicted full scale intelligence and verbal intelligence at the age of 5 quite well (with around 50% of explained variance of full scale and verbal intelligence by cognitive development at age 2 or 3). On the other hand, the prediction of other aspects of intelligence, namely processing speed and especially performance intelligence, were predicted less well by cognitive development at age 2 or 3. It can be concluded that in order to distinguish between different aspects of cognitive development, follow-up until at least the age of 5 is needed. When all cognitive scores (cognitive development at the age of 2 and 3, and full scale, verbal and performance intelligence and processing speed at the age of 5) are dichotomised into normal and abnormal scores, 33% and 15% of the children had an abnormal score at the age of 2 or 3 respectively, while almost 50% scored abnormally on one of the intelligence measures at the age of 5. The fact that not all children with cognitive disabilities at age 5 are recognized as such at toddler age, underscores the importance of follow-up until at least the age of 5. On the other hand, early intervention is indicated when cognitive problems are clear at a younger age. Regarding the preferability of test age (2 or 3 years), the results of our study are equivocal. Associations between cognitive development at age 3 and intelligence at age 5 are somewhat stronger than between cognitive development at age 2 and intelligence at age 5. On the other hand, agreement between cognitive development at age 2 and intelligence at age 5 was somewhat better than agreement between cognitive development at age 3 and intelligence at age 5. In spite of this discrepancy, we consider the age of 2 to be preferable, because 1) the number of false negatives will be much lower and 2) priority should be given to the earliest possible age to start intervention in case of developmental problems.

Chapter 3 reports on neurocognitive functions other than intelligence. As the child grows up, these functions develop and can increasingly be distinguished and assessed. It was concluded that very preterm children are at risk for problems in a broad range of these neurocognitive functions. These functions are important for (later) school functioning. Follow-up assessment at the age of 5, in which neurocognitive functions other than intelligence are included can contribute to timely consideration of extra support in regular education or special education.

It can be concluded that it is useful to have two follow-up assessments, one at toddler age and one at early school-age. An early follow-up at age 2 is needed to diagnose children with developmental problems that can be identified at a young age already, so that these children can profit from early intervention. A later follow-up at age 5 is needed to help a large group of children with developmental problems that cannot be recognized at an earlier age, like specific neurocognitive problems.
2) Which developmental domains should be included in the follow-up of very preterm children?
In this study, we intended to acquire a broad picture of very preterm children's development. On the basis of previous research, we selected developmental domains that we regarded as essential for children's overall and school functioning, namely neurological, motor, behavioural, and broad neurocognitive development. Because of the high rate of disabilities on each of these domains, all should be assessed at follow-up assessments at the age of 5. Depending on the available means, this can be done preferably by having the child tested by paediatricians, child physiotherapists and child psychologists, or, alternatively make partly use of questionnaires. Certain neurocognitive abilities (executive functioning) can for example be screened for using the questionnaire Behavior Rating Inventory of Executive Function, although it should be kept in mind that agreement with well-established executive functioning tasks is modest at best.

Aspects of the parental environment that were regarded as essential for child development were assessed as well. We found that parents of very preterm children perceived their child as more vulnerable, and that this perception of vulnerability was associated with child behaviour problems (Chapter 5). Parental perception is reliably measured with a short questionnaire. It could be worthwhile to take the small effort to include the assessment of parental perception of child vulnerability into follow-up assessment.

Parental stress was not elevated in parents of very preterm children when compared to term born children (Chapter 5). However, parental stress was shown to play a role in behaviour problems in very preterm children. It might therefore be useful to assess parental stress using a questionnaire is behaviour problems in very preterm children are present. Outcome on such a questionnaire could add to the choice of an appropriate intervention.

Another aspect of the parental environment that was found to be problematic for very preterm children was the mother-child interaction, and specifically maternal respect for the child's autonomy (Chapter 6). Because the observation of mother-child interaction is time-consuming, it might not be a reasonable idea to include this into the follow-up assessment routinely. Alternatively, such an observation could be performed when mother-child dyads are especially at risk for interaction-problems (in case mother has a low level of education and child has a severe disability).

It can be concluded that ideally, follow-up assessments encompass all developmental domains that are shown to be affected in very preterm children: neurologic and motor functioning, behaviour, intelligence and broader neurocognitive functioning. Although assessments by professionals are to be preferred, questionnaires could be an alternative. Questionnaires could also be used to assess parental perception of child vulnerability, and, if child behaviour problems are present,
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parental stress. Assessments of mother-child interaction are time consuming; these could be done if risk factors for mother-child interaction problems are present.

3) What are possibilities for intervention aimed at improving developmental outcome in very preterm children?
As medical complications that are associated with preterm birth add to the risk of preterm birth itself for developmental problems, further improvements in neonatal care and reduction of complications will improve outcome. A (further) implementation of developmental care in the newborn intensive care unit, aimed at the reduction of experienced stress by preterm infants, could also improve outcome of very preterm children. Because this thesis focused on follow-up however, I will focus on interventions taking place after hospital discharge.

Chapter 2 shows that at the age of 5, 75% of very preterm children have at least one disability. Given this very high percentage, it can be concluded that preventive intervention is needed for all very preterm children. In a Cochrane meta-analysis, it was concluded that early intervention programs for preterm infants have a positive influence on cognitive development at infant and preschool age. Interventions that not only focused on infant development, but on parent-infant relationship as well, had the greatest impact in the child's cognitive development. This is in line with the results of Chapter 6, that showed a lower quality of mother-child interaction in very preterm children and their mothers as compared to term born children and their mothers, and with results of earlier studies, showing that quality of mother-child interaction is associated with later child development.

The aforementioned Cochrane meta-analysis showed little evidence for an effect of preventive intervention on motor outcomes. However, the 24-months follow-up of the IBAIP-intervention, of which only the 6-month follow-up was included in the meta-analysis, showed an effect on motor outcomes at 24 months. In this study, an effect on cognitive functioning was found for children with combined biological and social risk factors. A review on early stimulation programs for preterm born children reported that intervention programs seem to be more effective when offered to families that combine several risk factors as well. The current study showed that children with a combination of biological and environmental risk run the highest risk of disabilities. If it is not possible to implement a preventive intervention for all very preterm children, it should be considered to offer early preventive intervention for this most vulnerable group of children.

Whether regular preventive intervention has been implemented or not, long-term follow-up plays an important role in identifying those children that need more support. In our study cohort, regular preventive intervention had not yet been implemented. Interventions were indicated often in follow-up: 62% of the children in our study cohort received physiotherapy, speech therapy...
and/or occupational therapy. Also extra support in day-care or school or placement in special day-care or school were made regularly, namely in 19% of the children in our cohort. The high rate of children with neurocognitive problems that were reported in Chapter 3, underscores the need for the development of interventions aimed at improving neuropsychological functions.

The environment a child grows up in is an important factor in its development and this seems to be the case especially in preterm born children (Chapter 2 and 5). As was mentioned before, not only child development, but also problems in the parental environment should be a focus of follow-up and reason for referral. This is not always the case in current practice. Psychosocial support (by a social worker or psychologist) was offered in our study sample in only 13% of the cases. Chapter 5 showed that maternal perception of child vulnerability is a risk factor for behaviour problems in preterm born children, and that this is the case for children with and without true vulnerabilities. When children are developing behaviour problems and mothers have a heightened perception of child vulnerability, interventions may be focused on adjusting mothers perceptions and beliefs concerning the child’s vulnerability. One way of doing this may be via counselling, using for example techniques from cognitive behavioural therapy.

Another risk factor for behaviour problems is parental stress (which we measured as a combination of psychological distress and parenting stress, Chapter 5). Previous research showed that effects of a program in the first year after hospital discharge, directed at enhancing the parent-infant relationship, supporting the infant’s development and reducing psychological stress in parents, were a reduction of behaviour problems in the children and a reduction of anxiety and depression in parents. When parenting stress is high, a parenting program would the intervention of choice. A promising intervention for reducing stress and cultivating positive caregiving in parents of children with disabilities is mindfulness training.

In Chapter 6, it was shown that quality of mother-child interaction is affected in very preterm children and their mothers. As was mentioned before, parent-child interaction should be a focus of early preventive intervention. When mother-child interaction problems in combination with behaviour problems are found at the age of 5, it is not too late to start an intervention. Not only programs focusing on the parent-child interaction in the first year of life yielded positive results, but a program in later years as well.

It can be concluded that, given the high percentage of disabilities in very preterm children, the implementation of a preventive program for the whole group is advisable. According to the literature, such a program should focus on both child development and parent-child interaction. If child disabilities are found during follow-up assessment, a referral should be made for additional...
support in the form of physiotherapy, speech therapy, occupational therapy, or neuropsychological training. If problems in the parental environment are found a referral for extra support is indicated as well, in the form of for example a parenting program or a parent-child interaction therapy.

**Key messages concerning practical implications**

- Follow-up at the age of 5 should be added minimally to early follow-up at the age of 2.
- Follow-up of child development should ideally encompass assessments on the domains of neurological, motor, behavioural, and broad neurocognitive development.
- Assessment of the parental environment via questionnaires should also be a recurring part of follow-up. A more intensive assessment of mother-child interaction should be added in case of a combination of risk factors (low socioeconomic status and child disability).
- A preventive intervention program is indicated for all very preterm children. Such a program should focus on child development and parent-child interaction.
- Intensive preventive intervention is most important and can be expected to be most effective for children with a combination of high biological and environmental risk.
- Problems in child development and/or parental environment found in long term follow-up assessment should both be reason for referral for extra support.

**Study limitations**

The first limitation is the composition of our control group. We originally aimed to recruit a classmate as a control child matched for gender and age for each very preterm child who was attending a regular school. Soon, it became clear that our control group would remain too small if we held on to this procedure. We then stopped matching for gender, and started inviting not only classmates, but also schoolmates, (neighborhood) friends and family members. We did not recruit control children who were attending special schools. We wanted to compare the very preterm group with an unbiased control group, that also included but not overrepresented children with disabilities. The formation of an unbiased control group would have been achieved best if the recruitment of controls would have happened at the time of birth. The preterm and the control group as a whole differed in some of the sociodemographic variables, for example maternal education. This might partly be representative of a true difference between families of premature and term born children.\(^6\) The current study showed that sociodemographic characteristics play an important role in the development of very preterm children. Although we corrected statistically for sociodemographic factors in our study, it is probable that there is residual confounding.\(^7\) In spite of the fact that sociodemographic background of the control group children seems to be relatively favorable, developmental functioning of the control group children does seem to be comparable to the Dutch population. For example, both intelligence and motor mean scores are
in agreement with those of the norm groups of the tests. Very preterm children that were too disabled to undergo the test battery were excluded. Consequently, results of our study cannot be generalized to all low functioning children. Also, it should be kept in mind that if these children would have been included, the very preterm group as a whole would have scored even more deviant from the control group.

Another limitation in this study was the fact that examiners were not blinded for birth status. We have tried to prevent observer bias by using highly standardized tests.

Some limitations concerning the measures used need to be mentioned. We aimed to use the latest versions of the developmental tests. We for example used the second edition of the Movement Assessment Battery for Children that had just been released in the Netherlands, and we made use of the third version of the Wechsler Preschool and Primary Scale of Intelligence, that was not even officially released in the Netherlands yet. However, the third version of the Bayley Scales of Infant Development (BSID-III), was not available in the Netherlands when the children in our study group were aged 2 and 3. It is unclear whether our results concerning the BSID-II, can be generalized to the BSID-III. It is therefore important to further study the predictive value of the BSID-III. Regarding the observation of mother-child interaction, for practical reasons we had to make use of a large set of coders, which decreases reliability and attenuates associations, and may have limited the power.

We found it important to not only include the mother but father as well in the assessment of the parental environment. In order to make the examination attainable for the participating families, we decided however to limit the interaction observation to one parent. Because this parent was the mother in most cases, we did not include the father-child interaction observation in the analyses. It is important that father-child interaction observations will be studied in future research. Most of the questionnaires were administered to both mother and father. We chose to only administer one Strengths and Difficulties Questionnaire to both of the parents. It turned out that this questionnaire was in most cases filled in by the mother. Consequently, there was interdependence between parent-rated child behaviour and the questionnaires completed by the mother. Another limitation was the large amount of missing values on some of our neurocognitive measures. One of the tasks, the Stop Signal Task, seemed to be too difficult or too dysregulating for the very preterm group especially. As a consequence, results regarding inhibition and sustained attention were inconclusive.

Finally, the cross-sectional design of a large part of this study limited the possibilities of disentangling bidirectional associations between the parental environment and child functioning. This could be the focus of future longitudinal research.
Future directions

The current study showed that at the age of 5, as more complex functions can be measured, more very preterm children show disabilities than at the age of 2 and 3. The question is, whether, if this process proceeds as they get older. Will more and more of these children show impairment, as more and more skills are expected of them when they grow up? Broad assessments of neurocognitive functioning at later school age, adolescence and adulthood are needed to answer this question. In such research, the identification of biological risk factors for neurocognitive disabilities remains important. The consequences of improvements in treatment in the NICU’s should be examined not only with short term, but also with aforementioned long-time and detailed neurocognitive assessment.

It would be useful to add MRI-assessments to future studies on neurocognitive development. Previous research shows that brain abnormalities identified with MRI can be related to neurocognitive functioning. Future research could focus on the predictive value of MRI-scans. Besides the theoretical importance of this kind of research, it could also be useful for the identification of children who should receive preventive intervention.

Especially when children have disabilities, the importance of the (parental) environment remains high through time. This should therefore also be included in future research. Previous research shows that fathers play a different role in child development than mothers. Not only mother-child interaction, but also father-child interaction should be observed. The current study showed that there is an association between the parental environment and child functioning, which is probably reciprocal effecting one another, as was shown before for term born children. As was stated before, longitudinal research in very preterm born children could disentangle these bidirectional associations. Such a study could also answer the question what the consequences of diminished maternal respect for the child’s autonomy are for child development. A longitudinal study, taking into account parental perception of child vulnerability, other aspects of the parental environment and child (behavioural) functioning could shed light on the mechanisms behind the association between which maternal perception of child vulnerability and child behaviour.

The current study gave some directions for the development of psychosocial intervention. These should not only focus on the child, but also on mother-child interaction (and especially on maternal respect for autonomy) and parental perception of child vulnerability. It should be investigated which aspects of intervention are effective for which children, how children needing intervention can be identified as early as possible, what the long-term effects of intervention are and what the cost-effectiveness is.
REFERENCE LIST


