CHAPTER 7

General discussion
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The primary aim of this thesis was to assess the stability of development and behavior of moderately-and-late-preterm children (MLPs) in comparison with early-preterm (EPs) and fullterm children (FTs), and to determine which factors influence this stability. We divided this primary aim has been divided into five research questions (see Figure 1), covering two themes: A. stability of developmental problems of preterm children and B. stability of emotional and behavioral problems of preterm children. This chapter summarizes the main findings related to the research questions, the discussion of these findings in relation to the literature, the methodological considerations of our study, their implications and our conclusions.

Figure 1: Graphic overview of the research questions per chapter in this thesis
MAIN FINDINGS

A. Stability of developmental problems of preterm children

To assess developmental differences over time a valid and reliable questionnaire for different ages is essential. For this purpose we chose the Ages and Stages Questionnaires (ASQ), using the age-specific versions for ages 4 and 5 years. The Dutch ASQ 48 months version (age 4 years) has been shown to have a good validity and reliability. The validation of Dutch ASQ 60 months version (age 5 years) is described in Chapter 2.

Research question 1 (Chapter 2): How is the internal consistency and construct validity of the ASQ 60 months version, and what are the effects of three scoring-methods on this validity?

Our psychometric evaluation of the ASQ 60 months version revealed good internal consistency and validity. Concerning internal consistency, the Cronbach’s alpha for the ASQ total score was excellent, but the alphas for the separate domains were less optimal and lower than those of the versions in the other countries. Male gender, prematurity, low paternal education, low family income and small-for-gestational age (SGA) were associated with low ASQ total scores, confirming construct validity. ASQ outcomes can be classified with three different scoring methods: the ASQ domain score, the ASQ total score, and the ASQ total score with parental concerns. The ASQ total score is focused on overall development, and is scored as abnormal if the overall score is in the abnormal range. The ASQ domain score is the classical scoring method and is scored as abnormal if at least one domain score is in the abnormal range. The ASQ total score with parental concerns is abnormal if the ASQ total score is in the abnormal range or if parents reported concerns in the open ASQ questions. Of the three scoring methods, the ASQ total score had the best psychometric performance (highest specificity with good sensitivity) for identification of special education or special educational needs (as criterion for developmental problems). The ASQ domain score had a higher sensitivity but with a lower specificity.

When we were confident that the ASQ for age 5 had good psychometric properties, we used the ASQs for ages 4 and 5 to study the stability of developmental problems. Using the combinations of normal and abnormal ASQ scores at ages 4 and 5 years we constructed four stability categories: consistently normal, emerging, resolving, and persistent developmental problems (Figure 2).

Research question 2 (Chapter 3): What is the stability of developmental problems in EPs and MLPs compared with FTs at school entry? And, does the stability patterns vary per developmental domain?

Stability patterns – proportions of children with persistent, emerging and resolving problems – on overall development (ASQ total score) were comparable between MLPs and
FTs, whereas EPs had significantly higher rates of persistent and emerging problems. With regard to most underlying domains, stability patterns of MLPs were in between those of EPs and FTs. Both EPs and MLPs (but with lower rates) had mainly persistent and emerging motor problems, and resolving communication problems.

**Figure 2**: Visualization of the four stability patterns, which can be formed with normal or abnormal outcomes on a measuring instrument at two time points.

Research question 3 (Chapter 4): Which perinatal and social factors are predictive of persistent and emerging developmental problems of preterm children at school entry?
Various perinatal and social factors were associated with persistent and emerging developmental problems in MLPs and EPs. The strongest associations involved factors related to the social context of a child, such as having siblings (multiparity), and chronic mental illness of the mother. Of the perinatal factors, premature prolonged rupture of membranes was associated with more emerging problems in MLPs, and being small-for-gestational age for all preterm children with persistent and resolving problems. Moreover, boys more frequently had persistent and resolving problems than girls. Compared with prediction based solely on being born EP or MLP, the inclusion of all those mentioned factors in a final model greatly improved the prediction of the stability patterns of developmental problems.

B. Stability of behavioral and emotional problems of preterm children
Research question 4 (Chapter 5): What is the stability of emotional and behavioral problems in preterm children compared with FTs upon school entry? In addition, what is the variation in stability patterns within the preterm group?
Compared with FTs, preterm children had higher rates of persistent, resolving, and to a lesser extent, emerging emotional and behavioral problems between ages 4 and 5 years. In approximately half of both preterm and FT children with problems before school entry, problems were persistent after school entry. Within the preterm group, EPs had the highest
rates of persistent and emerging problems, and MLPs of resolving problems. Among preterm children, proportions of persistent externalizing and internalizing problems were fairly comparable. However, externalizing problems were also more frequently emerging than internalizing problems, and internalizing problems were more frequently resolving than externalizing problems.

**Research question 5 (Chapter 6):** *What is the level of executive functioning in MLPs as compared with FTs at ages 11 and 19 years? In addition, does the maturation of executive functioning differ between MLPs and FTs at ages 11 and 19?*

MLPs and FTs had comparable executive functioning on most subdomains at ages 11 and 19 years. The only difference was on attentional flexibility at age 19, but not at age 11. Both FTs and MLPs demonstrated better attentional flexibility at age 19 than at age 11, but the level of improvement of FTs was greater. Although between MLPs and FTs the attentional flexibility at age 19 differed, their maturation of attentional flexibility between ages 11 and 19 was comparable.

**DISCUSSION OF THE MAIN FINDINGS**

**A parent-completed questionnaire as measure to identify problems**

In Chapters 2-5 we identified problems by using parent-completed questionnaires instead of extensive clinical tests or clinical assessments; we used the ASQ for developmental problems, and the Child Behavior Checklist (CBCL) for emotional and behavioral problems. In Chapter 2, we demonstrated that the Dutch version of the ASQ for age 5 years, which had previously not been validated, had good internal consistency and validity to screen for developmental problems, also in a preterm population. The other versions of the ASQ, and the CBCL had already proved to be reliable and valid screening instruments.1-5 For large population studies, such as preterm populations, parent-completed questionnaires may be more suitable than extensive clinical tests because they are less expensive and less time consuming, and can be based on performance in a safe home environment. At present, clinical assessments and extensive tests are used routinely to determine development and behavior (before and) after school entry for high risk populations such as preterm children <30 weeks GA or children with severe postnatal complications. However, clinical assessment alone detects only 30% of the children with developmental problems,6 and fewer than 50% of those with serious emotional and behavioral problems.7 In addition, most clinicians in well-child care and neonatal follow-up tend to use their clinical judgment to monitor children’s performance, rather than employing screening tools.6 The development and behavior of most MLPs are monitored only in well-child care. In this setting, less time per child and less financial resources are available, and development and behavior are usually not assessed after school entry (although other aspects are). A parent-completed screening
instrument, such as the ASQ, may be of attributed value in both the clinical setting as in the well-child care for identifying (preterm) children with problems.

We demonstrated in Chapter 2 that the ASQ total score is more informative than the generally used ASQ domain score. When special education attendance was used as criterion for developmental problems, the ASQ domain score showed high sensitivity but quite low specificity, whereas the ASQ total score showed both high sensitivity and high specificity. The ASQ domain score and the ASQ total score showed similar differences on ASQ-versions for ages 1-43 months in comparison with the gold standard for development -- the Bayley Scales of Infant Development --, but the ASQ sensitivity scores were consistently much lower than our findings. This may also be because we assessed an ASQ-version for an older age category. The ASQ domain score may have a higher sensitivity but lower specificity, as this method already scores abnormal when there is a delay in only one domain. However, a delay in one domain may be due to natural variation, which is compensated by better performance in other domains. The ASQ total score agrees more with this clinical view on problems; This scoring method classifies a child as having a developmental delay if it has problems in several domains or a very severe delay. Therefore, based on our findings, the ASQ total score is to be preferred when higher specificity and good sensitivity are required.

The stability of development and behavior of preterm children
In Chapters 3, 5 and 6 we demonstrated that preterm children have more persistent, emerging and resolving developmental, emotional, behavioral, and executive problems than FTs. As mentioned in the General introduction, the stability patterns of these problems over time may be influenced by preterm children’s own capacities to improve and adapt their skills, but also by changes in their social context. For instance, at the age of 4 years children start attending school, and in adolescence they start with higher education and working, initiate intimate relationships, and make the transition to independent living. These changes in social context may stimulate their skills, resulting in resolving problems. However, a changing social context also increases the demands placed on a child’s skills, therefore becoming a turning point whereby demands may outgrow their skills, making them unable to keep up with their FT peers, and thereby resulting in emerging problems.

In this thesis we have also demonstrated stability patterns of development and behavior frequently differ between EPs and MLPs. Therefore, in the following paragraphs we will first describe these stability patterns (proportions of persistent, emerging and resolving problems) among MLPs and EPs separately. Thereafter we will compare the two groups with each other.

The stability of problems of MLPs
MLPs more often had persistent and resolving emotional and behavioral problems than FTs, but the stability patterns of development were rather similar (Chapters 3 and 5).
In contrast to what we found, we also expected that MLPs would have higher rates of persistent and changing developmental problems than FTs, because at preschool age MLPs had greater risks of such problems (emotional, behavioral, developmental).\textsuperscript{13,14} Previous small longitudinal studies also reported comparable or decreasing differences between preterm children 34-36 weeks GA and FTs on other outcome measures: e.g. on cognition, academic achievement, social skills, and emotional and behavioral problems between ages 4-12 years,\textsuperscript{15,16} and on general cognitive ability in adolescence.\textsuperscript{15,17,18} Our findings and these studies suggest that differences in developmental, emotional and behavioral problems between MLPs and FTs decrease after school entry.

In preadolescence and adolescence, MLPs and FTs had similar reaction times in most executive functioning tasks. This contrasted with their performance at earlier ages; several studies demonstrated that up to age 8 years MLPs had poorer executive functioning than FTs.\textsuperscript{19–21} As MLPs and FTs already had comparable outcomes at age 11, our results raise the question of most executive problems may resolve before age 11 years. In line with this, Tideman et al. reported poorer cognitive development (on Griffiths Total score) at age 4 years for 39 preterm children <35 weeks GA in comparison with 23 FTs, but comparable cognitive development at ages 9 and 19 years.\textsuperscript{22} Our results and those of Tideman et al. indicate that before age 11 MLPs improve their executive performance towards a level comparable to that of FTs on most domains of executive functioning. In line with our findings on developmental, and emotional and behavior problems, differences between MLPs and FTs on most domains of executive functioning seem to decrease with increasing age.

In overall development we found that MLPs had stability patterns comparable to those of FTs, but MLPs had more persistent and emerging problems on specific domains, including communication, gross motor, personal social, externalizing, internalizing, and attentional flexibility. In line with our findings, Sheehan et al. demonstrated that MLPs performance of complex planning tasks resembles that of FTs, but with less efficiency.\textsuperscript{23} These subtle and specific differences between MLPs and FTs may be related to MLPs’ reduced brain plasticity. After the disruption of brain development in the perinatal period, MLPs adapt by using compensatory neural pathways and reduced or simplified connections.\textsuperscript{10,24,25} Consequently, even preterm children born at 34-36 weeks GA without overt neuropsychological impairments may display alterations in prefrontal connectivity.\textsuperscript{26} These brain alterations will affect functioning in situations where MLPs have insufficient adaptive skills. This may, for instance, be the case when stimulation is limited, or when the complexity of demands increases. Consequently, differences between MLPs and FTs will not be detected in general tasks, but only on specific domains or in more complex tasks.\textsuperscript{10,27}
The stability of problems of EPs

In comparison with FTs and MLPs, EPs showed higher rates of persistent and emerging developmental, emotional, and behavioral problems. These findings are in line with previous studies which compared EPs and FTs but, in contrast with our findings, those studies also reported high rates of resolving problems.\textsuperscript{28–31} It is not surprising that EPs had higher rates of persistent and changing problems than MLPs and FTs, as EPs also had higher rates of developmental, emotional and behavioral problems at preschool and school age.\textsuperscript{32–35} They have thus higher chances to have problems at (least) one age, and thus have higher rates of persistent, emerging, and resolving problems than MLPs. However, our findings regarding resolving problems contradicted this: rates of resolving problems were usually comparable or lower among EPs in comparison with MLPs. EPs may have relatively lower rates of resolving problems than MLPs because of a more disrupted brain development. Their lower GA and their greater risk of postnatal complications associated with their lower GA increases the risk of more severely disrupted white matter maturation and neuronal connection formation of the brain, and decreases cortical plasticity.\textsuperscript{25,36,37} The combination of a greater risk of brain damage and poorer cortical plasticity implies that EPs have a more limited compensatory potential to improve their performance by the formation of alternative neural pathways.\textsuperscript{36} Consequently, problems are more likely to persist and emerge in EPs than in MLPs, and more likely to resolve in MLPs.

Influence of perinatal and social factors on stability

We demonstrated that prediction of persistent and emerging developmental problems based solely on EP or MLP birth is inadequate (Chapter 3). However, we also demonstrated that prediction can be improved by taking into account perinatal and social factors, especially factors related to the social context (Chapter 4). Multiple cross-sectional studies have reported that a less optimal social context increases the risk of developmental problems for preterm children.\textsuperscript{38–42} Moreover, although Roberts et al. reported that sociodemographic factors contributed to changes in cognitive outcomes among EPs between ages 2 and 8, they did not determine this association for MLPs, nor discussed these factors in combination with pregnancy-related and neonatal factors.\textsuperscript{28} A less optimal social context may increase the risk of developmental problems because brain development depends highly on positive and negative external stimulation.\textsuperscript{43} In families with a less optimal social context parents frequently have less time, ability and money to stimulate the children’s development than in families with a better social context.\textsuperscript{44} In the context of having siblings, parents must divide their attention and resources between the children. Siblings also spend time with each other, but this contact cannot match the quality of stimulation that parents provide, particularly if siblings are younger.\textsuperscript{45} Another negative effect of a less optimal social context is more frequent stressful events, which may also influence development.\textsuperscript{44} Consequently, developmental problems are more likely to persist or emerge in an unfavorable social
context. The influence of the social context on the stability of developmental problems may be even more important when children are vulnerable to developmental problems, as are preterm children. For instance, Potijk et al. showed that MLPs with a low socioeconomic status have a multiplied risk of developmental problems at age 4 in comparison with MLPs with a normal or high socio-economic status.38

Preterm boys had higher rates of persistent developmental problems than preterm girls, and MLP boys also of resolving problems (Chapter 4). In addition, male sex tended to be predictive of emerging problems, but with borderline statistical significance (P .05-.10). It is not surprising that preterm boys were more likely to have persistent, emerging and resolving developmental problems, as preterm boys also had greater risks of developmental problems at a specific age.40,42,47,48 In addition, male sex is not only a risk factor for developmental problems, but is also associated with increased risk of preterm birth,49 neonatal mortality,49 postnatal complications,49 externalizing problems,14 and poorer performance on most domains of executive functioning at primary school age.50 These differences between preterm boys and girls can be explained by the fact that boys differ in every level of organization of their brain -- morphological, neurochemical, and functional -- and boys are more vulnerable to pro-inflammatory responses.51–53 To conclude, preterm boys had greater risks of developmental problems than preterm girls, but sex is not a good predictor of persistence or change in these problems.

In Chapter 4 we found that more factors related to social context were associated with persistent and emerging developmental problems among preterm children, than factors related to the pregnancy and neonatal period. For MLPs only PPROM, and for all preterm children only being born SGA, had increased risks of persistent and emerging problems. These findings contrast with those of studies on the association between pregnancy-related and neonatal factors with developmental problems at a specific age before school entry.29,47,48,54,55 Our findings may differ from these studies because we determined the association of perinatal and social factors in one model, and assessed developmental problems after school entry. Pregnancy-related and neonatal factors may influence development at preschool age, but -- particularly the less severe neonatal conditions -- may with increasing age have a decreasing influence on development. Moreover, as previously stated in this discussion, with increasing age factors related to the social context may have an increasing influence on children’s skills. In a systematic review on EPs and preterm children <1250g, Linsell et al. reported that various social and perinatal factors were associated with global cognitive impairment before age 5, but that after age 5 (to age 13) only an association with parental education persisted.40 Both our findings and those of Linsell et al. suggest that with increasing age the social context becomes more important, whereas the influence of pregnancy-related and neonatal factors decreases.
A life-course perspective on the stability of preterms’ problems

From a life-course perspective, we provide evidence on the stability of preterms’ outcomes throughout childhood, i.e. between ages 4 and 5, and between ages 11 and 19 years, and on the associations between factors before, during and shortly after birth on the stability of developmental problems before and after school entry. Our findings suggest that the consequences of preterm birth are not so harmful for most EPs and MLPs than expected. However, among approximately 10-15% of the preterm children problems emerged and persisted after school entry (Chapters 3 and 5). Factors related to social context, and some perinatal factors, can help to pinpoint those preterm children at risk of persistent and emerging developmental problems after school entry (Chapter 4). These insights contribute to early detection of problems and give opportunities for interventions to increase the likelihood of better performance later in life.56–58

Currently, outcomes of MLPs and EPs after school entry are not the main focus of research among preterm children. Instead, research has become increasingly focused on preterm children born at GAs <30 weeks, or even younger -- and on lower birth weight children, i.e. of <1000g.59 In addition, outcomes of preterm children are usually assessed before school entry.59 Although preschool assessments may be applicable for evaluation of current neonatal care, more knowledge on long-term stability is required to improve counselling of parents and clinical decision making. Evaluation at primary school age is even more important, as problems both emerge and resolve after school entry. It is very likely that problems of preterm children are age-related. On the one hand, severe neurological abnormalities like cerebral palsy, mental retardation, blindness, and deafness are likely to persist, but those are present mainly in the youngest EPs. On the other hand, subtler problems – such as motor problems, and emotional and behavioral problems – can also emerge or resolve at later ages, even among MLPs. Therefore, cross-sectional observations at preschool age are not adequate to determine long-term outcomes of EPs and MLPs; these children need re-evaluation at later ages.

In adolescence, the executive functioning of MLPs was comparable to that of FTs. These findings may seem reassuring, but EPs, and to a lesser extent MLPs, have in adolescence and adulthood been shown to have still poorer performance on other domains, including a greater risk of psychiatric disorders, severe behavioral and emotional problems, impaired vision, hearing loss, epilepsy, and possibly a lower intelligence.60,61 Such impairments can lead to socio-economic disadvantages. Both EPs and MLPs more often have lower levels of education, poorer paid jobs, and greater dependence on social security benefits.61–63 In Norway, 8-11% of the EPs and 2-4% of the MLPs had social security benefits in comparison with 2% of the FTs.61 Preterm children were also less likely to have a partner and children.61 The consequences for preterms’ educational qualifications, wealth, and relationships, in adulthood are not only related to current problems, but also a consequence of their performance during primary school.63 Therefore, the performance of EPs and MLPs
at primary school may have far-reaching consequences for preterm children’s future educational qualifications, relations, and future wealth.

The increased risks of persistent and emerging problems of preterm children should be considered in perspective, as approximately 80% of the MLPs and EPs consistently had no developmental, emotional or behavioral problems before and after school entry. Moreover, approximately half of their problems resolved after school entry, and by adolescence the executive function of MLPs and FTs seem rather comparable. Other studies also reported high rates of stable normal performance,\textsuperscript{15,64} and high rates of resolving problems.\textsuperscript{31,65,66} Furthermore, not only preterm children with a relatively uncomplicated neonatal period but also children with postnatal complications had good outcomes; in Chapter 3 we demonstrated that only very few neonatal and pregnancy-related factors to be associated with the stability of developmental problems. Hack et al. also reported that 39% of the EPS and preterms born with a weight <1500 grams who had neurosensory impairment early on, had resolving developmental problems between ages 2 and 8 years.\textsuperscript{65} Moreover, executive functioning at ages 4-12 years (cross-sectional measures) was not associated with neonatal complications among EPs <30 weeks GA, whereas postnatal growth and level of parental education were.\textsuperscript{67} Thus, even for EPs with a complicated neonatal course, long-term development may still be normal.

METHODOLOGICAL CONSIDERATIONS

For this thesis we used data from the LOLLIPOP and TRAILS study. In this section, we will discuss and compare methodological issues of both studies, divided over the following subheadings: quality of the study samples, quality of the obtained data, and causality and confounding.

Quality of the study samples

Chapters 2-5 are based on the LOLLIPOP cohort study and Chapter 6 on the TRAILS cohort study. The strengths of both samples are their large size, community-based nature, and high participation rates (79% and 76%, respectively). They are therefore both validly representative samples of the general Dutch population. Rates of preterm children are in the TRAILS sample as in a general population whereas the LOLLIPOP study has an overrepresentation of EPs and MLPs. With this overrepresentation of preterm children we were thus able to compare differences within the whole range of GAs (24-42 weeks).

Our samples also had some limitations. Due to the focus of the TRAILS study on a general population, its study sample consisted mainly of FTs (1677 of the 1805, 93%). Consequently, the number of EPs (n=16) was too small for further analyses. A limitation of the LOLLIPOP sample was that it did not include children born at 36 and 37 weeks GA, but we expect this to have a limited effect, as problems decrease with increasing GA,\textsuperscript{33} and we did include FTs.
In both studies selection bias may have occurred, but we expect this to have a minor influence because participation rates were high. Furthermore, it is possible that the children with the most problems refused to participate because they were already spending a lot of time with health professionals. Concerning the TRAILS study, in comparison with the participants the non-participants more often had unsatisfactory school performance, and their parents more frequently had a low educational level. However, the non-participants and participants did not differ significantly in socioeconomic status and mental health problems. Concerning the LOLLIPOP study, compared with the parents of the participants the parents of the non-participants more frequently had a non-Dutch background and lower education. However, there were no differences between the non-participants and participants regarding sex and SGA. Consequently, in the current samples of the LOLLIPOP and TRAILS studies, children with problems may have been underrepresented and rates of persistent problems may have been underestimated. In the LOLLIPOP study, selection bias might have occurred in the EP group if we did not include EPs via the neonatal intensive care units, because the youngest EPs and those with severe postnatal complications may not visit well-child care as they are also monitored in neonatal follow-up in the hospital. The EPs sampled via well-child care may, therefore, have had relatively less severe problems. However, it is also possible that children with problems are overrepresented, because parents who were concerned about their child’s development may have more motivation to participate. In both samples there was loss to follow-up between both measurements, although participation rates remained high. The children lost to follow-up in the LOLLIPOP study more frequently had an abnormal ASQ score at age 4, comparable rates of abnormal scores on the CBCL, and more frequently parents with a low education. In addition, rates of loss to follow-up were similar for preterm and FTs for both the TRAILS and the LOLLIPOP studies. Consequently, the effect of loss to follow-up on differences between preterm and FT children is likely to be small.

**Quality of the obtained data**

The outcome measures that we used were developmental problems, measured by the ASQ at ages 4 and 5; emotional and behavioral problems, measured by the CBCL at ages 4 and 5; and executive functioning, measured by the Amsterdam Neuropsychological Tasks (ANT) at ages 11 and 19. The ASQ and CBCL are parent-completed questionnaires, whereas the ANT is an extensive clinically assessed test.

We have already discussed above the advantages of parent-completed questionnaires for studies of large populations. Extensive clinical assessment tests can, on the other hand, objectively measure specific problems. The ANT is such an extensive test, and has proved to be a sensitive and valid tool to measure executive functioning in both non-referred and referred samples. Furthermore, the ANT included exactly the same basic tasks at both time points. It was therefore possible to determine improvement and deterioration
between the ages when the ANT was performed. Furthermore, by using more basic tasks we were able to determine performance on separate domains without contamination by other cognitive processes; more complex tasks are assumed to rely on multiple cognitive processes.72

Our measures also had some limitations. We used a parent-completed questionnaire to determine developmental, emotional, and behavioral problems, but despite its good psychometric properties such a questionnaire is not equal to a diagnosis by an extensive test.1–3,73,74 However, the disadvantage of the ANT is that, as it focuses on basic executive skills, it may not detect more subtle problems and subtle changes over time. To determine these subtle differences requires age-adapted tests for ages 11 and 19. Another limitation of our measures is that we measured only at two ages. Consequently, resolving problems may also include problems that vary around the cut-off point of the measurement. However, with scatter plots in Figure 1 of Chapter 5 and the low rate of small changes (less than 1SD score difference) in Chapter 4, we showed that this was usually not the case for the measures at ages 4 and 5. Moreover, if children change over such a short period of time (one year), changes might even be greater if measures were further apart in time. In short, these potential limitations are unlikely to have a major impact on our findings.

Causality and confounding
A major strength of the LOLLIPOP and TRAILS studies is that data were longitudinally collected. This allowed us to determine the stability of preterms’ outcomes throughout childhood, including between ages 4 and 5, and ages 11 and 19 years. We focused mainly on changes over a relatively short period, i.e. from ages 4 to 5 years with school entry as major event; this largely reduces the potential impact of other life events. A limitation of our analyses was that we could only assume that changes between ages 4 and 5 are causally related to school entry. To exclude other explanations such as further maturation, our findings should be replicated in a country where children go to school at age 6 years. By repeating our analysis of changes between ages 4 and 5 years in such a population we would be able to determine the effect of ageing one year from age 4 years onwards, without the impact of school entry.

Because of our large sample sizes and the availability of information regarding a wide range of perinatal and social factors we were able to adjust for a large variety of confounders. In addition, we collected our data on perinatal and social factors via several sources: medical reports from the hospital of both child and mother (only in LOLLIPOP study), medical reports from well-child care, and extensive parent-reported questionnaires regarding the family situation and perinatal period of the children. However, we may still have missed some confounders, as many factors could have influenced stability. For instance, between both measurements we did not adjust for interventions, although these could have affected stability. Furthermore, in Chapter 4, we constructed a prediction model
using multivariable analyses with backward selection. In these analyses we included many perinatal and social factors. The prevalence of some factors was different for EPs and MLPs, but we adjusted for those differences. To conclude, we expect uncontrolled confounding factors to have very limited effects on our findings.

**IMPLICATIONS**

**Implications for clinical practice and policy**

Our findings have implications for clinical practice and for policy regarding developmental screening, follow-up of preterm children, and neonatal care. First, we demonstrated that the ASQ was a valid and reliable measure to determine developmental problems. Our findings suggest that the ASQ could be a useful instrument in clinical practice and well-child care, to identify developmental problems. In addition, as this questionnaire is parent-completed, it will cost less time during visits and can even be completed in the safe home environment. Of the three scoring methods of the ASQ, the ASQ total score should be preferred for determining more overall and severe problems and for cases when high specificity is needed, as in well-child care. The ASQ domain score should be preferred for determining problems on specific domains or when high sensitivity is needed, as in the clinical setting. The ASQ is thus useful for identifying children at risk of developmental problems, and is applicable in various settings.

In this thesis, we demonstrated that although consequences of preterm birth are limited for most EPs and MLPs, among approximately 10-15% of the preterm children problems emerged and persisted after school entry (Chapters 3 and 5). In addition, we identified risk factors which improved prediction of those preterm children who were at risk of persistent and emerging developmental problems (Chapter 4). These insights could augment early identification of problems, thereby allowing early interventions to increase children’s possibilities of better performance later in life. For EPs and MLPs at risk of persistent and emerging problems, follow-up after school entry may improve early identification. We will discuss this implication in more detail below.

School entry seems to be a critical period in the stability of problems for both EPs and MLPs, but follow-up of most preterm children after school entry is currently not a routine practice. According to the Dutch guidelines only EPs <30 weeks GA and children with severe postnatal complications are included in neonatal follow-up until after school entry (age 5 or 9 years). This means that as almost all MLPs and also some EPs are followed only in well-child care, their development and behavior are usually not assessed after school entry. Therefore, for preterm children at risk of persistent and emerging problems but who are currently not included in neonatal follow-up, it would be useful to consider continuing follow-up after school entry. However, such a step should be preceded by research into its feasibility and effectiveness.
Targeted follow-up is important because the majority (±80%) of EPs and MLPs consistently had no problems, and problems were resolving at later ages in approximately half of the preterm children. We demonstrated that preterm children at greatest risk of persistent and emerging developmental problems were those with a less optimal social context, children born SGA, boys, MLPs born after PPROM, and children with problems at preschool age. Although we included many neonatal and pregnancy-related factors, we found more and stronger associations for factors related to social context (e.g. multiparity and chronic mental illness of the mother). Therefore, follow-up after school entry should be considered for at least all EPs, and for MLPs who have problems at preschool age, live in a less optimal social context, or were born SGA or after PPROM.

Monitoring of vulnerable preterm children who are not included in neonatal follow-up should be performed in well-child care until after school entry. We suggest monitoring these children in well-child care, instead of in clinical pediatric care, for three reasons. First, monitoring a large number of MLPs would be a too great workload for clinical pediatric care. Second, MLPs are usually admitted to non-academic hospitals, where clinical pediatric follow-up is less standardized than in well-child care. Third, well-child care professionals have much more experience in evaluating development and behavior than pediatricians in non-academic hospitals. They can therefore more easily identify the poorly performing children in the large preterm group. However, for adequate screening, well-child physicians must be able to refer directly to medical specialists and receive adequate reporting from them. Regular knowledge exchange between well-child care and clinical pediatric care would help to facilitate this process. Furthermore, supplementary assessment tools are needed to identify problems among preterm children after school entry, as the currently used Baecke Fassaert Motor test for ages 5 to 6 years deals only with motoric problems. To conclude, well-child care professionals and policy makers should consider extending monitoring to after school entry for those preterm children at risk of persistent and emerging problems and who are not monitored in the neonatal follow-up. The feasibility and effectiveness of such monitoring call for additional study.

Implications for future research
Our findings also have implications for future research. In this thesis we focused on the stability between two ages, but the trends before and after these ages are unclear. We hope that future research will determine the stability of development and behavior of preterm children over a longer period of their life course. In the near future, we also hope to study outcomes of (a part of) the LOLLIPOP cohort in adolescence.

For MLPs and FTs in preadolescence and adolescence, executive functioning was similar on most domains. These findings are hopeful, as they are more favorable than those at earlier ages, but they should be confirmed in other MLP cohorts. In addition, it might be
useful to determine whether MLPs also show comparable outcomes on other and more complex executive tasks (e.g. accuracy instead of reaction time) and on goal setting. We found several predictors of persistent and emerging developmental problems but could not address the pathways leading to these associations. Among these factors, PPROM and factors related to social context could possibly be influenced in clinical and well-child care. To realize this, we must better understand the pathways connecting predictors with persistent/emerging problems. Future studies should also focus on the predictive value of perinatal and social factors on the stability of emotional and behavioral problems, and of executive functioning.

Extension of monitoring of vulnerable preterm children until after school entry may require the development of new evidence-based tools to identify and deal with these problems. Moreover, optimal organization of such monitoring in the system of preventive care for children in the Netherlands and elsewhere requires further research.

CONCLUSIONS
This thesis shows that both EPs and MLPs have greater risks than FTs of persistent and changing developmental, emotional and behavioral problems, but with different stability patterns. Problems of MLPs are more frequently persistent and resolving, whereas problems of EPs are more persistent and emerging. In addition, MLPs have more problems on specific domains, whereas EPs have more overall problems. Furthermore, the social context plays an important role in persistent and emerging developmental problems among preterm children, and perinatal and social factors improve prediction of the stability patterns of these problems. Therefore, to improve early identification of problems we recommend extending the monitoring of preterm children at greatest risk in well-child care until after school entry.

REFERENCES
8. Steenis LJP, Verhoeven M, Hessen DJ, van Baar AL. Parental and professional assessment of early


44. Brito NH, Noble KG. Socioeconomic status and structural brain development. Front Neurosci 2014;8:1-12.


