CHAPTER 1

General introduction
CHAPTER 1 | General introduction

Preterm children are at increased risk of problems with development and behavior, but it is unclear whether these problems persist or change over time. The general aim of this thesis was therefore 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.

For our research we first determined the validity and reliability of the developmental screener, the Ages and Stages Questionnaire (ASQ) 60 month version. Using the ASQ at ages 4 and 5 years we determined the stability of development of preterm children and FTs between before and after school entry, and the perinatal and social factors which predict this stability. We also determined the stability of behavior by measuring emotional and behavioral problems of preterms and FTs upon school entry, and the stability of executive functioning of MLPs and FTs during adolescence. This first chapter will provide some background information regarding short-term and long-term consequences of preterm birth, explain why the stability of problems is important, present the research questions, introduce the main outcome measures of this thesis, and present an outline of the thesis.

Preterm birth and its consequences

Normally one expects a baby to be born at approximately 40 weeks’ gestational age (GA). However sometimes, by medical indication or spontaneously, children are born earlier. Preterm deliveries are defined as those that occur before 37 weeks GA. Rates of preterm-births in various countries vary: from 5% in most European countries, 7% in the Netherlands, 12% in the USA, to 18% in some developing countries. The majority (80%) of these children are MLP born, with a GA between 32-36 weeks, and the rest (20%) are EP born, with a GA below 32 weeks.

After birth, preterm babies have a hard time: for instance their lungs are not ready to function properly, their immature immune system struggles to defeat infections, and their liver has problems to break down bilirubin. EPs usually have a long postnatal hospital stay, which in high-income countries starts at the neonatal intensive care unit (NICU). MLPs predominantly have fewer postnatal complications than EPs. Consequently their hospital stay is shorter and they are not usually admitted to the NICU. Due to improvements in preterm care, survival rates of preterm children are increasing.

On the long-term, both EPs and MLPs seem to have more problems with development and behavior than FTs, and their risks increase with lower GA. Long-term problems with development include motoric and cognitive problems as well as problems with behavior, including emotional, behavioral and executive problems.
Stability of problems and the influence of school entry

Many studies have determined long-term outcomes at a specific time point, but less is known regarding the stability patterns – persistence and change – of these problems over time. This is important because when problems change, those preterm children with problems at one age may not be the same children as those with problems at another age. Identification of preterm children at risk of persistent and emerging problems could facilitate early interventions, thereby increasing the likelihood of improved performance in later life.\textsuperscript{14–16} As preterm children have higher rates of problems at most ages, we would also expect higher rates of persistent, emerging, and/or resolving problems. However, these stability patterns among EPs and MLPs are unclear.

Stability patterns over time are influenced by the capacities of the preterm child to improve and adapt its skills, and may also be influenced by changes in the social context. Important changes in the social context include starting primary school, pursuing higher education, working, initiating intimate relationships, and making the transition to independent living. These changes in social context may have both negative and positive influences. An example is the primary school entry at the age of 4. On the one hand, school may be a stimulating environment in which problems resolve through stimulating activities and interaction with other children. On the other hand, school entry may also lead to the emergence of problems when the higher demands made by more complicated tasks exceed their capacities so that they cannot keep up with their FT peers.

Use of measurement instruments to assess the stability of problems

Currently only high risk populations, such as preterm children <30 weeks GA or children with severe postnatal complications, are routinely monitored in neonatal follow-up with clinical assessments and extensive tests until after school entry (age 9). On the other hand, the development and behavior of most MLPs and EPs 30-31 weeks GA are followed only in well-child care, and most intensively only until school entry. A parent-completed questionnaire may help to determine in well-child care and neonatal follow-up which children are, or are not, likely to have persistent and emerging problems. A parent-completed questionnaire has the advantage of being less time consuming and less expensive than extensive diagnostic tests, and can be completed in the safe home situation. Such questionnaires may therefore be very useful for assessing a greater number of children, for instance in well-child care. However, although a parent-completed questionnaire allows for quick and economical screening to discover which children are likely to have specific problems, it is not diagnosis test. Instead, those children found to be at risk of problems on a parent-completed questionnaire can undergo more extensive diagnostic tests.

Stability and change of problems can be determined by repeating the same parent-completed questionnaire at different ages. When using a measurement instrument with
dichotomous outcomes, the combination of the results at two ages -- age A and age B -- forms a classification in four categories, as depicted in Figure 1.

**Figure 1**: A visualization of the four stability categories, which can be formed with normal or abnormal outcomes on a measuring instrument at two time points.

- **a. Consistently normal**: normal scores at both ages;
- **b. Resolving problems**: abnormal score at age A, normal score at age B;
- **c. Emerging problems**: normal score at age A, abnormal score at age B;
- **d. Persistent problems**: abnormal scores at both ages

The ASQ as developmental screening instrument

The Ages and Stages Questionnaire (ASQ) is one of the most frequently used developmental screeners worldwide. The ASQ can be completed by the parents in approximately 10-15 minutes, and is easy to understand. Nineteen age-adapted ASQ versions are available for ages 4 to 60 months. Each ASQ version covers five domains: communication, gross motor, fine motor, problem solving, and personal-social. Each domain is assessed using six questions about reaching milestones. At the end of the questionnaire, parents can indicate if they have concerns about development and the current skills of the child as compared with other children.

The psychometric properties of most age forms of the ASQ have been confirmed in various studies, but strong evidence for the 60 months’ version (ASQ-60) is lacking. Previous ASQ-60 studies in the US (original version), Korea and Norway had relatively small samples. Evidence is thus too weak to support use of the ASQ-60 in routine well-child care. In addition, outcomes may vary in other countries because of differences in language and culture. The Dutch version of the ASQ at age 4 (48 months’s version) has already been validated, but the psychometric properties of the Dutch ASQ at age 5 (60 months’ version) have not yet been determined.
Developmental problems and their stability

Developmental problems include problems with communication, gross motor function, fine motor function, problem solving, and personal social skills. At preschool age, 15-24% of the EPs and 8-25% of the MLPs have developmental problems in comparison with 4-14% of the FTs. The developmental problems of EPs at age 4 may involve all developmental domains, whereas at MLPs have mainly problems with communication, fine motor function, and personal social skills.

Concerning the stability of developmental problems of preterm children between before and after school entry, most evidence concerns EPs and evidence on MLPs is lacking. Developmental problems of EPs and/or children with low birth weight (<1500 g) are both emerging and resolving at primary school age. However, the evidence on the stability per developmental domain among EPs is inconsistent.

Perinatal and social factors may also affect the stability of developmental problems. Although several studies showed associations between perinatal conditions and developmental problems at one age, the influence of these factors differed over time. This may be due to changing effects of these factors with increasing age. However, it is unclear to which degree perinatal and social factors affect the stability of developmental problems of individual preterm children from before to after school entry.

Emotional and behavioral problems and their stability

Emotional and behavioral problems are also denoted as internalizing and externalizing problems, respectively. Internalizing problems include anxious, withdrawn, and depressive behavior; these reflect emotional distress as adaption to the environment. Externalizing problems include aggressive behavior and attention problems; these reflect acting out as reaction to conflicts with others. Preterm children have increased risks of both internalizing and externalizing problems, particularly attention problems, hyperactivity, anxiety/depression, social problems, and somatic complaints. The prevalence rates of emotional and behavioral problems among preterm children vary between 8 and 39%, depending on their GA, whereas in FTs these rates vary between 5 and 10%.

Concerning the stability of emotional and behavior problems of preterm children from before to after school entry, most evidence has to do with persistent problems, and there is little evidence on emerging and resolving problems. At primary school age EPs and/or extremely low birth weight children have greater risks of persistent emotional and behavioral problems. In contrast, between ages 4 and 12 MLPs do not seem to have more persistent problems than FTs. However, this evidence is based on a small study sample or a sample involving combinations of MLPs and EPs. We conclude that current knowledge of the stability patterns of emotional and behavioral problems, especially of MLPs, is limited.
CHAPTER 1 |

Executive functioning and its stability

Executive functioning is a set of cognitive skills which mediate the ability to organize thoughts and behavior in a goal-directed manner.\(^{42}\) Executive functioning can be divided into four domains, each consisting of different components: attentional control (such as sustained attention and inhibition), information processing (such as baseline speed), cognitive flexibility (such as working memory and attentional flexibility), and goal setting.\(^{42}\) EPs demonstrate poorer executive functioning at primary school age and adolescence.\(^{43–46}\) Less is known about the executive functioning of MLPs. MLPs at primary school age have been shown to have poorer executive functioning on the domains attention control and cognitive flexibility,\(^{10–12}\) but evidence is lacking regarding the persistence and change of these problems during adolescence. This knowledge is relevant because, as executive functioning matures throughout the whole course of childhood, including adolescence,\(^{47}\) problems in executive functioning may both persist or resolve during adolescence.

RESEARCH QUESTIONS

The primary aim of this thesis is to assess the stability of development and behavior of MLPs in comparison with EPs and FTs, and to determine which factors influence this stability. This primary aim has been divided into five research questions, covering two themes:

A. Stability of developmental problems of preterm children

1. 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? (Chapter 2)

2. What is the stability of developmental problems in EPs and MLPs compared with FTs at school entry? In addition, does the variation in stability patterns differ per developmental domain? (Chapter 3)

3. Which perinatal and social factors are predictive for persistent and emerging of developmental problems of preterm children at school entry? (Chapter 4)

B. Stability of emotional and behavioral problems of preterm children

4. What is the stability of emotional and behavioral problems in preterm children compared with FTs at school entry? In addition, what is the variation in stability patterns within the preterm group? (Chapter 5)

5. What is the executive functioning in MLPs in comparison with FTs at ages 11 and 19 years? In addition, do MLPs and FTs differ in maturation of executive functioning between ages 11 and 19 years? (Chapter 6)
STUDY SAMPLES

In this thesis we used data of two different study samples: the LOLLIPOP study cohort, and the TRAILS study cohort. An comparison of both studies is shown in Table. A more detailed description of each of these studies is described below.

The LOLLIPOP study (Dutch: Pinkeltje)

Articles 1-4 are based on data from the Longitudinal Preterm Outcome Project (LOLLIPOP), a Dutch cohort study focusing on the growth and development of MLPs. The LOLLIPOP study was approved by the UMCG institutional review board. From a community-based preventive child health care cohort of 45,455 children, born in 2002 and 2003, we included all children with a GA <36 weeks, at ages 43 to 49 months at their last routine well-child visit before starting school. For every second preterm child sampled, we selected for comparison the next FT child from the same preventive child health care cohort. The cohort was expanded with EPs born in 2003 who had been admitted to 5 of the 10 neonatal intensive care units (NICUs) in the Netherlands. The EPs from the NICUs were included at...
CHAPTER 1 |

the same ages. A total of 677 children (20.4%) refused to participate, could not be traced, or missed the invitation. Furthermore, 112 children (3.4%) were excluded because of major congenital malformations, congenital infections, or syndromes (n = 28), an unclear or missing GA (n = 37), loss to follow-up (n = 27), or other reasons (n = 20). The total LOLLIPOP sample included 2517 children (76.1% of the original sample): 698 EPs (among them 434 from the NICU enrichment), 1145 moderately-and-late children, and 674 fullterm children.

A month before the child’s well-child visit at age 43 to 49 months, parents received written information about the LOLLIPOP study as well as several questionnaires about family and perinatal characteristics, developmental problems (the ASQ) and emotional and behavioral problems (the Child Behavioral Checklist, CBCL). Parents returned the completed questionnaires at their well-child visit. After obtaining informed parental consent, we retrospectively recorded perinatal characteristics taken from discharge letters of child and mother, reports of the well-child care visits, and information from birth registers. We crosschecked data using various sources, where available. As a matter of routine, children in the Netherlands start school at exactly age 4. Approximately 4 to 6 weeks before the child’s fifth birthday, thus 1 year after school entry, parents again received the ASQ and CBCL, which they returned by mail.

The TRAILS study

Article 5 is based on data from the Tracking Adolescents’ Individual Lives Survey (TRAILS), a Dutch cohort study focusing on the psychological, social and physical development of adolescents and young adults. The Central Dutch Medical Ethics Committee approved the study. At 122 primary schools in five municipalities in the north of the Netherlands we approached all children born between October 1, 1989 and September 30, 1990. In total, 2230 children participated in the TRAILS study. When the children reached the age of 11, we sent an information brochure and an introduction letter to both parents and child, and informed the children at school. After receiving consent, well-trained interviewers visited one of the parents or guardians at home to administer an interview covering a wide range of topics, including perinatal factors and family composition. Additionally, most parents (81.6%) allowed us to use the reports of the child’s well-child visits; these gave us more detailed information about the child’s GA and birth weight in grams. Furthermore, at school, in designated testing centers, or at home a number of trained undergraduate psychology students tested the children regarding their executive functioning. When the children were 19 years old we again tested their executive functioning, using the same testing methods. We used data only of MLPs and FTs.
Table 1: Comparison of study samples used in this thesis: samples from the LOLLIPOP and TRAILS studies

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>LOLLIPOP study</th>
<th>TRAILS study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus</td>
<td>Preterm children</td>
<td>General population</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Growth and development</td>
<td>Psychological, social and physical development</td>
</tr>
<tr>
<td>Cohort</td>
<td>Community based cohort &amp; enrichment via NICUs</td>
<td>Community based cohort</td>
</tr>
<tr>
<td>Location</td>
<td>Distributed over the Netherlands</td>
<td>North of the Netherlands</td>
</tr>
<tr>
<td>Inclusion via</td>
<td>Well-child care</td>
<td>Primary schools</td>
</tr>
<tr>
<td>Ages of measures</td>
<td>4 &amp; 5 years</td>
<td>11 &amp; 19 years</td>
</tr>
<tr>
<td>Regarding this thesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA groups</td>
<td>688 MLPs, 376 EPs, 403 FTs</td>
<td>98 MLPs, 1832 FTs</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Development, emotional &amp; behavioral problems</td>
<td>Executive Functioning</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Perinatal and social factors</td>
<td>Social, cognition, some perinatal</td>
</tr>
<tr>
<td>Ages at measurements</td>
<td>4 &amp; 5 years</td>
<td>11 &amp; 19 years</td>
</tr>
<tr>
<td>Chapters of this thesis</td>
<td>Chapter 2-5</td>
<td>Chapter 6</td>
</tr>
</tbody>
</table>

GA: gestational age; LOLLIPOP: Longitudinal Preterm Outcome Project; TRAILS: Tracking Adolescents’ Individual Lives Survey

THESIS OUTLINE
In Chapter 2, we evaluated the internal consistency and construct validity of the ASQ 60 months’ version and the effects of three scoring methods on this validity. In Chapter 3 we assessed the stability of developmental problems as well as differences per developmental domain, in EPs and MLPs in comparison with FTs upon school entry. In Chapter 4 we assessed the predictive value of perinatal and social factors on the stability of developmental problems of preterm children upon school entry. In Chapter 5 we assessed the stability of emotional and behavioral problems in preterm children compared with FTs upon school entry, as well as variation in this stability within the preterm group. In Chapter 6 we assessed executive functioning of MLPs in comparison with FTs at ages 11 and 19, and changes between these ages.
REFERENCES


