Development of moderately preterm-born children

Jorien M. Kerstjens

The studies presented here are part of a larger cohort study on the development, growth, and health of preterm-born children, known as the Pinkeltje/LOLLIPOP study (controlled-trials.com ISRCTN 80622320). LOLLPOP is part of the study programme of the Postgraduate School of Behavioral and Cognitive Neurosciences, University of Groningen, the Netherlands. It is supported by the research foundation of the Beatrix Children's Hospital, the Cornelia Foundation for the Handicapped Child, the A. Bulk Preventive Child Health Care Research Fund, the Dutch Brain Foundation, and unrestricted investigator initiated research grants from FrieslandCampina, Friso Nederland, Abbott, and Pfizer Europe.

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	Prof. dr. P.J.J. Sauer

“There are two lasting bequests we can give our children.

One of these is roots, the other, wings.”

(William Hodding Carter)

Paranimfen:	Liesbeth ten Vergert Elianne Vrijlandt
Ceremoniemeester:	Jan Bouma

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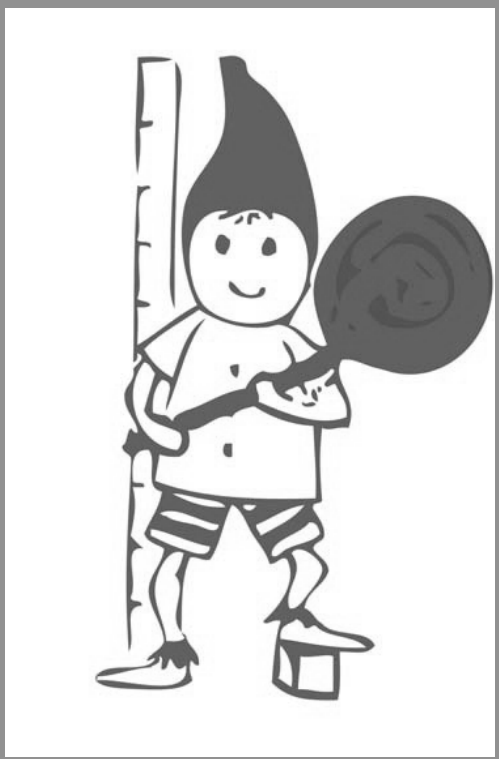
Chapter 1

General Introduction



Jorien M. Kerstjens

INTRODUCTION

The main aim of the research reported on is thesis was to establish developmental outcome in moderately preterm-born children (moderate preterms) at school-entry (age 4) and school age (age 7), and to determine which children in this group were at highest risk of developmental problems. There is no consensus of opinion in international publications on the definition of "moderately preterm birth": the lower boundary varies from 32 to 34 weeks of gestation and the upper boundary varies from 34 to 37 weeks of gestation.[1,2] By contrast, "early preterm birth" or "very preterm birth" is defined precisely as birth before 32 weeks of gestation.[1] To complicate matters even further, the entire group of moderate preterms, or of some subgroups within it, have also been referred to as "macropremies", "mild preterm", "near-term", or "late preterm". Nowadays, however, the term "late preterm" is usually restricted to birth between 34 and 37 weeks of gestation.[3,4] All gestational age boundaries may be arbitrary anyway if the risk of developmental problems were not to start increasing from a set gestational threshold but actually increases from fullterm down.

Worldwide, moderate preterms comprise a large and ever increasing group within the total number of live births. [1,2] Until a few years ago, moderate preterms were not considered at risk of developmental problems as a result of their being born preterm. Evidence is gradually emerging that this assumption was incorrect.[5-7] More knowledge on the prevalence of developmental problems in specific domains at school-entry in this group is, therefore, urgently needed. Because the group of moderate preterms is so much larger than the group of early preterms, the economic and social consequences of even a slight increase in developmental problems following moderately preterm birth might be huge, and in effect much larger than for the early preterm-born group.[8,9] Moreover, more knowledge about which children within the large group of moderate preterms are at highest risk of developmental problems may lead to improved chances of early detection.[10] Hopefully this will also lead to more opportunities for early intervention for children born four to eight weeks too early (before term).[11-14]

In this introduction we discuss the entity "moderately preterm birth", the evidence on developmental outcomes in this group at the time we started our research, and the predictive factors associated with developmental risk. We summarize current developmental follow-up practices for moderate preterms. The introduction concludes with a summary of our main aim and the associated research questions. This is followed by a description of the study sample.

Moderately preterm birth

In this thesis we have defined moderately preterm birth as a birth between 32^{+0} and 35^{+6} weeks of gestation. During the last decades, the incidence of both spontaneous and induced moderately preterm births has risen considerably, and now amounts to 6% to 11% of all live births.[10,15] By contrast, the incidence of early preterm births (less than 32 weeks of gestation) has risen only slightly and remains fairly constant at just under 2.0% of all live births.[10,15] Moderate preterms now account to 70% to 85% of all preterm-born children.[10,15]

The increase in moderately preterm births is due to changes in obstetric care (more induced births in high-risk pregnancies), changes in the lifestyle of fertile women, including the increase of maternal obesity and delayed childbearing, and an increase in the rate of children conceived by artificial reproduction techniques.[16] The number of moderate preterms has also increased due to the assumption that inducing birth "a few weeks early" has no long-term consequences.[7] Moderate preterms have long been considered "near-term"[3,17,18] implying that being born somewhat earlier was not expected to cause additional problems. Most moderate preterms are born in regional (secondary) hospitals, they appear relatively healthy at birth, have near-normal birth weights and usually only encounter mild postnatal morbidities before discharge. Severe postnatal complications warranting admission to a tertiary Neonatal Intensive Care Unit (NICU) are rare. These factors all added up to the fact that "near-term" was considered as being equal to "not at risk of developmental problems".

Development and predictive factors

Development is an on-going process the assessment of which requires different measures for each specific age.[19] Development at school-entry encompasses domains like motor functioning, communication, problem solving capacities, and personal-social skills. It is difficult to assess development at school-entry because children are still rather young and have problems sitting still and concentrating during extended test sessions. As they grow older, and their development proceeds, children can concentrate for longer periods of time. This allows for more reliable assessment of neuro-psychological functions like memory, attention, executive functioning, and visual-spatial skills.[20] Children with initial problems may improve and will experience fewer developmental problems over time (temporary developmental delay). Conversely, their problems may also be on-going or even worsen as they become older (developmental disability).[20]

When we designed our study, between October 2004 and March 2005, no knowledge was available about the extent to which moderate preterms may have problems in the various developmental domains at school entry. Moreover, at the time there was no information on the variety and extent of developmental problems at school-entry nor had any investigations been carried out to examine whether developmental problems persisted after school-entry. The general belief was that even if they did have some developmental problems at first, moderate preterms were most likely to catch up on that delay and that they would have no or only a few problems later on. This contrasted with early preterm-born children (early preterms) in whom developmental problems at school-entry and later on have been studied exten-sively.[21-30] At school-entry early preterms have developmental problems in various domains.[23,24,26] What is more, the developmental problems of early preterms quite often deteriorate or the problems only emerge after they become older, when more difficult tasks are required of them. At school age, 40% to 60% of early preterms have problems due to a lower IQ, and problems with visual-motor functioning, attention, memory, executive functioning, and gross or fine motor functioning. Behavioral problems like ADHD also exist quite often.[21,23,31,32] These problems may occur singly, but quite often combinations of developmental and behavioral problems are present.[33,34] As a result, 50% to70% of early preterms have special educational needs at school.

For moderate preterms, knowledge was also lacking on factors that might be associated with developmental problems, if any, at school-entry. Some studies argued that not moderately preterm birth but low socio-economic status (SES), which is known to increase the risk of moderately preterm birth, completely explains the differences between moderately preterm and fullterm-born children. Once again, this contrasts with early preterms for whom several antenatal factors, both fetal and maternal, are known to be associated with the risk of developmental problems.[35,36] These antenatal factors include pregnancy complications, lack of antenatal steroids, multiple pregnancies, being born small for gestational age (SGA), and male gender.[35,36] Several postnatal complications like septicemia, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and necrotizing enterocolitis are also known to be associated with increased risk of developmental delays in early preterms.[35] Finally, among early preterms, low SES is also associated with developmental risk, in particular after the age of two years.[37]

At the onset of our study it was unclear whether we could extrapolate the antenatal, postnatal, and socio-economic factors associated with developmental risk in the early

preterm-born group to the moderately preterm-born group, because moderate preterms are less preterm, their birth is induced for different reasons (partly elective reasons, having to do with expected problems of mother or child), and they have different postnatal morbidities than early preterms. Without it being based on research findings the general belief was that the small group of moderate preterms who suffered from such severe morbidities that they had to be admitted to a NICU, would be at greatest risk of developmental problems later on.[38]

Developmental monitoring in the Netherlands

In most countries, the development of early preterms is routinely monitored during infancy and toddler age by means of structured, hospital-based, NICU follow-up programs.[39] To establish the prevalence and nature of developmental problems these programs use validated neuro-developmental tests.[39] Because the tests are both expensive and time-consuming and need to be administered by trained professionals, it is not feasible to use them for large groups of children outside the academic setting. Traditionally, the main purpose of the NICU follow-up was to evaluate the neonatal treatment the early preterms had received, and to answer fundamental research questions. Besides, if follow-up revealed any developmental problems in a child, he or she was referred to a general pediatrician or other specialists for further treatment nearby home.

Routine, well-child health care in the Netherlands for fullterm-born children involves developmental monitoring between 0 and 4 years of age through structured visits to preventive child healthcare (PCH) clinics. Development of these fullterm-born children is monitored according to the "Van Wiechen Schema"(vWS),[40,41] and according to clinical assessment. When a PCH physician is concerned about a child's development, the child is referred to a pediatrician, or other specialist, for further diagnosis and treatment. PCH clinics, therefore, predominantly monitor children at low risk, whereas pediatricians mainly monitor children with an increased risk of developmental problems. The current PCH strategy seems to be shifting from equal monitoring of all children, to a more targeted approach whereby more attention is given to and more resources are spent on those children at increased risk of developmental problems.

Since it was unclear whether moderate preterms were indeed at increased risk, additional clinical follow-up over and above routine PCH monitoring has not been formalized for this group. Monitoring the development of a moderate preterms

therefore usually encompasses one, two, or at most three visits to a general pediatric out-patient clinic, ending before or on the child's first birthday. Subsequently, these moderate preterms visit PCH clinics, where, with the exception of a few local initiatives, they are monitored equal to fullterm-born children. Evidence on the effectiveness of the vWS for monitoring the development of moderate preterms in the PCHCs is lacking.[40-42]

Additional tools to monitor development: the Ages and Stages Questionnaire

Other developmental monitoring instruments, sometimes called "developmental screeners", may be adequate and affordable additional tools to monitor development in children at risk.[19] Several developmental screeners have been validated in different settings, including the home setting (parent-completed screeners), and screeners handled by professionals only. Parent-completed developmental screeners were found to show strong agreement with neuropsychological tests, and may help to engage parents actively in the development of their child[19,42,43] Currently, one of the most widely used parent-completed developmental screeners is the Ages and Stages Questionnaire (ASQ).[19,44,45] It has proven to be an inexpensive, easy to complete questionnaire with excellent psychometric properties.[46] The ASQ is widely used in preventive child healthcare in the United States of America as a first screening tool to identify children whose development may be at risk. Using a developmental screener in a different language and cultural setting than for which it was developed, not only requires an accurate translation, but should also include a structured analysis of its psychometric properties.[47,48] If, for example, a question in a Chinese questionnaire asking parents whether their four-year-old can already eat with chopsticks were to be translated into Dutch literally, then that would certainly lead to problems. Moreover, cut-off points for typical and atypical development may also vary between cultures.[49] The psychometric properties of the Dutch translation of the ASQ had not been studied when we started our research project.

In Summary

There were gaps in our knowledge about whether moderately preterm-born children are indeed at increased risk of developmental problems, which developmental domains are involved at school-entry, and whether problems persist after school-entry. In addition, knowledge was lacking on antenatal, postnatal, and socio-demographic factors associated with developmental problems in moderate preterms.

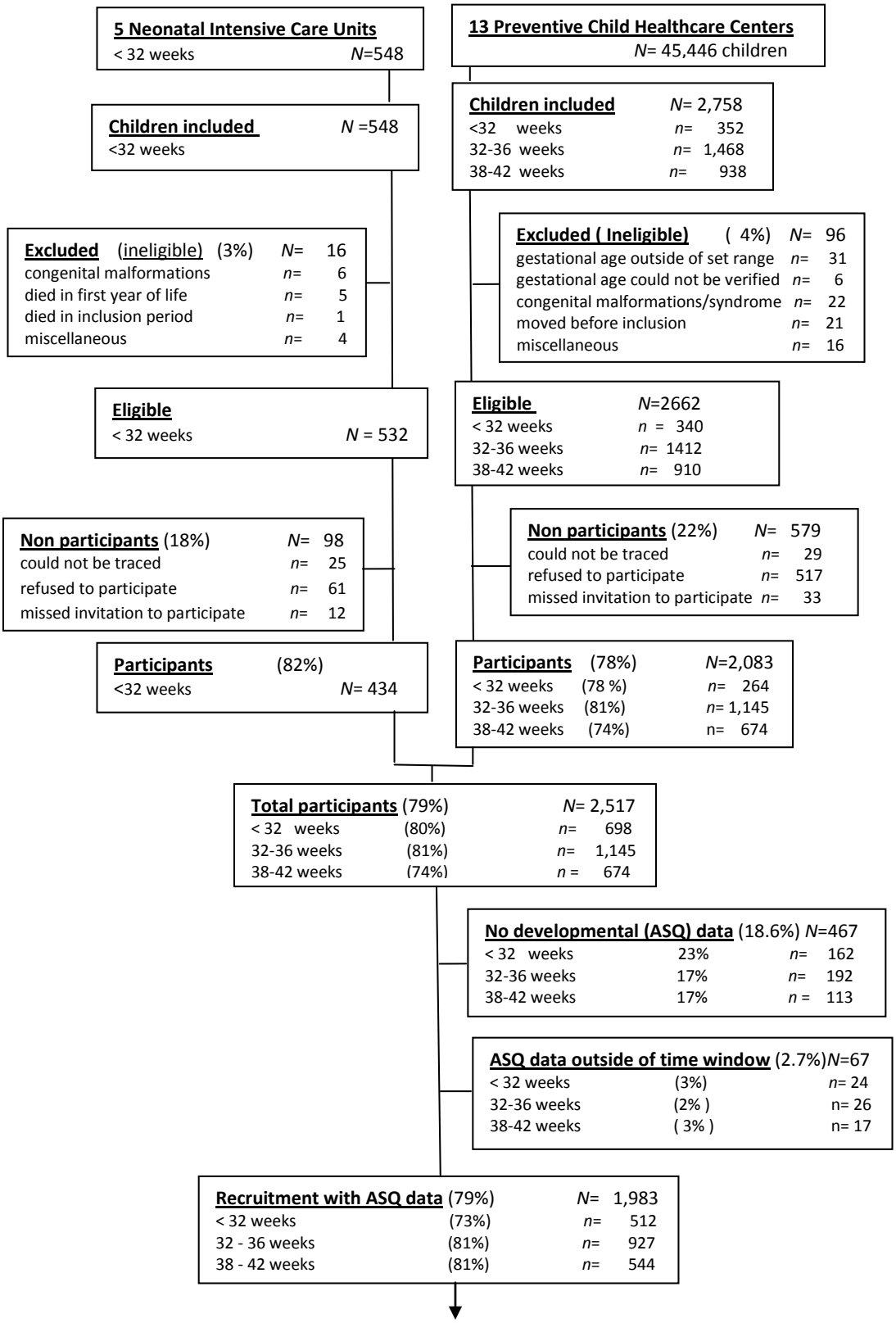
A better understanding of the factors associated with developmental risk may enable us to uncover possible underlying causal mechanisms. This in turn may lead to further research and ways of improving the antenatal and postnatal care of this particular group. Finally, we need to be able to identify those children within the large group of moderate preterms at highest risk of developmental problems, in order to follow these particular children in a more structured manner. As moderate preterms constitute such a large group, identifying a subgroup at increased risk would be helpful in cases where resources are limited and the more structured follow-up could target a smaller subgroup. This might improve the chances of early detection followed by early intervention, and hopefully, improve these children's' chances at school-entry and beyond.

The main aim of this thesis was, therefore, to establish developmental outcome in moderately preterm-born children at school-entry and at school age, and to determine which children in this group were at the highest risk of developmental problems.

This aim led to the following research questions:

1. What are the psychometric properties of the Dutch translation of the ASQ 48 months version? (*Chapter 2*)
2. Do moderately preterm-born children have more developmental problems at the age of four than fullterm-born children, which developmental domains are involved, and how do they compare to early preterm-born children? (*Chapter 3*)
3. What is the association between decreasing gestational age and risk of developmental problems at the age of four? (*Chapter 4*)
4. Which antenatal factors are associated with developmental problems in moderately preterm-born children at the age of four? (*Chapter 5*)
5. Which postnatal factors are associated with developmental problems in moderately preterm-born children at the age of four? (*Chapter 6*)
6. Do moderately preterm-born children have more neuropsychological and motor problems than fullterm-born children at the age of seven? (*Chapter 7*)

Chapter 8 provides a general discussion of the results and some perspectives for the future. In *Chapters 9 and 10* we summarize our findings in English and Dutch, respectively.


5 Neonatal Intensive Care Units
< 32 weeks N=548
13 Preventive Child Healthcare Centers
N= 45,446 children
Children included N =548
<32 weeks
Children included N= 2,758
<32 weeks n= 352
32-36 weeks n= 1,468
38-42 weeks n= 938
Excluded (ineligible) (3%) N= 16
congenital malformations n= 6
died in first year of life n= 5
died in inclusion period n= 1
miscellaneous n= 4
Excluded (Ineligible) (4%) N= 96
gestational age outside of set range n= 31
gestational age could not be verified n= 6
congenital malformations/syndrome n= 22
moved before inclusion n= 21
miscellaneous n= 16
Eligible
< 32 weeks N = 532
Eligible N=2662
< 32 weeks n = 340
32-36 weeks n= 1412
38-42 weeks n= 910
Non participants (18%) N= 98
could not be traced n= 25
refused to participate n= 61
missed invitation to participate n= 12
Non participants (22%) N= 579
could not be traced n= 29
refused to participate n= 517
missed invitation to participate n= 33
Participants (82%)
<32 weeks N= 434
Participants (78%) N=2,083
< 32 weeks (78 %) n= 264
32-36 weeks (81%) n= 1,145
38-42 weeks (74%) n= 674
Total participants (79%) N= 2,517
< 32 weeks (80%) n= 698
32-36 weeks (81%) n= 1,145
38-42 weeks (74%) n = 674
No developmental (ASQ) data (18.6%) N=467
< 32 weeks 23% n= 162
32-36 weeks 17% n= 192
38-42 weeks 17% n = 113
ASQ data outside of time window (2.7%) N=67
< 32 weeks (3%) n= 24
32-36 weeks (2%) n= 26
38-42 weeks (3%) n= 17
Recruitment with ASQ data (79%) N= 1,983
< 32 weeks (73%) n= 512
32 - 36 weeks (81%) n= 927
38 - 42 weeks (81%) n= 544

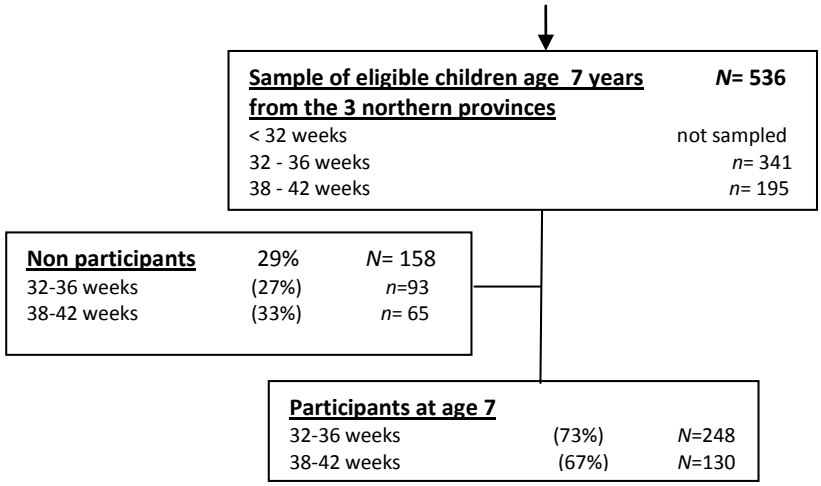


Figure 1. Overview of sampling procedures for the LOLLIPOP study.

The study sample

We drew a stratified sample from a community-based cohort of 45 446 children aged 43 to 49 months, born in 2002 and 2003, from the catchment area of thirteen preventive child healthcare (PCH) organizations. This longitudinal cohort study is known in Dutch as "Pinkeltje", after the children's books by Dick Laan about the adventures of the pixie Pinkeltje, but was reworded to "LOLLIPOP" (Longitudinal Preterm Outcome Project) for international purposes. We selected all children born before 36^{+0} weeks' gestation, plus a sample of fullterm-born children. (**Figure 1**)

We did not sample children born at 36^{+0}-36^{+6} weeks' gestation. Our decision to refrain from sampling children born at 36^{+0}-36^{+6} weeks' gestation was based on logistic reasons. As we sampled all preterm-born children within the catchment area of the PCH centers , and the group born between 36^{+0}-36^{+6} weeks' gestation is by far the largest within the range 32^{+0} -36^{+7} weeks' gestation, including this group born at 36^{+0}-36^{+6} weeks would have roughly led to an additional 1000 children sampled in our preterm PCH cohort, which was not doable within our resources. Furthermore we expected children born at 36^{+0}-36^{+6} weeks' gestation to have relatively few problems compared to fullterm-born children when we designed our study.

The fullterm-born control group comprised the first child from the same birth year with a gestational age (GA) between 38^{+0} and 41^{+6} weeks that was filed after each second preterm child by the same PCH. We enriched the sample with children from

five of the ten NICUs in the Netherlands, who were born at a gestational age of less than 32 weeks in 2003. All children were included at their last routine visit to their own PCH clinic before starting school.

Data on antenatal factors were collected from a general parental questionnaire at inclusion (age 4), from medical records (kept by NICUs and PCH clinics) as well as from national registers (PRN). These antenatal factors included pre-existing maternal, pregnancy-related maternal, fetal, and delivery-related factors. Data on postnatal factors were collected from the same sources and included hospital and NICU admissions, as well as common neonatal morbidities like hypoglycemia, hyperbilirubinemia, and respiratory or circulatory insufficiency. Data on socio-demographic factors were collected from the PCHC records, the general questionnaire, and birth registers. Socio-demographic factors included multiparity, country of birth of the mother, educational level and occupation of both parents, family income, smoking and alcohol during pregnancy, and single parent status. As outcome measures, data on developmental problems were collected with the ASQ (age 4) and neuropsychological tests for a subgroup (age 7). Neuropsychological tests included the short version of the Wechsler Intelligence Scale (WISC), and parts of the Rey Auditory Verbal learning Test (AVLT), Developmental Neuropsychological Assessment Battery (NEPSY), Test of Everyday Attention for Children (TEACH), and the parent-completed Behavior Rating Inventory of Executive Functions (BRIEF), as well as the Dutch version of the Movement ABC.

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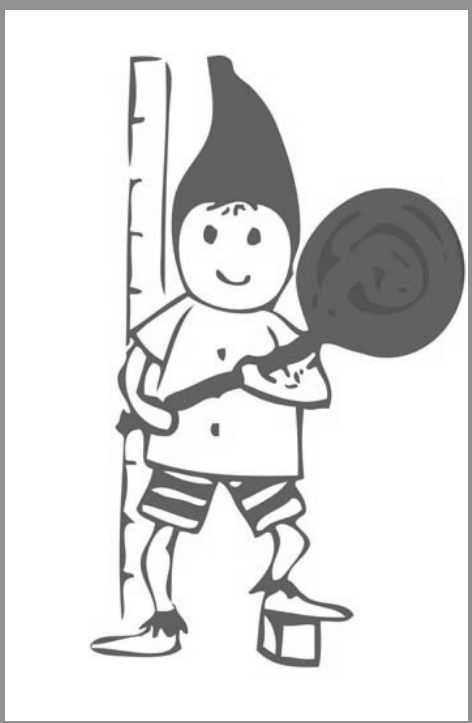
Chapter 2

Support for the global feasibility of the Ages and Stages Questionnaire as developmental screener



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ABSTRACT

Objective: To investigate the psychometric properties of the Dutch version of the 48 months Ages and Stages Questionnaire (D_ASQ_48).

Design: Prospective cohort study of a community-based sample of children born in 2002 and 2003 whose parents filled out the D_ASQ_48 and a questionnaire on school status at 60 months. The ASQ was translated into Dutch and back-translated into English by three independent translators.

Setting: Well Child Centers covering 25% of the Netherlands.

Participants: Parents of 1510 preterm and 562 term children born in 2002–2003 attending routine Well Child visits at age 45–50 months.

Main outcome measures: Reliability, validity and mean population scores for D_ASQ_48 compared to other countries.

Results: Mean population scores for the D_ASQ_48 were mostly similar to those in the USA, Norway and Korea. Exceptions (effect sizes of difference > 0.5) were problem solving (USA) and fine motor (Korea). Reliability was good for the total score (Cronbach alpha 0.79) and acceptable for all domains (0.61–0.74). As expected, infants born at gestational age < 32 weeks, children from low income families, of low educated mothers, and boys were more likely to fail on several domains (odds ratios ranging from 1.5 to 4.9). The only unexpected association concerned children from one-parent families. Sensitivity to predict special education at five years of age was 89% and specificity 80%.

Conclusions: The good psychometric properties of the Dutch ASQ_48 and the small differences when compared to other countries support its usefulness in the early detection of developmental problems amongst children worldwide.

INTRODUCTION

An estimated 5–10% of all children have a developmental disability.[1] The benefits of early intervention-therapy for young children at risk of developing a disability have been shown in randomized controlled trials.[2-6] Several countries are now setting high standards for the detection and treatment of developmental delay in children before school entrance.[7-9] However, detecting developmental delay with limited resources in the community setting is difficult.[10] Only 30% of children with developmental problems are identified before school age when relying solely on clinical judgment.[11]

Developmental screening can help the pediatrician to identify more children with a possible developmental delay or disability. Screening is "a brief assessment procedure designed to identify children who should receive more intensive diagnosis or assessment".[1,7,8] Child development is a dynamic process, and includes various streams of development, namely fine and gross motor, language, cognitive and adaptive behavioral components which are all interrelated and therefore quite complex. Developmental screening has limited ability to predict future functioning but is a valid and reliable way to assess subject skills in a variety of domains. Developmental screening tools undergo extensive testing for validity, reliability and accuracy and are standardized with a population representative sample. Sensitivity and specificity are measured by comparing the test to a gold standard developmental evaluation tool, and should both be between 70 and 80%, because of the nature and the complexity of measuring the continuous process of child development[1,7,8] This always leads to over-referral, and under-referral. But children who are not picked up by a first screen might well be found a next time if screening occurs periodically, and children who are over-referred often still benefit from more close surveillance.[12] Some well known examples of developmental screeners that can be utilized by trained professionals are the Denver II screening test, the Bayley Neurodevelopmental screener and the Batelle Developmental Inventory. The major disadvantage of these tests is that they take relatively much time and effort to administer and interpret.

In the past, parental reporting of current skills and concerns was considered to be too inaccurate to be used in screening, but in the last twenty years several studies have shown that parent-completed screening tools are highly accurate in detecting true problems.[13] Examples of parent-completed screening tools are the Parents' Evaluation of Developmental Status,[14] the Child Development Inventories,[15] and the Ages and Stages Questionnaires.[16] The parent based developmental screeners

that can be completed by parents in the home setting are being used more and more frequently, due to the fact that they are relatively inexpensive and accurate.[1] Amongst the parent-completed questionnaires for young children, the Ages and Stages Questionnaire (ASQ) is currently the most widely used.[18,20] It consists of 19 different questionnaires covering the age-range of 4 to 60 months. The reading level that is needed to fill in the various ASQ questionnaires is grade 4–6, thus ensuring easy parental comprehension. The ASQ takes 10–15 min to complete. The questionnaires cover five different domains: communication, gross motor, fine motor, problem solving and personal social skills. Each domain is assessed by six questions on developmental milestones. They are chosen so as to represent a developmental quotient of 75–100%. Parents can answer them with “yes”, “sometimes” or “not yet”, with a respective score of 10, 5 or 0 points. Referral for further assessment is advised when the score on any domain falls below the cut-off point, which is set at 2 standard deviations below the mean of the reference group.

The original ASQ has been proven to be reliable and cost-effective with excellent psychometric properties. Concurrent validity ranges from 76 to 88%.[19] Overall sensitivity and specificity are 75% and 86%, respectively. In a recent multinational trial involving 18 countries in Asia, Africa, Europe, North- and South-America, sensitivity was 88% and specificity was 82.5%.[17,20] Test–retest reliability within two weeks was 94% for the original version. Interobserver reliability between parents and professional examiners was 94%.

The ASQ is widely used in preventive and curative health care programs in the US and in Canada. It has been translated into Spanish, Korean, Chinese, French, Danish and Norwegian, and several other local translations exist.[21-26] Although the ASQ is translated and used all over the world, few studies have examined its psychometric properties in their own cultural setting after translation.[21,24,26,27]

For our study, we have selected the four year questionnaire of the ASQ, because it will help to identify children which have been missed by early developmental screening programs, who might still benefit from more formal neurodevelopmental testing at this young age. We believe that identifying children with possible developmental delays at the start of formal schooling, instead of waiting for serious problems to arise later on, could help to prevent unnecessary hardship for these children and their parents. In our country this age (4 years) coincides with a routine visit to our Well Child Preventive Health Care Clinics. The aim of this study was

to determine the psychometric properties of the Dutch 48 months ASQ questionnaire (D_ASQ_48) in a large community-based sample of children, as the first step towards determining the psychometric properties of the entire series of ASQ questionnaires in the Netherlands.

METHODS

Population

We drew a stratified sample from a community-based cohort of 45,446 children born in 2002 and 2003 from 13 Preventive Child Healthcare (PCH) organizations. In the Netherlands, 96% of all children attend routine Well Child Clinics offered by the PCH organizations.[28] All children born before a gestation of 36 completed weeks (further mentioned as preterm children) were selected, plus a sample of term-born children. The latter group comprised the first child from the same birth year with a gestational age (GA) between 38^{+0} and 41^{+6} weeks that was filed after each second preterm child. We enriched the sample with children from five of the ten newborn intensive care Units (NICUs) in the Netherlands who were born at a gestational age of < 32 weeks in 2003. Children with major congenital malformations, chromosomal abnormalities and syndromes were excluded. The demographic and socioeconomic background of the children enrolled in the study are shown in **Table 1**.

Procedure

The ASQ was translated into Dutch using the Guilléman method with three separate forward and backward translations.[29] The final version was reached through a consensus discussion involving an expert panel. Efforts were made to keep the exact meaning of the original items. Parents, with their child, were invited to participate in the study. The invitation was sent by mail, 4 weeks before the scheduled PCH visit for the age group of 45–50 months. Parents received an explanatory letter, the Dutch ASQ_48 and a general questionnaire with regard to their child's health and socio-demographic background.

Children who did not keep their appointment were traced, (as far as was possible) by the PCH. Questionnaires were returned to the research center. When their child reached five years of age, the parents who had completed the ASQ, once more received a general questionnaire by mail.

Table 1. Demographic and socioeconomic background of the sample by gestational age groups: numbers (% of gestational age group)

	N	< 32 wks	32-36 wks	38-42 wks	*p*-value
Number of children	2072	541 (26.1)	969 (46.8)	562 (27.1)	
Gestational age in weeks *Mean (range)*	2072	29^{+2} (23^{+6}-31^{+6})	34^{+0} (32^{+0}-35^{+6})	39^{+2} (38^{+0}-41^{+6})	< 0.001
Gender Boys	2072	276 (51.0)	554 (57.2)	279 (49.6)	*< 0.01*
Girls		265 (49.0)	415 (42.8)	283 (50.4)	
Child age at completing ASQ *(days)* Mean	2014	1390	1391	1390	
Range		1278-1811	1090-1789	1090-1811	
Educational level mother	2062				n.s
Maximum lower vocational[a] < 12 yrs		150 (27.8)	292 (30.3)	145 (25.9)	
Medium level 13-16 years		228 (42.3)	416 (43.2)	243 (43.4)	
(Applied) university > 16 years		161 (29.9)	255 (26.5)	172 (30.7)	
Household composition	2050				< 0.05
Two parents		500 (93.8)	896 (93.5)	540 (96.8)	
Single parent		33 (6.2)	62 (6.5)	18 (3.2)	
Ethnicity mother	2039				n.s
Mother born in the Netherlands		504 (94.7)	904 (94.8)	527 (95.3)	
Mother born outside the Netherlands		28 (5.3)	50 (5.2)	26 (4.7)	
Monthly family income	1622				< 0.001
< 1150 euros		26 (5.9)	63 (8.6)	23 (5.1)	
1151-3050 euros		277 (63.1)	520 (70.8)	316 (70.4)	
> 3050 euros		136 (31.0)	151 (20.6)	110 (24.5)	
Mother's age in years	2067				n.s
< 20		5 (0.9)	12 (1.2)	3 (0.5)	
20-35		465 (86.1)	827 (85.7)	468 (83.3)	
36-46		70 (13.0)	126 (13.1)	91 (16.2)	
Type of pregnancy	2059				< 0.001
Singleton		350 (64.7)	688 (71.7)	548 (98.2)	
Twin		184 (34.0)	254 (26.5)	10 (1.8)	
Triplet/Quadriplet		7 (1.3)	18 (1.9)	0 (0)	

P-values of chi-square tests for trends; *n.s. = not statistically significant.*

The parents were asked if their child was in mainstream education, had special educational needs within mainstream education, or was attending a school for children with special educational needs.

The data were coded according to standard practices for maintaining confidentiality. The study was approved by the local Institutional Review Board

Analyses

We first assessed the background characteristics of the study samples. Next, we compared mean scores for the Dutch ASQ_48 with those from the US, Korean, and Norwegian ASQ 48 months versions.[19,21,25] We limited these analyses to children for which the Dutch ASQ_48 had been filled in within two months of their fourth birthday, in a similar fashion to the Danish and international Magpie trials that employed the ASQ.[17,20,22] Moreover, we weighted our sample to reflect the total Dutch population with regard to gestational age.[30,31] Thirdly, we assessed internal consistency as a measure of reliability for the Dutch ASQ by computing Cronbach alpha coefficients; we compared our findings with those of the US ASQ. Fourthly, we assessed validity by defining cut-off points for deviant scores at 2 SDs below the mean for the reference group, in accordance with the ASQ manual.[32]

Because the distributions of the child-ages at which the Dutch ASQ_48 had been completed did not differ between groups, we used all the data when comparing the preterm and term-born control children. We used the following methods to assess validity:

- Content validity and cultural appropriateness were checked by an expert panel.
- Construct validity was analyzed using the following biological and environmental criteria: early prematurity (gestational age < 32 weeks), child's gender, mother's educational level, mother's age, household situation and family income.
- Predictive validity was assessed using the child's educational status at 5 years. We used enrolment in special education, or having special educational needs in mainstream education as criteria for developmental disability.

All analyses were done using SPSS for Windows 14.0. All tests were two-sided and considered to be statistically significant if $p<0.05$.

RESULTS

Sample and mean scores

Of the 3175 eligible children 2508 (79%) participated in the whole study, of which the parents of 2072 children completed the Dutch ASQ_48. Eventually 605 children (438 preterm infants and 167 term infants) completed the Dutch ASQ_48 within the time frame of 46–50 months. The other children were older or younger due to random variations in the dates of the Well Child visits due to logistical reasons.

The mean scores of Dutch children for all domains except for the fine motor domain differed significantly from the US mean scores. Moreover, Dutch mean scores were statistically significantly lower than the Norwegian scores in all domains. The Dutch and Korean children differed significantly with regard to the fine and gross motor domains. Differences were generally small, being only clinically relevant (effect sizes (Cohen's delta) >0.5, or differences in raw scores >5 points, the smallest possible increment in domain scores) in the problem solving domain (US) and the fine motor domain (Norway and Korea). Results are summarized in **Table 2**.

Table 2. Comparison of Dutch mean scores with US, Norwegian and Korean scores on the ASQ 48 months form.

	Dutch (N=605)		***US (N=336)***		***Norwegian (N=100)***		***Korean (N=224)***	
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
Communication	53.5	8.7	56 ***	9	56 ***	6	52.6	9.7
Fine motor	44.7	13.1	44	14	50 *** #	13	52.5 *** # $	8.3
Gross motor	49.5	10.6	52 ***	10	54 ***	9	51.1*	10.0
Problem solving	52.0	9.0	57 *** # $	8	54 *	9	52.1	8.7
Personal social	53.0	9.2	49 ***	13	56 ***	7	53.9	7.3

** p< 0.05, ** p<0.01, *** p< 0.001, # raw difference ≥ 5 points, $ Cohen's delta> 0.5.*

Internal consistency

Cronbach alpha for the total Dutch ASQ_48 score was 0.79. For domain scores, it ranged from 0.61 to 0.73. Cronbach alphas for the five domains and the total ASQ score in the Dutch and US samples are shown in **Table 3**. Item deletion did not improve standardized alpha coefficients.

Table 3. Reliability (Cronbach alphas) for domain scores Of the Dutch and US ASQ 48 months forms among term children.

Cronbach alphas	*Dutch*	*US*
Total score	0.79	-
Communication	0.74	0.71
Fine motor	0.69	0.69
Gross motor	0.64	0.77
Problem solving	0.61	0.67
Personal social	0.61	0.56

Content validity and cultural appropriateness

All items were discussed at length by an expert panel. This consisted of a leading Dutch researcher and professor in preventive child healthcare, a leading researcher and professor in neonatology, three child healthcare doctors and a general pediatrician. No major concerns were raised regarding the cultural or age-appropriateness for Dutch children in any item of the Dutch ASQ_48. All items were then discussed with a group of seven parents of children in the appropriate age group each with varying levels of education. No problems were encountered.

Construct validity

Dutch cut-off points were constructed according to the ASQ manual,[16] results are shown in **Table 4**. Children born at a gestational age of <32 weeks failed on the total and all domain scores significantly more often than controls, with clinical and statistical significance. Odds ratios (OR) ranged from 2.5 to 4.9. Children in low income families were more likely to have deviant scores on communication (OR 4.7), problem solving (OR 3.4), personal social (OR 3.3), and total score (OR 4.7). Children from one-parent families were less likely to have deviant scores on communication (OR 0.3) problem solving (OR 0.2) and total score (OR 0.3). Children of lower educated mothers were more likely to fail on fine motor (OR 1.7), problem solving (OR 1.9), personal social (OR 2.1) and also total score (OR 1.8).

Table 4. Cut-off scores for the domains of the Dutch ASQ 48 months form in a community-based sample.

Domain	*Cut-off score*
Total score	36.6
Fine motor	18.6
Communication	36.0
Gross motor	28.4
Problem solving	34.3
Personal social	34.7

These differences only reached statistical significance for personal social and total scores. Boys scored below the cut-off for all domain scores and total score significantly more often than girls (OR 1.5–4.7). Maternal age at delivery had no significant association with Dutch ASQ_48 scores. Results are summarized in **Table 5**.

Predictive validity

The Dutch ASQ_48 correctly identified 25 out of 28 children who were in special education or medical child care centers at the age of 5 years, i.e. an outcome showing severe developmental impairment one year later. Among those not identified, one was in special education because of behavioral problems and one because of medical problems related to having a tracheotomy. Sensitivity in our sample was 89% and specificity 80%. Negative (NPV) and positive predictive values (PPV) were 99.7% and 9.1%, respectively. When having special educational needs in mainstream education was added to the predictive criterion, sensitivity was 76%, specificity 81%, NPV 98.8% and PPV 13.5%.

Table 5. Associations of deviant scores on domains of the Dutch ASQ 48 months form with criteria for validity. (odds ratios and 95% confidence intervals).

Criterion	*Communication*	*Fine Motor*	*Gross Motor*	*Problem Solving*	*Personal Social*	*Total*
< 32 weeks	***4.05 (2.33-7.07)******	***4.25 (2.19-8.26)******	***4.89 (2.72-8.80)******	***2.48 (1.33-4.62)****	***4.38 (2.21-8.67)******	***4.59 (2.51-8.42)******
Male gender	***1.49 (1.15-3.47)****	***4.69 (2.82-7.81)******	***2.23 (1.48-3.35)******	***2.32 (1.44-3.72)******	***2.36 (1.47-3.78)******	***3.30 (2.11-5.15)******
Low income	***4.65 (2.09-10.3)******	*n.s.*	*n.s.*	***3.32 (1.30-8.45)****	*n.s.*	***4.74 (2.08-10.8)******
One-parent family	***0.23 (0.23-0.64)****	*n.s.*	*n.s.*	***0.17 (0.04- 0.75)****	*n.s.*	***0.29 (0.11-0.78)****
Low educ. mother	*n.s.*	*1.72 (0.99-2.98)*	*n.s.*	*1.85 (0.97-3.53)*	***2.09 (1.09-4.00)****	***1.82 (1.02-3.27)****

** p < 0.05, ** p <0.01, *** p < 0.001, n.s. = not statistically significant*

COMMENT

This study assessed the reliability and validity of the Dutch version of the ASQ_48 months questionnaire. Its results show that the Dutch ASQ_48 months has a good reliability. Mean scores are lower than in some other countries but most of the differences are small. Performance of the Dutch ASQ_48 months questionnaire on a number of aspects of validity generally confirmed validity. There was only one exception which was the unexpected lower percentage of children from one-parent families who failed the Dutch ASQ_48 months with regard to communication, problem solving and total score when compared to children from two parent families.

Despite the fact that 10 out of 15 comparisons of mean scores with other countries yielded statistically significant differences, most cross-country differences between the mean domain scores were remarkably small. Only three cross-country comparisons showed clinically relevant differences, the remainder probably being due to our large sample size and the resultant high power to detect relatively minor, clinically unimportant, differences. Problem solving scores were higher in the US sample. Fine motor scores were higher in the Norwegian and Korean samples. This was the only domain without a statistically significant difference in mean scores when comparing the Dutch and US data. We have no real explanation for these differences. The striking similarity between most mean scores and the failure to find more consistent clinically relevant cross-country differences suggests that the few differences that were found might be explained by chance. However, true differences in child rearing practices between countries could also contribute. The small effect size of most of the differences, and the absence of more clinically relevant differences, support the cross-continental usefulness of the ASQ.

Despite the fact that there are very few cross cultural differences, there is still the need for careful adaptation and validation of developmental screeners for different cultural settings and languages.[32]

The effect of prematurity, maternal education, and family income were consistent with previous studies,[33] reflecting the validity of the Dutch ASQ_48. The reduced risk of having a score below the cut-off score on communication, problem solving and total score for children from one-parent families might be explained by the fact that these children possibly receive more attention at a young age in the household situation. The absence of an association with teenage pregnancies was probably due to small numbers, reflecting the low rate of teenage pregnancy in the Netherlands.[34]

Girls in this study scored higher on all domains, which reached statistical significance for fine motor functioning, personal social, problem solving and total domain score. These differences are consistent with the Norwegian findings.[24,25] The "gold standard" neurodevelopmental tests have identical cut-off points for boys and girls in this age group.[35,36] It could be debated whether separate cut-off points are required for girls and boys, as is the case with behavioral measures like the Child Behavior Checklist.[37]

Strengths and limitations

A major strength of our study is that the normative data were based on a large, random sample from the community, using PCHs with extremely high (> 95%) attendance rates as sampling framework. The response rate of 65% is high compared to other validation studies of the ASQ 48 months. This response percentage includes the randomly chosen control children. Due to our large sample we could also perform a separate analysis on a sample with close age-boundaries regarding the age of completing the ASQ.

A limitation is that we could not compare the Dutch ASQ with a gold standard in developmental testing at 48 months, and had to rely regarding predictive validity of Dutch ASQ_48 scores on problems at school entry. Sensitivity and specificity of the predictions were acceptable. The Dutch ASQ_48 indeed identified almost all children with problems of a severity that already had led to (school) problems at this age, shown by the very high NPV. The test characteristics as found might even have been better if we had taken a time point at 7 or 8 years, when developmental delay has become even more pronounced.

CONCLUSIONS

Our results show that the ASQ 48 months questionnaire is a short parental developmental screener with excellent psychometric properties, which can be used in community settings outside the USA, to identify children who might benefit from more extensive developmental testing. The reliability and validity of the Dutch ASQ 48 months questionnaire, and the striking similarities with the data from the Norwegian and Korean validation studies are the first step in confirming the feasibility of the Ages and Stages Questionnaire for industrialized countries in general. Cross cultural studies on the entire series of questionnaires of the ASQ are needed to confirm these findings.

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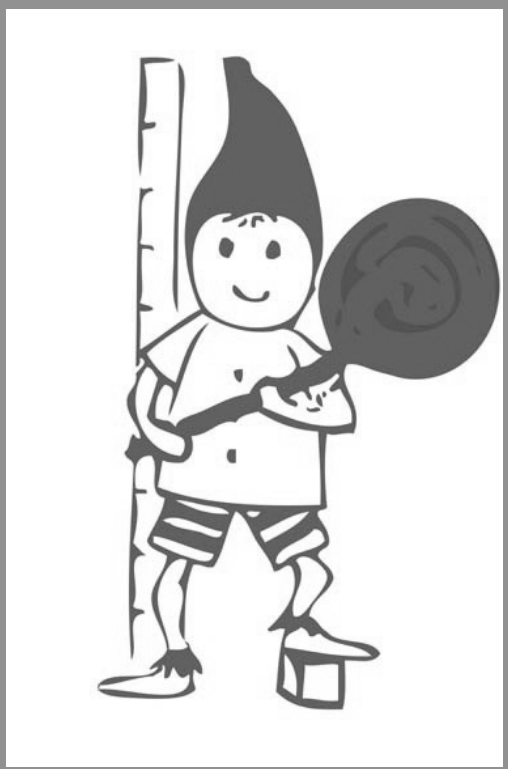
Chapter 3

Developmental delay in moderately preterm-born children at school entry



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ABSTRACT

Objective: To determine the prevalence and nature of developmental delay at preschool age in children born moderately preterm compared with those born full-term and early preterm.

Study Design: Parents of 927 moderately preterm-born children (32-35^{+6} weeks gestation), 512 early preterm-born children (<32 weeks gestation) and 544 fullterm-born children (38-41^{+6} weeks gestation), completed the Ages and Stages Questionnaire (ASQ) when the child was aged 43-49 months. We analyzed rates of abnormal ASQ scores and odds ratios (ORs) for abnormal ASQ-scores in both preterm groups compared with the fullterm group. We repeated the analyses after adjustment for socioeconomic status, sex, being part of a multiple birth and small for gestational age status.

Results: Abnormal (ie, >2 SDs below the mean) ASQ total scores were noted in 8.3% of moderately preterm-born children, in 4.2% of fullterm-born children, and in 14.9% of early preterm-born children. ORs of abnormal ASQ total scores were 2.1 (95% CI, 1.3-3.4) for moderately preterm-born children and 4.0 (95% CI, 2.4-6.5) for early preterm-born children. Both moderate and early preterm-born children had more frequent problems with fine motor, communication, and personal-social functioning compared with fullterm-born children. Compared with fullterm-born children, moderately preterm-born children did not have a greater prevalence of problems with gross motor functioning and problem solving, whereas early preterm-born children did. Socioeconomic status, small for gestational age status, and sex were associated with abnormal ASQ scores in moderately preterm-born children.

Conclusions: At preschool age, the prevalence of developmental delay in moderately preterm-born children was 2-fold of that in fullterm-born children and one-half of that in early preterm-born children.

INTRODUCTION

Moderately preterm-born children, born after 32 weeks gestational age, have been considered at low risk for long-term developmental consequences of their preterm birth. However, several recent epidemiologic studies have reported that compared with fullterm–born children, moderately preterm-born children are more likely to have problems in kindergarten, show less school readiness, repeat grades more often in mainstream education, and receive more special education.[1-4] Moderately preterm-born children as a group merit special attention given the increasing incidence of moderately preterm birth in the United States, from 7.4% of live births in 1983 to 10.4% of live births in 2003.[5,6] During the same period, the incidence of early preterm births (<32 weeks gestational age) remained constant at 1.8%-2.0% live births.[6] In Europe, the incidence of moderately preterm birth is 6%-9%.[6] The rising incidence and the possibility of long-term developmental impairments have triggered growing concerns about the economic consequences of moderate prematurity for society.[7,8]

The development of moderately preterm-born children before school age has not been widely studied, whereas that of early preterm-born children has been studied extensively. Early preterm-born children are at risk of developmental delay at an early age. Compared with fullterm-born children, they are more likely to have delays in fine and gross motor functioning, sensory integration, cognitive functioning, and communication and to have behavioral and socio-emotional problems.[9-12] The extent to which the developmental risk profile of early preterm-born group can be generalized to moderately preterm-born group is unclear. The aim of the present study was to determine the prevalence and nature of developmental delay at preschool age in children born between 32 and 36 weeks gestation compared with both fullterm-born and early preterm–born children. We hypothesized that the moderately preterm-born children would have more developmental problems than the fullterm-born children, but fewer developmental problems than early preterm-born children.

METHODS

Longitudinal Preterm Outcome Project (LOLLIPOP) is a large prospective cohort study on the growth, development, and general health of preterm-born children.[13] The study's main focus is on moderately preterm-born children, born between 32 and 35^{+6}

weeks gestation. The LOLLIPOP cohort comprises a community-based sample of early and moderately preterm (born before 36 weeks gestation) children and a random sample of fullterm-born children seen at preventive child healthcare centers (PCHCs), enriched with a sample of early preterm-born children from neonatal intensive care units (NICUs). Cohort size was based on estimates of data needed to compile growth charts for Dutch preterm-born children, leading to a planned inclusion of 1000 moderately preterm, 500 early preterm, and 500 fullterm-born children. Children were assessed at age 43-49 months. Prospective data on growth, development, and family characteristics were matched with retrospective data on pregnancy and birth from files maintained by PCHCs, pediatricians, and obstetricians. The LOLLIPOP study was approved by the local institutional review boards. In this article, we present the results of the assessment of the children's development at age 4 years. **Figure 1** provides an overview of both sampling procedures.

The community-based sample came from Dutch PCHCs, which monitor 90%-95% of all children at regular intervals from birth until age 4 years.[14] Thirteen PCHCs participated in the study. The PCHCs were randomly selected and stratified by region (north vs south), to balance differences in children's heights between these regions. Together the PCHCs monitored 45 446 children, representing 25% of the 4- year-olds in the Netherlands. Eight PCHCs checked the files of all children born between January 1 and December 31, 2002, and 5 PCHCs checked the files of all children born between June 1, 2002, and May 31, 2003. All children born before 36^{+0} weeks gestation without major congenital malformations, congenital infections, or syndromes were sampled. After each second preterm child sampled, the next term-born child (gestational age 38^{+0}-41^{+6} weeks) without the aforementioned exclusion criteria was drawn from the same files to serve as a control. The PCHCs sampled a total of 2758 children for the study. Oversampling of early preterm-born children was done by 5 tertiary NICUs covering a larger portion of The Netherlands. These NICUs sampled all early preterm-born children born between January 1 and December 31, 2003, discharged alive from their unit, and not meeting the exclusion criteria. After removing all children that had been double-sampled, we tracked the local PCHCs of these children (32 additional centers), and asked them to join the study for the children involved. The NICUs sampled an additional 548 early preterm-born children for the study.

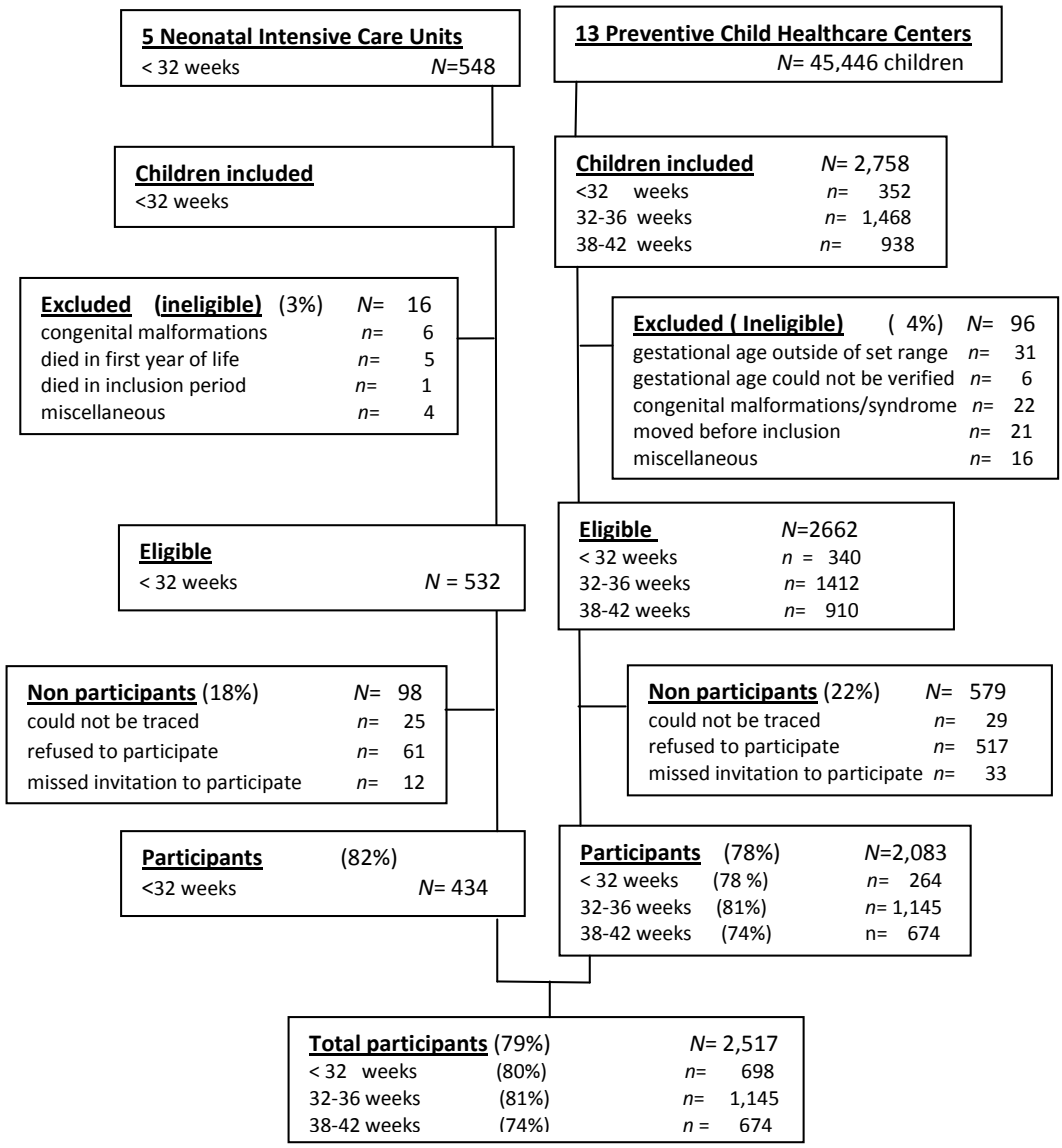

Figure 1. Overview of sampling procedures for the LOLLIPOP study.

Parents were invited to participate with their child in the study by mail at 4 weeks before the scheduled PCHC visit at age 43-49 months. The parents received an informational leaflet on the study, an informed consent form, and several questionnaires. They also received detailed instructions on completing the Ages and Stages Questionnaire (ASQ). The questionnaires were collected at the PCHC physician's visit. Parents of children who did not attend their regular visit were invited again and if necessary reminded by telephone or by a home visit (following routine PCHC procedures). Data were coded following standard practices for maintaining confidentiality.

Measures

Gestational age was confirmed by early ultrasound measurements in > 95% of cases. In the remaining cases, only clinical estimates based on last menstrual date were available, and these were checked against clinical estimates of gestational age after birth. Children whose gestational age could not be confirmed were excluded from the analysis. Development was assessed using the Dutch version of the age 48-month form of the ASQ, a validated parent-completed developmental screening tool.[13,15] The ASQ covers 5 developmental domains: communication, fine motor function, gross motor function, personal-social functioning, and problem solving.[15] Each domain has 6 questions on developmental milestones. Parents evaluate whether the child has achieved a milestone (yes, 10 points), has partly achieved the milestone (sometimes, 5 points), or has not yet achieved the milestone (no, 0 points). ASQ total score is calculated by adding all the domain scores and dividing the total by 5. The ASQ domain and ASQ total scores were dichotomized at 2 SD below the mean score of the Dutch reference group as normal/abnormal.[13] The ASQ domain and ASQ total scores were analyzed for children whose parents had completed the ASQ within a time window of 3 months around the median age for completing the ASQ in this study. Uncorrected calendar age was used for age calculations, following the ASQ manual.[15] The ASQ 48-months form was used because it was the most proximate to the age of children at the scheduled PCHC visits.

Data also were obtained on the parents' socioeconomic status (SES) and on the children's births. Mothers' and fathers' educational level, age at birth, country of birth, and family composition were assessed via a general questionnaire at study enrollment and matched with data from the PCHC records. Birth weight, small for gestational age (SGA) status, and multiple birth status were assessed via the same

general parental questionnaire and matched with data from retrospective files. SGA was defined as a birth weight below the 10th percentile of the Dutch Kloosterman growth charts.[16] PCHC physicians completed a questionnaire eliciting data on background characteristics for non-participating children.

Statistical Analyses

We first compared the rate of abnormal ASQ scores of moderately preterm-born children (32-35^{+6} weeks) with that of early preterm-born children (<32 weeks) and full-term-born children (38-41^{+6} weeks). In a sub-analysis, we divided moderately preterm-born children into those born at 32^{+0}-33^{+6} weeks and those born at 34^{+0}-35^{+6} weeks. Differences were tested using Pearson χ^2 statistics. We then used multivariate logistic regression analyses to examine the relationships between gestational age group and abnormal ASQ scores, leading to Odds Ratios (ORs) for abnormal ASQ scores. Finally, to assess whether maternal age at birth, mother's birth country, parental education, single-parent family, sex, multiple birth, and SGA added to the differences in ASQ scores by gestational group, we adjusted the logistic regression analyses for all factors that were possibly associated ($P < 0.20$) with development and gestational age in at least one of the ASQ domains in univariate analyses. Repeating these analyses using a stepwise backward procedure yielded similar results (data not shown). All analyses were done using SPSS version 16.0 (SPSS Inc, Chicago, Illinois). All tests were two-sided and were considered statistically significant at $P < .05$.

RESULTS

A total of 2517 of the 3194 eligible children (78.8%) were recruited for the study. Parents of 2050 of these children (81.4%) completed the ASQ. In > 95% of cases, the mother filled out the ASQ. The median age of the children at completion of the ASQ was 46 months. Of the 2050 questionnaires, 1983 (97%) were completed within 3 months of the median age at completion (43-49 months). The final analyses were performed on this group, referred to hereinafter as ''participating children.'' **Table I** presents background characteristics of the participating children. Compared with the participating children, the non-participating children had a greater proportion of lower SES (low education, 40.4% vs 28.9%; non-Dutch, 15.6% vs 5.4%; both, $P < 0.001$). Sex and SGA did not differ significantly between the two groups. The prevalence of multiple birth was higher in the participating children (22.4% vs 18.8% in non-participating children; $P <0 .05$).

Table 1. Background characteristics of participating children.

Variable	< 32 weeks	32-36 weeks	38-42 weeks	*P*
Total Group *n*(%) *N*=1983	512 (25.8)	927 (46.7)	544 (27.4)	
Inclusion rate, %	59	66	60	<0.0001
gestational age weeks, mean	29^{+2}	34^{+0}	39^{+5}	< 0.0001
range	24^{+0} -31^{+6}	32^{+0}-35^{+6}	38^{+0}-41^{+6}	
Gender				< 0.01
Male	263 (51.4)	532 (57.4)	270 (49.6)	
Female	249 (48.6)	395 (42.6)	274 (50.4)	
Birthweight g, mean (range)	1299	2248	3546	< 0.0001
Range	505-2360	705-3900	1660-5490	
Age at completing ASQ[a] (N=1925)				0.18
43-44 months	210 (42.1)	339 (38.0)	197 (37.0)	
45-46 months	233 (46.7)	417 (46.7)	259 (48.6)	
47-49 months	56 (11.2)	137 (15.3)	77 (14.4)	
Mother's educational level (N=1973)				0.23
Maximum lower vocational[b] <12 years	142 (27.8)	276 (30.0)	140 (25.8)	
Medium level 13-16 years	214 (42.0)	398 (43.2)	237 (43.7)	
(Applied) university 17+ years	154 (30.2)	247 (26.8)	165 (30.4)	
Father's educational level (*N*=1914)				< 0.05
Maximum lower vocational[b] <12 years	145 (29.2)	314 (35.4)	151 (28.5)	
Medium level 13-16 years	204 (41.0)	307 (34.6)	201 (38.0)	
(Applied) university 17+ years	148 (29.8)	267 (30.1)	177 (33.5)	
Household situation, n (%) (N=1975)				<0.01
Two parents	476 (93.3)	857 (92.6)	523 (96.9)	
Single parent	34 (6.7)	68 (7.4)	17 (3.1)	
Ethnicity mother, n (%) (N= 1976)				0.52
Mother born within the Netherlands	481 (94.1)	872 (94.4)	517 (95.6)	
Mother born outside the Netherlands.	30 (5.9)	52 (5.6)	24 (4.4)	
Mother's age in years, n (%) (N=1981)				0.24
< 20 years	5 (1.0)	11 (1.2)	3 (0.6)	
20-35 years	440 (86.1)	794 (85.9)	453 (83.4)	
36-46 years	64 (12.9)	119 (12.9)	87 (16.0)	
Part of a multiple pregnancy (N=1983)				
Singleton	334 (65.2)	668 (72.1)	538 (98.9)	<0.0001
Twin	171 (33.4)	243 (26.2)	6 (1.1)	
Triplet/Qaudruplet	7 (1.4)	16 (1.7)	0 (0.0)	
SGA < P10, n (%) (N=1983)	97 (19.1)	85 (9.2)	45 (8.4)	<0.0001

[a] *In 58 children, the ASQ was completed within the set time window, but no exact date could be determined.*

[b] *Lower vocational education levels finished high school.*

Figure 2 shows the rates of abnormal ASQ total and ASQ domain scores for the three gestational age groups studied. The rate of abnormal ASQ total score was 8.3% in the moderately preterm-born children, compared with 4.2% in the full-term children and 14.9% in the early preterm-born children. The moderately preterm-born children had higher rates of abnormal scores in the fine motor, communication, and personal social functioning domains than full-term children, but lower rates of abnormal ASQ total score and all domain scores than early preterm-born children.

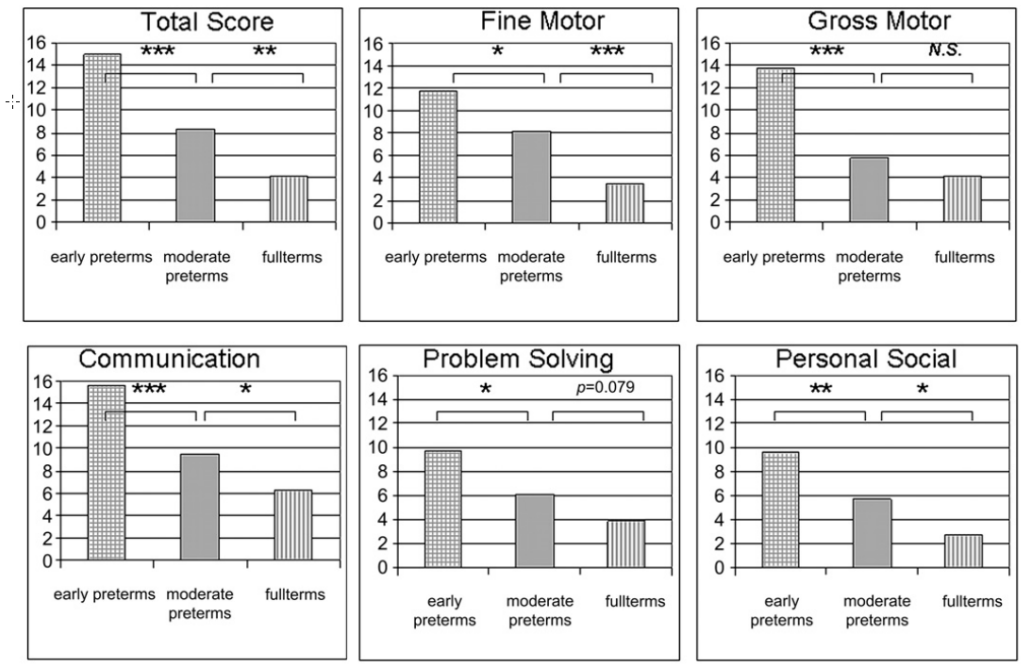

Figure 2. Percentages of children with abnormal scores on ASQ total score and ASQ domains for moderately preterm and early preterm-born children compared with term-born children at age 4 years.

**; P< 0.05, ** P < 0.01, *** P ≤ 0.0001 , n.s not significant*

Table 2. Crude and adjusted Ors and 95% CIs for abnormal scores on ASQ total score and ASQ domains for early and moderate preterms compared with fullterms, with adjustment for maternal and paternal education, mother's country of birth, SGA, sex, and being part of a multiple birth.

	Early Preterms			**Moderate Preterms**			**fullterms**	**32-33^{+6} weeks**			**34-35^{+6} weeks**		
	OR	C.I.	*p*	OR	C.I.	*p*	OR	OR	C.I.	*p*	OR	C.I.	*p*
Total score crude	**4.0**	**2.44-6.53**	**0.000**	**2.1**	**1.27-3.38**	**0.004**	1.0	**2.1**	**1.12-3.76**	**0.019**	**2.1**	**1.24-3.48**	**0.005**
Total score adjusted	**3.2**	**1.88-5.37**	**0.000**	1.5	0.89-2.52	0.128	1.0	1.5	0.81-2.92	0.187	1.5	0.84-2.52	0.177
Fine motor crude	**3.7**	**2.15-6.22**	**0.000**	**2.4**	**1.44-4.04**	**0.001**	1.0	**2.8**	**1.55-5.21**	**0.001**	**2.2**	**1.29-3.83**	**0.004**
Fine motor adjusted	**3.6**	**2.02-6.38**	**0.000**	**2.0**	**1.17-3.54**	**0.011**	1.0	**2.5**	**1.32-4.87**	**0.005**	**1.8**	**1.01-3.22**	**0.047**
Gross motor crude	**3.8**	**2.29-6.18**	**0.000**	1.4	0.85-2.37	0.176	1.0	1.0	0.50-2.11	0.937	1.6	0.94-2.74	0.081
Gross motor adjusted	**3.5**	**2.04-5.94**	**0.000**	1.3	0.75-2.21	0.357	1.0	1.0	0.46-2.06	0.947	1.4	0.81-2.50	0.216
Communication crude	**2.8**	**1.82-4.27**	**0.000**	**1.6**	**1.04-2.40**	**0.031**	1.0	**2.0**	**1.19-3.28**	**0.008**	1.4	0.89-2.20	0.141
Communication adjusted	**2.3**	**1.45-3.68**	**0.000**	1.3	0.84-2.08	0.224	1.0	1.6	0.94-2.81	0.081	1.2	0.74-1.93	0.475
Problem solving crude	**2.6**	**1.56-4.48**	**0.000**	1.6	0.95-2.7	0.081	1.0	**1.9**	**1.04-3.62**	**0.037**	1.4	0.81-2.47	0.219
Problem solving adjusted	**2.4**	**1.34-4.23**	**0.003**	1.2	0.68-2.09	0.538	1.0	1.7	0.87-3.27	0.123	1.0	0.53-1.81	0.983
Personal social crude	**3.7**	**2.05-6.71**	**0.000**	**2.1**	**1.18-3.78**	**0.012**	1.0	**2.1**	**1.003-4.23**	**0.049**	**2.1**	**1.15-3.94**	**0.016**
Personal social adjusted	**3.2**	**1.70-6.07**	**0.000**	**1.9**	**1.001-3.48**	**0.050**	1.0	1.8	0.82-3.79	0.149	**1.9**	**0.999-3.66**	**0.050**

Table 2 presents crude ORs for abnormal ASQ total and ASQ domain scores for early and moderately preterm-born children compared with full-term children. The crude ORs for moderately preterm-born children were at least one-half of those for early preterm-born children in all domains except gross motor function. In univariate analyses, a poor developmental outcome was more likely in children with low maternal and paternal education, non-Dutch maternal birth country, two-parent family, SGA, male sex, and multiple birth ($P < 0.05$), but not in those with young maternal age at birth ($P > 0.20$)

Consequently, all demographic and socioeconomic risk factors except maternal age at birth were included in the final multivariate model. Adjustment for the aforementioned factors decreased the ORs for abnormal scores in all gestational age groups (**Table 2**). Although all ORs remained >1, in moderately preterm-born children only ORs for the fine motor domain and the personal-social domain (borderline) were statistically significant, whereas in early preterm-born children ORs were significant for all ASQ domains.

Crude and adjusted ORs for ASQ total scores were similar in the two moderate preterm subgroups. The younger moderate subgroup did worse than the older moderate subgroup in some, but not all, ASQ domains.

DISCUSSION

This study demonstrates a 2-fold greater prevalence of developmental delay at pre-school age in moderately preterm-born children compared with term-born children, and half the prevalence compared with early preterm–born children. At preschool age, moderately preterm-born children were more likely than full-term children to have problems with fine motor, communication, and personal-social functioning. In these 3 domains, moderately preterm-born children had problems similar to those of early preterm-born children, but to a lesser degree. At preschool age, moderately preterm-born children did not have a higher rate of problems with gross motor function or problem solving compared with full-term children, whereas early preterm-born children did. Socioeconomic and demographic factors partly explained the differences between the moderately preterm and full-term children.

This study simultaneously assessed several developmental domains at preschool age in a large, community-based, longitudinal cohort of moderately preterm-born children. The few previous studies on the development of moderately

preterm-born children at preschool age involved either a specifically selected high risk group of late preterm-born children (34-36^{+6} weeks gestation)[17] or a group of relatively healthy late preterm-born children.[4] Moreover, a comparison of studies is difficult, given that the studies used a variety of cutoff points for ''moderately'' preterm birth. Previous studies on developmental outcomes beyond the preschool period have reported more grade retention and more special educational needs at age 5-10 years,[2-4,18] poorer performance in adulthood, and lower job-related incomes in moderately preterm-born children compared with full-term children.[19-21] These findings indicate long-lasting developmental consequences of moderately preterm birth.

Our results demonstrate that several of these developmental problems can be detected at preschool age. Our results also reveal some details regarding the nature of the developmental problems in the moderately preterm group. First, the prevalence of abnormal fine motor scores was higher in this group. This might well be the origin, at least in part, of the writing problems seen in higher grades.[3,4,18] Second, these children had a higher prevalence of abnormal ASQ scores in the communication domain. Persistent language problems may lead to reading and spelling problems and poorer verbal fluency in adulthood.[1,3,18] Baron et al[17] reported reduced noun fluency and action verb fluency, but no receptive or expressive language delays, in late preterm–born children. Third, moderately preterm-born children had more problems with personal-social functioning, which measures the capacity to function in a group. A child with a delay in this domain seems likely to encounter problems at school-entry.

The moderately preterm-born children did not have increased rates of abnormal scores in the ASQ domains of gross motor functioning and problem solving. The only indirect measure of problems in gross motor function was reported by Huddy et al,[3] who found problems with physical education at age 7 in 33% of his moderately preterm group. The ASQ problem solving domain might be interpreted as giving a first estimate of executive functioning and IQ. If so, then our results of no important differences are consistent with two previous reports. Baron et al[17] found no difference in general conceptual ability between late preterm and full term children, and Van Baar et al[2] found only a small difference (ie, 3 IQ points) between moderate preterm and full-term children at school age.

Our findings do not offer an explanation for the increased incidence of developmental problems on parental report in the moderately preterm group. There may be several explanations. Given that only 60% of the human brain volume is

present at 32 weeks gestation,[22] hypoxia, hypotension, and several noxious stimuli in the extrauterine environment might disrupt various maturational processes, including increased neuronal connectivity, dendritic arborization, formation of synaptic junctions, and maturation of neurochemical and enzymatic processes.[2,23] Postnatal maturational processes might not be the only processes involved; spontaneous preterm birth itself might be caused by prenatal events that are part of a larger underlying cascade that trigger preterm birth and simultaneously cause or predispose the infant to neurologic injury.[8] Further research is needed to unravel these complicated matters.

In this study we compared moderately preterm-born children not only with full-term children, but also with early preterm-born children. Early preterm-born children had more developmental delays than moderately preterm-born children in all ASQ domains, in concordance with their more immature brain at birth and greater susceptibility to both perinatal and postnatal complications. The influence of gestational age on development was also suggested within the moderately preterm subgroup analysis. ORs for abnormal ASQ scores were higher in the subgroup born after 32-33 weeks gestation in 3 out of 5 domains. Therefore, our data for early and moderately preterm children support the theory of the influence of declining gestational age on development.[24]

In our study we corrected for several well-documented confounders for developmental delay.[25] Poorer developmental outcomes of the moderately preterm-born children were associated with other risk factors, including SES, sex, and SGA. Moderately preterm birth and an unfavorable SES provide a ‘‘double hit.’’

Major strengths of the study are its community-based design, the use of a wide range of sources of information, the exclusion of children with major congenital malformations and syndromes, and the collection of information on a wide range of potential confounders.[26] We also recognize some limitations of the study. For one, we used a screening instrument instead of a more extensive test to measure development. But several authors have argued that developmental screening tests are reliable measures for identifying developmental problems in high-risk populations,[27] and using this instrument allowed us to examine a large population of preterm children. Another limitation is that we did not include children born at 37 weeks gestation in the full-term group, which might have magnified the differences among groups. Kramer et al[28] have shown that children born at 37-38 weeks do worse than children born at

39-40 weeks. A third limitation is the low inclusion percentage (64%) of the eligible children (for ASQ data). Nonparticipating children were more likely to have a less favorable SES. Because low SES added to the risk of abnormal scores, this might have lead to underestimation of the prevalence of developmental delay.

Our findings have several implications. For every early preterm-born child with a developmental delay as measured by the ASQ on entering school in the Netherlands, there will be two moderate preterm–born children of the same age with a similar developmental delay. Thus, identifying preconceptual, prenatal, and postnatal risk factors associated with long-term developmental delay in moderate preterm-born children, and intervening if possible, are urgently needed. Furthermore, when weighing decisions on terminating pregnancies before term, obstetricians and pediatricians should be aware of the risks of long-lasting developmental consequences of mode-rately preterm birth.[29] Finally, the developmental problems in our children at age 4 years are likely to be precursors of problems in later life. Thus, our findings might provide an opportunity for targeted early intervention at a young age, and could improve the chances of getting off to a successful start at school for this large group of children.

Acknowledgements

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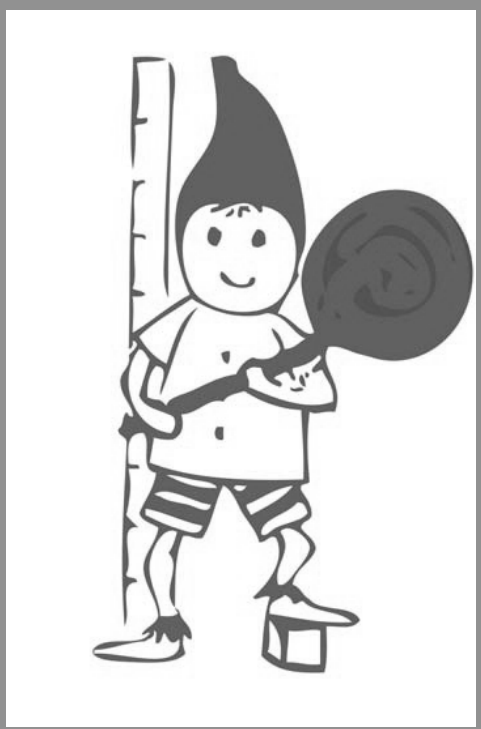
Chapter 4

Risk of developmental delay increases exponentially as gestational age of preterm infants decreases: a cohort study at age 4 years



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WHAT THIS PAPER ADDS

- Among children born from 25 to 36 weeks of gestation, risk of developmental delay at age 4 increases exponentially with decreasing gestational age.
- This holds true for the domains of fine motor, gross motor, communication, problem-solving, and personal–social functioning of the Ages and Stages Questionnaire.
- Adjustment for covariates did not alter the pattern of exponential risk.

ABSTRACT

Aim The aim of the study was to assess the influence of decreasing gestational age on the risk of developmental delay in various domains at age 4 years among children born at a wide range of gestational ages.

Method In a community-based cohort, the parents of 1439 preterm-born children (24^{+0} to 35^{+6} wks) and 544 term-born children (38^{+0} to 41^{+6} wks) born in 2002 and 2003 completed the Ages and Stages Questionnaire (ASQ) when their child was 43 to 49 months old. The prevalence rates of abnormal scores on the ASQ total-problems scale were compared in preterm and term-born children and the resulting odds ratios for gestational age groups were calculated and adjusted for social and biological covariates.

Results The prevalence rates of abnormal scores on the ASQ total-problems scale increased with decreasing gestational age: from 4.2% among term-born children to 37.5% among children born at 24–25 weeks' gestation ($p<0.001$). The risk of abnormal ASQ-total score increased exponentially with decreasing gestational age compared with children born at term (odds ratio per week gestation 1.14, 95% confidence interval 1.09–1.19). A similar exponential pattern was seen on all underlying ASQ domains, both before and after adjustment.

Interpretation The risk of developmental delay increases exponentially with decreasing gestational age below 36 weeks' gestation on all developmental domains of the ASQ. Adjustment for covariates did not alter the pattern of exponential increase in developmental risk with decreasing gestational age. We speculate that both direct perinatal cerebral injuries and tropic and maturational brain disturbances are involved.

INTRODUCTION

Two recent meta-analyses reported a pattern of continuously decreasing IQ scores with decreasing gestational age.[1,2] By and large, in these meta-analyses the results for children born at between 32 and 36 weeks' gestation, that is moderately preterm children, were arrived at by extrapolation, as relatively few studies on long-term development have been carried out in this particular group.[3,4] Recently, we demonstrated that moderately preterm children are also at increased risk of developmental delay at school entry.[5]

Studies on the effect of decreasing gestational age on development in early childhood that cover the entire preterm gestational age range are few and inconclusive regarding the increased risk of developmental delay with decreasing gestational age.[6,7] Further, most studies examining the association between decreasing gestational age and increasing developmental problems focus solely on global IQ scores or on rates of specific school problems such as difficulties in reading and mathematics, or failure to complete school at all.[2,8,9] To our knowledge, no study has addressed the effect of decreasing gestational age over the entire preterm gestational age range on the developmental domains that may underlie these problems at school entry.

Most studies included in meta-analyses of the relation between gestational age and development of children born below 32 weeks of gestation control only for a limited number of biological and social covariates.[1,2] This may be an important limitation, since several studies have demonstrated that biological and social covariates influence the likelihood of both preterm birth and adverse long-term developmental outcomes.[9,10] This is particularly true for the effect of socio-economic status beyond the age of 2 years.[11]

The aim of our study was, therefore, to assess the influence of decreasing gestational age on the risk of developmental delay in a variety of developmental domains at age 4 years. We compared a group of preterm children born at a wide range of gestational ages with term-born children. We analyzed crude data and data adjusted for biological and social covariates.

We hypothesized that the prevalence of developmental delay would show a pattern of continuous increase with decreasing gestational age in several developmental domains, independent of biological and social covariates.

METHODS

Participants

This study was part of the Dutch Longitudinal Preterm Outcome Project (LOLLIPOP).[5,12] From a community-based preventive child healthcare (PCHC) cohort of 45 455 children born in 2002 and 2003, we sampled all children with a gestational age of less than 36 weeks. For every second preterm child we sampled, we selected the next term-born child (38^{+0} to 41^{+6} weeks' gestation) from the same PCHC cohort as a comparison. The cohort was expanded with very preterm children (< 32wks gestation) born in 2003 who had been admitted to any of five tertiary neonatal intensive care units that cater for all very preterm children in their region. These very preterm children accounted for 17.8% of the study cohort. The cohort size of the complete LOLLIPOP sample was based on estimates of numbers needed to compile the growth charts for Dutch preterm-born children. This led to a planned inclusion of 1500 preterm children and 500 term-born comparison children.

The children were recruited during a routine visit to their local PCHC centre at the age of 43 to 49 months (inclusion period 2005–2007): 95% of all Dutch children are routinely seen at a PCHC centre at this age.[13] Children with major congenital malformations, syndromes, and congenital infections were excluded. The study was approved by the Ethics Review Board of the University Medical Center Groningen. Written informed consent was obtained from all parents. In total, 79% of eligible children (*n*=2517) participated in the LOLLIPOP study. We have previously published a detailed description of the LOLLIPOP study design.[5,12]

Measures: Assessment of developmental delay

We used the Dutch 4 years version of the Ages and Stages Questionnaire (ASQ) to assess development.[12] The ASQ is a parent-completed, validated developmental screening instrument. It measures development in five domains: fine motor, gross motor, communication, problem-solving, and personal–social functioning.[14] The scores of these five domains are summed to obtain an ASQ total-problems score. The original ASQ has proved to be a reliable and cost-effective screening instrument with excellent psychometric properties.[14] Concurrent validity ranges from 76% to 88%.[14] Overall sensitivity and specificity are 75% and 86%, respectively. ASQ scores were based

on the children's uncorrected calendar age in accordance with the ASQ manual and the recommendations of the American Academy of Pediatrics.[14,15] A score of more than 2SD below the mean score for the term-born children was considered abnormal.[12]

The ASQ was completed by the parents of 81.4% of the children who participated in the study (*n*=2050). The median age of the children for whom the ASQ was completed was 46 months. Ninety-seven per cent of the parents (n=1983) completed the ASQ within a time window of 46 months (SD 3 months). We based our analyses on this group, hereafter referred to as the participating children. In comparison with the participating children, the mothers of the non-participating children were more often of a lower socio-economic status (lower vocational level 40.4% vs 28.9%, non-Dutch 15.6% vs Dutch 5.4%, both $p<0.001$). The sex ratio and rate of small for gestational age (SGA) status were not significantly different in the participating and non-participating children.

Measures: gestational age, biological, and social covariates

We compared the data on gestational age provided by the PCHC physicians with the data supplied by the paediatricians, obstetricians, midwives, and parents. In the case of conflicting data, we retrieved the original data from the paediatricians' records. We expressed gestational age in completed weeks of gestation. The children's biological and social details, collected from the parental questionnaires, were cross-matched with the data from the medical sources. The biological covariates included the child's sex, multiple birth, and SGA. We defined SGA, as a proxy for intrauterine growth restriction, as birth weight below the 10th centile of the Dutch Kloosterman growth curves.[16] The social covariates comprised the level of education of both parents, mother's age, and mother's country of birth.

Statistical analyses

We compared the prevalence of abnormal scores on the ASQ total-problems scale and on each of the ASQ domains for preterm children of each gestational week and term-born children (38^{+0} to 41^{+6} weeks' gestation). As there was only one child with a gestational age of 24 weeks, we included this child in the group of children born at 25 weeks' gestation. Next, we computed the crude odds ratios for abnormal scores on

ASQ-total problems scales and ASQ domains for decreasing gestational age as a continuous variable (defined as 'number of weeks born too early', ranging from 5 to 15 weeks). We compared these scores with those for term-born comparison children (38^{+0} to 41^{+6} wks), for whom gestational age was set at 'zero weeks too early'. Adding 'number of weeks too early' as a continuous variable to the model led to the assessment of an exponential association between risk of developmental delay and decreasing gestational age because of the statistical properties of the logistic model. Subsequently, in order to examine whether the model was truly exponential, we added the quadratic term ('number of weeks born too early' *x* 'number of weeks born too early') to the model. We examined the goodness-of-fit for both models with the Hosmer–Lemeshow test.[17]

We repeated the analyses omitting the child born at 24 weeks of gestation. As there is considerable discussion about whether being born at 'early term gestational age' (i.e. 38–39 weeks' gestation) might also have negative developmental consequences,[18] we also repeated the analyses with the comparison group limited to the children born at 40^{+0} to 41^{+6} weeks' gestation. In this model, we categorized the children born at 38 and 39 weeks as born 1 and 2 weeks too early, respectively. Finally, we performed a multivariable logistic regression analysis, with adjustment for all biological and social covariates that had a possible relation (p <0.20) with developmental outcome for ASQ-total-problems in the univariate analyses, in the model with all term-born comparison children (38^{+0} to 41^{+6} wks) grouped together. The covariates we entered in the univariate analysis were sex, multiple birth, SGA, level of maternal and paternal education, mother's age and her country of birth.

We used SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) for all the analyses. All analyses were two-sided and *p*-values below 0.05 were considered statistically significant.

RESULTS

Prevalence of developmental delay

Demographic data of the participating children are presented in **Table 1**. The children are grouped according to the dichotomous outcome of the ASQ total-problems score. The groups differed significantly on almost all covariates.

Table 1. Numbers and percentages of children (N(%)) with normal and abnormal ASQ-total problem scores for biological and social variables.

	Abnormal ASQ score		Normal ASQ Score		
	N	%	N	%	*P* value
Sex					<0 .001
Male	132	(12.9)	895	(87.7)	
Female	38	(4.3)	849	(95.7)	
Multiple birth					0.027
Singleton	120	(8.1)	1361	(91.9)	
Part of a multiple	50	(11.5)	383	(88.5)	
SGA[a]					<0.001
≥ 10th centile	129	(7.6)	1566	(92.4)	
< 10th centile	41	(18.7)	178	(81.3)	
Maternal education[b]					<0.001
Low	65	(12.3)	465	(87.7)	
Medium or high	104	(7.6)	1272	(92.4)	
Paternal education[b]					<0.001
Low	71	(12.2)	509	(87.8)	
Medium or high	89	(7.0)	1183	(93.0)	
Mother's age at birth of child					0.726
> 19 years	168	(8.8)	1732	(91.2)	
< 20 years	1	(12.5)	7	(87.5)	
Country of birth of mother					0.050
Netherlands	156	(8.6)	1654	(91.4)	
Non-Netherlands	14	(14.4)	83	(85.6)	
Age at completing ASQ					0.030
43-46 months	156	(9.4)	1496	(90.6)	
47-49 months	14	(5.3)	248	(94.7)	

[a]*SGA; below 10th centile according to Dutch Kloosterman growth curves*
[b]*Low education equals primary school or less and/ or low-level technical and vocational training. Medium Level equals high school or medium level technical and vocational training for 12-16 years. High level equals university or high-level technical and vocational training for more than 16 years.*
ASQ, Ages and Stages Questionnaire;
SGA, small for gestational age

In **Figure 1** we present the prevalence rates of abnormal ASQ total-problems scores by week of gestation. The prevalence rate of abnormal ASQ total-problems scores increased with decreasing gestational age below 36 weeks (p <0.001, χ^2 for trend test). Overall, the prevalence rate rose from 4.2% among term-born children to 37% among children born at 24 to 25 weeks' gestation. The same pattern of increasing prevalence of developmental delay with decreasing gestational age from 36 weeks was reflected in the scores on all ASQ domains (all p-values <0.001, χ^2 for trend test).

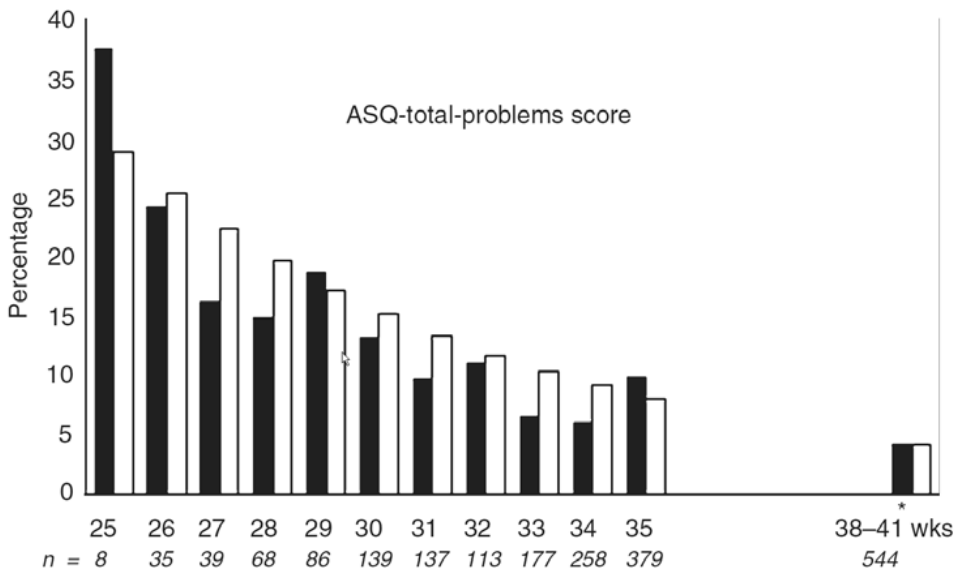

Figure 1: Percentages of children born at each gestational week with abnormal Ages and Stages Questionnaire (ASQ) total-problems scores at age 4 years. Black bars, percentages of children with abnormal ASQ total-problems scores; open bars, percentages of children with expected abnormal ASQ-total-problems scores according to the exponential model; *n* total number of children per gestational age group.

**The rate of term-born children with an abnormal ASQ total-problems score was more than 2.3% because of a non-normal distribution of the ASQ scores.*

Odds ratios for the number of weeks born too early

Table 2 shows the crude and adjusted odds ratios (OR) for abnormal scores on the ASQ total-problems scale and on all the ASQ domains for decreasing gestational age measured as a continuous variable (number of weeks born too early). The odds ratio risk of preterm children having an abnormal score on the ASQ total-problems scale compared with term-born children increased by 1.14 for each week by which gestation was reduced (95% confidence interval [CI], 1.09–1.19; p <0.001). This implies that the odds ratio for an abnormal ASQ total-problems score rises from 1.14^5 (OR 1.93) for a child born 5 weeks too early to 1.14^{15} (OR 7.14) for a child born 15 weeks too early. Model fit, as tested with the Hosmer– Lemeshow statistic (HL test), was good (χ^2 7.25, degrees of freedom (df) 5, p=0.20). Adding the weeks born too early as an additional quadratic term did not improve the fit of the model (HL-test: χ^2 7.36, df 5, p=0.20), indicating that no deviations from the exponential association occurred.

As shown in **Table 2** for separate ASQ domains, the odds ratios for 'number of weeks born too early' ranged from 1.10 to 1.14. This resulted in the odds ratios for children born 15 weeks too early varying between 4.17 (1.10^{15}) and 7.14 (1.14^{15}). These models for each of the five separate underlying ASQ domains also had a good fit. Adding the quadratic term 'number of weeks born too early' did not improve the fit on any of the ASQ domains.

Table 2. Odds ratios (OR), Confidence intervals (CI) and *P*-values of univariate and multivariate logistic regression analyses for gestational age as a continuous variable on ASQ total-problems and ASQ domains compared to term-born children[a].

	Univariate			Multivariate [b]		
Domain	**OR**	**CI**	***p***	***O*R**	**CI**	***p***
Total Problems	1.14	1.09-1.19	< 0.0001	1.13	1.08-1.18	< 0.0001
Fine Motor	1.12	1.07-1.17	< 0.0001	1.13	1.08-1.18	< 0.0001
Gross Motor	1.14	1.09-1.19	< 0.0001	1.13	1.08-1.19	< 0.0001
Communication	1.10	1.06-1.14	< 0.0001	1.08	1.04-1.13	< 0.0001
Personal Social	1.14	1.08-1.19	< 0.0001	1.13	1.07-1.19	< 0.0001
Problem-solving	1.10	1.05-1.15	< 0.0001	1.10	1.05-1.16	< 0.0001

[a] *term-born children (38^{+0}- 41^{+6} weeks), defined as zero weeks too early*

[b] *Adjusted for gender, SGA, father's education, mother's education, mother's birth country, and multiple birth*

Next, we repeated the analyses to assess whether we would obtain similar results if we were to make different choices in our models. In the model excluding the child born at 24 weeks' gestation and in the model with the control group restricted to children born at 40^{+0} to 41^{+6} weeks' gestation, the odds ratios for decreasing gestational age and model fit were very similar to those in our first set of models. Adding the quadratic term did not improve model fit in these models either.

As all covariates, except maternal age, had a significant or borderline association with developmental outcome on ASQ total-problems, all covariates, except maternal age, were added to the final multivariable logistic regression models. Adjustment for these covariates hardly affected the odds ratios for developmental risk by week born too early, for both ASQ total-problems and ASQ domains. Adjustment for age at completing the ASQ did not change our results (not shown).

DISCUSSION

This study demonstrates that the risk of developmental delay increases exponentially as gestational age decreases in the range 25 to 36 weeks. This is demonstrated by abnormal scores on both the ASQ total-problems scale and all five underlying ASQ domains, that is fine motor, gross motor functioning, communication, problem-solving, and personal-social functioning. Adjustment for covariates did not alter the pattern of exponential increase in developmental risk with decreasing gestational age.

Our finding that the risk of developmental delay increased exponentially as the number of weeks born too early increased is in contrast with the findings of other studies on the association between increasing weeks too early and developmental outcome. Other authors studying the association in very preterm-born children found linear associations between decreasing gestational age and global IQ measures.[1,2] However, probably as a result of the limited range of gestational ages in their studies, they were unable to discriminate between a linear and an exponential association. Our study covered a much wider range of preterm gestational ages.

Several reviews on the outcomes of preterm birth have mentioned stepwise increases in developmental disabilities with decreasing gestational age in broad gestational age groups, but without providing data by week of gestational age.[19,20] Two research groups that did study a wide range of preterm gestational ages per week gestational age did find non-linear associations between decreasing gestational age and global developmental outcome, but neither labelled the association exponential.[6,7] Wolke et al.[6] described a stepwise association between decreasing gestational age and

global IQ score in a German cohort born between 27 and 42 weeks' gestation. Mathiasen et al.[7] presented two straight regression lines with different slopes to model the association between decreasing gestational age and the risk of not finishing basic education for preterm-born Danish children, one for children born at 24 to 31 weeks' gestation and one for those born at 32 to 41 weeks' gestation.

We found only one recent study, by Mackay et al.[21], showing results that could lead one to conclude that an exponential relation might exist between decreasing gestational age and special educational needs as a proxy for developmental problems. In a series of logistic regression analyses for each week of gestation between 24 and 43 weeks, Mackay et al. analyzed the association between gestational age and the proportion of children with special educational needs. They presented their results on a logarithmic scale.

Our findings also deviated from those of other studies concerning the association between the risk of developmental delay and decreasing gestational age with regard to the measure used to assess development. Instead of looking at global IQ measures, or global school problems, we studied specific developmental domains that might underlie these problems at the age of 4 years. We found exponential associations between decreasing gestational age and the risk of abnormal scores on all five of the developmental domains of the ASQ, with relatively small differences in effect sizes. This might well explain the wide variety of high-prevalence/low-severity developmental disabilities and educational problems found in preterm children at school age.[22]

Adjusting for biological and social covariates did not alter the exponential increase in the developmental risk associated with decreasing gestational age, as measured by score on the ASQ total-problems scale and ASQ domains. In effect, differences in the odds ratios of scores on the ASQ total-problems scale and ASQ domains before and after adjustment were small. This shows that the exponential relationship is a real effect of gestational age, and not confounded by these factors. If social factors have an impact on this relationship, then this occurs in parallel with the effect of gestational age.

The explanation for the exponential association between the risk of developmental delay and the number of weeks born too early might be found in the rapid growth of the brain during the third trimester of pregnancy. Between 24 and 40 weeks of gestation, cortical volume increases fourfold. This corresponds with increasing synaptogenesis, neuronal and axonal growth, myelination, and focused

apoptosis, all leading to exponentially increasing brain connectivity.[23] The conditions necessary for all the different maturational processes of the brain that lead to increased brain connectivity are more favourable in utero than after birth. Direct brain destruction caused by perinatal insults and maturational and trophic disturbances of normal brain development after preterm birth might be involved in the exponentially increasing risk of developmental delay.[2,23]

Strengths and limitations

Our study has several strengths. Firstly, it is based on a large, prospective, community-based sample involving a wide range of preterm and term gestational ages. Secondly, gestational ages were determined by several methods, enhancing reliability. Finally, we excluded children with congenital malformations, syndromes, and congenital infections. Excluding these children, which usually is not possible in birth register cohorts, might be important as children with congenital malformations and syndromes are more often born preterm.

We also recognize limitations of our study. We measured developmental outcome with a parent-completed screening instrument rather than more extensive neuropsychological tests. Even so, developmental screens are considered to be reliable measures for identifying developmental problems in large high-risk populations.[24] Another limitation is that we did not include in our study design children born at 36 and 37 weeks' gestation. In the Netherlands, children born at 36 weeks are considered to be preterm and children born at 37 weeks are considered to be born at term. The fact that both our first model with term-born comparison children born between 38^{+0} and 41^{+6} weeks and the restricted model with term-born comparison children born between 40^{+0} and 41^{+6} weeks yielded similar results, including a good model fit, confirms the hypothesis of an effect of decreasing gestational age below 40 weeks' gestation, even in the early term range.[20,21] Thus, these findings are in line with those of other recent studies that found an effect of decreasing gestational age below 40 weeks of gestation.[19–21] None of them, however, formally assessed its exponential nature.

Implications

Our study may have several implications. Firstly, it emphasizes that professionals (obstetricians, paediatricians) and parents should be aware that there is no clear preterm gestational threshold below which risk of developmental delay starts to

increase. In fact, the increase is exponential. Evidence that the prevalence of developmental delay increases exponentially with decreasing gestational age, even in the moderately preterm age range, might influence the delicate balance between the advantages and disadvantages involved in planning a birth before term. Secondly, knowledge about specific developmental domains already affected at preschool age should lead to a closer link with prevention and early treatment. Finally, since we presume that problems in these developmental domains on entering school may be precursors to problems persisting into late childhood and adulthood, early, targeted intervention might also have long-lasting socio-economic implications for society.[25] Some studies have found that very preterm children seem to do better when entering adulthood.[19,20] Whether the pattern of exponential increase of developmental disabilities with decreasing gestational age will persist into adulthood therefore deserves additional study.

CONCLUSION

With decreasing gestational age from 36 to 25 weeks, the prevalence of parent-reported developmental delay of preterm-born children at the age of 4 years increases exponentially in five domains: fine motor, gross motor, communication, problem-solving, and personal-social functioning.

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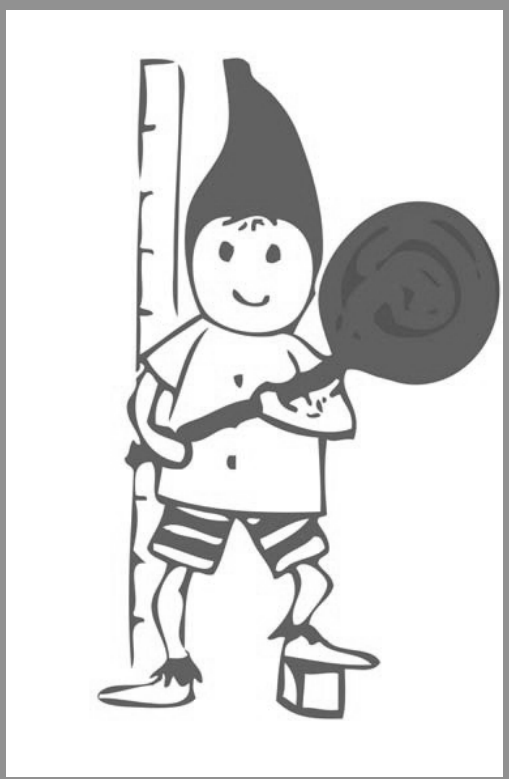
Chapter 5

Maternal and pregnancy-related factors associated with developmental delay in moderately preterm-born children



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PRECIS

For moderately preterm-born children, only intrauterine growth restriction, maternal obesity, being one of a multiple, and sex are associated with developmental risk in early childhood.

ABSTRACT

Objective: To estimate the association between preexisting maternal and pregnancy-related factors and developmental delay in early childhood in moderately preterm-born children.

Methods: We measured development with the Ages and Stages Questionnaire at age 43–49 months in 834 moderately preterm-born (between 32^{+0} and 35^{+6} weeks' gestation) children born in 2002–2003. We obtained data on pre-existing maternal, maternal pregnancy-related, fetal, and delivery-related factors. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) and attributable risks for developmental delay adjusted for sociodemographic and lifestyle variables.

Results: Attributable risk for developmental delay for small-for-gestational-age (SGA, as a proxy for intrauterine growth restriction [IUGR]) was 14.2% (SGA 21.9%, no SGA 7.7%, P<0.05, adjusted OR 2.75, CI 1.25–6.08), for pre-existing maternal obesity 10.5% (obesity 18.0%, no obesity 7.5%, P<0.01, adjusted OR 2.73, CI 1.35–5.52), for multiple pregnancy 4.2% (multiple 12.0%, singleton 7.8%, P<0.05, adjusted OR 1.86, CI 1.02–3.42), and for male sex 9.3% (male 13.0%, female 3.8%, P<0.001, adjusted OR 4.20, CI 2.09–8.46). No other pre-existing or pregnancy-related maternal factors or any delivery-related factors were associated with increased risk of developmental delay.

Conclusions: Of all pre-existing maternal and pregnancy-related factors studied, SGA, maternal pre-pregnancy obesity, being one of a multiple, and male sex were associated with the risk of developmental delay in early childhood after moderately preterm birth. Reinforced focus on prevention of IUGR, preconception lifestyle interventions aiming at weight reduction in fertile women, and reinforced efforts to reduce rates of multiple pregnancies in assisted reproduction may all contribute toward more favorable developmental outcomes in moderately preterm-born children.

INTRODUCTION

The incidence of both spontaneous and induced moderately preterm births (32^{+0}–35^{+6} weeks of gestation) has risen in the last decades from 6% to 9% of all life births worldwide and accounts for 70–85% of all preterm-born children.[1] Moderately preterm-born children have more developmental and behavioral problems in kindergarten and primary school,[2–6] increased special educational needs,[4,7] and more social disabilities as adults than term-born children.[8] Because of the large share of moderately preterm-born children within all life births, even slightly increased risks of long-term developmental problems in this group have important economic and social implications.

Several pre-existing maternal and pregnancy-related factors have been shown to increase the risk of moderately preterm birth, neonatal mortality, and early neonatal morbidity before discharge.[10–13] It is unknown whether these same factors also increase the risk of developmental delay in early childhood for this particular group. Knowledge on this subject may help optimize antenatal obstetric care and may also be helpful for obstetricians who need to counsel parents in case of considering induced moderately preterm delivery. The same knowledge may also help pediatricians to identify those children within the large moderately preterm group who may have an increased risk of developmental delay in early childhood and who could, therefore, benefit from more structured follow-up assessments.

The aim of this study was to estimate, for moderately preterm-born children, which pre-existing maternal and pregnancy-related factors were associated with developmental delay in early childhood.

MATERIALS AND METHODS

This study was part of the Longitudinal Preterm Outcome Project (LOLLIPOP) on growth and development of preterm children.[6,14] In a community-based cohort of 45,455 children born in 2002 and 2003, all children with a gestational age between 32^{+0} and 35^{+6} weeks of gestation were sampled. We based the size of our cohort on estimates of the numbers needed to compile growth curves for Dutch preterm-born children.[14]

All children were included during their regular visit to a preventive child health care center at the age of 43–49 months (uncorrected age, inclusion from

October 2005 to September 2007). At this age, 95–97% of all Dutch children are routinely seen at a preventive child health care center.[15] Children with major congenital malformations, congenital infections, and syndromes were excluded.
Eventually 960 moderately preterm-born children included in the growth part of the LOLLIPOP study also participated in the developmental part of the LOLLIPOP study. The institutional medical ethical review board at Groningen approved the entire study and we obtained written informed consent from all parents. Further details on the LOLLIPOP study were provided previously.[6,14]

Before their planned visit to the preventive child health care center, parents were asked to fill out the Dutch version of the 48-month Ages and Stages Questionnaire, a parent-completed developmental screening tool.[16] Reliability and validity of the Ages and Stages Questionnaire has been documented in several studies.[16,17] The Ages and Stages Questionnaire measures development in five domains: communication, fine motor, gross motor, problem-solving ability, and personal–social functioning. The scores on each domain add up to an Ages and Stages Questionnaire total score.[17] An Ages and Stages Questionnaire total score of more than two standard deviations below the mean of the Dutch reference group was considered to indicate developmental delay (dichotomous yes or no). We set the time window for the parents to have completed the Ages and Stages Questionnaire between 43 and 49 months (3 months on either side of the median).[6]

We expressed gestational age in completed weeks of gestation. We collected the data on pre-existing maternal and pregnancy-related factors of children participating in this part of the LOLLIPOP study in a controlled manner from the hospital records of both mothers and children, preventive child health care center records, the Dutch Central Perinatal Registration, and a parental questionnaire at age 4 years. We crosschecked data from different sources whenever possible. Pregnancy-related factors were divided into three categories; maternal, fetal, and delivery-related. This led to a final categorization of all factors into one of four categories: maternal pre-existing, maternal pregnancy-related, fetal, and delivery-related factors. Because pre-existing diabetes was very rare in our sample, we pragmatically included pre-existing diabetes into the corresponding pregnancy-related category gestational diabetes. Within the category of fetal factors, small for gestational age (SGA), as a proxy for intrauterine growth restriction (IUGR), was defined as a birth weight below the 10th percentile of the Dutch Kloosterman growth charts.[18] All variables are specified in **Table 1.**

Table 1. Variables within the pre-existing maternal, pregnancy-related, and sociodemographic and lifestyle categories.

	N	*Abnormal*	*%*	*Definition of the variable*
Pre-existing maternal				
Somatic illness	*834*	*46*	*5.5*	Pre-existing somatic illness in the mother (auto-immune, renal, cardiac, pulmonary, other)
Mental illness	*834*	*13*	*1.6*	Pre-existing mental illness in the mother (depression, psychosis, other)
Pre-pregnancy obesity	*790*	*91*	*11.5*	Pre-pregnancy obesity, BMI greater than 30kg/m^2
***Pregnancy-related* maternal**				
Maternal age	829	5	0.6	Maternal age younger than 20 years.
Hypertension	834	162	19.4	HELLP or (pre)-eclampsia
Diabetes	834	20	2.4	Pre-existing or gestational diabetes treated with diet or insulin
Ante partum hemorrhage	834	97	11.6	Abruptio, placenta previa, placental bleeding or all in the second trimester or third trimester or both
Antenatal steroids	834	159	19.1	Full course antenatal steroids (2 shots , and greater than 48 hours after first shot)
IVF	834	60	7.2	In vitro fertilization or intracytoplasmic sperm injection (ICSI)
Fetal				
SGA	834	76	9.1	SGA less than P10 according to Dutch growth charts
Male sex	834	471	56.5	Male sex
Multiple	834	243	29.1	Being part of a multiple birth
Lower gestational age	834	269	32.3	Lower gestational age within the moderately preterm range (ergo 32-33 weeks)
Delivery-related				
Infection	834	125	15.0	Clinical infection mother, child, or both perinatally, or proven placental infection
P_PROM	834	194	23.3	Prolonged premature rupture of membranes (greater than 24 hrs before delivery)
Breech presentation	834	124	14.9	Breech presentation during delivery

Delivery-related (continued)				
Induced birth	834			Induced birth categorical
spontaneous		604	72.4	Non induced
fetal		70	8.4	Fetal
maternal		73	8.8	Maternal
fetal and maternal		53	6.4	Fetal and maternal combined
elective		34	4.1	Elective
fetal indication	834	123	14.8	Fetal or (fetal + maternal) indication of delivery
C-section	834	300	36.0	Primary or secondary C-section
Assisted delivery	834	75	9.0	Forceps and or vacuum
Apgar score	827	32	3.9	5 minute Apgar score below 7
Social demographic/ lifestyle				
Multiparity	833		35.3	Mother who has gone through a previous pregnancy
Non-Dutch ethnicity[a]	832		5.4	Mother not born within the Netherlands
Maternal education	825		29.8	Low maternal education (< 12 years of formal education)
Paternal education	797		35.9	Low paternal education (< 12 years of formal education)
Family income	805		6.8	Low family income (≤ €850 ($1,087) per month)
Alcohol	826	40	4.8	Alcohol; more than 1 unit per week
Smoking	820	183	21.9	Smoking; any

Data are n (%) unless otherwise specified

BMI, body mass index; HELLP, hemolysis, elevated liver enzymes, and low platelet count;

SGA, small for gestational age;

PROM, premature rupture of membranes.

[a] *Children, mainly white*

Data on sociodemographic and lifestyle variables were collected from the general questionnaire and crosschecked with medical data. These data included multiparity, socioeconomic status, ethnicity, smoking, and alcohol consumption during pregnancy (Table 1). For socioeconomic status, we computed a composite continuous score based on the average of the following five indicators: educational level of both parents, occupational level of both parents, and family income.19 Low socioeconomic status was defined as the lowest 25% of the continuous socioeconomic status score; the middle 50% and highest 25% were combined into non-low socioeconomic status.

We first calculated the prevalence rates of all pre-existing and pregnancy-related (maternal, fetal, delivery-related) and sociodemographic and lifestyle variables in our cohort of children with and without abnormal Ages and Stages Questionnaire scores. Second, we analyzed the association of all pre-existing and pregnancy-related variables with rates of abnormal Ages and Stages Questionnaire scores in univariable logistic regression analyses. Furthermore, we calculated attributable risks. Third, we constructed a multivariable model including all variables with *P* values <.20. In this model, we combined induction of birth for solely fetal reasons with induction for "combined fetal and maternal reasons." Together they formed a new variable, "fetal indication." Finally, we adjusted for differences in sociodemographic and lifestyle parameters with a *P* value <.20 in univariable analyses. We constructed one additional model. In this additional model, we removed SGA as a variable from the model. We chose to do so because non-reassuring fetal parameters (signs of fetal distress) leading to induced moderately preterm birth are often found in growth-restricted fetuses. This implies that SGA and induced birth for fetal indication may be partial proxies.

All regression analyses were done using multilevel techniques to account for the clustering of risk factors in members of multiples.[20] All analyses were done using SAS 9.2. The threshold for statistical significance was set at *P* <.05.

RESULTS

A total of 927 (97%) of the 960 Ages and Stages Questionnaires were completed within the set timeframe. For 10% (*n*=93) of these children, we were unable to retrieve data on antenatal factors as a result of logistic reasons and missing records. The final sample, therefore, consisted of 834 children.

Table 2. Children with and without risk factors with abnormal ASQ Scores.

Risk factor	Children without risk factor N	%	Children with risk factor N	%	*P* -value
Pre-existing maternal factor					
Somatic illness	65/752	(8.6)	7/46	(15.2)	0.18
Mental illness	69/785	(8.8)	3/13	(23.1)	0.10
Pre-pregnancy obesity	50/671	(7.5)	16/89	(18.0)	**< 0.01**
Pregnancy-related maternal factor					
Maternal age	71/792	(9.0)	1/5	(20.0)	0.38
Hypertension	56/642	(8.7)	16/156	(10.3)	0.55
Diabetes	70/779	(9.0)	2/19	(10.5)	0.69
Ante-partum hemorrhage	62/706	(8.8)	10/92	(10.9)	0.51
Antenatal steroids	59/641	(9.2)	13/158	(8.3)	0.72
IVF	71/738	(9.6)	1/60	(1.7)	**0.04**
Fetal factor					
SGA	56/725	(7.7)	16/73	(21.9)	**<0.001**
Male gender	13/345	(3.8)	59/453	(13.0)	**<0.001**
Multiple	44/564	(7.8)	28/234	(12.0)	0.06
Lower gestational age	49/539	(9.1)	23/259	(8.9)	0.92
Delivery related factor					
Infection	63/682	(9.2)	9/116	(7.8)	0.61
Preterm-PROM	58/612	(9.5)	14/186	(7.5)	0.42
Breech presentation	56/678	(8.3)	16/120	(13.3)	0.07
Induced birth					
Spontaneous (reference)	44/577	(7.6)			0.13
Fetal			11/69	(15.9)	
Fetal +maternal			7/51	(13.7)	
Maternal			6/68	(8.8)	
Elective			4/33	(12.1)	
Fetal indication	54/678	(8.0)	18/120	(15.0)	**0.01**
C-section	37/512	(7.2)	35/286	(12.2)	**0.02**
Assisted delivery	70/729	(9.6)	2/72	(2.8)	**0.05**
Apgar score	69/765	(9.0)	3/30	(10.0)	0.75
Socio Demographic and Lifestyle					
Multiparity	32/522	(6.1)	40/275	(14.5)	**<0.001**
Low SES	44/594	(7.4)	28/204	(13.7)	**<0.01**
Ethnicity	67/754	(8.9)	5/44	(11.4)	0.58
Smoking	52/614	(8.5)	18/176	(10.2)	0.49
Alcohol	67/759	(8.8)	3/33	(9.3)	0.99

Bold data indicate statistical significance
Data are n/N (%) unless otherwise specified.

SGA, small for gestational age; PROM, premature rupture of membranes.

The children not included in the final sample (*n*=126) more often had mothers who were non-Dutch (15.0% compared with 5.4%, P<0.001). They did not differ significantly on sex, gestational age, SGA, maternal education, or percentage of multiples (results not shown).

Prevalence rates of all factors are shown in **Table 1**. For 72% of the cohort, birth occurred after spontaneous rupture of membranes or spontaneous onset of labor, whereas 24% were induced births for fetal, maternal, or both indications, and 4% were elective births.

Seventy-two children (8.6%) had an abnormal Ages and Stages Questionnaire score. Prevalence rates of abnormal Ages and Stages Questionnaire scores for children with and without antenatal factors are shown in **Table 2**.

We present the results of the univariable analyses in **Table 3**. With regard to both pre-existing and pregnancy-related maternal factors, only pre-pregnancy obesity was associated with increased risk of developmental delay at age 4 years. Furthermore, the fetal factors, SGA and male sex, as well as the delivery-related factors cesarean delivery and "fetal indication" were associated with an increased risk of developmental delay. Several other factors in all four categories had borderline positive or negative associations with developmental delay and were, therefore, also included in the multivariable models.

Attributable risk for developmental delay for SGA (as a proxy for IUGR) was 14.2% (SGA 21.9%, no SGA 7.7%, P< 0.05), for pre-existing maternal obesity 10.5% (obesity 18.0%, no obesity 7.5%, P< 0.01), for multiple pregnancy 4.2% (multiple 12.0%, singleton 7.8%, P< 0.05), and for male sex 9.3% (male 13.0%, female 3.8%, *P*< 0.001).

Table 3 contains the results of the unadjusted and adjusted multivariable multilevel models. In the unadjusted model (*Model 1*), pre-pregnancy obesity, SGA, and male sex remained associated with an increased risk of developmental delay with statistical significance, and being one of multiple was also associated with an increased risk of developmental delay. Adjustment for sociodemographic and lifestyle factors hardly influenced the strength of the associations (*Model 2*). Repeating the analyses excluding SGA did not influence the results either (results not shown).

Legend Table 3 (continued)
SGA, small for gestational age; PROM, preterm rupture of membranes.
Data are odds ratio (95% confidence interval).

Table 3. Abnormal Ages and Stages Questionnaire Scores for maternal, fetal, and delivery-related factors in univariable and multivariable multilevel analyses.

	Univariate		Multivar. Model 1		Mulitvar. Model 2	
	OR	CI	OR	CI	OR	CI
Pre-existing maternal factor						
Somatic illness	1.88	0.76-4.64†	1.38	0.45-4.20	1.50	0.49-4.60
Mental illness	2.88	0.67-12.4†	2.49	0.15-12.1	1.32	0.14-12.3
Pre-pregnancy obesity	**2.72**	**1.41-5.26****	**2.69**	**1.34-5.39****	**2.73**	**1.35-5.52****
Pregnancy related maternal factor						
Maternal age	3.42	0.29-41.0				
Hypertension	1.23	0.67-2.28				
Diabetes	1.16	0.24-5.63				
Ante-partum hemorrhage	1.26	0.60-2.66				
Antenatal steroids	0.91	0.47-1.76				
IVF	0.16	0.02-1.22#	0.14	0.02-1.10	0.18	0.02-1.46
Fetal factor						
SGA	**3.22**	**1.66-6.24*****	**2.48**	**1.13-5.46***	**2.75**	**1.25-6.08***
Male gender	**3.86**	**2.04-7.31*****	**4.28**	**2.13-8.61*****	**4.20**	**2.09-8.46*****
Multiple	1.60	0.94-2.74#	**2.09**	**1.14-3.83***	**1.86**	**1.02-3.42***
Lower gestational age	0.99	0.57-1.71				
Delivery related factor						
Infection	0.84	0.39-1.78				
Preterm Prom	0.78	0.41-1.47				
Breech presentation	1.71	0.91-3.20#	1.28	0.63-2.62	1.25	0.02-1.46
Induced birth						
Spontaneous (ref)	1.00					
Fetal	**2.41**	**1.12-5.20***				
Fetal +maternal	1.96	0.79-4.88†				
Maternal	1.20	0.47-3.07				
Elective	1.75	0.55-5.59				
Fetal indication	**2.10**	**1.14-3.87***	1.20	0.53-2.70	1.15	0.50-2.62
C-section	**1.81**	**1.08-3.03***	1.26	0.65-2.45	1.42	0.72-2.78
Assisted delivery	0.27	0.06-1.15#	0.37	0.08-1.64	0.56	0.12-2.52
Apgar score	1.17	0.33-4.12				

Model 1, unadjusted multivariable model;
Model 2, multivariable model adjusted for socioeconomic status and parity.
**: P <0.05, **: P <0.01, ***: P < 0.001, (univariable; #: P < 0.10, † P < 0.20)*

DISCUSSION

In this cohort of moderately preterm-born children, SGA, prepregnancy obesity, being one of a multiple, and male sex increased the risk of developmental delay in early childhood. We did not find an association between any pregnancy-related maternal factors or delivery-related factors and risk of developmental delay.

The association between SGA and developmental risk is also in line with other studies both in full-termborn and early preterm-born children.[20–22] Although SGA remains only a proxy for IUGR,[22,23] many of those born SGA will have had chronic deficits in nutritional and oxygen needs during the fetal period.[22] These chronic deficits may alter brain structure permanently, thus compromising development.

The association between maternal prepregnancy obesity and developmental risk is also in line with a study on early preterms[20] and consistent with findings from an experimental animal model.[24] This may indicate that maternal obesity not only increases the risk of preterm birth,[25] but also increases the risk of adverse development later on.

The third fetal factor that increased the risk of developmental delay in our cohort was multiple pregnancies. Twins are known to have poorer developmental outcomes than singletons, but it has been argued that this is solely the result of higher rates of IUGR and preterm births in multiples. [26] In our cohort, results for multiples were not explained by IUGR or by gestational age within the moderately preterm range.

The final factor strongly associated with developmental risk was male sex. It has been postulated that early preterm-born boys have a higher biological baseline risk for developmental delay as well as a higher risk of postnatal complications that also leads to developmental delay.[27] Our findings suggest that this male disadvantage also holds true for moderately preterm-born boys.

In our multivariable models, we found no association between any maternal pregnancy-related or delivery-related factors and risk of developmental delay, which is in line with a study on early preterms.[20]We found several delivery-related factors (cesarean delivery, breech presentation, assisted delivery, fetal indication) that showed significant or nearly significant associations with developmental delay in the univariable analyses to lose significance in the multivariable models, including the model without SGA as a variable. It implies that predominantly fetal factors, and not the final indication for earlier delivery or mode of delivery, is associated with the

increased risk of developmental delay. It is reassuring that we could not demonstrate an association between prolonged premature rupture of membranes and risk of developmental delay. Even so, this lack of association has to be interpreted with caution, because we did not have data on placenta histology.

The strengths of our study are its community-based approach, the large number of children that participated, and the data collection from various sources. We also recognize some limitations. We measured developmental outcome with a parent-completed screening tool instead of submitting the children to extensive neuropsychologic tests. Nevertheless, developmental screeners are considered to be reliable measures for identifying developmental problems in high-risk populations.[28] Furthermore, many etiologic factors and phenotypic entities within the complex "preterm birth syndrome" are intricately entwined, making it difficult to assess separate variables in the cascade leading to moderately preterm birth.[29,30] Our study may also have been underpowered to find associations for some of the rarer antenatal factors. Finally, children who were not included in the analyses more frequently had mothers born outside The Netherlands. Because of the universal access to care in The Netherlands, we think that this difference will not have influenced our results, but it might reduce the generalizability of our results.

Our study may have important implications. Until recently, perinatal care focused on secondary prevention of preterm birth, including moderately preterm birth in high-risk pregnancies, and the reduction of early neonatal morbidity after preterm birth. Most moderately preterm deliveries, however, are spontaneous without any evidence of fetal compromise and few or no postnatal complications. Therefore, more focus should be placed on primary prevention of spontaneous preterm birth as outlined in the guidelines of the Royal College of Obstetrics and Gynaecology.[31] These guidelines include issues on increasing health and healthy lifestyles in fertile women in general to reduce both IUGR and the risk of preterm delivery.[32] Our study however cannot answer the question whether earlier delivery within the moderately preterm range, aiming at preventing more severe IUGR, may be feasible [33]

Of all the pre-existing maternal and pregnancy-related factors studied, only SGA, maternal prepregnancy obesity, being one of a multiple, and male sex were associated with the risk of developmental delay in early childhood after moderately preterm birth. Current efforts to prevent IUGR, efforts to reduce weight

in fertile women by intervening in preconception lifestyle, and efforts to reduce rates of multiple pregnancies in assisted reproduction should be continued and where possible be reinforced. They may all contribute toward more favorable developmental outcomes in moderately preterm-born children.

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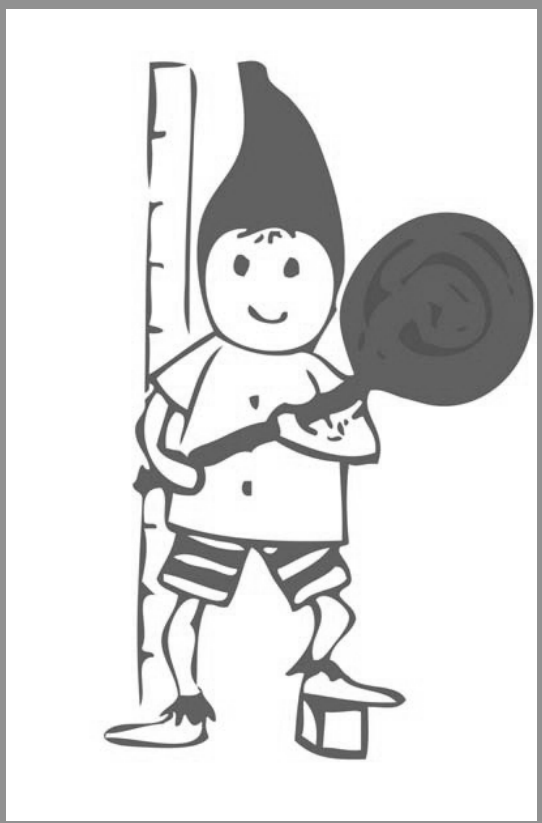
Chapter 6

Neonatal morbidities and developmental delay in moderately preterm-born children



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WHAT'S KNOWN ON THIS SUBJECT:

Moderately preterm-born children (32–35^{+6} weeks' gestation) are at risk for both neonatal morbidities after birth and developmental delays in early childhood. It is unknown whether neonatal morbidities contribute to the developmental delays of this particular group.

WHAT THIS STUDY ADDS:

Of all neonatal morbidities commonly seen in moderately preterm-born children, only hypoglycemia increased the risk of developmental delay after moderately preterm birth. A concerted effort to prevent hypoglycemia after birth might enhance developmental outcome in this group.

ABSTRACT

Background and objective: Children born moderately preterm (32^{+0} – 35^{+6} weeks' gestation) are at increased risk of both neonatal morbidities and developmental delays in early childhood. It is unknown whether neonatal morbidities contribute to the increased risk of developmental delay. The objective of this study was to determine the effect of neonatal morbidities after moderately preterm birth on development at preschool age.

Methods: In a community-based, stratified cohort, parents of 832 moderately preterm children born in 2002 or 2003 completed the Ages and Stage Questionnaire when their child was 43 to 49 months old. Data on Apgar scores, asphyxia, tertiary NICU admission, hospital transfer, circulatory insufficiency, hypoglycemia, septicemia, mechanical ventilation, continuous positive airway pressure, apneas, caffeine treatment, and hyperbilirubinemia were obtained from medical records. We assessed associations of neonatal characteristics with developmental delay, adjusted for gender, small-for-gestational-age status, gestational age, and maternal education.

Results: Hypoglycemia and asphyxia were associated with developmental delay; odds ratios (ORs) were 2.42 (95% confidence interval [CI]: 1.23– 4.77) and 3.18 (95% CI: 1.01–10.0), respectively. Tertiary NICU admission and hyperbilirubinemia had positive but statistically borderline nonsignificant associations with developmental delay: ORs were 1.74 (95% CI: 0.96–3.15) and 1.52 (95% CI: 0.94–2.46), respectively. No other neonatal morbidities were associated with developmental delay. In multivariate analyses, only hypoglycemia was associated with developmental delay (OR: 2.19; 95% CI: 1.08–4.46).

Conclusions: In moderately preterm-born children, only hypoglycemia increased the risk of developmental delay at preschool age. A concerted effort to prevent hypoglycemia might enhance developmental outcome in this group.

INTRODUCTION

Moderately preterm-born children (32^{+0}–35^{+6} weeks' gestation)[1,2] have a relatively high rate of neonatal morbidities.[3] These neonatal morbidities include asphyxia, respiratory insufficiency, circulatory insufficiency, septicemia, hypoglycemia, hyperbilirubinemia, apnea, hypothermia, and feeding problems.[3–6] Some of these morbidities are severe enough to warrant admission to a tertiary NICU. Apart from the risk of neonatal morbidities, moderately preterm-born children are also more likely to have developmental delays at preschool age.[7–9] Particularly in moderately preterm-born children, it remains unclear whether these neonatal morbidities are associated with the increased risk of developmental delay.[9]

In the general population, male gender, small-for-gestational-age (SGA) status at birth, decreasing gestational age, and low maternal education increase the risk of developmental delay. It might, therefore, be important to correct for these biological and environmental variables when studying the association between neonatal morbidities and developmental delays in moderately preterm-born children.[10–13] First, insight into the impact these neonatal morbidities have on this particular group of preterm-born children might help to direct future research on optimizing postnatal care for this group.[14] Second, it might help to predict which children in this group might be more likely to have developmental delays in early childhood.

The aim of the authors of this study was to determine for moderately preterm-born children which neonatal morbidities were associated with developmental delay at preschool age. We hypothesized that several neonatal morbidities would have an association with developmental delays in this group, independent of SGA status, gender, gestational age (within the moderately preterm range), and maternal level of education.

METHODS

Population and Participants

This study was part of the Longitudinal Preterm Outcome Project (LOLLIPOP) on growth and development in preterm children.[9,15,16] In a community-based cohort of 45 455 children born in 2002 and 2003, all children with a gestational age between 32^{+0} and 35^{+6} weeks' gestation were sampled. We based the size of our cohort on the estimates for the numbers needed to compile growth curves for Dutch preterm-born children, because for that part of the LOLLIPOP study we needed the largest number of children. To detect a difference in growth restraint of 10% between term and

preterm children per week of gestation, separately for boys and girls, with a power of 80% at $P < 0.05$, we needed to include 1000 moderately preterm-born children.[16] In this context, growth restraint was defined as $<10^{th}$ percentile for fullterm children.

All the children were included during their regular visit to a preventive child health care center (PCHC) at the age of 43 to 49 months (inclusion from October 2005 – September 2007). At this age, 95% to 97% of all Dutch children are seen routinely at a PCHC.[17] Children with major congenital malformations, congenital infections, and all children with syndromes were excluded. Eventually, after removal of the excluded children, 1145 moderately preterm-born children were included in the study.

The study was approved by the local institutional review board, and written informed consent was obtained from all parents. A detailed description of how the LOLLIPOP study was conducted has been described previously.[9,15,16]

Variables and Procedures

Parents completed several questionnaires, including the Dutch version of the 48 months Ages and Stages Questionnaire (ASQ) before their planned visit to the PCHC. The ASQ is a parent-completed developmental screening tool.[18,19] Its reliability and validity have been documented in several studies.[19–22] The ASQ measures development in five domains: communication, fine motor, gross motor, problem-solving ability, and personal-social functioning.[18] The scores on each domain add up to an ASQ total-problems score. A score of > 2 SDs below the mean score for the Dutch reference group was considered to indicate developmental delay (dichotomous yes/no). Reliability, validity, mean scores, and cut-off values of the Dutch 48 months ASQ version had been determined earlier in a larger part of the LOLLIPOP cohort consisting of a sample of 1510 early and moderately preterm-born children and 562 term-born controls.[15] For the purpose of this study and in accordance with the ASQ manual and American Academy of Pediatrics recommendations, the ASQ scores were based on the children's uncorrected calendar age.[15,23]

Data on neonatal morbidities of children participating in this part of the LOLLIPOP study were collected from hospital records, bedside charts, and preventive child health care records. We based our choice of neonatal morbidities to be collected on general clinical knowledge on the admission of moderately preterm-born children and on a search of the available literature.[3] In the Netherlands, deliveries between 32 and 37 weeks' gestation are conducted in regional hospitals. After birth, glucose values, oral intake, daily weight gain, and jaundice are monitored according to

local protocols. Only when the mother is critically ill or the expected birth weight of the child is <1200 g will mothers be admitted antenatally to a tertiary hospital center. Whenever a child needs mechanical ventilation after birth or is otherwise critically ill, the child is stabilized in the regional hospital and then transferred to a tertiary NICU. Neonatal morbidities were categorized as birth-related, admission-related, and other neonatal variables. Definitions of the variables are described in **Table 1**.

Table 1. Definitions of variables concerning neonatal morbidities grouped into birth-related, admission-related, and other neonatal variables, and the definitions of the biological and environmental variables.

Variable	Definition
Birth-related	
Low Apgar score	Apgar score < 7 after 5 minutes
Asphyxia	Asphyxia documented in the conclusion of the discharge letter
Admission-related	
Not admitted	Not admitted to any pediatric ward, stayed with mother in the maternity ward
Tertiary NICU	Admission to a tertiary neonatal intensive care unit (NICU)
Transportation	Transfer from a regional hospital to a tertiary NICU within 72 hrs after birth
Other neonatal	
Circulatory insufficiency	Inotropics including dopamine, dobutamine or (nor)adrenaline
Respiratory insufficiency	
- CPAP*	CPAP for longer than initial stabilization in the delivery room only
-Ventilation	Mech. ventilation for a longer duration than initial stabilization in the delivery room only
-CPAP and/or vent.	CPAP and/or mechanical ventilation with same definitions
Apnea	Apnea in discharge letter or documented on bedside-charts
Caffeine	Treatment with caffeine for apnea
Septicemia	Both clinical symptoms and at least 1 positive blood culture result
Hypoglycemia	At least one plasma glucose value > 1.7mmol/L (30 mg/dL), within first 72 hours of life
Hyperbilirubinemia	Peak bilirubin value > 340 µmol/L (20mg/dL) and/or any value requiring phototherapy
Biological and environmental factors	
SGA	Birth weight below P10 according to the Dutch growth curves
Male Gender	Male gender
Low gestational age	< 34 weeks' gestation (i.e. 32^{+0} - 33^{+6} weeks)

CPAP; continuous positive airway pressure

We did not include rare neonatal morbidities (morbidities with a prevalence of < 0.5% in moderately preterm-born children) in the analyses because of a lack of power to detect their effects, however severe. Such rare morbidities include high-grade intraventricular hemorrhages, bronchopulmonary dysplasia, necrotizing enterocolitis, and convulsions.

ANALYSES

We first analyzed the prevalence rates of all birth-related, admission-related, and other neonatal variables as well as the prevalence rates of biological and environmental variables of our study group. Subsequently, we analyzed the association between all the variables and rates of abnormal ASQ total-problems scores in univariate logistic regression analyses. Finally, all risk factors with univariate associations of $P < 0.10$ were included simultaneously in a multivariable logistic regression model. Because we expected to find an association between SGA status and several neonatal morbidities, such as hypoglycemia, we had decided beforehand to repeat the analyses without the children who were SGA. For those neonatal morbidities that had significant associations in the multivariate analyses, we also assessed which ASQ domains were involved and carried out further investigations concerning the variable and the children affected. All analyses were done by using SPSS version 18.0 (SPSS Inc, Chicago, IL).

RESULTS

The parents of 84% (*N* = 960) of the 1145 participating moderately preterm-born children completed the ASQ. The median age of these children was 46 months. Of these 960 questionnaires, 97% (*N* = 927) were completed within the time window, which we had set at 43 to 49 months. We did not retrieve data on neonatal morbidities for 10% (*N* = 95) of these 927 children. This fact was partly due to logistic reasons, because we did not visit small regional hospitals that were very far away from the coordinating research center, and partly due to missing records.

The final sample eventually consisted of 832 children with ASQ data within the set time window and neonatal data. The non-included children in the final sample (N = 313) more often had mothers who were non-Dutch (15.0% vs 5.4%, $P < 0.001$). They did not differ significantly concerning gender, gestational age, SGA status, maternal education, or percentage of multiples (results not shown). Demographics of the children in the final sample are shown in **Table 2**. The prevalence rates of the neonatal morbidities we studied ranged from 1.1% to 46%.

Table 2. Prevalence rates for all birth-related, admission-related, other neonatal, biological, and environmental variable for different gestational ages.

Variable	32-35 wk		32-33 wk		34-35 wk		
	N=832		*N*=268		*N*=564		
	N[a]	%	N	%	N	%	
Birth-related							
Low Apgar score	32	3.7	14	5.2	18	3.2	
Asphyxia	17	2.0	8	3.0	9	1.6	
Admission-related							
Not admitted to a pediatric ward	5	0.6	0	0	5	0.9	
Tertiary NICU	119	14.3	74	27.6	45	8.0	*
Transportation	37	4.4	22	8.2	15	2.7	*
Other neonatal							
Circulatory insufficiency	25	3.0	12	4.5	13	2.3	
Respiratory insufficiency							
CPAP (0-13 days)	139	16.7	82	30.6	57	10.1	*
Ventilation (0-23 days)	62	7.5	40	14.9	22	3.9	*
CPAP and/or Ventilation	153	18.4	91	34.0	62	11.0	*
Apnea	193	23.3	119	44.4	74	13.2	*
Caffeine	94	11.4	74	27.6	20	3.6	*
Septicemia	30	3.6	17	6.3	13	2.3	*
Hypoglycemia[b]	67	8.1	24	9.0	43	7.7	
Hyperbilirubinemia[c]	361	46.4	147	55.1	214	38.0	*
Biological and environmental							
SGA (< 10th percentile)	76	9.1	25	9.3	51	9.0	
Male Gender	471	56.6	145	54.1	326	57.8	
Low maternal education	246	29.7	91	34.1	155	27.7	*

CPAP, continuous positive airway pressure.

[a] *All variables: ≤ 9 children with missing data.*

** P < 0.05 for differences between both gestational groups in χ2 analysis.*

[b] *At least 1 recorded plasma glucose value < 1.7 mmol/L (30 mg/dL). Range, lowest recorded value: 0.4–6.4 mmol/L.*

[c] *Peak bilirubin value of >340 µmol/L (20 mg/dL) or any value requiring phototherapy. Range, highest recorded value: 34–421 µmol/L.*

Univariate Analyses

Within our total study group of 832 moderately preterm-born children, 73 (9.1%) had abnormal ASQ total-problems scores, as opposed to 4.2% of the term-born children in the original LOLLIPOP cohort.[9] **Table 3** shows the results of both the univariate and multivariate logistic analyses. Two neonatal morbidities, hypoglycemia and asphyxia, had a positive association with developmental delay as measured by the ASQ total-problems score in the univariate analyses; odds ratios (ORs) were 2.42 (95% confidence interval [CI]: 1.23–4.77) and 3.18 (CI: 1.01–10.0), respectively. Tertiary NICU admission and hyperbilirubinemia had positive albeit statistically non-significant associations

with developmental delay ($0.05 < P < 0.10$). No other neonatal morbidities were associated with developmental delay. Regarding biological and environmental risk factors, both gender and SGA were associated strongly with developmental delay, whereas maternal educational level and a lower gestational age (within the age range for moderately preterm-born children) were not. Repeating our analyses with gestational age as a continuous variable did not change our results with respect to the effect of gestational age.

Multivariate Analyses

As shown in **Table 3**, hypoglycemia remained associated with an increased risk of developmental delay as measured by the ASQ total-problems score in the multivariate model, with an OR of 2.19 (CI: 1.08–4.46). Male gender and SGA status also retained strong associations with developmental delay in the multivariate model. The multivariate analyses without the children who were SGA showed similar results; in the model without the children of SGA status, the OR of hypoglycemia for abnormal ASQ total-problems scores was 2.64 (CI: 1.23–5.65).

Looking at the group of children with hypoglycemia (N = 67) in more detail, we found that > 90% had not been admitted to a tertiary NICU, and none had had asphyxia, circulatory insufficiency, or a bilirubin value of > 340 μmol/L. Two children (3%) with hypoglycemia were mechanically ventilated, 4 children (6%) had a septicemia, and 8 (12%) were born SGA. Rates of SGA status, tertiary NICU admittance, hyperbilirubinemia, septicemia, mechanical ventilation, and asphyxia did not differ statistically between children with and without documented hypoglycemia.

Table 3. Odds ratios (OR), 95% Confidence intervals (CI), and *P* values for abnormal ASQ total-problems scores for birth-related and admission-related or other neonatal variables and biological and environmental variables.

Variable	Univariate Analysis			Multivariate Analyses[a]		
	OR	(CI)	*P*	OR	(CI)	*P*
Birth-related						
Low Apgar score	1.11	(0.33-3.75)	0.87	-		
Asphyxia	**3.18**	**(1.01-10.0)**	**0.05**	2.67	(0.74-9.60)	0.13
Admission-related						
Not admitted	0.81	(0.10-6.59)	0.85	-		
Tertiary NICU	1.74	(0.96-3.15)	0.07	1.22	(0.61-2.42)	0.57
Transportation	1.26	(0.43-3.15)	0.67	-		
Other neonatal						
Circulatory insufficiency	0.47	(0.05-3.05)	0.38	-		
Respiratory insufficiency						
CPAP	0.85	(0.44-1.67)	0.65	-		
Ventilation	1.04	(0.45-2.64)	0.84	-		
CPAP and/or ventilation	0.76	(0.39-1.48)	0.65	-		
Apnea	0.85	(0.44-1.67)	0.65	-		
Caffeine	0.76	(0.39-1.48)	0.41	-		
Septicemia	1.56	(0.53-4.60)	0.42	-		
Hypoglycemia[b]	**2.42**	**(1.23-4.77)**	**0.01**	**2.19**	**(1.08-4.46)**	**0.03**
Hyperbilirubinemia[c]	1.52	(0.94-2.46)	0.09	1.48	(0.89-2.46)	0.13
Biological/environmental						
SGA (< 10th percentile)	**3.30**	**(1.78-6.12)**	**< 0.001**	**2.62**	**(1.36-5.05)**	**< 0.001**
Male Gender	**3.54**	**(1.94-6.46)**	**< 0.001**	**3.12**	**(1.70-5.75)**	**< 0.001**
Low gestational age[d]	0.95	(0.57-1.60)	0.85	-		
Low maternal education	1.31	(0.79-2.18)	0.30	-		

[a] *All variables with univariate associations at P < 0.10 were entered in the multivariate model simultaneously.*

[b] *At least 1 plasma glucose value < 1.7 mmol/l (30mg/dl).*

[c] *Peak bilirubin value of > 340 µmol/l (20mg/dl) or any value requiring phototherapy.*

[d] *Low gestational age within the study group; that is 32^{+0}-33^{+6} weeks' gestation.*

Twelve of 67 children with a glucose value < 1.7 mmol/L (30 mg/dL) had abnormal ASQ total-problems scores; 12 of 73 children with abnormal ASQ total-problems scores had a glucose value < 1.7 mmol/L (30 mg/dl). In a subanalysis, we found that ORs for abnormal ASQ total-problems scores increased with decreasing glucose values (**Table 4**).

Finally, we examined the association between hypoglycemia and underlying ASQ domains. Hypoglycemia had positive but statistically nonsignificant associations with all 5 underlying ASQ domains, as shown in **Table 5.**

Table 4. Odds ratios (OR), 95% Confidence intervals (CI), and *P* values for abnormal ASQ Total-Problems scores for different ranges of hypoglycemia.

Variable	N	OR	CI	*P*
Glucose < 1.1mmol/L (20mg/dL)	25	3.04	1.03-9.00	0.045
Glucose 1.1-1.7 mmol/L (20-30mg/dL)	42	2.50	0.98-6.40	0.055
Glucose 1.7-2.2 mmol/L (30-40mg/dL)	120	1.40	0.66-3.00	0.38
Glucose 2.2-2.8 mmol/L (40-50mg/dL)	109	1.31	0.59-2.92	0.41

Table 5. Odds ratios (OR), 95% Confidence intervals (CI), and *P* values for abnormal ASQ domain scores for hypoglycemia.

ASQ Domain	OR (CI)	*P*
Fine Motor	1.7 (0.81-3.61)	0.16
Gross Mtor	2.0 (0.87-4.71)	0.10
Communication	1.7 (0.81-3.40)	0.16
Problem-solving	2.1 (0.94-4.37)	0.07
Personal-social	2.2 (0.93-5.05)	0.08

DISCUSSION

The authors of this study demonstrated that in a group of moderately preterm-born children, only hypoglycemia was associated with parent-reported developmental delay at preschool age, controlling for SGA status and gender. No other neonatal morbidities we studied were associated with developmental delay in this group.

Our finding that only hypoglycemia was associated with an increased developmental risk in moderately preterm-born children was unexpected. A documented glucose value < 1.7mmol/L (30 mg/dL) was rather common (8.1%) and increased the risk of developmental delay from 9.1% to almost 20%. There is no consensus among pediatricians on the absolute threshold values for hypoglycemia that will lead to brain injury.[25–28] There also is no consensus on specific operational thresholds for different gestational ages below which extra measures to prevent hypoglycemia should be undertaken.[25,26] There is considerable debate on the effect of short-lasting low plasma glucose levels at higher values than 1.7 mmol/L, that is, in the range between 1.7 and 2.5 mmol/L (30–45 mg/dL).[25–27] We chose a relatively low cut-off point to enable us to study even short periods of hypoglycemia.

Hypoglycemia is only a proxy for energy failure in the brain. The effect of hypoglycemia on the brain, even if it occurs only during a short period, also depends on many other factors. These factors include cerebral blood flow, cerebral glucose utilization, and the presence of alternative substrates such as lactate and ketone bodies.[25–29] Comorbidity among the children with hypoglycemia was not increased significantly, suggesting that they were not the sicker children. Moreover, excluding children of SGA status from the analyses did not change our results. The effects on development of hypoglycemia in moderately preterm-born children seemed to be due to the hypoglycemia in itself. Furthermore, risk of developmental delay increased with decreasing glucose values, with a steeper incline below 1.7 mmol/L (30 mg/dL), suggesting an increased risk of brain injury below this value. There are relatively few studies published on the effect of neonatal hypoglycemia on development in early childhood. In a systemic review on this subject, the authors concluded that no valid estimate of the effect of neonatal hypoglycemia on development could be given based on the 18 studies included in their review.[30]

Data on the underlying pathologic substrate of hypoglycemia on the brain are rare and derive mostly from adult studies, animal studies, or studies on term-born infants.[27,28] MRI findings in these few studies have shown that both diffuse cortical and

subcortical injuries, hemorrhages, infarction, and basal ganglia and thalamus abnormalities are related to hypoglycemia.[27,28] Our findings on the effects of hypoglycemia on developmental delay across all five developmental domains measured by the ASQ are in agreement with these findings of injuries in a wide range of cerebral regions.

The high risk for hypoglycemia in moderately preterm-born infants can be explained by the fact that in comparison with healthy term-born infants, they have less glucose stores, less alternative substrates, and less well-developed hormonal counter-regulatory mechanisms to sustain adequate glucose levels after birth.[25–29] They also have more difficulties in starting to feed orally and in achieving adequate feedings than term-born infants do.[3,5] Moreover, in contrast to early preterm-born infants, moderately preterm-born infants do not always routinely receive intravenous glucose infusions after birth.

In our moderately preterm-born study group, we found no association between other common neonatal morbidities such as respiratory insufficiency, circulatory insufficiency, and septicemia and developmental delay. This finding is contrary to our hypothesis and in contrast with findings on early preterm-born children, for whom several of these neonatal morbidities were linked to an increased risk of developmental delay.[31–33] The differences in the effects of these neonatal morbidities on developmental delays in both groups might be due to the fact that the severity of several neonatal morbidities is usually lower in the moderately preterm-born group. No child was ventilated for > 2 weeks, and bilirubin values of > 340 µmol/L (20 mg/dL) were rare. Furthermore, we speculate that the brain of moderately preterm-born children is perhaps more resilient to injury caused by neonatal morbidities than the brain of early preterm-born children.

The strengths of our study were the community-based approach and the large number of children who participated. We also recognize several limitations of our study. We measured developmental outcome with a parent-completed screening tool instead of submitting the children to extensive neuropsychological tests. Nevertheless, developmental screeners are considered to be reliable measures for identifying developmental problems in high-risk populations.[34] A second limitation was the retrospective design for collecting data on neonatal morbidities. It is possible that for some children, hypoglycemia had not been measured according to the national guidelines or had been recorded in sources we were unable to trace. A third limitation concerned the low prevalence of some of the risk factors, such as asphyxia, circulatory insufficiency,

not being admitted to neonatal care, and intraventricular hemorrhages. This low prevalence leads to a relatively low power to detect differences in developmental outcome.

Still larger population-based studies are needed to estimate the effect of such severe, but rare, neonatal morbidities on risk of developmental delay. Finally, more children who were not included in the final analyses had mothers born outside the Netherlands. The latter children are unlikely to have had different neonatal morbidities. Furthermore, all children born in the Netherlands get equal medical care at birth regardless of the insurance of their parents. We therefore think these differences in rates of mothers born outside the Netherlands will not have influenced our results.

Our study may have important implications. We were surprised to find that 8.1% of the moderately preterm-born children we studied had at least 1 documented glucose value of < 1.7 mmol/L (30 mg/dL), which occurred despite the guidelines to prevent hypoglycemia in this group. These guidelines include recommendations to monitor glucose regularly during the first 24 hours, and administering early, frequent enteral feedings. Controlled, prospective studies with interventions aiming at enhanced prevention of severe hypoglycemia in moderately preterm-born children are needed to confirm that the chance of developmental delay can be modified by stricter glucose control.[35] The next implication is that our results might help to further unravel the complex cascade of biological, environmental, prenatal, perinatal, and postnatal events that might all lead to developmental delay in moderately preterm-born children.[2,10,12]

We found that the effects of SGA status and male gender were more important than all the neonatal morbidities we examined. Our study, therefore, does not support the view that neonatal morbidities have a large influence on developmental outcome in the group of moderately preterm-born children.

CONCLUSIONS

Hypoglycemia after moderately-preterm birth is associated with an increased risk of parent-reported developmental delay at age 4. Stricter monitoring and timely treatment of hypoglycemia after birth might benefit the large group of moderately preterm-born children.

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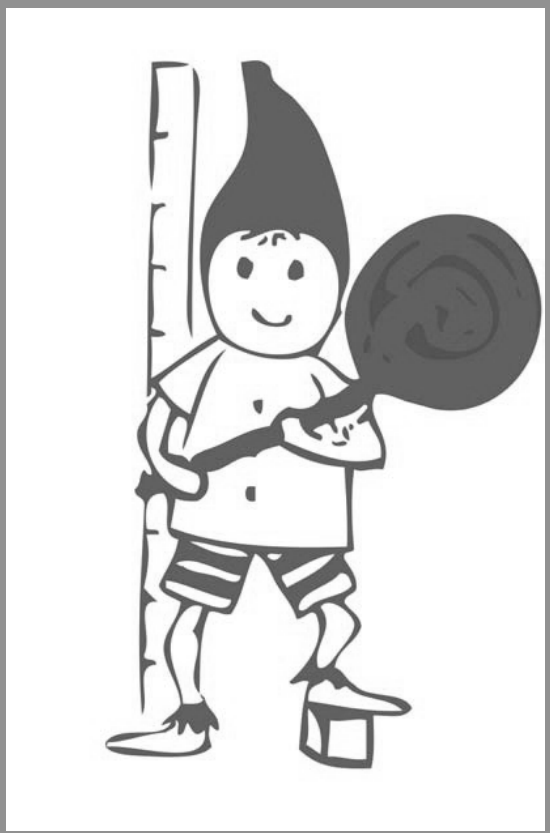
CHAPTER 7

Functioning of 7-year-old children born at 32 to 35 weeks' gestational age



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WHAT'S KNOWN ON THIS SUBJECT:

Approximately 80% of all preterm children are born moderately preterm (32–36 weeks' gestation). Moderately preterm children are at increased risk for developmental delays, but the specific neuropsychological functions that may underlie these delays are unknown.

WHAT THIS STUDY ADDS:

Moderately preterm birth is associated with poorer performance in intelligence, attention, visuospatial reasoning, and executive functioning. Using gender-specific norms, our data suggest that preterm boys catch up, whereas preterm girls lag behind their peers at 7 years of age.

ABSTRACT

Objective: To compare neuropsychological functions in moderately preterm (32–35 weeks' gestation) and full-term children at the age of 7 years and identify gender differences.

Methods: Community-based prospective cohort study of 248 moderately preterm children (138 boys) and 130 full-term children (58 boys). Neuropsychological tests included IQ, memory, attention, visual perception, motor skills, visuomotor skills, and parental report of executive functioning.

Results: The moderately preterm group performed significantly worse on total and performance IQ, visuospatial reasoning, attention control, inhibition, and executive functioning. No differences were found in verbal IQ, verbal memory, and visuomotor and motor skills. Preterm children were at higher risk for scores <10th percentile on intelligence, visuospatial reasoning (relative risk ratio both: 1.69 [95% confidence interval: 1.29–2.28]), and executive functioning problems (relative risk: 1.94 [95% confidence interval: 1.51–2.57]). Using gender-specific norms, preterm boys performed significantly worse than fullterm boys on visuospatial reasoning ($P < 0.01$); preterm girls performed significantly worse than full-term girls on visuospatial reasoning, intelligence, attention, and executive functioning ($P < 0.05$).

Conclusions: Moderately preterm birth is associated with lower intelligence and poorer neuropsychological functioning at early school age. No differences in motor skills and verbal memory were found. Using gender-specific norms, our data suggest that moderately preterm boys catch up, whereas moderately preterm girls lag behind their peers on various neuropsychological functions by the age of 7 years.

INTRODUCTION

Moderately preterm infants born at ≥32 weeks' gestational age (GA)[1] currently make up over 80% of all preterm births in developed countries.[2] Approximately 7% of all births in Europe (6.3% in the Dutch population) and 10% in the United States are moderately preterm, and the incidence is rising.[3,4] Although moderately preterm infants seem to be almost fully developed, studies reveal a greater risk for mortality and morbidity than full-terms associated with immaturity-related complications.[5] The increased risk for medical complications has fueled concern about the long-term outcome after moderately preterm birth.[6] In infants born very preterm (GA<32 weeks), neurologic and physiologic immaturity has been associated with clear deficits in a number of key neurodevelopmental areas in childhood.[7,8] These deficits have been associated with poorer school performance.[9] Although more mature than infants born very preterm, moderately preterm-born infants are considerably less mature than infants born at full-term.

The brain almost doubles in size in the 8 weeks before full-term age as differentiation proceeds throughout the cortex and myelination of central brain regions continues.[10] This may increase the risk for disruptions of brain growth and development in preterm-born infants. Evidence has been accumulating that behavioral problems,[11] neurodevelopmental delays or deficits,[6,12–16] and learning difficulties[17,18] occur more frequently in children born between 32 and 36 weeks' GA. Neuropsychological outcome at preschool age has been investigated in 3 cohorts of moderately preterm-born children born in the last 10 years.[12,13,15] Information on outcome at school age in children born in this period is, however, missing. Furthermore, most previous studies used global measures of cognition or school outcome with the result that little is known about the specific neuropsychological deficits that may underlie the global deficits and school performance that have been identified. Because learning is a school-aged child's primary task, we assessed both global intelligence and a range of specific neuropsychological functions in the domains of memory, attention, executive functioning, visuospatial reasoning, and motor skills, which can be considered to be central to effective learning in class.[19]

Finally, although male gender is considered a risk factor in very preterm children,[20] only Romeo et al[12] have addressed the issue of gender differences in outcomes in children born moderately preterm. They found that girls performed better than boys at 12 to 18 months of age, suggesting that male gender is also a risk factor in moderately preterm-born children.[12]

Our aim was to compare moderately preterm-born children with full-term born peers at early school age on neuropsychological and motor outcomes, with particular attention to gender differences.

METHODS

Subjects, Study Design, Sampling Procedure, and Sampling Criteria

The Longitudinal Preterm Outcome Project (LOLLIPOP) is a large, prospective follow-up study on growth, development, and general health in preterm-born children. From a community-based cohort of 45 446 children born in 2002 and 2003 in the Netherlands, 1843 preterm (<36 weeks) and 674 fullterm children (38^{+0}–41^{+6} weeks) were included. Children were recruited from 1 of 13 Dutch preventive child health care centers. GA was calculated from the date of last menstruation, and confirmed in the majority of cases by early ultrasound measurements. Exclusion criteria were major congenital malformations, congenital infections, or syndromes. After each second preterm child was identified, the next full-term born child who did not meet the exclusion criteria was drawn from the same files as a control. Full-term children were thus from the same preventive child health care centers and in the same age range as the preterm children. Sampling procedures, inclusion and exclusion criteria, study conduct, participants and nonparticipants in the LOLLIPOP study have been described in detail elsewhere.[13,21]

For the current study, we selected all moderately preterm-born children (32– 35^{+6} GA) and full-term controls (38^{+0}-41^{+6} GA) from the LOLLIPOP cohort who were currently living in the 3 northern provinces of the Netherlands. This included 341 children born moderately preterm and 195 full-term, age-matched controls. In total, 248 children born moderately preterm (138 boys; 110 girls; median GA: 34 weeks in both groups) and 130 full-terms (58 boys; 72 girls; median GA: 40 weeks in both groups) agreed to participate in this study, a response rate of 73% for children born moderately preterm and 67% for controls. Mean age was 6.9 years (range, 6.4–7.3).

A power calculation had revealed that we needed 250 moderately preterm children and 125 full-term controls to detect a clinically relevant difference in mean IQ, here set at 5 points or one-third of the SD of the IQ-distribution in the population, at $P = .05$ and 80% power. Regarding the power to detect gender differences, we performed a post hoc power analysis. This revealed that we needed 64 preterm boys and 64 girls to detect 5 IQ points difference, being more than half the SD in

our sample, as SD of IQ was 9.7 points in our preterm group. A possible explanation of why SD was lower than the expected 15 IQ points is the limited number of IQ subtests used. Thus, the power calculations confirmed the sample size was appropriate for our goals.

Medical data were extracted from hospital charts. Demographic and perinatal data are presented in **Table 1**. All children had normal or corrected to normal vision. The study was approved by the Ethical Review Board of the University Medical Center of Groningen (UMCG). Examinations were performed in accordance with the institutional (UMCG) and international (Declaration in Helsinki, 1964, European Union Council Directive 86/609/EEC) ethical standards, including written informed consent.

Table 1. Demographic and perinatal characteristics of the moderately preterm and full-term groups.

Characteristic	**Preterm group** ***n*=248**	**Full-term group** ***n*=130**	***P*- value**
Age, *y*	6.9 (0.1)	6.9 (0.1)	
Boys:girls	138/110	58/72	< 0.05
Gestational age, *wk*	33.9 (1.1)	39.7 (0.9)	
Birth weight, *g*	2237 (489)	3583 (516)	<0.01
SGA[a] birth weight < 10^{th} centile	31 (12.5)	11 (8.5)	0.352
NICU admission	40 (16,1%)	1 (0.8%)	<0.001
Length of hospital admission[b] (d)	19 (12.6)	0.4 (1.1)	<0.0005
Range	0-116	0-6	
Apgar score at 5' < 6 (n=330)	7 (2.8%)	0 (0%)	0.059
Maternal age, *y*	31.3 (4.4)	31.4 (3.7)	0.762
Maternal education level (n=359)			0.064
Low	66 (28%)	21 (17.1%)	
Middle	92 (39%)	52 (42.3%)	
High	78 (33%)	50 (40.6%)	
Paternal education level (n=350)			0.066
Low	78 (34%)	27 (22.5%)	
Middle	84 (36.5%)	47 (39.2%)	
High	68 (29.5%)	46 (38.3%)	

Data are mean (SD) or number or range or percentages (%). P-values of the t-test and $\chi 2$ test.

[a] *SGA, small for gestational age.*

[b] *Mean of total hospital admission time including NICU and neonatal ward*

Measures and Procedure

The children and their parents were invited to visit the UMCG or a well-infant clinic in their neighborhood for a 3-hour assessment comprising a number of standardized

neuropsychological tests and questionnaires. Each child was tested individually by a trained psychologist who was blind to group assignment while parents completed the questionnaires in the waiting room. We used a short version of the Wechsler Intelligence Scale, Third Edition, Dutch Version[22] consisting of 2 verbal subtests and 2 performance subtests to estimate total IQ (TIQ), verbal IQ (VIQ), and performance IQ (PIQ). We assessed verbal memory by using the Dutch version of the Rey Auditory Verbal Learning Test.[23] We used the design copying subtest of the Developmental Neuropsychological Assessment battery[24] to assess visuomotor functioning. We assessed the attentional skills that are required for effective functioning at school, using 3 subtests from the Test of Everyday Attention for Children, Dutch version[25]: Map Mission, Score!, and Same world/ Opposite world. To measure motor skills required in everyday life, we used the Dutch version of the Movement Assessment Battery for Children.[26] Behavior regulation and meta-cognitive functioning, key aspects of executive functioning, were assessed by using the parent's form of the Behavior Rating Inventory of Executive Functions, Dutch version (BRIEF).[27] A more detailed description of each component of the assessment is provided in **Table 2**.

Statistical Analysis

χ^2 tests and *t* tests were used to assess differences between the groups in demographic characteristics. Because the main outcome measures were normally distributed, we used analysis of variance (ANOVA) on all total scores in a 2 x 2 design (preterm versus term; boy versus girl) to detect differences between the groups in Neurodevelopmental outcomes. We repeated the analyses adjusting for parental ducational level. Then, to minimize the impact of the gender differences that are often present in typically developing children, gender-specific *z* scores were computed for each neuropsychological domain for boys and girls separately. The z scores were based on the data of the full-term control groups. ANOVAs were conducted on the gender-specific *z* scores to investigate differences between preterm and full-term boys, and preterm and full-term girls. Finally, the prevalence of clinical scores in the different Neurodevelopmental domains in the preterm group was investigated. The 10th percentile, defined as a *z* score below -1.28, was the cutoff.[28] The relative risk (RR) then is defined as the ratio of the percentages of preterm and of term children with a *z* score below the 10th percentile.

Table 2. Measurements, related cognitive and motor functions, and referring names.

Test / Scale names	Functions	Referring name
WISC-III-NL	Short version of Intelligence test	Intelligence
Verbal IQ	Verbal intelligence	VIQ
Similarities	Abstract reasoning	Abstract reasoning
Vocabulary	Comprehension of words	Comprehension
Performance IQ	Performance intelligence	PIQ
Picture arrangement	Chronological ordering	Ordering
Block design	Visuospatial reasoning	Visuospatial reasoning
Total IQ	Global intellectual level	TIQ
AVLT	Verbal memory	Verbal memory
Immediate recall	Short-term memory and learning	Recall
Delayed recall	Active long-term memory	Delayed recall
Recognition	Passive long-term memory	Recognition
NEPSY-2 design copying	visuomotor functioning	Visuomotor
TEA-Ch-NL	Everyday attention in children	Attention
Map mission	selective visual attention	Selective attention
Score!	sustained auditory attention	Sustained attention
Same world	attention control	Attention control
Opposite world	response inhibition	Inhibition
BRIEF	Executive functioning in everyday life	Executive function
Behaviour regulation index	Modulate and control: Inhibition, Shift cognitive set, emotional control	BRI
Meta-cognition Index	Problem-solving: Initiate, working memory, plan/organise, organisation of materials, monitor	MCI
Global Executive Composition	Total of BRI and MCI subscales.	GEC
Movement ABC	Motor skills in everyday situations	Motor Skill
Fine motor	Manual dexterity	Manual dexterity
Ball	Object control	Object control
Balance	Postural control	Postural control
Total score	Motor proficiency	Total M-ABC

AVLT, Rey Auditory Verbal Learning Test; BRI, behavioral regulation index; GEC, global executive functioning; MCI, meta cognition index; Movement ABC, Movement Assessment Battery for Children; NEPSY-2, Developmental Neuropsychological Assessment; TEA-Ch-NL, Test of Everyday Attention for Children; WISC-III-NL, Wechsler Intelligence Scale, 3d Edition, Dutch version.

RESULTS

Cognitive and Motor Outcomes in the Preterm and Control Groups

The mean scores are presented in **Table 3**. The moderately preterm group performed more poorly than the full-term group on every measure. The differences reached statistical significance for TIQ, PIQ, visuospatial reasoning, attention control, and inhibition. On the BRIEF, preterm children's parents reported significantly more difficulty on global executive functioning and the behavioral regulation index but not on the meta-cognition index.

Repeating the analyses with adjustment for parental education level revealed slight increases in most P values but did not affect the statistical significance (P<0.05) regarding any outcome (**Table 3**).

Gender Differences

Regarding demographic and perinatal characteristics, no differences existed between boys and girls. Only the numbers of preterm children born small for GA were higher for boys (n = 21) than for girls (n = 8; P = 0.047). Girls performed significantly better than boys in the areas of verbal memory, visuomotor skills, sustained attention, attention control, and 2 aspects of motor skill: manual dexterity and posture control (**Table 4**). They also performed better on executive functioning, but the difference failed to reach statistical significance. Boys performed better than girls on visuospatial reasoning, but this difference also did not reach statistical significance. None of the interactions between gender and group was statistically significant. Adjustment for parental education level hardly affected the P values of the gender differences and did not affect the statistical significance (P < 0.05) of any gender difference (**Table 4**).

Table 3. Cognitive and motor results in the moderately preterm and full-term groups, mean differences, and statistical significances of group differences before and after adjustment for parental education.

Measures	Preterm	Full-term	Mean difference	*P*	P^a
	***N*=248 (SD)**	***N*=130 (SD)**	**SD (95%CI)**		
INTELLIGENCE (TIQ)	101.2 (9.7)	103.9 (10.3)	-2.7 (-4.8, -0.6)	0.011	0.033
Abstract reasoning, SS	10.8 (2.7)	11.2 (3.1)	-0.4 (-1.0, 0.2)	0.208	0.319
Ordering, SS	9.7 (2.9)	10.0 (2.9)	-0.3 (-0.9, 0.3)	0.318	0.457
Visuospatial reasoning, SS	9.7 (2.9)	10.8 (3.2)	-1.1 (-1.7, -0.5)	0.001	0.004
Comprehension, SS	10.5 (2.4)	10.9 (2.9)	-0.3 (-0.9, 0.2)	0.232	0.377
VIQ	103.6 (10.6)	105.7 (13.2)	-2.0 (-4.5, 0.4)	0.108	0.184
PIQ	98.7 (12.3)	102.3 (11.8)	-3.6 (-6.2, -1.0)	0.007	0.024
VERBAL MEMORY					
Recall	34.3 (8.6)	35.8 (9.5)	-1.5 (-3.4, 0.4)	0.121	0.322
Delayed recall	7.4 (2.5)	7.7 (2.7)	-0.3 (-0.8, 0.3)	0.340	0.678
Recognition	27.9 (2.8)	28.1 (2.1)	-0.2 (-0.8, 0.3)	0.432	0.410
VISUOMOTOR ATTENTION	8.1 (2.2)	8.4 (2.5)	-0.3 (-0.8, 0.2)	0.188	0.389
Selective attention	11.9 (4.7)	12.7 (4.6)	-0.8 (-1.8, 0.2)	0.129	0.142
Sustained attention	6.4 (2.4)	6.8 (2.1)	-0.3 (-0.8, 0.2)	0.192	0.375
Attention control	36.9 (10.7)	34.2 (8.6)	2.7 (0.6, 4.9)	0.013	0.048
Inhibition	49.5 (19.5)	44.4 (11.7)	5.1 (1.5, 8.8)	0.006	0.021
EXECUTIVE FUNCTIONS					
GEC	104.1 (22.3)	99.3 (19.7)	4.7 (0.2, 9.3)	0.042	0.048
BRI	40.0 (9.8)	37.6 (9.0)	2.4 (0.4, 4.5)	0.020	0.020
MCI	64.1 (22.3)	61.8 (12.8)	2.3 (-0.7, 5.3)	0.127	0.149
MOTOR SKILLS					
Total M-ABC	4.7 (5.0)	4.3 (4.2)	0.3 (-0.7, 1.4)	0.497	0.742
Manual dexterity	1.2 (2.0)	1.0 (1.5)	0.2 (-0.2, 0.6)	0.254	0.381
Object control	2.0 (1.1)	2.0 (2.1)	0.0 (-0.4, 0.4)	0.962	0.817
Posture control	1.5 (2.5)	1.3 (2.1)	0.2 (-0.3, 0.7)	0.502	0.569

Data are mean (SD). P values of the F tests in ANOVA.

[a] P values adjusted for parental education in ANOVA.

Higher scores represent better performance on the subtests,except for Attention control, Inhibition, all Executive functioning and all Motor skills, where higher scores indicate poorer performance.

***BRI**, behavioral regulation index;* ***GEC,** global executive functioning;*

***MCI**, meta-cognition index;* ***SS,** standard score (mean = 10; SD = 3).*

Table 4. Cognitive and motor results in the moderately preterm and full term groups by gender, and statistical significance of gender difference after adjustment for gestational age category, and * after adjustment for gestational age category and parental education.

Measures		**Preterm** ***N*****=248 (SD)**	**Full-term** ***N*****=130 (SD)**	***F***	***P***	F^a	P^a
INTELLIGENCE (TIQ)	boy	101.9 (10.4)	103.8 (9.8)	0.763	0.383	1.226	0.269
	girl	100.4 (8.7)	104.1 (10.7)	-----	-----	-----	-----
Abstract reasoning SS	boy	11.1 (2.7)	11.0 (3.0)	0.406	0.524	0.659	0.417
	girl	10.6 (2.6)	11.4 (3.1)	-----	-----	-----	-----
Ordering, SS	boy	9.7 (3.0)	9.7 (3.2)	0.953	0.330	0.653	0.420
	girl	9.8 (2.8)	10.3 (2.5)	-----	-----	-----	-----
Visuospatial	boy	9.9 (3.2)	11.2 (3.4)	2.972	0.086	3.679	0.056
reasoning SS	girl	9.5 (2.5)	10.5 (2.9)	-----	-----	-----	-----
Comprehension SS	boy	10.6 (2.3)	10.9 (2.9)	0.299	0.585	0.302	0.583
	girl	10.5 (2.4)	10.8 (3.0)	-----	-----	-----	-----
VIQ	boy	104.4 (10.9)	105.5 (12.7)	0.666	0.415	0.991	0.320
	girl	102.7 (10.2)	105.8 (13.7)	-----	-----	-----	-----
PIQ	boy	99.2 (13.2)	102.3 (12.8)	0.447	0.504	0.727	0.394
	girl	98.0 (10.9)	102.2 (11.0)	-----	-----	-----	-----
VERBAL MEMORY	boy	33.4 (8.8)	33.0 (8.2)	11.822	0.001	12.225	0.001
Recall	girl	35.5 (8.1)	38.1 (9.9)	-----	-----	-----	-----
Delayed recall	boy	7.0 (2.6)	7.0 (2.1)	16.779	<0.001	15.411	<0.001
	girl	7.9 (2.3)	8.3 (3.0)	-----	-----	-----	-----
Recognition	boy	27.4 (3.3)	27.7 (2.1)	10.979	0.001	11.626	0.001
	girl	28.4 (1.9)	28.4 (2.0)	-----	-----	-----	-----
VISUOMOTOR	boy	7.6 (2.1)	7.8 (2.5)	19.525	<0.001	17.532	<0.001
ATTENTION	girl	8.7 (2.2)	8.9 (2.3)	-----	-----	-----	-----
Selective attention	boy	11.8 (4.9)	12.0 (4.2)	1.384	0.240	1.541	0.215
	girl	12.0 (4.3)	13.3 (4.8)	-----	-----	-----	-----
Sustained attention	boy	6.1 (2.4)	6.5 (2.4)	9.171	0.003	8.401	0.004
	girl	6.9 (2.3)	7.0 (1.9)	-----	-----	-----	-----
Attention control	boy	37.9 (11.4)	36.1 (10.4)	5.716	0.017	5.222	0.023
	girl	35.8 (9.8)	32.8 (6.7)	-----	-----	-----	-----
Inhibition	boy	49.9 (14.6)	47.0 (14.5)	1.545	0.215	1.289	0.257
	girl	49.0 (24.4)	42.3 (8.3)	-----	-----	-----	-----

EXECUTIVE	boy	104.7 (23.3)	104.1 (23.9)	3.094	0.079	2.425	0.120
FUNCTIONS (GEC)	girl	103.3 (20.9)	95.5 (14.6)	-----	-----	-----	-----
BRI	boy	40.1 (10.3)	39.6 (11.3)	1.797	0.181	1.660	0.198
	girl	39.9 (9.2)	36.0 (6.2)	-----	-----	-----	-----
MCI	boy	64.6 (15.1)	64.5 (14.6)	3.195	0.075	2.292	0.131
	girl	63.4 (13.6)	59.5 (10.7)	-----	-----	-----	-----
MOTOR SKILLS	boy	5.4 (5.6)	5.1 (4.2)	10.314	0.001	9.058	0.003
Total M-ABC	girl	3.8 (3.8)	3.7 (4.2)	-----	-----	-----	-----
Manual dexterity	boy	1.7 (2.3)	1.3 (1.6)	20.299	<0.001	18.434	<0.001
	girl	0.7 (1.5)	0.7 (1.4)	-----	-----	-----	-----
Object control	boy	2.0 (2.2)	1.9 (2.0)	0.069	0.793	0.00	0.983
	girl	1.9 (1.8)	2.0 (2.2)	-----	-----	-----	-----
Posture control	boy	1.8 (2.7)	1.7 (2.4)	8.064	0.005	8.494	0.004
	girl	1.1 (2.1)	1.0 (1.8)	-----	-----	-----	-----

Data are mean (SD). Higher scores represent better performance on the subtests, except for Attention control, Inhibition, allExecutive functioning and all Motor skills, where higher scores indicate poorer performance.

F and P values concern gender differences adjusted for (preterm or term) group, derived from F tests in ANOVA.

BRI, behavioral regulation index;

GEC, global executive functioning;

MCI, meta-cognition index; SS, standard score (mean = 10; SD = 3).

[a] *F and P values adjusted for parental education*

Gender-Specific z Scores

Significant differences between preterm and full-term children were more frequent in girls than boys (**Fig 1**). *Z* score profiles of the preterm group revealed that preterm boys performed significantly more poorly than full-term boys on only 1 test, visuospatial reasoning ($F_{1,195}$ = 9.82, *P* = 0.002, η^2 =0.048). Preterm girls performed significantly more poorly than full-term girls on visuospatial reasoning ($F_{1,181}$ =11.35, *P* = .001, η^2 = 0.059), intelligence ($F_{1,181}$ = 13.12, *P* =0 .001, η^2 = 0.068), attention ($F_{1,181}$ = 7.14, *P* = .008, η^2 = 0.038), and executive functioning ($F_{1,181}$ = 9.82, *P* = 0.002, η^2 = 0.052). We found a significant group x gender effect for executive functioning ($F_{1,375}$ = 10.67, *P* =0.001, η^2 = 0.028): preterm girls performed more poorly than full-term girls on executive functioning than preterm boys compared with full-term boys.

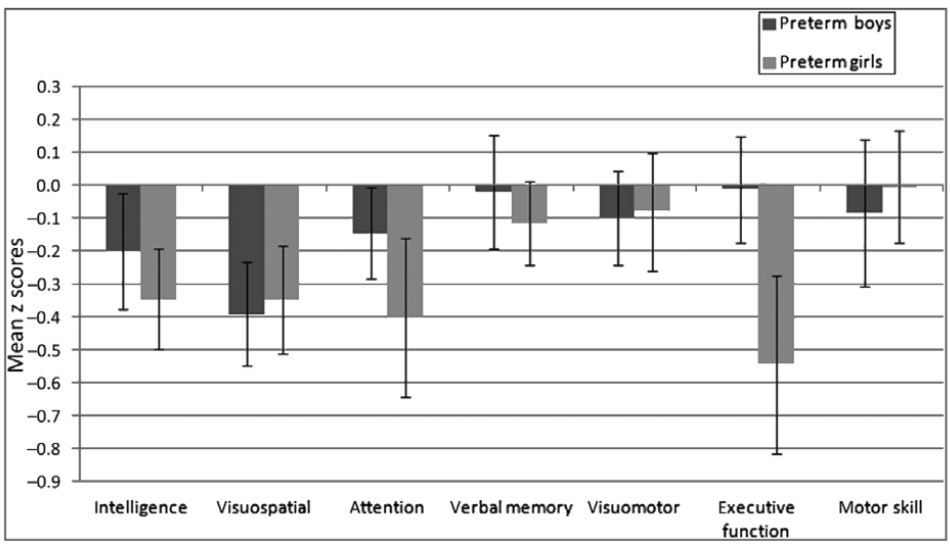

Figure 1 . The z-score profiles with 95% confidence intervals for the preterm boys and preterm girls. Z-scores were calculated for the preterm group with reference to the control group data for each gender. The mean Z-scores for the control group are zero by definition.

Relative Risk

Moderately preterm-born children were at higher risk for clinically significant poor (<10th percentile) scores on measures of intelligence, visuospatial reasoning (both RR ratios: 1.69 [95% confidence interval (CI): 1.29– 2.28]) and executive functioning (RR: 1.94 [95% CI: 1.51–2.57]).

DISCUSSION

In a detailed investigation of outcomes in a broad range of neuropsychological domains, we found that a moderately preterm group of 7-year-olds scored worse on tests of TIQ, PIQ, visuospatial reasoning, attention, and executive functioning than full-term controls. After adjustment for parental education level, the differences were largest for visuospatial reasoning and executive functioning, up to one-third SD lower, which might not be clinically significant but could be important if magnified to a whole population. The RR of impairment for the moderately preterm children was 1.69 for intelligence and visuospatial reasoning and 1.94 for executive functioning. On tests of VIQ, verbal memory, and visuomotor and motor skills, no differences were found between the groups

When using raw scores, there were no gender differences in the differences between moderately preterm and term children (ie, no statistically significant gender x GA interaction). Moderately preterm boys and girls performed equally poorer than their full-term counterparts for all outcomes. This is consistent with previous studies.[12,29] However, when using gender-specific norms, preterm boys performed poorer than full-term boys only on the test of visuospatial reasoning, whereas preterm girls performed significantly worse on tests of visuospatial reasoning, intelligence, aspects of attention, and executive functioning than fullterm girls.

We identified differences in both global and specific neuropsychological functions. First, consistent with previous studies,[6,12,15] we found small but significant differences between moderately preterm and full-term children in global intelligence. In very preterm children without serious neurologic complications, the severity of impairments is associated with declining GA.[29] In a study of 7- to 9-year-old moderately preterm children, van Baar et al[6] found scores within the normal range, but on average 3 IQ points lower than full-term controls. In our study, although their scores were in the normal range, the preterm children as a group scored 2.7 IQ points lower than full-term age-mates. Unexpectedly, the difference in TIQ scores between preterm and full-term children was greater for girls than for boys: 4 vs 2 points. Male gender is considered a risk factor in very preterm children.[9,12,20] Romeo et al[12] found that girls performed better than boys on the mental developmental index at 12 to 18 months, suggesting that male gender is also a risk factor in late preterm (between 34 and 36^{+6} GA) preschool children. However, at early school age, we found no difference between girls' and boys' performances in the moderately preterm group for TIQ. Further, intelligence scores were significantly lower in the preterm girls than in the full-term girls, whereas they did not differ between preterm and fullterm boys. The absence of the advantage of the preterm girls over preterm boys at school age,

and the differences between their performance and that of the full-term girls suggest that the moderately preterm boys catch up and/ or the moderately preterm girls lose some of their advantage on measures of global intelligence, falling behind fullterm girls by early school age.

Second, we found that the moderately preterm group performed considerably more poorly on PIQ and visuospatial reasoning. The block design subtest assessing visuospatial reasoning is a multidetermined subtest, because its score depends on various functions including visuospatial reasoning and fine motor control. As noted above, motor and visuomotor scores did not differ between the 2 groups, indicating that the basis for the difference was poorer visuospatial reasoning rather than poorer motor skills. Given Baron et al's[15] finding of poorer visuospatial reasoning in a group of preschoolers born between 34 and 36 weeks' GA, and our finding of a similar deficit in 7-year-olds born between 32 and 36 weeks' GA, we suggest that poorer visuospatial reasoning persists at least until early school age. Visuospatial reasoning is an indicator of nonverbal abilities, and many preterm children display nonverbal learning disabilities.[29] The effects of this type learning disorder, which is considered to be on a continuum with executive functioning and attention disorders, may hamper academic performance as well as social interactions.[30]

Our moderately preterm children also performed more poorly than their fullterm peers on measures of attention control, inhibition, and executive functioning. Previous studies have revealed poorer executive functioning in children born moderately preterm at 4 years of age.[15] Visuospatial, attention, and executive functioning problems have consistently been found in children born very preterm[31–34] and have been associated with white and gray matter lesions.[34,35] We speculate that these lesions are also the basis of the deficits that we found in moderately preterm-born children.[36]

In typically developing children, girls tend to have a general developmental advantage over boys of the same age,[37] particularly in the areas of attention and executive functions.[37,38] In our study, this was indeed the case in the control group but not in the preterm group, where differences in specific domains were more pronounced among girls. This suggests that moderately preterm girls have lost their developmental advantage and perform more poorly than full-term girls and at approximately the same level as moderately preterm boys. A first alternative explanation may be selection bias (ie, above average abilities in our full-term girls). However, this is unlikely because the full-term girls' scores, although above the mean for their age, were not significantly higher than the Dutch normative scores. A second alternative explanation may be lower GA in the preterm girls because decreasing GA

is associated with neuropsychological deficits.[8] However, this is also unlikely because mean and median GA did not differ significantly between the preterm boys and girls

Adjustment for parental education level hardly affected the size of the differences between the moderately preterm and term group. It also did not alter significance on any outcome regarding gender differences. Previous research has consistently revealed that parental socioeconomic status, in particular parental education level, is positively associated with cognitive development.[13,39,40] This was also the case in our cohort, but parental education level did not confound or mediate any association we found.

An important strength of this study is the direct assessment of a wide range of neuropsychological outcomes, using carefully selected, well-established measures, in a large community-based sample of moderately preterm-born children. A limitation is the use of the BRIEF, a questionnaire measure rather than a direct test of executive functioning. However, we selected the BRIEF because the parents' report covers the child's behavior in daily life evaluated over the previous 6 months. At 7 years of age, this is likely to be a more valid measure than laboratory tasks carried out at a single moment in the child's life.

The neuropsychological domains found to be affected in moderately pretermborn children matched those in very preterm-born children in all areas investigated except visuomotor skills and verbal memory. This suggests that, although less vulnerable than very preterm-born children, moderately preterm-born children are more vulnerable than full-term peers, and that the vulnerability of brain development to the disruptions that may accompany preterm birth persist between 32 and 36 weeks' GA, albeit at a reduced level. Although the differences in performances between moderately preterm born and term-born children were only clinically relevant on measures of visuospatial reasoning and executive functioning, we believe that the consistently poorer performance of the moderately preterm-born group on all measures, which are called on by school learning, may disadvantage them compared with their full-term classmates.

Preterm birth is an increasing public health problem in developed countries.[2,5,6] Therefore, clinicians and caretakers should be aware that moderately preterm birth significantly affects neuropsychological functioning of at least some of the children involved and may lead to impaired performance at early school age. Moderately preterm girls seem to be more vulnerable at this age. An important question that remains is what explains the gender-differences in the effect of preterm birth on cognitive outcomes and what the underlying mechanisms leading to neurologic impairment may be.

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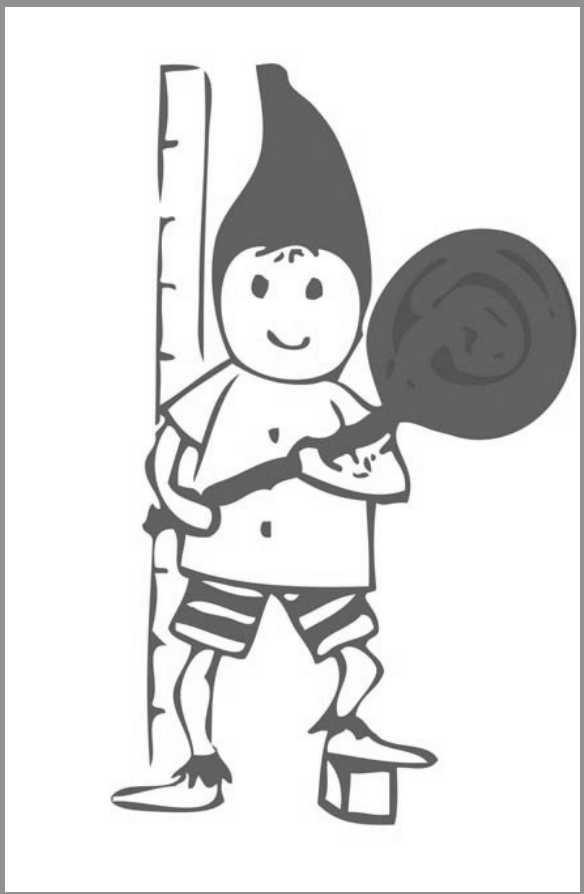
Chapter 8

General Discussion



Jorien M. Kerstjens

GENERAL DISCUSSION

Our main aim was to establish developmental outcome in moderately preterm-born children at school-entry (age 4) and school age (age 7) and to determine which children in this group were at highest risk of developmental problems.

We translated our aims into the following research questions:

1. What are the psychometric properties of the Dutch translation of the ASQ 48 months version? (**Chapter 2**)
2. Do moderately preterm-born children have more developmental problems at the age of four than fullterm-born children, which developmental domains are involved, and how do they compare to early preterm-born children? (**Chapter 3**)
3. What is the association between decreasing gestational age and risk of developmental problems at the age of four? **(Chapter 4)**
4. Which antenatal factors are associated with developmental problems in moderately preterm-born children at the age of four? **(Chapter 5)**
5. Which postnatal factors are associated with developmental problems in moderately preterm-born children at the age of four? **(Chapter 6)**
6. Do moderately preterm-born children have more neuropsychological and motor problems than fullterm-born children at the age of seven? (**Chapter 7**)

In the discussion, we first answer our research questions and provide a summary of our main findings. Next, we compare our results to other studies and offer possible explanations for our findings. After a discussion on strengths and limitations, we discuss the implications of our results, both in terms of healthcare and research. The discussion concludes with some future perspectives.

Main findings

1.What are the psychometric properties of the Dutch translation of the ASQ 48 months version?

We found excellent psychometric properties for the Dutch ASQ 48 months version. The Cronbach alphas, a measure of internal consistency, were high on the ASQ “total-problems” score and acceptable on all ASQ domain scores. The mean Dutch ASQ domain scores were similar to the mean domain scores from other countries.

Only three out of fifteen between-country comparisons showed clinically relevant differences. Construct validity was confirmed by the fact that preterm-born children, boys, children from low-income families, and children of low-educated mothers more often had abnormal ASQ scores. Predictive validity at age 4 was excellent for special education and good for special educational needs at age 5. Furthermore, fullterm-born boys had abnormal ASQ scores more often than fullterm-born girls.

2. Do moderately preterm-born children have more developmental problems at the age of four than fullterm-born children, which developmental domains are involved, and how do they compare to early preterm-born children?

Developmental problems at school-entry occurred twice as often in moderately preterm-born children (moderate preterms) than in fullterm-born children (fullterms), and half as often when compared to early preterm-born children (early preterms). The percentage of children with developmental problems was 8.3% for moderate preterms, 4.2% for fullterms , and 14.9% for early preterms. In the domains fine motor functioning, communication, and personal-social skills moderate preterms had problems more often than fullterms, but less often than early preterms. As a group moderate preterms did not encounter problems in gross motor functioning or problem-solving more often than fullterms, whereas early preterms did.

3. What is the association between decreasing gestational age and risk of developmental problems at the age of four?

The association between decreasing gestational age and the risk of developmental problems at school-entry increased exponentially as the range of gestational ages decreased from 36 to 25 weeks. Developmental problems concerned problems on the ASQ “total-problems” score, and problems on ASQ fine and gross motor functioning, communication, problems-solving and personal-social skills. Adjustment for gender, small for gestational age (SGA) status, both parents’ educational levels, mother’s country of birth, and multiple birth did not alter the pattern of exponential increase in developmental problems with decreasing gestational age.

4. Which antenatal factors are associated with developmental problems in moderately preterm-born children at the age of four?

For moderate preterms we found that almost all fetal factors, i.e. SGA, male gender, being one of a multiple, as well as one maternal pre-existing factor (pre-pregnancy

obesity) were associated with a higher risk of developmental problems at the age of four. We found no association between any pregnancy-related or delivery-related factors and the risk of developmental problems among moderate preterms. Induced birth for fetal indication increased the risk of developmental delay only if the factor SGA birth was not included in the model.

5. Which postnatal factors are associated with developmental problems in moderately preterm-born children at the age of four?

For moderate preterms, hypoglycemia, defined as at least one documented glucose value below 1.7 mmol/l, was associated with a higher risk of developmental problems at the age of four. We found no association between any other common neonatal morbidity (respiratory or circulatory insufficiency, asphyxia, hyperbilirubinemia, septicemia, low Apgar score, apnea, caffeine treatment) or NICU admission and developmental problems at school-entry for moderate preterms.

7. Do moderately preterm-born children have more neuropsychological and motor problems than fullterm-born children at the age of seven?

When they were seven old, moderate preterms scored worse than fullterms on tests of total intelligence, performance intelligence, visuospatial reasoning, attention control, inhibition, and executive functioning, but not on tests of verbal intelligence, verbal memory, and visuomotor and motor skills. Differences were largest for visuospatial reasoning and executive functioning (up to one-third SD). Furthermore, moderate preterms were at increased risk of clinically significant poor scores (< P10) on measures of intelligence, visuospatial reasoning and executive functioning. Using gender-specific norms, moderately preterm-born boys performed poorer than fullterm-born boys only on visuospatial reasoning, whereas moderately preterm-born girls performed significantly worse on visuspatial reasoning, intelligence, aspects of attention, and executive functioning than fullterm-born girls.

General Discussion

Psychometric properties of the ASQ.

Our finding of the excellent psychometric properties of the Dutch ASQ (48 months version) including reliability and several measures for validity, i.e. content, construct, and predictive validity) were in line with several other validation studies.

Our findings, therefore, strongly supported the feasibility of the Dutch ASQ as a developmental screener.[1-5] The few mean scores that differed between countries may be due to differences in child-rearing practices, as was suggested in the case of Norwegian and Korean validation studies.[2,3] These differences also underline the necessity of cross-cultural validation studies[6,7] as they may lead to larger differences for different countries. The gender differences in the ASQ scores we found in our fullterm-born reference group were also consistent with the Norwegian findings on gender differences in their ASQ validation study.[3] Differences by gender may exist in other countries as well. Should this occur in more settings, it may be warranted to consider introducing separate gender norms for the ASQ.

Developmental problems at the ages of four and seven.

We found more developmental problems at the ages of four and seven among moderate preterms than among fullterms, which was in line with several studies published since the inception of this project.[8-16] Almost all studies on pre-school ages (ages one to four) found that moderate preterms had an increased risk of developmental problems compared to fullterm-born children, even though definition of moderate prematurity, inclusion criteria, and age at assessment differed somewhat between studies. We found that moderate preterms had roughly twice the rate of developmental problems when compared to fullterm-born children, and approximately half that of early preterms. Despite this higher rate among early preterms, the economic and social consequences for society of prematurity will be due mostly to the moderately preterm-born group because this group is considerably larger than the group of early preterms.

Our study also showed which developmental domains in particular were involved at the age of four, whereas other studies on preschool-ages mainly presented rather broad developmental measures such as special educational needs,[11,13,15] school problems,[9,13] or global IQ.[8,10,11] The developmental domains we found to be affected most, i.e. fine motor functioning, communication, personal-social skills, and ASQ “total-problems” score, constituted, in our opinion, the precursors of problems at school. If so, this information offers potential targets for interventions. The increased risk of developmental problems at age four was confirmed by the neuropsychological assessment at the age of seven of a subsample of the moderate preterms. This ruled out, that the finding at the age of four of an increased rate of problems on the parent-completed ASQ, was due only to information bias stemming

from parental concern. Moreover, our finding of increased rates of problems of moderate preterms at the age of seven also confirmed that the developmental problems of moderate preterms may persist after school entry, and was in agreement with several other recent studies.[9,13,15,17,18] All these studies found increased rates of school problems and special educational needs for moderate or late preterms at school-entry. This implied that developmental problems of moderate preterms at school-entry were not merely "transient", and suggests that early intervention might really be worthwhile. Of the different developmental domains we examined, we briefly discuss general IQ.

Our results on the IQs of moderate preterms at the age of seven showing small differences of three to four points in comparison to fullterm-born children, were in agreement with two other studies,[8,11] which also reported small IQ deficits at group level at ages two and eight. In our study all moderate preterms scored within the normal range (IQ > 70 (>P2.3)). Nevertheless, at the age of seven, we found that when compared to fullterm-born children moderate preterms had an increased risk of clinically significant poor scores (< P10) on several IQ measures. Results from other studies that emerged during the same period as ours, showed conflicting results, with some reporting more IQ scores below 85, or below 70, and others not reporting increased rates of low IQ scores.[20-22] Even so, for moderate preterms all recent studies found increased rates of special educational needs, repeating grades, or difficulties with reading, spelling, and arithmetic .[20-22]

Pattern of association between gestational age and developmental problems

We found an exponential association between decreasing gestational age and the risk of developmental delay at school-entry not described previously. Most studies reported linear relationships between developmental measures and gestational age.[23,24] These studies extrapolated their data from the early preterm age range to the moderately preterm age range for lack of data on this particular group. The findings of the few studies that did assess a broad range of preterm age ranges and that did include data on a moderately preterm-born group, are inconclusive, and only examined broad developmental measures.[17,25] Our results were not explained by the early preterm-born group, since the same exponential pattern remained when the early preterms were excluded from the analyses.

The exponential relationship we found was not limited to overall development but included all developmental domains measured by the ASQ. We found exponential

associations for all five domains of the ASQ with relatively small differences in odds ratios. This suggested that developmental problems in several domains at once, might not only occur in early or extremely early preterms but in moderate preterms
as well.[26] An explanation for the exponential pattern of developmental risk per week of gestational age might be found in the rapidly increasing brain connectivity between 24 and 40 weeks of gestation. During this time brain volume increases fourfold[27] (only 60% of the human brain volume is present at 32 weeks of gestation). This corresponds with increasing synaptogenesis (neural networking), neuronal and axonal growth, dendritic arborization, myelination, gyral and sulcal infolding, maturation of neurochemical and enzymatic processes, and focused apoptosis.[28,29]

Antenatal factors associated with risk of developmental problems

As far as antenatal factors are concerned, we found an association between developmental problems and several fetal factors and maternal preexistent obesity. The developmental problems were not associated with maternal pregnancy-related illnesses and delivery-related factors. The three fetal factors that were associated with the risk of developmental problems, i.e. SGA, male gender, and being one of a multiple birth, were also found to associate with developmental risks in early preterms and in fullterm-born children,[30-31] and are, therefore, not unique for moderate preterms. We briefly discuss each of the three fetal factors mentioned.

The first fetal factor we found to be associated with developmental risk was SGA. Even though SGA remains only a proxy for intra-uterine growth restriction (IUGR),[32,33] chronic deficits in nutritional and oxygen needs during the fetal period may alter brain structure permanently, with the oligodendrocytes in a prominent role.[29]

Male gender was the second fetal factor we found to be associated with developmental risk. For early preterms this male disadvantage seems to be due to both an increased biological risk of being a male, and an increased risk of neonatal complications for males.[34,35] In a post-hoc analysis, moderate preterm-born boys proved to be more susceptible to hypoglycemia, which confirmed that the male disadvantage was also present with regard to neonatal complications in moderate preterm boys. We no longer found a male disadvantage for moderate preterms at age seven. Whether this male disadvantage is permanent, or only temporary due perhaps to a difference in the timing of achieving developmental milestones, needs to be

studied in more detail. At the age of seven, moderately preterm-born girls had relatively more lower scores compared to fullterm-born girls, than moderately preterm-born boys had compared to fullterm-born boys. Despite the larger *z* score differences for moderately preterm-born girls, at the age of seven the scores of moderately preterm-born girls were not worse than those of moderately preterm-born boys. This might be explained in terms of the general developmental disadvantage of fullterm-born boys compared to fullterm-born girls at age four mentioned previously. This would suggest that moderately preterm-born girls lose some of their gender advantage. To our knowledge, we were the first to examine specific gender differences in moderately preterm-born boys and girls compared to their fullterm-born peers. Only one study on cerebral palsy (fullterm-born children and preterms) found that females performed better on IQ measures at the age of four, but that this was no longer the case at ages six to seven.[36] The underlying mechanisms are unknown, but may involve hormonal differences in utero and after birth, and a different architecture and timing between the genders of cerebral brain connections.[36] It would be interesting to know whether using gender-specific norms on developmental tests at young ages reduces the male preterm disadvantage which is seen in most studies concerning both early and moderately preterm-born children.

The third fetal factor we found to be associated with developmental risk was being born as one of a multiple. Our findings contradicted the hypothesis[37] that the higher developmental risks of multiples is explained entirely by prematurity and IUGR, since the increased risk of multiples remained virtually unchanged between the univariate and multivariate models in our group of moderately preterm-born children.

In our study we only found one maternal factor that was associated with developmental risk: maternal pre-pregnancy obesity. This finding was relatively new, since maternal obesity had not been associated with developmental problems in offspring until fairly recently.[38] We were aware of only one other study, a cohort of predominantly early preterms,[30] where a similar association between maternal obesity and IQ scores was found at the age of two, independent of socioeconomic status (SES). Conflicting data exist on the effect of maternal obesity on the development of fullterm-born children.[38,39] The mechanisms underlying the effect of maternal obesity on the development of offspring are not completely understood, but might include residual environmental factors despite controlling for SES and lifestyle,[39] genetic and metabolic causes, and chronic low grade placental inflammation.[38]

In an animal model with mice, the brains of offspring of obese female mice developed differently compared to offspring of non-obese female mice.[40]

The fact that no other maternal pregnancy-related or delivery-related factors were associated with developmental problems led us to suggest that only maternal pregnancy-related factors, which lead to chronic deficits in oxygen and nutritional requirements which in turn lead to intra uterine growth restriction, were associated with the increased risk of developmental problems in the early childhood of this group. Our finding of no other maternal factors related with developmental problems was in accordance with results of Helderman et al.[30] in a cohort of early preterms.

Associations between postnatal factors and developmental risk.

Regarding the associations between the risk of developmental problems and factors after birth in moderate preterms, we only found hypoglycemia to be associated with an increased developmental risk. For three reasons this unexpected finding may be due to the effect of hypoglycemia itself: 1) The children with hypoglycemia were not the sickest children. 2) There was a dose-response effect between the lowest glucose value and the risk of developmental delay, with a steeper decline below 1.7 mmol/l. 3) The effect of hypoglycemia did not change when SGA born children were excluded. Several factors contribute towards moderate preterms being more susceptible to hypoglycemia than fullterms. These factors include diminished glucose stores and alternative substrates, less well-developed hormonal counter-regulatory mechanisms to sustain adequate glucose levels after birth, difficulties in achieving adequate feedings, and the lack of routine IV glucose infusion after birth, the latter in contrast to routine practice in the care of early preterms.[41,42] Whether neonatal hypoglycemia eventually has an effect on development in early childhood may depend on factors like cerebral blood-flow, glucose utilization, and alternative substrates.[41-46] Data on the underlying pathologic substrate of hypoglycemia however, are sparse, and for the most part based on animal studies, studies on adults, or fullterm-born children.[44,46] MRI findings in these few studies revealed very diverse cerebral substrates.[44,46]Our findings on the effects of hypoglycemia on the developmental delay across all five developmental domains measured by the ASQ were in agreement with the diversity found in anatomical substrates.

Apart from hypoglycemia, we found no other common neonatal morbidity that increased the risk of developmental problems in our moderately preterm-born group. In contrast with studies on early preterms, [47-50] respiratory insufficiency,

circulatory insufficiency, and septicemia were not associated with developmental delay in moderate preterms. We did not find an association with NICU admission either, which was in line with a recent publication by McGowan et al.[51], even though it was in contrast with another small study (*N*=118).[52] We speculated that the differences in the effects of the common neonatal morbidities on the developmental delays between early and moderate preterms might be related to the different points of time during gestation at which the morbidities occur. Across the range of preterm gestational ages, the vulnerability of the developing brain might change, in the light of the cerebral trophic and maturational processes that occur during the last trimester of pregnancy.

Effect of SES

We assessed whether differences in developmental outcomes between moderate preterm and fullterm-born children might be due to differences in SES. This seemed not to be the case, since adjustment for SES at both four and seven years decreased these differences only to a limited degree. Whether this also implied that SES had no association at all with developmental problems of moderate preterms, is a topic for future research.

Summary

In summary, we found that moderately preterm-born children had developmental problems twice as often as term-born-born children at school-entry. Therefore, this group of children should indeed be considered as being at increased developmental risk because of their moderately preterm birth. Moderate preterms had developmental problems half as often as early preterms at the age of four. At the age of seven, moderate preterms performed less well than fullterm-born children on a select set of neuropsychological domains, but not on motor functioning. We found an exponential relationship between decreasing gestational age and the risk of developmental problems. Only hypoglycemia, maternal pre-pregnancy obesity, and three fetal factors, i.e. SGA, male gender, and being one of a multiple birth, were associated with developmental risk in moderate preterms. These factors might help to predict which children within the moderately preterm-born group are at highest risk of developmental problems. The role low SES plays in the increased prevalence of developmental problems of moderate preterms has to be elucidated, but did not seem to be predominant.

Strengths and limitations

Major strengths of our study were its large community-based sample with over 1000 moderate preterms, and the two large control groups of both fullterm and early preterm-born children, from the same cohort. In addition, we studied several developmental domains instead of global developmental measures like IQ or the rate of school problems. Finally, we assessed developmental problems in two ways: by means of the ASQ, a parent-completed questionnaire, and by extensive neuropsychological assessment. In doing so, we were able to rule out that our findings were due simply to information bias. We assessed a wide array of developmental domains and were able to show the added value of using the ASQ as a parental questionnaire. The ASQ is a screening tool that can also be readily used in preventive child healthcare and community pediatric settings.

Our study also had limitations. One limitation concerned the inclusion method. Inclusion took place at PCH clinics. This possibly led to excluding the most severely handicapped children since their parents often skip routine PCH visits. We did not expect this to have had a strong effect on our results.

A second limitation was that we did not include children born between 36 and 37 weeks in our moderately preterm-born group. This may have limited the comparability of our study with other studies on *late* preterms (34^{+0} to 36^{+6} weeks of gestation). When we designed our study, the phrases “moderate preterm” and “late preterm” had yet not been introduced and published[53] and our main goal was to analyze the development of “non-early” preterm-born children. Even so, all boundaries for distinguishing one group of preterms from the next, or from fullterm-born children, remain arbitrary.[54,55]

A third and final limitation was that we obtained information on prenatal and perinatal factors from medical records. This may have caused some underestimation of real effects due to incomplete recordings.

Implications

Our study had three important implications: increasing awareness of the developmental consequences of preterm birth, enhanced prevention of moderately preterm birth, and structured monitoring of moderate preterms.

First, our findings emphasized the necessity of raising awareness of the developmental consequences of moderately preterm birth. Our findings refuted the assumption that born “just a few weeks early” or “near-term” does not have

developmental consequences. By implication, obstetricians, parents, and pediatricians should more often weigh the possible long-term disadvantages against short-term postnatal advantages of induced preterm birth. In the same line, we might perhaps want to reconsider the strict definitions of early preterm, moderately preterm, near-term, early-term, etc. as if they are really separate entities; it muddles the issue. In fact, there is no "safe" preterm gestational threshold beyond which preterm birth may not have developmental consequences.

Second, enhancing prevention of moderate preterm birth should concern both primary and secondary prevention. Primary prevention includes lifestyle changes and reducing the number of multiples in multiple births. Promoting a healthy lifestyle in fertile and pregnant women might include attempts at reducing maternal obesity and unhealthy lifestyles associated with the risk of IUGR, such as smoking and alcohol. This shift towards primary prevention is in agreement with recent recommendations of the American College of Obstetricians and Gynecologists.[56] An attitude change in subfertility treatments aiming at reducing the number of multiples might form another challenge. In this respect we also need to encourage mothers to consider bearing their children at an earlier age, thus reducing artificial fertilization requests. Secondary prevention aims at reducing iatrogenic births whenever possible, but short-term and long-term benefits and the risks for child and mother will always have to be weighed against each other when inducing delivery before term.

Third, structured monitoring also implies a shift in attitude. Our results imply that moderate preterms deserve more attention than they have received until now in follow-up care. More awareness, e.g. checking an extra box on a risk sheet, might improve the effectiveness of the follow-up of this group. Assessing developmental outcome serves two purposes: first, the developmental assessment ensures the most optimal developmental chances for children and their parents and second, the developmental assessment evaluates obstetric and neonatal treatment strategies. We will have to find ways to combine the efforts of obstetricians, neonatologists, PCH physicians, and pediatricians in order to reach both goals at the same time in a cost effective manner.

Future perspectives

Future perspectives concern further clinical research, early intervention after discharge, feasibility of the ASQ in the PCH setting, and a revision of the current views on effective follow-up of preterm-born children.

First, future research concerns both pediatric and obstetric studies. Our retrospective study should be duplicated in prospective randomized controlled trials, involving stricter recommendations to prevent hypoglycemia in moderate preterms, with extended follow-up (until school age) with several developmental and behavioral outcome measures. These prospective trials might prove whether hypoglycemia can be prevented further, and whether the developmental chances in moderate preterms can indeed be improved with tighter glucose control (causality). Obstetric trials aiming at primary secondary, or tertiary prevention of preterm birth, should not only have the rates of preterm or IUGR birth and NICU admission as their primary outcome measures, but should also target long-term developmental outcome assessments in the offspring.

Second, more insight is needed into the efficacy of early intervention strategies after discharge, aiming at facilitating normal development. As far as early intervention is concerned, all our efforts are now aimed at minimizing short-term complications after preterm birth, with many expensive high-tech interventions. Relatively little effort is spent on intervention strategies after discharge which may, potentially, be just as worthwhile. More emphasis on, and commitment to, large trials aiming at proving the efficacy of early intervention for larger groups of preterms should definitively be placed higher on our list of priorities, even though they are much more difficult to conduct than short-term intervention studies prior to discharge. As yet, firm evidence on the sustained efficacy of early intervention strategies is scarce, and pertains only to early preterm-born children.[57-60]

Third, with regard to the ASQ, prospective trials could target the introduction of the ASQ as an additional measure for monitoring development in preterm-born children, both in the pediatric and the PCH setting. These trials should study feasibility, efficacy, and implementation. The ability to issue one or several ASQs as an additional measure besides the “Van Wiechen Schema” and clinical evaluation by the PCH physician might enhance chances of early detection, and referral during the window of opportunity for early intervention.

Finally with regard to follow-up, the findings reported on in this thesis constitute an invitation to rethink our entire preterm follow-up system. Until now, we have followed only early preterm-born children in a structured manner, because their risks are well known and they are an easily accessible group. Even for this group, both gestational thresholds for NICU follow-up and the length of follow-up are declining due to funding issues. Follow-up of the much larger and ever increasing group of "non-early" or moderately preterm-born children is unstructured and incidental, shifting between pediatricians and PCH physicians. Perhaps we should start thinking about a more globally targeted follow-up, in which we can combine care for and research on larger groups of children at risk of developmental problems before or at school-entry in a more cost-effective manner. As resources dwindle and the rates of preterms continue to rise, this requires better collaboration among obstetricians, general pediatricians, and PCH physicians. Perhaps we could initiate a two-tier developmental screening whereby only the children with abnormal test results on developmental screeners go on to neurodevelopmental testing. This might be doable, but involves a shift of focus, a shift of resources, implementation studies, and structured collaboration between all the disciplines involved. As 6% to 11% of all children are born preterm world-wide, we should encourage "a call for action". This might help to ensure that further research on optimal treatment before and after birth, and research on optimizing follow-up and targeted intervention strategies for the entire preterm group, are given a higher ranking on the European as well as global agenda.[61] The above call for action coincides with the recent white paper issued by the March of Dimes Foundation on prevention of preterm birth and its consequences.[62]

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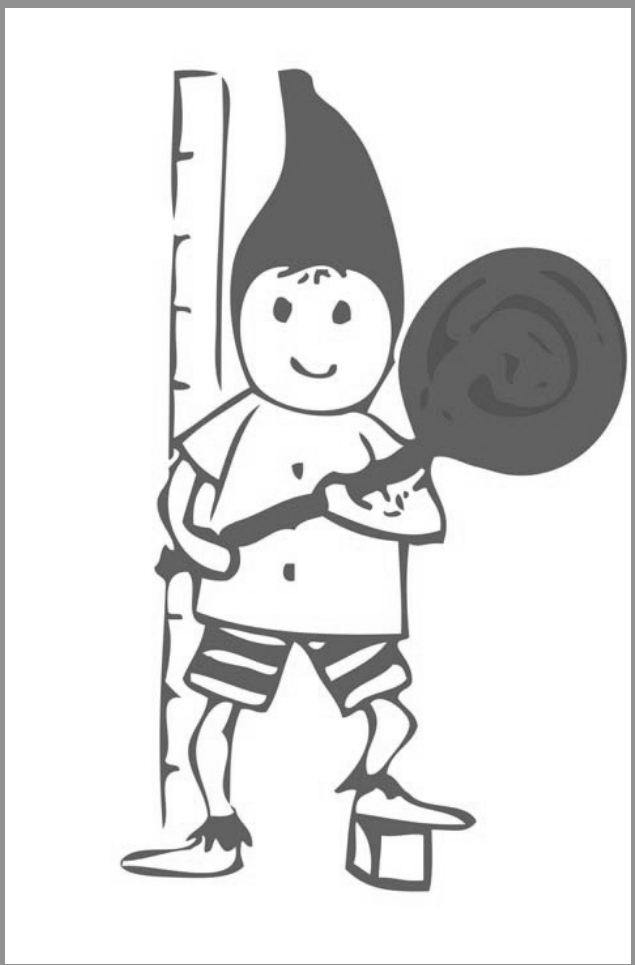
Chapter 9

English Summary



Jorien M. Kerstjens.

ENGLISH SUMMARY

General Introduction

The main goal of the research reported on is thesis was to establish developmental outcome in moderately preterm-born children at school-entry (age 4) and school age (age 7) and to determine which children in this group were at highest risk for developmental problems.

There is no consensus of opinion in international publications on the definition of "moderately preterm birth": the lower boundary varies from 32 to 34 weeks of gestation and the upper boundary varies from 34 to 37 weeks of gestation. In this thesis, we have defined moderately preterm birth as a birth between 32^{+0} and 35^{+6} weeks' gestation (moderate preterms). By contrast, "early preterm birth" or "very preterm birth" is defined precisely as birth before 32 weeks of gestation (early preterms). The incidence of moderately-preterm birth has risen considerably during the last decades. Moderate preterms now account for 70% to 85% of all preterm-born children, and equal 6% to 11% of all life births worldwide.

The increase in moderately preterm births is due to changes in obstetric care (more induced births in high-risk pregnancies), changes in the lifestyle of fertile women, including the increase of maternal obesity and delayed childbearing, and an increase in the rate of children conceived by artificial reproduction techniques.[16] The number of moderate preterms has also increased due to the assumption that inducing birth "a few weeks early" has no long-term consequences for the child. Moderate preterms are born in regional (secondary) hospitals, they appear relatively healthy at birth, have near normal birth weights, and usually only encounter mild postnatal morbidities before discharge. Because of the assumption of not being at increased developmental risk, their follow-up after discharge is transferred to routine monitoring in preventive child healthcare. They thereby contrast to early preterms, which are known to be at increased developmental risk compared to fullterm-born children (term-borns), and are therefore entered in structured, hospital–based follow-up programs after discharge.

Evidence is gradually emerging that the assumption of no increased developmental risk for moderate preterms was incorrect. More knowledge on the extent of problems in specific developmental domains for moderate preterms at school-entry and beyond, and more knowledge about which children within this

large group are at highest risk, may lead to improved chances for early detection in a subgroup followed by effective early intervention. Increased knowledge might also help to unravel possible underlying causal mechanisms.

The main aim of this thesis was, therefore, to establish developmental outcome in moderately preterm-born children at school-entry and at school age, and to determine which children in this group were at the highest risk of developmental problems. To examine developmental outcome, we first translated and validated a Dutch version of the 48 months form of the Ages and Stages Questionnaire (ASQ).

The main aim led to the following research questions;

1. What are the psychometric properties of the Dutch translation of the ASQ 48 months version? (*Chapter 2*)
2. Do moderately preterm-born children have more developmental problems at the age of four than fullterm-born children, which developmental domains are involved, and how do they compare to early preterm-born children? (*Chapter 3*)
3. What is the association between decreasing gestational age and risk of developmental problems at the age of four? (*Chapter 4*)
4. Which antenatal factors are associated with developmental problems in moderately preterm-born children at the age of four? (*Chapter 5*)
5. Which postnatal factors are associated with developmental problems in moderately preterm-born children at the age of four? (*Chapter 6*)
6. Do moderately preterm-born children have more neuropsychological and motor problems than fullterm-born children at the age of seven? (*Chapter 7*)

To achieve our goals we drew a stratified sample from a community-based cohort of 45,446 children aged 43-49 months, born in 2002 and 2003, from the catchment area of 13 Preventive Child Healthcare (PCH) organizations. This longitudinal cohort study is known in Dutch as “Pinkeltje” and as “LOLLIPOP” (Longitudinal Preterm Outcome Project) for international purposes. We selected all children born before a gestation of 36^{+0} weeks, plus a sample of term-born children (38^{+0}-41^{+6} weeks’ gestation). We did not sample children born at 36^{+0}-36^{+6} weeks’ gestation. Our decision to refrain from sampling children born at 36^{+0}-36^{+6} weeks’ gestation was

based on logistic reasons. We enriched the sample with early preterms children from five of the ten NICUs in the Netherlands, also born in 2003. Eventually, the PCHCs included 2,517 children at their last routine visit to the PCHC (43-49 months). Data on antenatal postnatal and socio-economic factors were collected from a general parental questionnaire at inclusion (age 4), from medical records (kept by NICUs and PCH clinics) as well as from national registers (PRN). As outcome measure. Data on developmental problems were collected with the Ages and Stages Questionnaire (ASQ) at school-entry and neuropsychological tests for a subgroup at school age (age 7).

Psychometric properties of the ASQ.

The Ages and Stages Questionnaire (ASQ) is a parent-completed developmental screening measure (sometimes called a developmental screener), which has been developed in the United States in 1980-1990. The ASQ is currently one of the most widely used developmental measures in preventive child healthcare in the United States of America as a first screening tool to identify children whose development may be at risk.

We evaluated the psychometric properties of the Dutch translation of the ASQ 48 months form, before using it as outcome measure in our research project (*chapter 2)*. We found excellent psychometric properties for the Dutch ASQ 48 months version. In an expert panel of professionals and parents, we found no problems regarding content validity or cultural appropriateness of the Dutch ASQ version. The Cronbach alphas, a measure of internal consistency were high on ASQ total-problems and acceptable on all ASQ domains. The mean Dutch ASQ domain scores were remarkably similar to the mean scores from other countries, with only three out of fifteen between-country comparisons showing clinically relevant differences. Construct validity of the Dutch ASQ version was confirmed by the fact that preterm-born children, boys, children from low income families and children of low-educated mothers more often had abnormal ASQ scores. Finally, the predictive validity of the Dutch ASQ version at age 4 was excellent for special education a year later at age 5, and good for special educational needs at age 5. Furthermore, fullterm-born boys had abnormal ASQ scores more often than fullterm-born girls. Our finding of excellent psychometric properties of the Dutch ASQ version were in line with several other validation ASQ studies and therefore strongly support the feasibility

of the Dutch ASQ as developmental screener. The ASQ might be a cheap and easy to complete additional measure to screen for developmental problems in both the PCHC and general pediatric setting.

Development of moderate preterms at age 4, comparison with other gestational groups, and pattern of association

Evidence lacked on the extent to which moderate preterms may have problems in the various developmental domains at school-entry. This contrasts with early preterms, for whom evidence was abundant. For early preterms, 40 to 60% had been shown to have problems with lower IQs and neuropsychological functioning (such as memory) at school-entry and at school age.

In *Chapter 3*, We showed that moderate preterms had roughly twice the rate of developmental problems when compared to fullterm-born children, and approximately half that of early preterms. The percentage of children with developmental problems was 8.3% for moderate preterms, 4.2% for fullterms , and 14.9% for early preterms. In the Netherlands, at age 4, because the group is so much larger, there will be twice as many moderate preterms as early preterms with developmental problems. In the domains fine motor functioning, communication, and personal-social skills moderate preterms had problems more often than fullterms, but less often than early preterms. As a group moderate preterms did not encounter problems in gross motor functioning or problem-solving more often than fullterms, whereas early preterms did.

We found an exponential association between decreasing gestational age (per week gestation) and the risk of developmental delay at school-entry (*chapter 4*). Developmental problems concerned problems on the ASQ-total score, and on all ASQ domains, and remained unaltered after adjustment for several confounders. This implies that there is no “safe” preterm gestational threshold above which preterm birth will not have developmental consequences, and also that preterm birth at the threshold of viability will have the largest consequences by far.

Association with antenatal factors.

Previous research has shown that several antenatal factors, both fetal and maternal, increased the risk of moderately-preterm birth, neonatal mortality, and early neonatal morbidity before discharge. These factors included maternal age, maternal

hypertension, maternal antepartum hemorrhage, maternal obesity, gestational diabetes, male gender, intrauterine growth retardation (IUGR), multiple pregnancy, lower gestational age within the moderately preterm range, chorioamnionitis, lack of antenatal steroid administration, and (emergency) Cesarean section. For early preterms, we already knew that several of these same factors are also associated with developmental outcome, but we did not know if we could extrapolate in the early preterm group to the moderately preterm group, because moderate preterms are less preterm, and are born for different reasons than early preterms. For moderate preterms we found that three fetal factors, i.e. small for gestational age (SGA), male gender, being one of a multiple, as well as one maternal pre-existing factor (pre-pregnancy obesity) were associated with a higher risk of developmental problems at the age of four. We found no association between any pregnancy-related or delivery-related factors and the risk of developmental problems among moderate preterms. (*chapter 5*).

The three fetal factors that were associated with the risk of developmental problems, i.e. SGA, male gender, and being one of a multiple birth, were also found to associate with developmental risks in early preterms and in fullterm-born children,[30-31] and are, therefore, not unique for moderate preterms.

The first fetal factor we found to be associated with developmental risk was SGA. Even though SGA remains only a proxy for IUGR, chronic deficits in nutritional and oxygen requirements during the fetal period leading to intra-uterine growth restriction may permanently alter brain structure, and therefore be associated with developmental problems. The second fetal factor we found to be associated with developmental risk was male gender, which probably reflects both an increased biological risk, as well as an increased risk of neonatal complications, as also seen in early preterms. The third fetal factor we found to be associated with developmental risk was being part of a multiple. Our study therefore contradicts the hypothesis that the higher developmental risk of multiples is completely explained by prematurity and IUGR. The final antenatal factor associated with developmental risk concerned maternal pre-pregnancy obesity. The mechanisms underlying the effect of maternal obesity on the development of offspring are not completely understood, but might include residual environmental factors despite controlling for SES and lifestyle,[39] genetic and metabolic causes, and chronic low grade placental inflammation.

In summary, this implies that being born a few weeks early is especially associated with risk of developmental problems for boys, multiples, intra-uterine growth-restricted children and children of obese mothers.

Associations between postnatal factors and developmental risk.

Moderate preterms have a relatively high rate of non-severe "common" neonatal morbidities, including (mild) asphyxia, respiratory insufficiency, circulatory insufficiency, septicemia, hypoglycemia, hyperbilirubinemia, apnea, hypothermia, and feeding problems. Only a few of these morbidities are severe enough to warrant admission to a tertiary NICU. For all of these morbidities there was a lack of knowledge on associations with (long term) developmental consequences for moderate preterms.

We found that for a range of postnatal factors, only hypoglycemia (defined as at least one documented glucose value below 1.7 mmol/l) was associated with a higher risk of developmental problems at age 4 for moderate preterms (*Chapter 6*).

Concerning hypoglycemia, we found a dose response effect between lowest glucose value and risk of developmental problems with a steeper incline below 1.7mmol/l. We found no association between any other common neonatal morbidity (respiratory or circulatory insufficiency, asphyxia, hyperbilirubinemia, septicemia, low Apgar score, apnea, caffeine treatment) or NICU-admission and developmental problems at school-entry among moderate preterms. This lack of association contrasts to the findings for early preterms.

The fact that only hypoglycemia was associated with developmental problems refutes the common assumption, that "those moderate preterms sick enough to be admitted to a NICU will be the ones with developmental problems later on". The association we found between hypoglycemia and developmental risk might also have important implications if replicated in prospective trials aiming at reducing the incidence of hypoglycemia after moderately preterm birth.

Development of moderate preterms at age 7.

Apart from the fact that we found moderate preterms to have more developmental problems at age 4, we also wanted to know if developmental problems would persist at school age. We found that when they were seven years old, moderate preterms scored worse than fullterms on tests of total intelligence, performance intelligence, visuospatial reasoning, attention control, inhibition,

and executive functioning, but not on tests of verbal intelligence, verbal memory, and visuomotor and motor skills. Differences were largest for visuospatial reasoning and executive functioning (up to one-third SD). Furthermore, moderate preterms were at increased risk of clinically significant poor scores (< P10) on measures of intelligence, visuospatial reasoning and executive functioning. Using gender-specific norms, moderately preterm-born boys performed poorer than fullterm-born boys only on visuospatial reasoning, whereas moderately preterm-born girls performed significantly worse than fullterm-born girls on visuspatial reasoning, intelligence, aspects of attention, and executive functioning.

Despite the larger z score differences for moderately preterm-born girls, at the age of seven the scores of moderately preterm-born girls were not worse than those of moderately preterm-born boys. This might be explained in terms of the general developmental disadvantage of fullterm-born boys compared to fullterm-born girls at age four mentioned previously. This would suggest that moderately preterm-born girls lose some of their gender advantage. Our results of more neuropsychological problems for moderate preterms at age 7 are in agreement with several recent studies which all found increased rates of school problems and special educational needs for moderate or late preterms at school age, and give more insight into the neuropsychological domains involved. These findings at age 7 also confirm that developmental problems of moderate preterms may persist after school-entry and imply that early intervention might be worthwhile, especially aiming at enhancing visuospatial reasoning, attention, and executive functioning.

Implications

The studies as presented in this thesis, have three important implications for the care for moderate preterms: increasing awareness of the developmental consequences of moderately preterm birth, enhanced prevention of moderately preterm birth (including reducing numbers of multiples) and structured monitoring of moderate preterms.

First and foremost, our findings refuted the assumption that being born “just a few weeks early” or “near term” does not have developmental consequences. By implication, obstetricians, parents, and pediatricians should more often weigh the possible long-term disadvantages against short-term postnatal advantages of induced preterm birth. In the same line, we might perhaps want to reconsider the strict definitions of early preterm, moderately preterm, near-term, early-term, etc.

as if they are really separate entities; it muddles the issue. In fact, there is no “safe” preterm gestational threshold beyond which preterm birth may not have developmental consequences.

Second, enhancing prevention of moderate preterm birth should concern both primary and secondary prevention. Primary prevention includes lifestyle changes and reducing the number of multiples in multiple births. Promoting a healthy lifestyle in fertile and pregnant women might include attempts at reducing maternal obesity and unhealthy lifestyles associated with the risk of IUGR, such as smoking and alcohol. This shift towards primary prevention is in agreement with recent recommendations of the American College of Obstetricians and Gynecologists. An attitude change in subfertility treatments aiming at reducing the number of multiples might form another challenge. In this respect we also need to encourage mothers to consider bearing their children at an earlier age, thus reducing artificial fertilization requests. Secondary prevention aims at reducing iatrogenic births whenever possible, but short-term and long-term benefits and the risks for child and mother will always have to be weighed against each other when inducing delivery before term. All these measures will serve a double purpose as they will lead to fewer moderately preterm births and fewer children with developmental consequences of their moderately preterm birth.

Third, structured monitoring also implies a shift in attitude. Our results imply that moderate preterms deserve more attention than they have received till now in follow-up care. Early identification of moderate preterms at the highest risk, based on antenatal, postnatal and sociodemographic factors, could lead to a labeling of moderate preterms at “ increased risk’”. Increased attention for this group could lead to more timely identification, followed by possibilities for early intervention. Hopefully, we will also find ways to intertwine the efforts of obstetricians, neonatologists, PCH physicians and pediatricians to combine patient care, with follow-up care for research purposes, for the large group of moderate preterms in an appropriate and cost-effective manner.

Future perspectives

Future perspectives concern further clinical research, early intervention after discharge, assessment of the feasibility of using the ASQ in the PCH setting, and a revision of the current views on effective follow-up of preterm-born children.

First, regarding clinical research, the associations with developmental risk for moderate preterms that we found in our cohort study, should be replicated in large prospective studies with detailed information from both obstetricians and pediatricians with long follow-up (up till school age).

Second, more insight is needed into the efficacy of early intervention strategies after discharge. We now aim all our efforts at preventing preterm birth and its short-term complications before discharge home, with expensive high-tech interventions, and spend relatively little effort and money on intervention strategies (in the home setting) after discharge , which potentially might be just as worthwhile.

Third, prospective trials are needed on the introduction of the ASQ as additional measure to monitor development in preterm-born children in both the pediatric and the PCH setting. These trials should study feasibility, efficacy, and reliability in routine practice. The availability to issue one or several ASQs as additional measure besides the Van Wiechen Schema and the clinical evaluation by the PCH physician and/or pediatrician, might enhance chances of early detection, and referral during the window of opportunity for early intervention.

Finally with regard to follow-up, the findings reported on in this thesis constitute an invitation to rethink our whole preterm follow-up system. Up till now, we have followed only early preterm-born children in a structured manner, because their risks are well known and they are an easily accessible group. Perhaps we should start thinking about a more globally targeted follow- up, in which we combine care and research on larger groups of preterm-born children at risk for developmental problems in a more cost-effective manner. This requires better collaboration between obstetricians, neonatologists, general pediatricians, and PCH physicians, as resources dwindle, and rates of preterms continue to rise. This might be doable, but involves a shift of focus, a shift of resources, implementation studies, and structured collaboration between all disciplines involved.

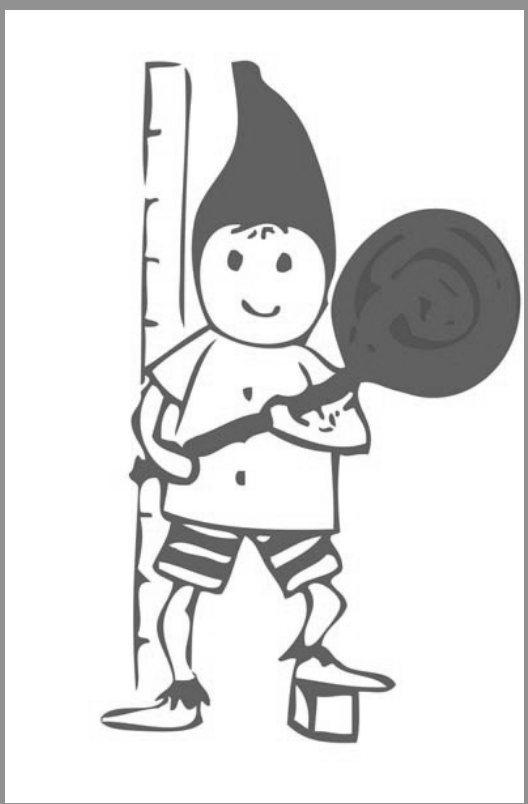
As worldwide an estimated 6- 11% of all children are born early or moderately preterm, we should encourage further research on optimal treatment before and after preterm birth. This fits in the recent call for action (European white paper) on prevention of preterm birth and its consequences.

Chapter 10

Nederlandse Samenvatting

Dankwoord

Lijst JGZ Instellingen



Jorien M. Kerstjens.

SAMENVATTING

Het hoofddoel van dit proefschrift was het vaststellen van ontwikkelingsuitkomsten op de leeftijd van 4 jaar (start school) en 7 jaar (schoolleeftijd) voor "matig te vroeg" geboren kinderen en daarnaast het bepalen welke kinderen in deze groep het hoogste risico lopen.

"Matige vroeggeboorte" wordt op verschillende manieren gedefinieerd in de internationale literatuur. In dit proefschrift hebben we er voor gekozen om matige vroeggeboorte te definiëren als geboorte tussen 32^{+0} en 35^{+6} weken zwangerschapsduur (matig te vroeg geboren kinderen). Dit komt overeen met 4 tot 8 weken te vroeg. Matige vroeggeboorte contrasteert met "veel te vroege vroeggeboorte", waarvan de definitie is vastgesteld op geboorte vóór 32 weken zwangerschapsduur (veel te vroeg geboren kinderen).

De incidentie (hoe vaak het voorkomt) van matige vroeggeboorte is in de laatste decennia sterk toegenomen. Op dit moment zijn 70% tot 85% van alle kinderen die te vroeg geboren worden matig te vroeg geboren kinderen, wat overeenkomt met 6% tot 11% van alle levend geboren kinderen wereldwijd. De toename in de incidentie van matige vroeggeboorte is een gevolg van frequenter obstetrisch ingrijpen in hoog-risico zwangerschappen, veranderingen in gezondheidsgedrag van vrouwen in de vruchtbare leeftijd, toename van de leeftijd waarop vrouwen zwanger worden, en een toename van het aantal kinderen geboren met behulp van kunstmatige reproductie (voortplantings) technieken. De toename in incidentie is daarnaast ook een gevolg van de veronderstelling dat het "een paar weken" voor de uitgerekende datum opwekken van de geboorte geen consequenties heeft voor de ontwikkeling van het kind later.

Matig te vroeg geboren kinderen worden grotendeels geboren in regionale ziekenhuizen, zien er bij de geboorte relatief gezond uit, hebben een bijna normaal geboortegewicht, en hebben meestal geen ernstige complicaties waarvoor ze moeten worden opgenomen op een neonatale intensive care unit (NICU). Na ontslag worden ze – vanwege de veronderstelling van geen verhoogd risico op ontwikkelingsproblemen – al snel overgedragen aan de preventieve jeugdgezondheidszorg. Dit is in tegenstelling tot de nazorg voor veel te vroeg geboren kinderen die na ontslag geprotocolleerd plaatsvindt in academische ziekenhuizen juist vanwege het bekende verhoogde ontwikkelingsrisico.

In de laatste tien jaar is er toenemende zorg dat de aanname over de afwezigheid van een verhoogd ontwikkelingsrisico voor matig te vroeg geboren

kinderen wel eens onjuist zou kunnen zijn. Uitbreiding van de kennis over de mate waarin problemen voorkomen op specifieke ontwikkelingsdomeinen voor matig te vroeg geboren kinderen bij het naar school gaan en daarna, en van de kennis over welke kinderen in deze grote groep het hoogste risico lopen, kan aangrijpingspunten opleveren voor een betere vroeg-opsporing (gevolgd door vroegbehandeling) voor de subgroep met de grootste kans op problemen in de ontwikkeling. Toegenomen kennis kan ook helpen om onderliggende oorzaken en mechanismen te ontrafelen.
Het hoofddoel van dit proefschrift was dan ook het vaststellen van ontwikkelings-uitkomsten voor matig te vroeg geboren kinderen bij het naar school gaan en later, alsook bepalen welke kinderen in deze groep het hoogste risico lopen.
Als instrument voor het vast stellen van ontwikkelingsuitkomsten hebben we gekozen voor de “Ages and Stages Questionnaire” (ASQ). We hebben eerst de 48-maanden versie van de ASQ vertaald in het Nederlands en gevalideerd, voordat we hem konden gebruiken in ons verdere onderzoek.

Dit hoofddoel leverde de volgende onderzoeksvragen.

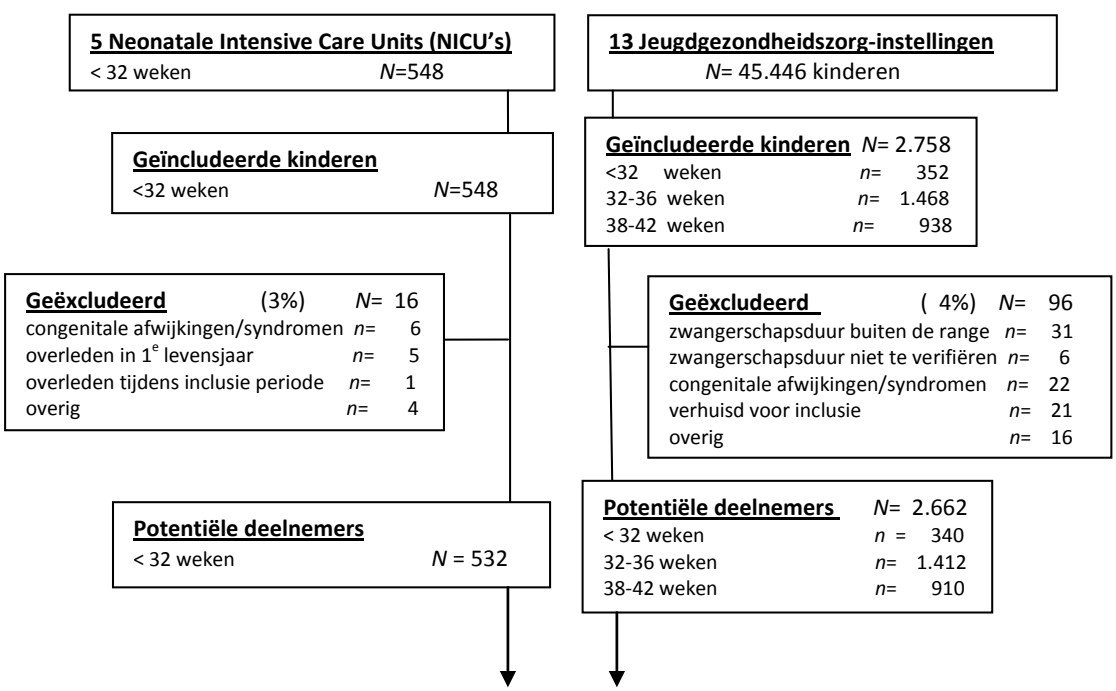
1. Wat zijn de psychometrische eigenschappen van de Nederlandse vertaling van de 48 maanden versie van de ASQ?
2. Hebben matig te vroeg geboren kinderen meer ontwikkelingsproblemen dan op tijd geboren kinderen op de leeftijd van 4 jaar, welke domeinen betreft dit, en hoe zijn ze te vergelijken met veel te vroeg geboren kinderen?
3. Wat is het verband tussen afnemende zwangerschapsduur en risico op ontwikkelingsproblemen op de leeftijd van 4 jaar?
4. Welke antenatale factoren zijn voor matig te vroeg geboren kinderen geassocieerd met ontwikkelingsproblemen op de leeftijd van 4 jaar?
5. Welke postnatale factoren zijn voor matig te vroeg geboren kinderen geassocieerd met ontwikkelingsproblemen op de leeftijd van 4 jaar?
6. Hebben matig te vroeg geboren kinderen meer neuropsychologische en motorische problemen dan op tijd geboren kinderen op de leeftijd van 7 jaar?

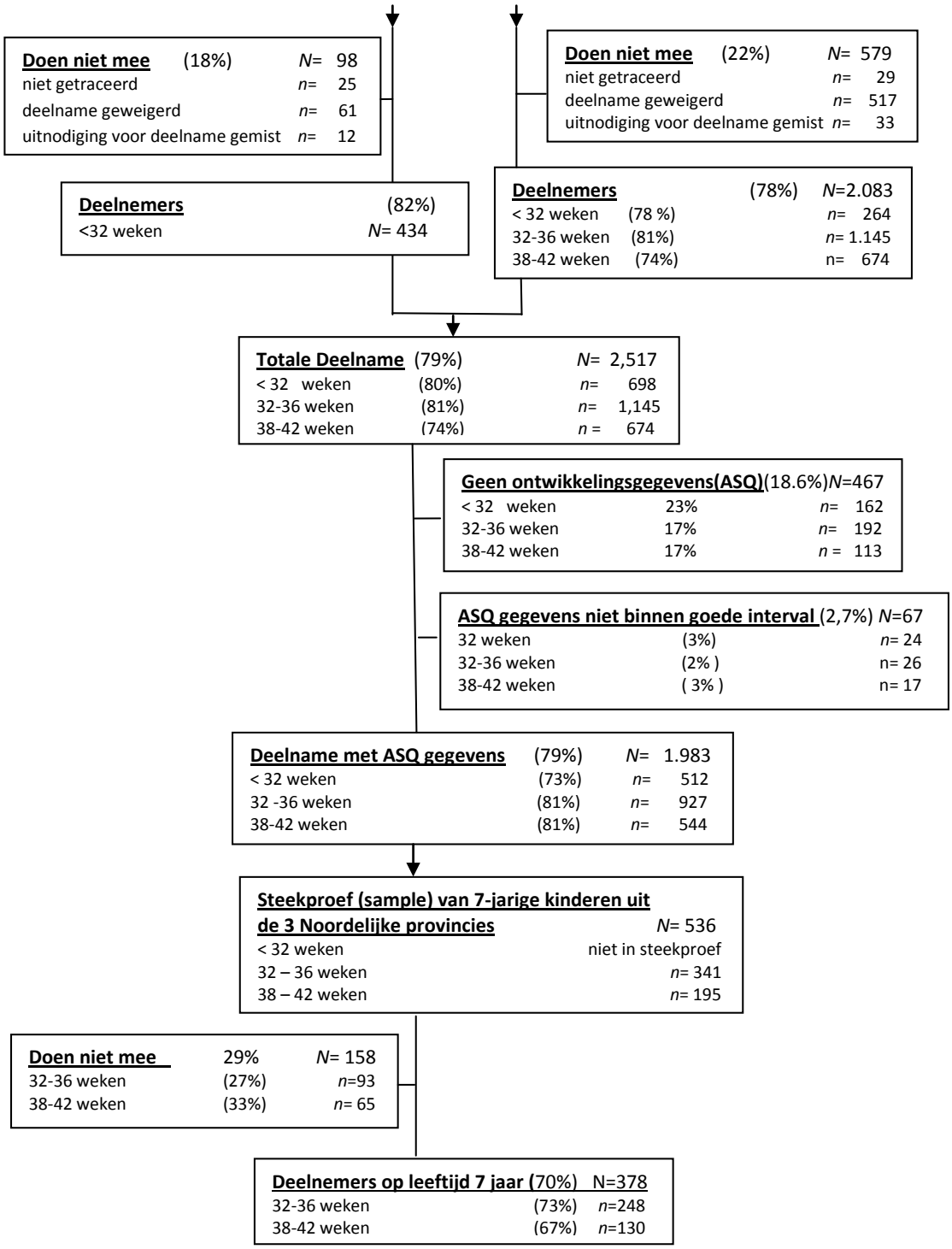
Om antwoord te krijgen op onze vragen hebben 13 Nederlandse instellingen voor Jeugdgezondheidszorg (JGZ) een gelaagde steekproef voor ons genomen uit een jaarcohort van kinderen geboren in 2002 of 2003. De dossiers van alle kinderen geboren in één jaar werden bekeken. Om logistieke redenen was dit per JGZ instelling van 1 januari 2002 t/m 31 december 2002 of van 1 juni 2002 t/m 31 mei 2003.

In totaal waren dit 45.446 dossiers. Alle kinderen geboren met een zwangerschapsduur van minder dan 36 weken, zonder congenitale afwijkingen, infecties of syndromen werden geïncludeerd. Na iedere twee te vroeg geboren kinderen werd het eerstvolgende op tijd geboren kind uit dezelfde kaartenbak (zwangerschapsduur 38- 42 weken) zonder bovenstaande exclusiecriteria, als 'controle' geïncludeerd. Dit prospectieve cohort onderzoek staat in Nederland bekend als "Pinkeltje" en heeft later voor internationale publicaties de naam "LOLLIPOP" (Longitudinal Preterm Outcome Project) gekregen.

Om ook voldoende veel te vroeg geboren kinderen in ons onderzoek te betrekken, hebben we deze steekproef verrijkt met alle veel te vroeg geboren kinderen die geboren waren tussen 1 januari 2003 en 31 december 2003 in vijf van de tien Nederlandse NICU's, voor zover ze niet ook al in de steekproef van de JGZ instellingen waren opgenomen. Ook deze kinderen zijn geincludeerd via de JGZ.

De JGZ instellingen hebben voor ons de ouders van al deze geselecteerde kinderen (*N*=3306) benaderd tijdens hun laatste geplande bezoek aan het consultatie-bureau op de leeftijd van 43-49 maanden. Uiteindelijk hebben er van deze selectie 2517 kinderen meegedaan aan het Pinkeltje onderzoek, waarvan de ouders van 2050 kinderen niet alleen aan het onderzoeksdeel over groei hebben meegedaan maar ook aan het onderzoeksdeel over ontwikkeling. Inclusie procedures zijn weergegeven in **figuur 1**.





Figuur 1. Overzicht van inclusie procedures voor de Pinkeltje studie.

De ouders van deze kinderen hebben voor hun bezoek aan het consultatiebureau een algemene vragenlijst over antenatale, postnatale en sociaaldemografische kenmerken ingevuld. Daarnaast hebben ze de ASQ ingevuld. Verder hebben we gegevens van deze kinderen opgevraagd bij de regionale en academische ziekenhuizen (*N*=60) waar de kinderen na hun geboorte waren opgenomen, en bij alle betrokken jeugdgezondheidszorg (JGZ) instellingen. Door de toevoeging van de veel te vroeg geboren kinderen vanuit de NICU's hebben uiteindelijk 46 JGZ instellingen in Nederland met één of meerdere kinderen meegedaan. Ook hebben we gegevens over de kinderen en hun moeders verzameld uit de geboorteregisters van de "Perinatale Registratie Nederland" (PRN). Tenslotte zijn de matig te vroeg geboren en op tijd geboren kinderen uit de drie noordelijke provincies (Groningen, Friesland en Drenthe) neuropsychologisch getest op de leeftijd van 7 jaar (*N*=378).

Psychometrische eigenschappen van de Nederlandse 48 maanden versie van de ASQ.
De "Ages and Stages Questionnaire" (ASQ) is een vragenlijst waarmee de voortgang van de ontwikkeling van kinderen vanaf 2 maanden tot 5 jaar kan worden vervolgd. Voor de verschillende leeftijden zijn er aparte versies. Deze vragenlijst is ontwikkeld in de USA tussen 1980 en 1990 en wordt ook wel een "ontwikkelings-screener" genoemd. De ASQ kan door ouders thuis worden ingevuld. De ASQ wordt zeer frequent gebruikt in de Amerikaanse preventieve jeugdgezondheidszorg om kinderen te identificeren die een verhoogd risico hebben op ontwikkelingsproblemen. We hebben de ASQ 48 maanden versie professioneel laten vertalen en vervolgens de psychometrische (test) eigenschappen van deze versie van de ASQ onderzocht, alvorens deze vragenlijst te gebruiken als uitkomstmaat in ons onderzoek *(hoofdstuk 2).*

In een panel van experts (professionals en ouders) vonden we geen problemen wat betreft inhoudsvaliditeit en culturele geschiktheid van de items. Cronbach alpha's als maat voor interne consistentie waren hoog voor de ASQ-totaal score en voldoende hoog voor alle domeinscores. De gemiddelde Nederlandse ASQ scores kwamen opmerkelijk overeen met de gemiddelde scores in andere landen, waarbij maar drie van de 15 paarsgewijze vergelijkingen van scores voor verschillende landen klinisch relevante verschillen lieten zien. De begripsvaliditeit van de Nederlandse vertaling van de ASQ was goed, overeenkomstig die van de Amerikaanse versie, blijkend uit het feit dat te vroeg geboren kinderen, jongens, kinderen uit laag inkomen gezinnen, en kinderen van laag opgeleide moeders vaker afwijkende

ASQ resultaten hadden. En tenslotte werd de goede predictieve (voorspellende) validiteit bevestigd door het feit dat de uitkomsten op de Nederlandse ASQ op de leeftijd van 4 jaar uitmuntend voorspelden welke kinderen op de leeftijd van 5 jaar speciaal onderwijs volgden, en goed voorspelde welke kinderen op de leeftijd van 5 jaar extra hulp nodig hadden op school (rugzakje).

De uitstekende psychometrische eigenschappen die we vonden voor de Nederlandse versie van de ASQ komen overeen met de bevindingen in meerdere andere validatie studies van een vertaalde versie van de ASQ, en ondersteunen daarmee de bruikbaarheid van de Nederlandse ASQ als ontwikkelings-screener. De ASQ kan een goedkope en makkelijk inzetbare aanvulling vormen bij de vroege opsporing (voegsignalering) van ontwikkelingsproblemen in de JGZ en in algemene kindergeneeskundige settings.

Ontwikkeling van matig te vroeg geboren kinderen op de leeftijd van 4 jaar in vergelijking met veel te vroeg en op tijd geboren kinderen.

Er is weinig bekend over de mate waarin matig te vroeg geboren kinderen problemen hebben op verschillende ontwikkelingsdomeinen op het moment dat zij voor het eerst naar school gaan. In tegenstelling daarmee, was het voor veel te vroeg geboren kinderen wel bekend dat 40% tot 60% problemen heeft met een lager IQ of problemen heeft op specifieke neuropsychologische domeinen (zoals geheugen) bij het naar school gaan, alsook op latere schoolleeftijd. In *hoofdstuk 3* laten we zien dat ontwikkelingsproblemen bij het naar school gaan van matig te vroeg geboren kinderen twee keer zo vaak voorkomen als bij op tijd geboren kinderen, en ongeveer half zo vaak als bij veel te vroeg geboren kinderen. Matig te vroeg geboren kinderen hadden vaker problemen met fijne motoriek, communicatie en persoonlijk sociaal functioneren (functioneren in een groep). Matig te vroeg geboren kinderen hadden niet vaker problemen dan op tijd geboren kinderen met grove motoriek of probleem oplossen, wat bij veel te vroeg geboren kinderen wel het geval was. Concluderend hadden matig te vroeg geboren kinderen op meerdere domeinen vaker problemen, wat zich ook vertaalde in meer afwijkende ASQ-*totaal* scores vergeleken met op tijd geboren kinderen.

Deze resultaten hebben twee implicaties. Ten eerste dat in absolute aantallen (omdat de groep zoveel groter is) er minstens twee keer zoveel matig te vroeg geboren kinderen als veel te vroeg geboren kinderen met ontwikkelingsproblemen zijn op de

leeftijd van 4 jaar in Nederland. Ten tweede, dat matig te vroeg geboren kinderen meer aandacht verdienen qua follow-up dan dat zij nu gewoonlijk krijgen.

Deze uitkomsten resulteerden vervolgens ook in de vraag of risico op ontwikkelingsproblemen lineair toeneemt met afnemende zwangerschapsduur, of dat er een soort drempelwaarde bestaat bij een bepaalde zwangerschapsduur. In *hoofdstuk 4* tonen we aan dat het risico op ontwikkelingsproblemen exponentieel toeneemt met afnemende zwangerschapsduur tussen 25 en 36 weken. Ontwikkelingsproblemen betroffen hierbij de ASQ-totaal score en scores op alle onderliggende ASQ domeinen. Deze resultaten veranderden niet na correctie voor meerdere confounders. Dit impliceert dat er geen "veilige" grens is wat betreft zwangerschapsduur, waarboven vroeggeboorte niet kan leiden tot ontwikkelingsproblemen, en daarnaast dat extreme vroeggeboorte op de grens van de levensvatbaarheid bij uitstek de grootste kans op gevolgen zal hebben qua ontwikkeling.

Samenhang met antenatale factoren.

Eerder onderzoek heeft aangetoond dat meerdere pre-existente factoren van de moeder en meerdere zwangerschapsgerelateerde factoren het risico op matige vroeggeboorte, neonatale mortaliteit en vroege neonatale complicaties na de geboorte verhogen. Deze factoren betreffen onder meer leeftijd van de moeder, hypertensie (hoge bloeddruk), bloedverlies voor de geboorte, obesitas, (zwangerschaps)diabetes van de moeder, mannelijk geslacht van het kind, intra-uteriene groeiachterstand (IUGR), meerlingzwangerschap, lagere zwangerschaps-duur (binnen de range van matige vroeggeboorte), ontsteking van de vruchtvliezen (chorioamnionitis), niet toegediend zijn van steroïden voor de geboorte, en (spoed)keizersnede. Voor vroege prematuren was al bekend dat meerdere van deze factoren eveneens geassocieerd waren met ontwikkelingsproblemen later. Het was echter niet bekend of we deze kennis konden extrapoleren naar matig te vroeg geboren kinderen, omdat matig te vroeg geboren kinderen minder te vroeg geboren worden, en om andere redenen te vroeg geboren worden dan veel te vroeg geboren kinderen.

We vonden een samenhang tussen meerdere kenmerken van het kind en obesitas van de moeder en ontwikkelingsrisico voor matig te vroeg geboren kinderen (*hoofdstuk 5*). Verder was geen enkele andere maternale zwangerschaps-gerelateerde of bevallings-gerelateerde factor in ons onderzoek geassocieerd met ontwikkelings-

problemen later. De drie kind-factoren die bleken samen te hangen met het risico op ontwikkelingsproblemen waren dysmaturiteit (Small for Gestational Age, SGA), mannelijk geslacht, en het zijn van een deel van een meerling. Deze drie kind-factoren hangen ook bij veel te vroeg geboren kinderen en bij op tijd geboren kinderen samen met ontwikkelingsproblemen, en zijn daarmee niet uniek voor deze groep.

De eerste kind-factor die samenhing met ontwikkelingsrisico was SGA. Chronische tekorten in zuurstof en voedingsstoffen tijdens de foetale periode die leiden tot SGA kunnen mogelijk de groei en opbouw van het brein blijvend beïnvloeden, en daardoor ook leiden tot ontwikkelingsproblemen. De tweede kind-factor die samenhing met ontwikkelingsrisico was een mannelijk geslacht, wat waarschijnlijk wordt veroorzaakt door zowel een hoger biologisch risico, als door een verhoogd risico op postnatale complicaties, net zoals bij veel te vroeg geboren kinderen. De derde kind-factor die samenhing met ontwikkelingsrisico was het deel zijn van een meerling. Onze studie weerlegt daarmee de hypothese dat het verhoogd ontwikkelingsrisico van meerlingen volledig wordt verklaard door vroeggeboorte en intra-uteriene groei restrictie (IUGR). De laatste antenatale factor die samenhing met ontwikkelingsrisico was obesitas van de moeder tijdens de zwangerschap. Onderliggende mechanismen die het effect van obesitas van de moeder op de ontwikkeling van het kind verklaren zijn nog niet geheel duidelijk. Deze mechanismen zouden gerelateerd kunnen zijn aan een residu van omgevingsfactoren ondanks het controleren voor sociaaleconomische status en leefstijl factoren, genetisch of metabool bepaald kunnen zijn, of gerelateerd kunnen zijn aan een chronische “low grade” infectie van de moederkoek.

Samenvattend impliceren onze resultaten dat “een paar weken te vroeg” geboren worden met name voor jongetjes, meerlingen , groeivertraagde kinderen, en kinderen van obese moeders samenhangt met een verhoogd risico op ontwikkelings-problemen.

Associaties met postnatale factoren

Matig te vroeg geboren kinderen hebben een relatief hoge incidentie van niet ernstige, veel voorkomende neonatale problemen zoals zuurstoftekort tijdens de geboorte, respiratoire en/of circulatoire insufficiëntie (problemen met de bloeddruk of ademhaling), sepsis (infectie in het bloed), hypoglycemie (lage glucosewaarde in het bloed) , hyperbilirubinemie (geelzien), apneu (stoppen met ademen), onder-

temperatuur en voedingsproblemen. Slechts een beperkt aantal van deze problemen zijn ernstig genoeg om te resulteren in opname op een NICU. Van geen enkele van deze postnatale problemen wisten we of ze samenhingen met latere ontwikkelingsproblemen van matig te vroeg geboren kinderen. In *hoofdstuk 6* rapporteren we dat van een groot aantal postnatale problemen alleen hypoglycemie (gedefinieerd als minstens één gedocumenteerde glucose waarde onder de 1,7 mmol/l) samenhing met een verhoogd risico op ontwikkelingsproblemen op de leeftijd van 4 jaar voor matig te vroeg geboren kinderen. Wat betreft hypoglycemie vonden we bovendien een dosis-response effect tussen laagste gemeten glucose waarde en kans op ontwikkelingsproblemen, met een sterker verband bij waarden onder de 1,7 mmol/l. We vonden voor geen enkele ander veel voorkomend neonataal probleem (respiratoire of circulatoire insufficiëntie, asfyxie, geelzien, sepsis, lage Apgar score, apneu, behandeling met coffeïne) een verband met ontwikkelingsproblemen op de leeftijd van 4 jaar, en ook niet voor opname op de NICU, bij matig te vroeg geboren kinderen. Dit ontbreken van andere factoren die samenhangen met ontwikkelingsproblemen later contrasteert met de bevindingen hierover bij veel te vroeg geboren kinderen.

Het feit dat alleen hypoglycemie samenhing met ontwikkelingsproblemen weerlegt de algemene veronderstelling dat vooral de matig te vroeg geboren kinderen die zo ziek zijn dat opname op een NICU nodig was, degenen zullen zijn met problemen later. Dit kan belangrijke consequenties hebben voor zorg en preventie voor deze groep in de toekomst. Bevestiging in prospectief onderzoek is daarom gewenst.

Ontwikkeling op de leeftijd van 7 jaar.

We vonden dat matig te vroeg geboren kinderen meer ontwikkelingsproblemen hadden op de leeftijd van 4 jaar, maar we wilden vervolgens ook weten of deze problemen bleven bestaan op latere school leeftijd (7 jaar). In *hoofdstuk 7* beschrijven we dat matig te vroeg geboren kinderen slechter scoren dan op tijd geboren kinderen op testen van algemene intelligentie, visuospatieel redeneren, aandacht, en executieve functies, maar niet op testen van verbale intelligentie, verbaal geheugen, en (visuo)motorische vaardigheden. Executieve functies omvatten hogere controle functies van de hersenen zoals plannen, bijsturen, prioriteren, en gedrag en acties aanpassen aan een situatie. Visuospatieel redeneren omvat het mentaal manipuleren van visueel-ruimtelijke informatie, een voorbeeld hiervan is het reconstrueren van een blokpatroon of het leggen van een puzzel. De verschillen waren het grootst voor

visuospatieel redeneren (tot een derde standaard deviatie) en executieve functies. Matig te vroeg geboren kinderen hadden ook vaker klinisch relevante lage scores (< P10) op onderdelen van intelligentie, visuospatieel redeneren en executieve functies. Gemeten aan specifieke normen voor jongens en meisjes, bleken matig te vroeg geboren jongens alleen slechter te scoren op visuospatieel redeneren ten opzichte van op tijd geboren jongens, terwijl matig te vroeg geboren meisjes slechter scoorden op visuospatieel redeneren, intelligentie, onderdelen van aandacht en executieve functies ten opzichte van op tijd geboren meisjes. Ondanks de grotere verschillen tussen matig te vroeg en op tijd geboren meisjes, scoorden matig-vroeggeboren meisjes niet slechter dan matig-vroeggeboren jongens op de leeftijd van 7 jaar. Dit komt doordat op tijd geboren jongens gemiddeld een tragere ontwikkeling hebben dan op tijd geboren meisjes. Het kan worden geïnterpreteerd als dat matig te vroeg geboren meisjes een deel van hun 'geslachtsvoordeel' verliezen.

Onze resultaten wat betreft meer neuropsychologische problemen bij matig te vroeg geboren kinderen op de leeftijd van 7 jaar komen overeen met die van meerdere recente studies die allemaal een verhoogd percentage school problemen en/of van noodzaak van extra begeleiding op school (rugzakje) hebben gevonden voor matig te vroeg geboren kinderen, en leveren meer inzicht in de ontwikkelings-domeinen die hierbij betrokken zijn. Onze resultaten op de leeftijd van 7 jaar bevestigen ook dat problemen op de leeftijd van 4 jaar inderdaad kunnen blijven bestaan na de kleuterklassen, en suggereren daarmee dat vroegtijdige interventie nuttig zou kunnen zijn, vooral indien die aangrijpt op visuospatieel redeneren, aandacht en executieve functies.

Implicaties.

Onze onderzoeksresultaten leiden tot drie belangrijke implicaties (gevolgtrekkingen) voor de zorg van matig te vroeg geboren kinderen: het verhogen van het bewustzijn bij professionals en ouders over de mogelijke gevolgen voor de ontwikkeling van matige vroeggeboorte, het versterken van de preventie van matige vroeggeboorte (inclusief terugdringen van het aantal meerlingen), en het verbeteren van de ontwikkelings-monitoring van matig te vroeg geboren kinderen.

Ten eerste, en meest belangrijk, weerleggen onze resultaten de aanname dat "een paar weekjes te vroeg" of "bijna op tijd geboren" geen gevolgen voor de ontwikkeling heeft. Gynaecologen, ouders en kinderartsen zouden daarom vaker de

lange termijn complicaties van het opwekken van vroeggeboorte af moeten wegen tegen de korte termijn voordelen, omdat er geen “veilige” grens is qua zwangerschapsduur waarboven vroeggeboorte geen ontwikkelingsrisico zal opleveren.

Ten tweede zou de preventie van (matige) vroeggeboorte moeten worden versterkt door het bevorderen van gezond gedrag bij vrouwen in de vruchtbare leeftijd. Dit impliceert een afname van ongezond gedrag (ongezond eetgedrag, onvoldoende fit zijn, roken, aanhoudende stress vlak voor en tijdens zwangerschap) en het bevorderen van het krijgen van kinderen op jongere leeftijd. Een afname van het aantal kinderen met IUGR zal zowel leiden tot een afname van het aantal kinderen dat matig te vroeg geboren wordt, alsook tot een afname van het aantal kinderen binnen deze matig te vroeg geboren groep met ontwikkelingsproblemen later. Een afname van het aantal meerlingen bij onvruchtbaarheids-behandelingen vormt een volgende uitdaging, maar zou een afname van het aantal matig (en veel) te vroeg geboren kinderen kunnen opleveren, met daarnaast eveneens een afname van het aantal kinderen binnen de matig te vroeg geboren groep met ontwikkelingsproblemen later. Preventie impliceert ook een reductie (afname) van het aantal vroeggeboortes op medische gronden, voor zover mogelijk, waarbij het vinden van een goede balans tussen korte termijn en lange termijn voordelen voor zowel moeder als kind altijd lastig zal blijven.

Ten derde impliceren onze resultaten dat matig te vroeg geboren kinderen meer aandacht verdienen dan dat ze tot nu toe kregen in nazorg. Geprotocolleerde ontwikkelings-monitoring op het consultatiebureau (of in een gecombineerd nazorgbureau van de JGZ en kindergeneeskunde) zou aanvullende ontwikkelings-screening kunnen inhouden, mogelijk door het invoeren van de ASQ. Vroege herkenning van matig te vroeg geboren kinderen met het hoogste risico, gebaseerd op antenatale, postnatale en sociaal-demografische factoren, zou daarbij nuttig kunnen zijn. Meer aandacht voor deze groep zou tot vroegere opsporing van matig te vroeg geboren kinderen met daadwerkelijke problemen kunnen leiden, gevolgd door vroege interventie.

Toekomstperspectieven

Toekomstperspectieven behelzen nieuw klinisch onderzoek, vroege opsporing van ontwikkelingsproblemen, vroege interventie na ontslag, het onderzoeken van de haalbaarheid van het inzetten van de ASQ op het consultatiebureau, en het

ontwikkelen van een nieuwe visie op de meest effectieve nazorg voor te vroeg geboren kinderen.

Ten eerste zullen de verbanden die wij vonden in ons cohortonderzoek moeten worden bevestigd in groot prospectief, gecombineerd obstetrisch en kindergeneeskundig, onderzoek met een lange follow-up (tot in de schoolleeftijd).

Ten tweede is er meer inzicht nodig in het effect van vroege interventies in de zuigelingen en kleuterleeftijd. Nu focussen we vooral op het voorkomen van vroeggeboorte en van korte termijn complicaties daarvan voor ontslag naar huis. Op dit moment stoppen we relatief weinig energie (en geld) in interventiestrategieën in de thuissituatie na ontslag, die in potentie net zo belangrijk zouden kunnen zijn voor zowel ouders als voor hun kinderen.

Ten derde is onderzoek nodig naar het introduceren van de ASQ als aanvullend instrument om ontwikkeling te monitoren van te vroeg geboren kinderen in zowel de JGZ als de kindergeneeskunde. Dit onderzoek zou gericht moeten zijn de haalbaarheid, uitvoerbaarheid, effectiviteit en betrouwbaarheid van de ASQ als standaard ontwikkelings-screenings instrument bij hoog risico kinderen. De mogelijkheid om één of meerdere versies van de ASQ als aanvullend instrument naast het Van Wiechen Schema door jeugdarts en/of kinderarts in te zetten, zou de kansen op vroege opsporing gevolgd door vroege verwijzing in de voor behandeling gevoelige periode kunnen verhogen.

Tenslotte kunnen onze resultaten een aanzet vormen om ons hele nazorg systeem voor te vroeg geboren kinderen te herijken. Tot nu toe zijn alleen veel te vroeg geboren kinderen op een geprotocolleerde manier vervolgd, omdat hun ontwikkelingsrisico bekend was, ze een goed omschreven, relatief kleine en gemakkelijk bereikbare groep vormen van kinderen die worden geboren in academische settings. Misschien zouden we moeten nadenken over een meer algemene follow-up van te vroeg geboren kinderen, waar we ook nog nazorg en follow-up voor evaluatie van ons eigen handelen voor een grotere groep prematuren op een meer kosteneffectieve manier weten te combineren. Dit vereist betere samenwerking tussen verloskundigen, gynaecologen, neonatologen, algemene kinderartsen, en jeugdartsen, in afstemming met ziektekostenverzekeraars. Dit kan haalbaar zijn, maar houdt wel in dat aandacht en beschikbare budgetten anders moeten worden gericht, en dat er een gestructureerde samenwerking dient te komen tussen alle partijen.

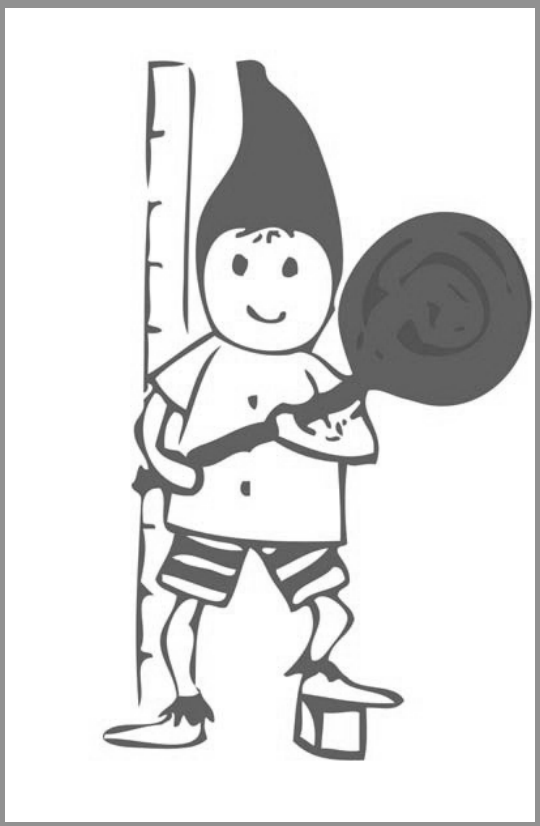
Aangezien geschat wordt dat wereldwijd 11% van alle kinderen matig of veel te vroeg geboren wordt, zouden we verder onderzoek met een weldoordachte onderzoeksagenda (met duidelijke prioritering) over optimale behandeling vóór en na vroeggeboorte moeten toejuichen. De recent uitgebrachte “call for action” (Europese “white paper”) over preventie van vroeggeboorte en de gevolgen van vroeggeboorte, sluit hier uitstekend bij aan.

Chapter 10

Nederlandse Samenvatting

Dankwoord

Lijst JGZ Instellingen



Jorien M. Kerstjens.

Dankwoord

Voor het Pinkeltje onderzoek werden meer dan 2500 kinderen op consultatiebureaus van Terschelling tot Maastricht geincludeerd. Een dergelijk grootschalig onderzoek kan alleen slagen dankzij inspanningen van enorm veel mensen. Het dankwoord vormt het uitgelezen moment om allen daarvoor te bedanken, ook al is het bijna onmogelijk om iedereen bij naam apart te noemen.

Allereerst ben ik heel veel dank verschuldigd aan alle ouders en kinderen die meegedaan hebben aan Pinkeltje. Zonder hun bereidwilligheid om ellenlange vragenlijsten in te vullen en hun kinderen te laten testen, was Pinkeltje nooit van de grond gekomen, en was er nu voor mij geen promotieplechtigheid!

Dit proefschrift kwam tot stand onder supervisie van mijn promotores Prof. dr. AF Bos en Prof. dr. SA Reijneveld en mijn copromotor Dr. AF de Winter.

Hoogeleerde Bos, beste Arie, jij hebt mij als hoofd van de afdeling neonatologie de vrijheid en ruimte gegeven, om matig te vroeg geboren kinderen als onderwerp van mijn promotie te kiezen, ondanks het feit dat dit onderwerp in feite grotendeels buiten de “academische neonatologie” ligt, dat waardeer ik zeer. Dat Pinkeltje uiteindelijk zo groot zou worden, hebben we, denk ik, geen van beiden aan het begin van dit project voorzien. We hebben binnen Pinkeltje samen veel ups and downs doorgemaakt, resulterend in dit boekje, en er volgen in ieder geval nog drie Pinkeltje proefschriften. Veel dank voor je kritische blik op de inhoud van dit gehele proefschrift, en het steeds terugkeren naar “wat is nu precies je onderzoeksvraag”, ik heb hier heel veel van geleerd!

Hooggeleerde Reijneveld, beste Menno,de gezondheidswetenschappen was een compleet nieuw gebied voor mij; ook van jou heb ik enorm veel geleerd, en zeer gewaardeerd hoe scherp en zorgvuldig (en snel) je steeds commentaar gaf op alle versies van de vele Pinkeltje artikelen die langskwamen. Jouw invalshoek van zowel arts, als epidemioloog met veel ervaring in het doen van grootschalig onderzoek, zijn van onschatbare waarde geweest voor Pinkeltje als onderzoek, en voor mij als persoon!

Weledelzeergeleerde de Winter, beste Andrea, jij kwam vanuit gezondheids-wetenschappen erbij als lid van het Pinkeltje team, op een moment dat ik toe was aan een doorstart. Je hebt me vol verve uit die pitstop geholpen, waar ik je oprecht dankbaar voor ben. Ik wens je succes als copromotor van de volgende Pinkeltje promovendi.

De leden van de beoordelingscommissie, prof. Dr. S.P. Verloove-Vanhorick, prof. Dr. P.J.J. Sauer, en prof. Dr. K Hoppenbrouwers van de Katholieke Universiteit Leuven:Ik ben jullie erkentelijk voor het willen beoordelen van dit proefschrift. Beste Pauline, LOLLIPOP (de Engelse naam van Pinkeltje) is ook wel “POPS 2” genoemd, ik zie dat als een compliment! Beste Pieter, ik herinner me nu nog onze eerste besprekingen samen met Arie op jouw kamer, (toen nog als afdelingshoofd), waar je zei dat “die late prematuren het best wel eens slechter zouden kunnen doen dan dat wij nu denken”, je kreeg gelijk! Hooggeleerde professor Hoppenbrouwers, ik waardeer het zeer dat juist ook vanuit de gezondheidswetenschappelijke hoek u heel secuur mijn proefschrift door hebt willen worstelen, en zie er naar uit u de 13^{e} mei ook in levende lijve te ontmoeten.

Het vele veldwerk voor het Pinkeltje werd gecoördineerd door Liesbeth ten Vergert, Marijke Broer van Dijk en Brigit van der Hulst. Beste Liesbeth, Brigit en Marijke; zonder jullie bezielende enthousiasme, toewijding, steun en voortdurende inspanningen, was Pinkeltje als onderzoek niet gelukt. Ik bewaar dierbare herinneringen aan de grote mokken thee tijdens de vele vergaderingen (met veel te veel agendapunten) met jullie drie ’s avonds bij mij thuis in Groningen Zuid.

In totaal hebben 13 JGZ instellingen integraal meegedaan aan Pinkeltje. Het coördineerwerk hiervoor werd vol verve verricht door een groot aantal CB artsen. Naast de al eerder genoemde Brigit (Icare), Marijke (Thuiszorg Groningen) en Liesbeth (Thuiszorg de Friese Wouden, Zuid-West Friesland en Het Friese Land), waren dit Brigitte de Pree en Helen de Langen (St. Groene Kruis Domicura), Marielle Jaminon (Thuiszorg Westelijke Mijnstreek), Ria van Berlo en Felicia van Berkel (Zorggroep Noord en Midden Limburg), Saapke Engel (St. De Zorgboog), Mint Arends (Carinova), Hinke Jeeninga (St. Thuiszorg Midden-Gelderland), Stineke Faber en Maya Touw (Rivas Zorggroep), en tenslotte Eveline Storchi, Marjan de Muynck en Irma Verweij (Opmaat). Verder hebben nog eens 27 andere thuiszorg-instellingen een of meerdere vroege

prematuren voor ons geincludeerd voor het tweede deel van het cohort. Het is ondoenlijk om iedereen die daarbij geholpen heeft apart te benomen, maar ik ben jullie wel allemaal persoonlijk dankbaar! Als bijlage is een lijst opgenomen van alle JGZ instellingen die met een of meerdere kinderen hebben meegedaan. Los van de coördinatoren is het eigenlijke echte inclusiewerk verricht door honderden consultatiebureau (CB) artsen, CB verpleegkundigen en CB assistenten. Deze grote groep mensen bij al deze thuiszorginstellingen hadden het daadwerkelijke patiëntencontact; zonder jullie consciëntieuze en positieve bijdrage hadden niet zoveel kinderen met hun ouders meegedaan aan Pinkeltje.

Ons project begon zonder projectleider, waarbij Rolof Gijtenbeek, de eerste student betrokken bij Pinkeltje -en dus pionier-, in een hoekje van een gedeelde stafkamer probeerde samen met mij het geheel op de rails te houden. Rolof, dank voor al dit werk! Uiteindelijk werd het Pinkeltje Office (PO), met vele meters stellingen met dossiers en 4 werkplekken. Gelukkig kwam er uiteindelijk toch een echte project-manager, wat onontbeerlijk is voor zo'n project: Maud Litjens; veel dank voor het stroomlijnen van duizenden ingaande en uitgaande Pinkeltje formulieren, ziekenhuisgegevens, PRN gegevens, en het coördineren van meetmoment 3.

Pinkeltje was ook niet groot gegroeid zonder de hulp van een lange rij studenten, die bezoldigd of onbezoldigd (in het kader van wetenschappelijke stages) meegeholpen hebben om Pinkeltje data te verzamelen, te schonen, uit te werken, of kinderen te testen. Rolof, Jelly, Grace, Kirsten, Sjors ,Marijke, Claudia, Marit, Bregitte, Kristian, Judith, Marieke, Sanja, Kim, Inge, Maud J, Amarens, Ard, Jorijn, Milou en Aniek; zonder jullie kluswerk waren we niet zover gekomen. Karin Veldman, jij verdient een aparte vermelding in dit rijtje, alleen al voor alle dierbare koppen koffie met "wat lekkers", naast het verzetten van bergen werk op PO.

Goede secretariële ondersteuning is onontbeerlijk voor iedere promovendus. De secretaresses, Janette, Hilde en later Heidi, jullie hulp voor de talloze malen dat ik weer belde vanuit thuis, voor een bestand (nog voor de dropbox-tijd) en voor alle andere Pinkeltje klussen is zeer gewaardeerd! Het zelfde geldt voor alle kinderartsen en secretaresses van andere NICU's en perifere ziekenhuizen die stapels dossiers voor ons opvroegen.

En dan een aparte alinea voor de neuropsychologen. Phillipa Butcher, die enorm hielp met uitwerken van de eerste ASQ data in SPSS (toen nog abracadabra voor mij), en de testbatterij voor meetmoment 3 ontwierp; thanks down under! Anke Bouma, en Reint Geuze, die (financiën en) enorme inzet leverden voor meetmoment 3; veel dank, en ik hoop dat de samenwerking zal blijven!
Renata, our multinational Pinkeltje postdoc student, I am proud and happy to include one of our joint articles in this thesis, and hope you will keep looking back at your Dutch time period with enthusiasm and nostalgia!
Koen, voor het superviseren van meetmoment 3, de uitleg over moeilijke neuro-psychologische begrippen, en de af en toe typisch Belgische opbeurende woorden op de gang, merci!

Inger, de 2e Pinkeltje-promovenda, en opvolger van Lies, heeft samen met Karin en mij een groot aantal kerngegevens uit Pinkeltje geschoond. Dit soort megaklussen bepalen mede het slagen van een onderzoek. Daarnaast heb je de verantwoordelijkheid gedragen voor het verzamelen (en invoeren) van alle ziekenhuisgegevens en gegevens uit PRN, en was je een tijdje datamanager. Fijn dat ook jouw proefschrift zo goed als af is, en succes met je opleiding tot kinderarts! En vervolgens Marieke, en nu ook Jorijn, heel veel succes met jullie promoties binnen Pinkeltje.

Hans, Ilse, Diane, René, en andere TCC medewerkers, jullie hebben heel veel tijd en energie in “het kleine Pinkeltje” gestopt, en ik weet dat het jullie vele hoofdbrekens heeft gekost. Veel dank dus voor het maken van teleformulieren, scannen, handmatig controleren en opbouwen van de retrieval.

Martin de Kleine ben ik erkentelijk voor zijn aanstekelijk enthousiasme over het hele Pinkeltje project, en een aantal goede suggesties, waaronder toevoegen links-rechts-handigheid aan de ASQ 5 jaar, en heus; het artikel word echt ooit geaccepteerd!

Anneke Bulk, medeauteur van het boek over nazorg van prematuren (wat de aanzet was naar Pinkeltje); je was vanaf de zijlijn zeer positief betrokken bij het Pinkeltje onderzoek, inclusief het doneren van geld uit je eigen A- Bulk-JGZ-stimulerings-fonds.

Ook dank ik Roy Stewart vanuit de gezondheidswetenschappen, die op het moment dat het statistisch echt “hogeschool" werd, fantastisch bijsprong, en onder meer de multilevel analyses uitwerkte.

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Een aantal kinderartsen, waar ik als mens en als arts veel van geleerd heb; Rob Tummers, (je stond ooit aan de wieg van mijn keus om kinderarts te worden) Sidarto Bambang Oetomo, Wim van Aalderen, Margreet Bink, en Wim Baerts, jullie wil ik hierbij apart noemen, maar dezelfde dank gaat natuurlijk net zo hard aan alle andere kinderartsen en neonatologen die mijn opleiding tot kinderarts en later tot neonatoloog verzorgden.

Mijn collegae, Peter, Elisabeth, Klasien, Nathalie (nu MCL), Anneke, Margriet, Jan, Henk, Hannah (nu MZH), Chris, en Lily, veel dank voor de steun, gezelligheid, en collegialiteit in het opvangen van afdelingstaken, als kliniek werkzaamheden en Pinkeltje zaken weer eens conflicteerden. Daarnaast de andere promovendi van Arie, merci voor congres-gezelligheid en de handige foefjes bij submitten!

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En dan in de reeks van de hoogwaardigheidsbeklеders wil ik ook graag mijn paranimfen, Liesbeth ten Vergert en Elianne Vrijlandt noemen.
Beste Liesbeth, (al eerder genoemd voor het vele werk voor Pinkeltje); het begon ooit in 1980 met een fietstocht naar een kamp, waarbij al mijn kleren over straat rolden, en je hielp sokken bij elkaar te grabbelen; dit werd het begin van een lange en dierbare vriendschap, en lang leve Vappetit!

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Huib en Mieke, jullie zijn allebei echt een enorme steun geweest (en nog steeds) in de lange tijd die ik met deze promotie bezig was. Alle etentjes, wijze woorden, spoed-overleggen, het leren relativeren, en de schouder om af en toe op uit te huilen, ik ben jullie daar intens dankbaar voor!
Jaap en Len, meer op afstand, maar ook altijd zeer geïnteresseerd, met een verfrissende visie op promoveren vanuit een totaal andere hoek, ook dank! Ik hoop dat we nu elkaar weer vaker zullen gaan zien!
Erik en Marijn, ook jullie horen in dit boekje, veel dank voor alle dierbare en leuke momenten die ik met jullie heb gedeeld, en ik hoop jullie te mogen blijven volgen in jullie verdere leven!

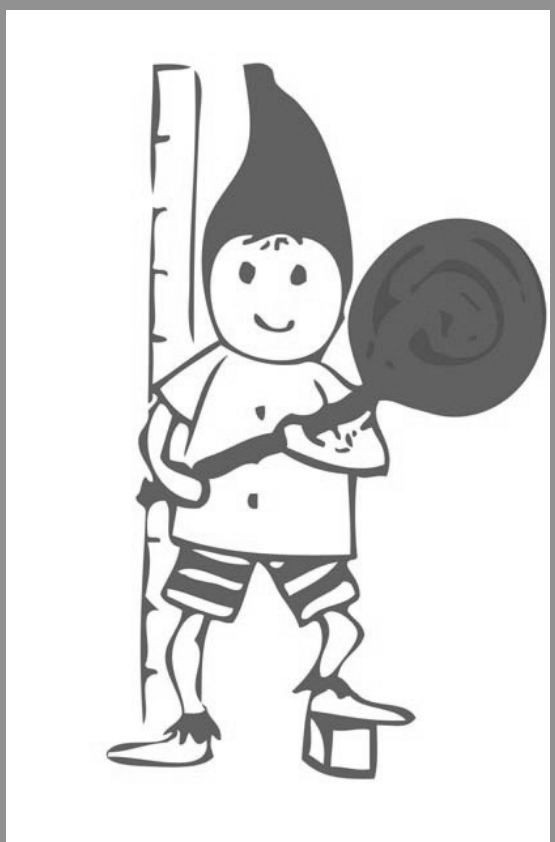
Lieve vader en moeder, jullie gaven me de mogelijkheden om te studeren en droegen bij aan mijn doorzettingsvermogen om kinderarts te worden. Ik heb genoten van hoe intens jullie meeleefden met alle fasen van dit soms eindeloos lijkende project. Vandaag promoveert jullie tweede kind; ik weet dat jullie daar trots op zijn!

Een aantal dierbare vriendinnen tenslotte, die altijd bereid waren om me weer een hart onder riem te steken “when the going got tough” Annet, Helen, Andrea, Gea en Monique; nu is weer meer tijd voor gezellige happeningen!

And last, but not least, lieve Jan, je had (gelukkig) nog geen idee wat Pinkeltje inhield toen we elkaar in het wedstrijd-laser veld tegenkwamen, en elkaar met “bakboord!” probeerden af te troeven. Pinkeltje heeft ons samen heel veel tijd en energie gekost. Samen met Raiza, onze trouwe viervoeter, heb je geprobeerd te zorgen dat de balans voor mij tussen werk en vrije tijd nog enigszins in evenwicht bleef. Jouw opmerkingen over “zit je nu alweer in je hok te werken” zijn nu hopelijk (grotendeels) verleden tijd. Ik hoop dat we samen, jij met nieuwe heup, en met Pinkeltje in rustiger vaarwater weer enorm kunnen gaan genieten van zon, zee en wind op de Zilverbeer, wandelen met de hond, en klussen in de tuin!

Chapter 9

Nederlandse Samenvatting
Dankwoord
Lijst JGZ Instellingen



Jorien M. Kerstjens.

LIJST JGZ INSTELLINGEN

Onderstaande thuiszorgorganisaties hebben destijds aan het Pinkeltje onderzoek meegewerkt. De namen van thuiszorgorganisaties zijn sindsdien door fusies en overnames deels veranderd. Het blijft mogelijk dat mede daardoor ondanks zorgvuldig nazoeken de lijst niet geheel compleet is.

Amant
Aveant
Carinova
Carint (CarintReggeland Groep)
GGD Amsterdam
GGD Gooi- en Vechtstreek
GGD Nijmegen
GGD Rotterdam
Corbis
Groenekruis Domicura
Icare
JongFlorence
Kruiswerk West Veluwe
Livio
Omring
Opmaat
Rivas Zorggroep
Stichting de Zorgboog
Stichting Thuiszorg Midden Gelderland
Thebe
Thuiszorg De Friese Wouden
Thuiszorg Groningen
Thuiszorg Het Friese Land
Thuiszorg Midden-Limburg
Thuiszorg Noord Oost Brabant
Thuiszorg Noord West Twente
Thuiszorg Oostelijk Zuid Limburg
Thuiszorg West Brabant
Thuiszorg Westelijke Mijnstreek
Thuiszorg Zuid West Friesland
Valent
Verian
Vierstroom
Vitras
Vivent
Yunio
Zorg en Welzijn
Zorggroep NoordLimburg
Zorggroep Oude en Nieuwe Land
Zuidzorg (inclusief de Kempenstreek)

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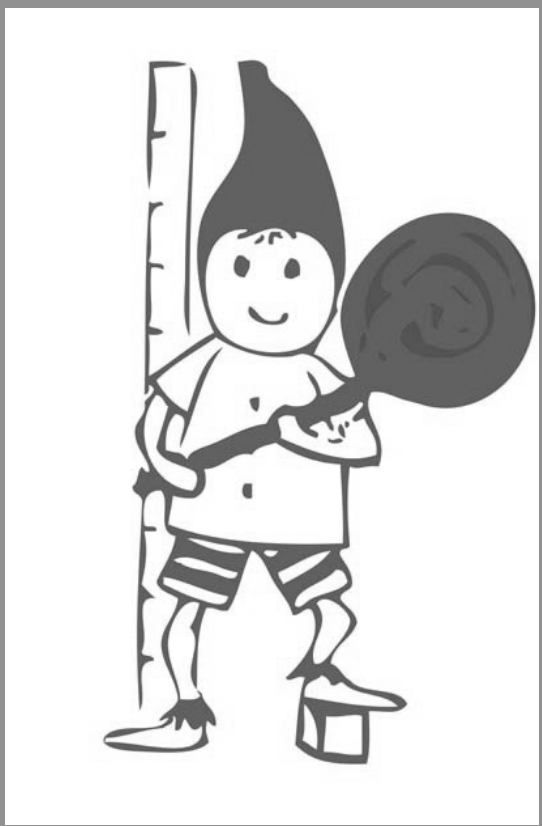

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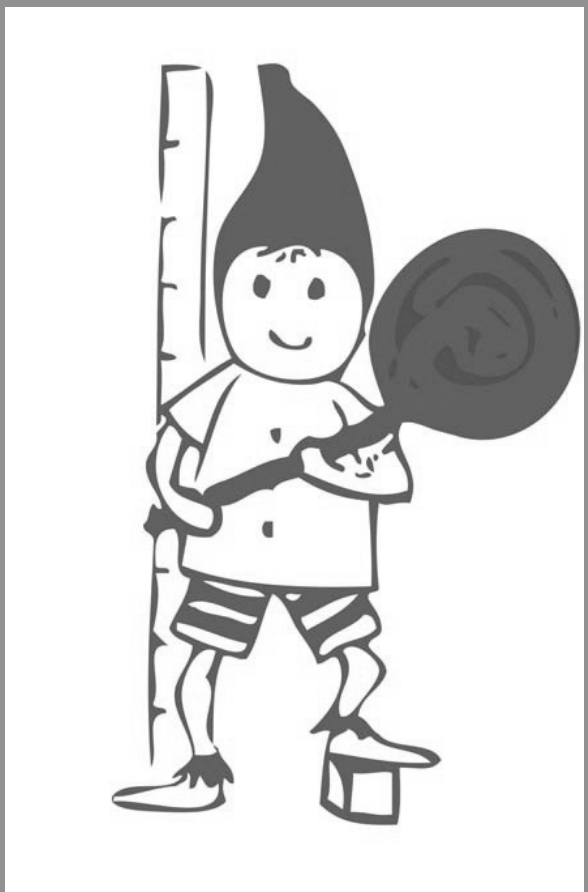

Jorien M. Kerstjens.

Jorien Maria Kerstjens was born on the 20th of August 1962 in Zwijndrecht, the Netherlands. She grew up in different parts of the Netherlands and lived briefly in the United States as a child. She graduated from the gymnasium of the Geert Groote College, a secondary school in Deventer. She studied Medicine in Groningen, with internships in Hospital Ziekenzorg (currently Medisch Spectrum Twente). She started her research career in the Emma Children's Hospital, division of Pediatric Pulmonology under supervision of R. Griffioen. After a brief interlude as senior house officer in General Surgery in Enschede, she started her training in Paeditiatrics in the Beatrix Children's Hospital in Groningen with clinical rotations in the Isala Clinics in Zwolle, and finished her last year of Paediatric training in the Sophia Children's Hospital in Rotterdam. She worked briefly as a Paediatrician in the Schieland Hospital in Schiedam (currently Vlietland Hospital). Afterwards she worked in the Pasteur Hospital in Oosterhout (now Amphia H.), and the Refaja Hospital in Dordrecht, (Albert Schweitzer Hospital). During this period she completed the Neonatal Individual Developmental Care and Assesment Program (NIDCAP), with a final examination in Lund in Sweden.

After 10 years in the general Paediatric setting, she completed a sabbatical year as a fellow in Neonatology, once more in the Isala Clinics in Zwolle. During this year she decided to move on to Neonatology and eventually finished her training in Neonatology in the Beatrix's Children's Hospital in Groningen. She currently is a staff member of the Neonatology section of the Beatrix Children's Hospital in Groningen.

Her interest in follow-up of preterm-born children started during the period she worked in Dordrecht, where she was one of the principal members in a transmural team that designed and initiatied the first Dutch "preterm follow up" poli (O3 project). In this project Preventive Child Healthcare and Paeditiatric hospital-based care were combined in a setting which also included other specialists in child health care. The goal of this project was to optimise developmental outcome for preterm-born children. This design has now been adapted in several other parts of the Netherlands. The O3 project, and the publication of her book "Follow-up of preterms" (nazorgboek prematuren) were the starting point for the Pinkeltje Project, and eventually resulted in this thesis. Jorien has presented her research at several international conferences.

Jorien lives with Jan Bouma in Zeegse and loves gardening and ocean sailing. It is her wish te continue doing research in developmental follow up of preterm-born children in the Beatrix Children's Hospital together with the Preventive Child Health Care.

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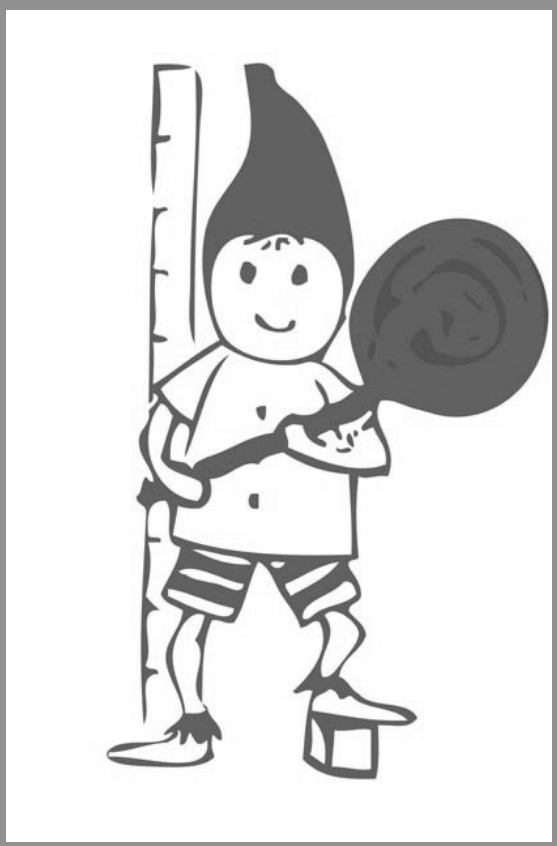

Jorien M. Kerstjens.

ABBREVIATIONS

ASQ	Ages and Stages Questionnaire
AVLT	Auditory Verbal Learning Test
BMI	Body Mass Index
BRI	Behavioral Regulation Index
BRIEF	Behavior Rating Inventory of Executive Functions
C-Section	Caesarian Section
CI	Confidence Interval
GA	Gestational Age
GEC	Global Executive Functioning
IUGR	Intrauterine Growth Restriction
LOLLIPOP	Longitudinal Preterm Outcome Project
MCI	Meta-Cognition Index
N	Number
NEPSY	Developmental Neuropsychological Assesment Battery
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PCH	Preventive Child Healthcare
PCHC	Preventive Child Healthcare Center
PIQ	Performance IQ
P-PROM	Prolonged Premature Rupture of Membrames
RR	Relative Risk
SD	Standard Deviation
SES	Socioeconomic Status
SGA	Small for Gestational Age
SS	Standard Score
Tea-CH-NL	Test of Everyday Attention for Children
TIQ	Total IQ
UMCG	University Medical Center Groningen
VIQ	Verbal IQ
WISC	Wechsler Intelligence Scale for Children