

Behaviour and development in 24-month-old moderately preterm toddlers

Marjanneke de Jong,¹ Marjolein Verhoeven,¹ Carole A Lasham,² Clemens B Meijssen,³ Anneloes L van Baar¹

¹Department of Child and Adolescent Studies, Utrecht University, Utrecht, The Netherlands

²Department of Pediatrics, Tergooi Hospital, Blaricum, The Netherlands

³Department of Pediatrics, Meander Medical Centre, Amersfoort, The Netherlands

Correspondence to

Marjanneke de Jong, Department of Child and Adolescent Studies, Utrecht University, P.O. Box 80.140, 3508 TC Utrecht, The Netherlands; M.deJong@uu.nl

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ABSTRACT

Objective Moderately preterm children (gestational age 32–36+6 weeks) are at risk of cognitive and behaviour problems at school age. The aim of this study was to investigate if these problems are already present at the age of 2 years.

Study design Developmental outcome was assessed at 24-months (corrected age) with the Bayley-III-NL in 116 moderately preterm (M=34.66±1.35 weeks gestation) and 99 term born children (M=39.45±0.98 weeks gestation). Behaviour problems were assessed with the Child Behaviour Checklist.

Results With age corrected for prematurity, moderately preterm children scored below term peers on Receptive Communication skills (11.05±2.58 vs 12.02±2.74, p=0.02). Without correcting age for prematurity, moderately preterm children scored below term born peers on Cognition (8.97±2.11 vs 10.68±2.35, p<0.001), Fine Motor (10.33±2.15 vs 11.96±2.15, p<0.001), Gross Motor (8.47±2.55 vs 9.39±2.80, p=0.05), Receptive Communication (10.09±2.48 vs 12.02±2.74, p<0.001) and Expressive Communication (10.33±2.43 vs 11.49±2.51, p=0.005) skills. Compared with term peers, more moderately preterm children showed a (mild) delay (ie, scaled score <7) in gross motor skills with age uncorrected for prematurity (20.7% vs 11.2%, p=0.04). Moderately preterm children had more internalising behaviour problems than term children (44.76±8.94 vs 41.54±8.56, p=0.03). No group differences were found in percentages of (sub)clinical scores.

Conclusions At the age of 2 years, uncorrected for prematurity, differences in cognition, communication, and motor development were present in moderately preterm children compared with term born peers. After correcting age for prematurity, a difference was only found for receptive communication skills. In addition, moderately preterm children show more internalising behaviour problems.

INTRODUCTION

Worldwide, 11.1% of all pregnancies end in preterm delivery before 37 weeks of gestation, of which 84% are born moderately preterm after a gestational age (GA) between 32 to 36 weeks and 6 days.¹ Although to a lesser extent than very and extreme preterm children, moderately preterm children still have more neonatal complications than term born children, such as respiratory distress, hypoglycaemia and feeding problems.² Long-term follow-up studies have shown that these children are at increased risk of cognitive, school and behaviour problems at (pre)school age.³ Little is known

What is already known on this topic

- ▶ Moderately preterm children are at risk for cognitive, school and behaviour problems.
- ▶ Little is known about moderately preterm born children at toddler age, especially with respect to standardised behavioural outcomes.
- ▶ Most previous studies studied American populations, less is known about the development of European moderately preterm children.

What this study adds

- ▶ Using chronological age, moderately preterm toddlers scored lower than term born peers on cognition, communication and motor skills.
- ▶ Even after correcting age for prematurity, moderately preterm 24-month-olds showed lower receptive communication scores (Bayley-III-NL).
- ▶ Moderately preterm children have more internalising behaviour problems (Child Behavior Checklist) already at toddler age.

about developmental and behavioural outcomes in moderately preterm children in their first 2 years of life, even though this may be a period during which the first signs of developmental delay appear. The aims of the current study are to investigate developmental and behavioural outcomes of 24-month-old moderately preterm children compared with term born peers.

Few studies have compared developmental outcomes (ie, cognitive, motor and/or communication skills) of moderately preterm with term born toddlers at this early age, using developmental tests. These studies showed inconsistent results, with some studies finding poorer outcomes for moderately preterm children,^{4–9} while others found no differences.^{4 5 7 10–12} The inconsistencies in these findings are most likely a result of the use of age correction for prematurity or not. Age correction is infrequently used in moderately preterm children, especially in the late preterm subgroup (ie, GA of 35–36 weeks). Most studies that found group differences did not correct age for prematurity,^{5–8} while the studies that found no differences did correct the ages.^{5 7 10–12} Two studies did find



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differences with scores based on corrected age.^{4–9} Hillemeier *et al*⁴ found that moderately preterm children had double the risk for scoring in the lowest 10% at 9 months of age, but by 24 months of age there was no increased risk in the moderately preterm children. Voigt *et al*⁹ found a difference, with lower scores for moderately preterm children, with a medium effect size at 24 months of age. In the current study, differences between moderately preterm and term born toddlers will be determined for corrected as well as uncorrected age.

Despite growing evidence that moderately preterm children show more problem behaviour at (pre)school age,^{3, 13–15} no studies have been published that have determined the prevalence of behavioural problems in this group at toddler age using standardised measures such as the Child Behaviour Checklist (CBCL 1½–5).¹⁶ In this study, standardised and up-to-date assessments were performed in moderately preterm and term born children at 2 years of age in order to compare functioning of both groups.

METHOD

This study is part of an ongoing longitudinal project on the development of Dutch moderately preterm children, the STAP Project (ie, Study on Attention of Preterm children). Parents of moderately preterm (32–36 weeks' gestation) and term born (>37 weeks' gestation) children were invited by letter by their paediatrician or midwife to participate in the study when their child was 10 months old. Children were born between March 2010 and April 2011 in nine hospitals in and around Utrecht. For both groups, exclusion criteria were dysmaturity (birth weight below the 10th centile according to Dutch reference curves¹⁷), multiple birth, severe congenital malformations, antenatal alcohol or drug abuse by the mother, and chronic antenatal use of psychiatric drugs by the mother. We also excluded children admitted to a tertiary neonatal intensive care unit (NICU), according to the admission criteria of the official guidelines from the Dutch Society for Obstetrics and Gynecology and the Dutch Pediatric Association, as this might be a specific subgroup. In the Dutch population in 2012, NICU treatment was needed in 29% of the children born after 32–33 weeks and only in 7% of infants born after 34–36 weeks.¹⁸

Informed consent was given by the parents. The children received a gift after the visit and parents received travel expenses.

Measures

Developmental level

At 24 months of age, corrected for prematurity, a trained examiner performed the Dutch version of the Bayley-III, the Bayley-III-NL¹⁹ to assess the developmental level of the children.

The Bayley-III-NL consists of five subtests: Cognition, Fine Motor, Gross Motor, Receptive Communication and Expressive Communication. Scaled scores based on Dutch norms were used, which vary between 1 and 19 with a mean of 10 and a SD of 3. Scores of 7–13 are considered normal; a score below 7 indicates a (mild) developmental delay,²⁰ and is therefore seen as a clinically relevant score in this study. The reliability and validity of the Bayley-III-NL is good.²⁰

Behaviour

Prior to the visit to the test location, mothers completed the Dutch version of the CBCL 1½–5¹⁶ to assess the child's behaviour problems. The CBCL 1½–5 consists of 100 items with descriptions of behaviour problems for which the mother

indicates to what extent this fits the child now or in the past 2 months ('not/never', 'somewhat/sometimes' and 'very/often'). The T-scores of the total problem scale, as well as the T-scores on the two broadband scales (ie, internalising and externalising behaviour) and the seven subscales (ie, emotional reactivity, anxious/depressed behaviour, somatic complaints, withdrawn behaviour, sleep problems, attention problems and aggressive behaviour) were used. For total problems and the broadband scales, T-scores below 60 are considered normal, between 60 and 64 is seen as borderline clinical, and 64 or higher as clinical scores.¹⁶ For the subscales, scores below 65 are considered normal, between 65 and 70 borderline clinical, and 70 or higher as clinical scores.¹⁶ Subclinical and clinical scores are considered as clinically relevant scores in this study. The reliability and validity of the CBCL 1½–5 is good.¹⁶

Neonatal and background characteristics

Neonatal characteristics regarding hypoglycaemia, phototherapy, oxygen requirements, and length of hospital stay were based upon the discharge letters in the hospital files. Background characteristics, such as maternal education level, maternal age at birth and ethnic origin of the child, were provided by the parents using a short questionnaire.

Data analysis

Group differences in scores were investigated using (Multivariate) Analyses of Covariance ((M)ANCOVAs). Group differences in percentages of clinically relevant scores were investigated with logistic regression analyses. Analyses were adjusted for background characteristics that differed between the groups. (Multivariate) Analyses of Variance and Pearson's correlations were used to explore the relationship between neonatal characteristics and outcome measures within the moderately preterm born group.

Power analysis using G*Power showed that to test a group difference with a medium effect size (Cohen's $f^2=0.15$), a significance level of $\alpha=0.05$ and a power of 0.80, using a MANCOVA with seven dependent variables, a sample of in total 104 was needed, with 52 children in each group.²¹ Partial η^2 was used as effect size estimate, with 0.01 indicating a small effect size, 0.06 a medium effect size, and 0.13 and above a large effect size.²²

RESULTS

Of the 333 parents of moderately preterm children that were eligible for this study in the participating hospitals, 123 consented (37%). The participating moderately preterm children did not differ from non-participants in GA, birth weight, number of days in hospital, additional oxygen requirement, phototherapy requirement, gender and percentage of first-born children. A slightly higher incidence of hypoglycaemia was observed in non-participants (11.2% vs 4.9%, $\chi^2=3.76$, $p=0.05$). For the 457 eligible term born children, parents of 103 children (23%) consented to participate. The participating term born children did not differ from non-participants in gender, GA, birth weight, number of days in hospital, additional oxygen requirement, phototherapy requirement, hypoglycaemia and percentage of first-borns. The distribution of GA in weeks of the preterm and term born sample did not differ significantly from that in the general Dutch population.¹⁸

Complete data was available for 116 (94%) moderately preterm children and for 99 (96%) term born children. Sample characteristics are shown in table 1. The groups differed in maternal education level and maternal age at birth, with more low and medium educated mothers and younger mothers in the

Table 1 Neonatal and demographic characteristics of the participants

	Term born GA 37–41 weeks (n=99)	Moderately preterm GA 32–36 weeks (n=116)	
<i>Neonatal characteristics</i>			
GA in weeks			
Mean (SD)	39.45 (0.98)	34.66 (1.35)	
32 weeks (%)		10.3%	
33 weeks (%)		11.2%	
34 weeks (%)		17.2%	
35 weeks (%)		24.1%	
36 weeks (%)		37.1%	
37 weeks (%)	4.0%		
38 weeks (%)	11.1%		
39 weeks (%)	32.3%		
40 weeks (%)	40.4%		
41 weeks (%)	12.1%		
Birth weight in grams			
Mean (SD)	3575 (460)	2575 (508)	
Range	2795–5330	1420–3850	
Days in hospital			
Mean (SD)	0.42 (1.01)	12.00 (9.84)	
Range	0–6	1–42	
Need for oxygen* (%)	0%	22.4%	
Phototherapy (%)	0%	35.3%	
Hypoglycaemia (%)	0%	5.2%	
<i>Demographic characteristics</i>			
			p Value†
Age in months‡			
Mean (SD)	23.71 (0.52)	23.60 (0.63)	0.20
Range	23–25	23–27	
Gender (% boys)	45.5%	57.8%	0.07
First-born (%)	51.5%	62.9%	0.09
Ethnic origin (% Dutch)	95.9%	96.5%	0.42
Maternal age at birth (years)			
Mean (SD)	32.52 (4.20)	31.04 (4.43)	0.01
Range	20–43	21–41	
Maternal educational level			
Low§	3.0%	7.8%	
Medium¶	12.1%	35.3%	<0.001
High**	84.8%	56.9%	

*That is, additional oxygen right after birth, nasal cannula and/or continuous positive airway pressure (CPAP; n=17).

†ANCOVAs used for child age and maternal age. χ^2 tests used for gender, first-born, ethnic origin and maternal educational level.

‡Age at Bayley-III assessment.

§No education, elementary school, special education or lower general secondary education.

¶High school or vocational education.

**College, university or higher.

ANCOVAs, analyses of covariance; GA, gestational age.

moderately preterm group. Therefore, we controlled for maternal education level and maternal age at birth in all analyses concerning group differences.

Developmental outcomes

The average scaled scores and the percentage of children with a (mild) developmental delay, which reflects a score below 7 on the subtests of the Bayley-III-NL are presented per group in tables 2 and 3, respectively. For the moderately preterm group, the results are presented separately for corrected and uncorrected age (for prematurity).

Group differences using age corrected for prematurity

A MANCOVA of the five subtests of the Bayley-III-NL showed no overall difference between moderately preterm and term

born children on the scaled scores after correcting age for prematurity and adjusting for maternal education level and maternal age at birth. However, moderately preterm children scored significantly lower than full term peers regarding Receptive Communication with a small effect size. No group differences were found in the percentages of children with a mild developmental delay, see table 3.

Group differences using uncorrected, chronological age

When age was not corrected for prematurity, the MANCOVA showed a significant difference between moderately preterm and term born children. Moderately preterm children scored significantly below term born children on all subtests, that is, Cognition, Fine Motor skills, Gross Motor skills, Receptive Communication and Expressive Communication with small to

Table 2 Developmental outcomes of the children on the Bayley-III-NL

	FT N=98	MPT—corrected age N=116			MPT—uncorrected age N=116		
	Mean (SD)	Mean (SD)	p Value*	Effect size†	Mean (SD)	p Value*	Effect size†
Cognition	10.68 (2.35)	10.01 (2.27)	0.26	0.01	8.97 (2.11)	<0.001	0.09
Fine motor	11.96 (2.15)	11.34 (2.06)	0.09	0.01	10.33 (2.15)	<0.001	0.11
Gross motor	9.39 (2.80)	9.26 (2.78)	0.88	0.00	8.47 (2.55)	0.05	0.02
Receptive communication	12.02 (2.74)	11.05 (2.58)	0.02	0.03	10.09 (2.48)	<0.001	0.11
Expressive communication	11.49 (2.51)	11.15 (2.54)	0.59	0.001	10.33 (2.43)	0.005	0.04

MANCOVA results for corrected age: Wilks' $\Lambda=0.96$, $F_{5,206}=1.80$, $p=0.11$, partial $\eta^2=0.04$;
MANCOVA results for uncorrected age: Wilks' $\Lambda=0.83$, $F_{5,206}=8.26$, $p<0.001$, partial $\eta^2=0.17$.
*Compared with full term group.†Partial η^2 .
FT, full term, GA 37–41 weeks; GA, gestational age; MANCOVA, multivariate analysis of covariance; MPT, moderately preterm, GA 32–36 weeks; analyses are adjusted for maternal education level and maternal age at birth.

medium effect sizes. A higher percentage of moderately preterm children showed a (mild) developmental delay regarding gross motor skills (see table 3). No group differences were found for the other subtests.

Behavioural outcomes

The CBCL T-scores are presented in table 4. Moderately preterm children did not differ from term children in total problem scores. A MANCOVA with the T-scores of the internalising and externalising scale also showed no significant group difference. However, moderately preterm children did have significantly higher internalising behaviour scores. No differences were found in externalising behaviour problems. A MANCOVA with the T-scores of the seven subscales of the CBCL showed no group differences. No group differences were found in the percentages of children with (sub)clinical scores, see table 4.

Neonatal characteristics in relation to outcome measures within the moderately preterm group

The analyses described above were repeated comparing only late preterm born children (ie, GA 34–36 weeks, $n=91$) with the term born group. All results remained the same (data not presented).

Within the moderately preterm group, GA (as continuous variable), birth weight and days in hospital were not related to developmental outcomes (using chronological age and corrected age) or behavioural outcomes; Pearson's correlations between these neonatal characteristics and the Bayley-III or CBCL scores were not significant and varied between 0.001 and 0.17, except for the correlation between birth weight and the sleep problems subscale of the CBCL that was significant with a small effect size ($r=0.19$, $p=0.05$). No differences on behavioural and

developmental outcomes were found between children who required additional oxygen and those who did not. Also, no differences were found between the 41 children who received phototherapy and those who did not, and between the 6 children who had hypoglycaemia and those who had normoglycaemia.

DISCUSSION

This study on outcome of moderately preterm children at 2 years of age showed that using uncorrected, chronological age, resulted in lower scores for cognitive, motor and communication skills, compared with scores of term born children. Even for the (large) subgroup of only late preterm children these results were found. This is in line with previous studies that used uncorrected age.^{5 7 8} When we did correct age for prematurity, the group differences generally were not statistically significant, although, overall, preterm children had lower scores than their term born peers. Moderately preterm children did not differ from term born peers in cognitive and motor skills when age-corrected scores were analysed, which is in accordance with some previous studies at infant and toddler age.^{4 5 7 10–12} However, even after correcting age for prematurity, a significant difference was found, showing that moderately preterm children scored somewhat below term born peers on receptive communication skills. It is difficult to compare these results with previous studies, as in most previous studies regarding prematurely born toddlers,^{4 6–11} language skills were not assessed by a separate subtest, except for the study by Morag *et al*,⁵ that found no difference between moderately preterm and term born children after correcting age for prematurity.

Little consensus exists whether correcting age for prematurity is needed in moderately preterm children and if so, until what

Table 3 Percentage of children with a (mild) developmental delay (ie, scaled score <7) on the Bayley-III-NL

	FT	MPT-corrected age				MPT-uncorrected age			
		OR	(95% CI)	p Value*	OR	(95% CI)	p Value*		
Cognition	3.1%	4.3%	0.89	(0.19 to 4.15)	0.89	8.6%	2.19	(0.56 to 8.63)	0.26
Fine motor	2.0%	0.9%	0.48	(0.04 to 6.36)	0.57	5.2%	2.13	(0.40 to 11.44)	0.38
Gross motor	11.2%	15.5%	1.61	(0.69 to 3.73)	0.27	20.7%	2.30	(1.03 to 5.13)	0.04
Receptive communication	2.0%	4.3%	2.07	(0.37 to 11.56)	0.41	6.9%	3.52	(0.69 to 17.82)	0.13
Expressive communication	6.1%	4.3%	0.48	(0.13 to 1.75)	0.26	7.8%	1.03	(0.33 to 3.17)	0.96

*Compared with full term group; analyses are adjusted for maternal education level and maternal age at birth.
FT, full term, GA 37–41 weeks; GA, gestational age; MPT, moderately preterm, GA 32–36 weeks.

Table 4 Behavioural outcomes of the children

	T score		% (sub)clinical						
	Mean (SD)								
	FT N=94	MPT N=111	p Value	Effect size*	FT (%)	MPT(%)	OR	(95% CI)	p Value
Total problems	43.34 (8.56)	46.06 (7.87)	0.08	0.02	3.2	5.4	1.37	(0.31 to 6.02)	0.68
Internalising problems	41.54 (8.56)	44.76 (8.94)	0.03	0.03	1.1	5.4	3.70	(0.41 to 33.09)	0.24
Externalising problems	46.80 (8.68)	48.80 (8.11)	0.24	0.01	4.3	9.0	1.88	(0.54 to 6.54)	0.32
Subscales									
Emotionally reactive	51.43 (2.98)	52.60 (4.59)	0.12	0.01	1.1	4.5	3.70	(0.40 to 34.22)	0.25
Anxious/ depressed	50.46 (1.55)	50.74 (1.88)	0.53	0.002	0	0	–	–	–
Somatic complaints	52.15 (4.23)	53.68 (5.49)	0.18	0.01	3.2	10.8	2.26	(0.58 to 8.83)	0.24
Withdrawn	51.87 (3.34)	52.23 (3.51)	0.70	0.001	1.1	0.9	0.76	(0.04 to 15.14)	0.86
Sleep problems	51.99 (4.09)	52.13 (3.89)	0.89	0.00	2.1	1.8	0.53	(0.06 to 4.43)	0.55
Attention problems	52.68 (4.58)	53.46 (5.26)	0.88	0.00	4.3	6.3	1.06	(0.28 to 4.04)	0.93
Aggressive behaviour	52.28 (3.58)	52.86 (4.60)	0.35	0.004	0	3.6	–	–	–

*Partial η^2 ; analyses are adjusted for maternal education level and maternal age at birth; ANCOVA results of the total problems score: $F_{1,201}=3.15$, $p=0.08$, partial $\eta^2=0.02$; MANCOVA results of the internalising and externalising scale: Wilks' $\Lambda=0.98$, $F_{2,200}=2.54$, $p=0.08$, partial $\eta^2=0.03$; MANOVA results of the subscales: Wilks' $\Lambda=0.98$, $F_{7,195}=0.59$, $p=0.76$, partial $\eta^2=0.02$.

ANCOVA, analysis of covariance; FT, full term, GA 37–41 weeks; GA, gestational age; MANOVA, multivariate analysis of variance; MANCOVA, multivariate analysis of covariance; MPT, moderately preterm, GA 32–36 weeks.

age. This study showed that correcting age for prematurity influences the findings, even in the subgroup of late preterm children. It is, however, as yet unknown which score (ie, corrected or uncorrected for prematurity) is most predictive for later functioning. A few studies examined the predictive value of corrected and uncorrected scores in very preterm children with inconsistent results.^{23–25} In two studies,^{23 24} no difference in predictive validity of corrected and uncorrected scores was found. In contrast, Rickards *et al*²⁵ reported that the corrected scores were most predictive of later outcomes. Further research is needed to investigate the predictive value of corrected and uncorrected scores in moderately preterm children.

The percentage of children showing a developmental delay was not higher in the moderately preterm group for most of the subtests, except for gross motor skills when age was uncorrected for prematurity. For both groups, the percentage of children showing a developmental delay was lower than expected for all subtests, except for gross motor skills. In addition, the mean scores of all subtests, except gross motor skills, were higher than the normative means. This might be explained by the fact that a sample of relatively highly educated mothers participated in this study and term healthy children of higher educated mothers have been found to show higher Bayley-III scores.²⁰

Moderately preterm 24-month-olds were found to show somewhat more internalising behaviour problems than full term peers. No differences between levels of externalising behaviours were found. Despite these higher mean levels of problem behaviour, moderately preterm children did not show a higher risk of (sub)clinical scores than term born children. Our findings are partly in accordance with the study of Potijk *et al*,¹⁴ who found significantly higher problem scores for 4-year-old moderately preterm children on all scales of the CBCL. It might be that the behaviour problems of moderately preterm children increase with age, as several studies showed at preschool^{13 14} and school age^{13 15 26} that moderately preterm children had a higher risk of subclinical scores for total behaviour problems,^{13 14} internalising behaviour,^{15 26} externalising behaviour,¹⁴ attention problems²⁶ and somatic complaints.¹⁴

A careful interpretation of our findings is important, as the mean scores of both groups of children, for developmental

outcome and behaviour problems, were within the normal range. A statistically significant difference of one point on the scaled score of the Bayley-III-NL, which was found for receptive communication skills after correcting age for prematurity, is not immediately clinically significant. Additionally, the effect sizes of the group differences were found to be small, except for uncorrected age scores. Group differences with medium to large effect sizes need immediate attention from professionals in order to try to reduce the developmental and behavioural problems found. Small sized group differences might, however, also be important, as these could be early indicators of later, more serious difficulties, having an effect on their functioning at school. Further study of development of these moderately preterm children from toddler age onwards is therefore needed to fully evaluate these findings.

The analyses in our study were adjusted for maternal education level. In our sample, more mothers of moderately preterm children had a low or medium education level than mothers of term born children. This is in accordance with population based studies showing that lower maternal education level is a risk factor for premature birth.^{27 28} Correcting for maternal education level might therefore also lead to overcorrection. However, the number of low educated mothers was small in our moderately preterm and term born sample, which is a limitation of this study.

The relationship between neonatal characteristics and long-term developmental outcome measures was explored to investigate if indications for specific subgroups could be found. Comparison of late preterm born children (ie, GA 34–36 weeks) with the term born group showed the same results as for the total group of moderately preterm children: even late preterm children differed from term born children on several aspects of development and behaviour. With respect to other neonatal characteristics, no relationships were found between GA, birth weight, days in hospital, need for additional oxygen, and developmental and behavioural outcomes. As only a small percentage of the children had problems like hypoglycaemia (5.2%) clearly indicated in their hospital discharge letters, our study had only limited power to find any differences between the subgroups of children with and without problems such as hypoglycaemia.

Therefore, when the focus needs to be on such neonatal problems in moderately preterm children, future studies should be specifically designed to examine these problems.

A final remark is that in this study, only moderately preterm children who were relatively healthy and did not need tertiary NICU admittance, were selected. However, in the Netherlands 10.2% of all moderately preterm children are admitted to the NICU.¹⁸ This specific subgroup might be at an even higher risk of developmental and behavioural problems, and therefore these children should also be studied in the future.

In conclusion, at 2 years of age, uncorrected for prematurity, moderately preterm children differed from their term born peers in cognitive, motor and communication skills. With age corrected for prematurity, they differed from their term born peers only on receptive communication skills. Already at 2 years of age, moderately preterm children show more internalising behaviour problems than term born peers. Although only subtle differences were found in this study, these findings may still be an indication for later difficulties of moderately preterm children in academic functioning and socioemotional development.

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