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Attainment of gross motor milestones by preterm children with normal development upon school entry☆

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ABSTRACT

Background: Little is known on the motor development of moderately preterm born (MPT) children, in comparison with early preterm born (EPT) children and fullterm born (FT), for children with normal motor outcomes at school entry.
Aims: To compare attainment rates of gross motor milestones reached between ages 1–24 months for MPT, EPT, and FT children, all with normal development upon school entry.
Study design: Prospective cohort study.
Subjects: We included 1247 preterm (PT) children (gestational age [GA] 24.0–35.6 weeks) and 488 FT children (GA 38.0–41.6 weeks), with normal gross motor development at 4 years according to the Ages and Stages Questionnaire.
Outcome measures: We assessed 11 gross motor milestones assessed in preventive child healthcare during six standardized visits at calendar age.
Results: During the first six months, all PT categories had lower milestone attainment-rates than FTs children (differences 9–60% for PTs compared with FTs children). For all PT categories attainment rates gradually increased during toddlerhood. For PT children with higher GA, differences in attainment rates compared with FTs children were smaller and attainment rates became comparable to FT children at an earlier age. At age 24 months only attainment rates for PT children born < 30 weeks GA remained lower than for FTs children (85% versus 95%, $P < 0.01$).
Conclusion: Milestone attainment rates are highly dependent on GA during the first two years. Differences between PT and FT children are larger and persist longer with lower GA. For PT children < 30 weeks GA, differences still occur at 24 months.
Clinical Trial registry name and registration number: controlled-trials.com, ISRCTN 80622320.

1. Introduction

Worldwide, the development of preterm-born (PT) children (gestational age [GA] < 37 weeks) is closely monitored by preventive child health care (PCHC). Monitoring is important, because PT children are at greater risk of developmental delay, [1–3] including motor delay

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[4–6]. Persistent problems in the motor domain have been linked to long-term difficulties in other developmental domains, such as poor adaptive and cognitive functioning, learning disabilities, and behavioral problems [7–9].

Developmental monitoring is a core task of PCHC, commonly implemented by assessing developmental milestone attainment. Early preterm-born (EPT) children (GA < 32 weeks) reach motor milestones later than do FT children during infancy and toddlerhood [10,11]. This may be due to ontogenetic differences in maturation as a consequence of a shorter period in the womb compared to fullterm (FT) children. In addition, EPT children experience more perinatal problems than FT children [12]. Both factors may also contribute to delayed attainment of milestones for moderately preterm-born (MPT) children (GA 32–36 weeks), who experience motor delay in early childhood more often than FT children as well [13–15]. However, for MPT children, evidence on rates of gross motor milestone attainment is limited.

In developmental monitoring in community pediatrics, age of assessment is generally adjusted for GA during the first two years of life as recommended by the American Academy of Pediatrics for EPT children [16]. For MPT children, there is no published guideline. Whether correction for GA should also be applied for MPT children when assessing gross motor milestones is unknown. Such knowledge can help clinicians in interpreting developmental findings on MPT children, potentially leading to timelier developmental interventions. Therefore, this study aimed to compare the rates of gross motor milestones attainment between 1 and 24 months calendar age by PT and FT children both with normal development upon school entry. Second, we aimed to assess differences in risk of failing gross motor milestones by degree of prematurity.

2. Methods

2.1. Participants

We used data from the Longitudinal Preterm Outcome Project (LOLLIPOP) study, a community-based cohort of children born in 2002–2003, with data on the growth and development of both EPT and MPT compared with FT children. From 13 PCHCs we checked a total of 45,446 child files, roughly 25% of all Dutch 4-year-olds within a complete year cohort. We selected all children with a GA < 36 weeks. After every second PT child, we selected the next FT child from the same birth year as a control. The cohort was enriched with all EPT children from 5 neonatal intensive care units (NICUs), also born in 2003, and alive upon discharge. PCHC physicians included all children upon their final visit at the age of 4 years. PCHC physicians were not blinded to the clinical history and GA of children. Children with major congenital malformations and syndromes were excluded. Eventually 2517 children participated in the LOLLIPOP study.

For 79% of the children developmental data were available (512 EPT [GA < 32 weeks], 927 MPT [GA 32–35.6 weeks] and 544 FT children [GA 38–41.6 weeks]). For the present study we included only children with a normal gross motor development upon school entry (N = 1735, 87.5%). The study was approved by the Ethics Review Board of the University Medical Center Groningen, and written informed consent was obtained from all parents.

2.2. Measures and procedure

2.2.1. Gross motor milestones in the first two years of life

PCHC physicians scored gross motor milestones between 1 and 24 months of age according to the protocol of the Dutch version of the Denver Developmental Screener (DDDS). The DDDS is a valid and reliable instrument to measure gross motor milestone attainment in the Dutch population [17]. Most gross motor milestones had to be actively observed by the PCHC physicians according to this protocol. We collected the scores retrospectively, upon inclusion of children in the LOLLIPOP study. According to local protocols, children were scored with the DDDS at standardized DDDS time-points between 1 and 24 months of age. We included six standardized DDDS time-points, comprising a total of 11 gross motor milestones (Table 1). The number of milestones that could be scored varied per time-point (from one to three). A child was categorized as failing a time-point if failing at least one milestone at that time-point. Both PT and FT children were assessed at calendar ages for milestone attainment, following the Dutch guidelines for PCHC; with prematurity subsequently taken into account during the interpretation of the findings.

Table 1
Developmental gross motor milestones of the Dutch version of the Denver Developmental Screener by time-points (months) and corresponding age ranges (weeks).

Developmental milestone	Time-point (months)	Age-range (weeks)
Raises chin for a moment	1	0–8
Raises chin to 45°	3	8–16
Looks around 90° with head raised	6	22–30
Flexes legs while being swung		
Sits stable unaided[a]	12	44–60
Crawls, abdomen on the floor[a]		
Pulls up to standing[a]		
Crawls, abdomen off the floor[a]	15	56–72
Walks along[a]		
Squats while picking up things	24	96–112
Walks well alone		

Children with missing individual milestone scores for a time-point with multiple milestones were excluded for that time-point.
[a] Parental information on attainment of this milestone sufficed.

2.2.2. Developmental outcome upon school entry

For the present study, we have included only children with normal gross motor development upon school entry. In this way, we could assess the developmental pattern that reflects only the transient motor delay because of prematurity, for which adjusting via correction for GA is appropriate. Normal gross motor development upon school entry was assessed using the parent completed Ages and Stages Questionnaire 48 months' form (ASQ-48). The ASQ-48 contains 30 questions on five developmental domains, including the gross motor domain. The Dutch ASQ has been shown to be a valid, reliable, cost-effective, fast and easy way to screen children for developmental delay [18]. We calculated an ASQ-48 gross motor domain score as the sum of the six gross motor scores. Following the ASQ manual, all ASQs were completed at calendar age, and a score below -2SD for the Dutch FT reference group was considered as abnormal [19].

2.2.3. Gestational age and covariates

GA was defined as the period between the mother's last day of menstruation and the child's day of birth, and was verified by early ultrasound measurements in over 95% of the cases. In all cases, estimates were checked against clinical indications of GA after birth. If GA could not be reliably established, children were excluded. For the present study, we categorized GA per 2 weeks, except for PT children with a GA < 30 weeks; these were combined into one category.

Our choice of covariates was based on the literature on risk factors related to both being born preterm and age of developmental milestone attainment [20,21]. As covariates we included gender, ethnicity, being born small-for-gestational-age (SGA, defined as < P10 on Dutch Kloosterman curves), [22] and maternal educational level. Information on all covariates was extracted from a general questionnaire and matched to both hospital files and PCHC files.

2.3. Statistical analyses

First, we assessed background characteristics of the participating children per GA category, testing differences using X^2 tests for trends

Table 2
Participants' characteristics per gestational age category.

GA categories:		< 30 N = 186	30–31 N = 230	32–33 N = 265	34–35 N = 566	> 38 N = 488	P-value
Gestational age (weeks), mean (SD)		27.8 (1.2)	30.5 (0.5)	32.6 (0.5)	34.6 (0.5)	39.6 (1.0)	**< 0.001**
Gender, N male (%)		81 (43.5)	115 (50.0)	145 (54.7)	318 (56.2)	237 (48.6)	**0.013**
SGA, N (%)		40 (21.5)	32 (13.9)	25 (9.4)	47 (8.3)	35 (7.2)	**< 0.001**
Ethnicity mother							
N Other (%)		14 (7.8)	12 (5.3)	18 (6.8)	30 (5.3)	22 (4.8)	
N Caucasian (%)		166 (92.2)	216 (94.7)	247 (93.2)	536 (94.7)	440 (95.2)	0.55
Education mother							0.083
N Middle/High (%)		136 (73.5)	161 (70.3)	173 (65.5)	403 (71.7)	365 (75.1)	
N Low (%)		49 (26.4)	68 (29.7)	91 (34.5)	159 (28.3)	121 (24.9)	
N (%) of children with milestone data per GA category per time-point	1 m	*	38 (16.5)	74 (27.9)	327 (57.8)	359 (73.6)	**< 0.001**
	3 m	56 (30.1)	77 (33.5)	121 (45.7)	342 (60.4)	356 (73.0)	**< 0.001**
	6 m	82 (44.1)	116 (50.4)	142 (53.6)	377 (66.6)	353 (72.3)	**< 0.001**
	12 m	92 (49.5)	116 (50.4)	122 (46.0)	238 (42.0)	183 (37.5)	**0.004**
	15 m	150 (80.6)	165 (71.7)	183 (69.1)	388 (68.6)	294 (60.2)	**< 0.001**
	24 m	107 (57.5)	130 (56.5)	149 (56.2)	372 (65.7)	301 (61.7)	**0.029**
Age in weeks per time-point, mean (SD)	1 m	*	6.6 (1.9)	5.6 (1.3)	4.8 (1.1)	4.4 (1.0)	**< 0.001**
	3 m	14.5 (2.5)	13.8 (2.0)	13.6 (1.6)	13.3 (1.3)	13.3 (1.2)	**0.002**
	6 m	26.2 (2.1)	26.6 (2.5)	26.5 (2.6)	26.1 (2.3)	26.1 (2.4)	0.12
	12 m	50.3 (3.2)	50.1 (2.7)	50.0 (3.0)	50.0 (3.7)	49.5 (2.8)	0.058
	15 m	63.0 (2.8)	62.5 (3.6)	62.7 (3.5)	61.5 (3.0)	62.2 (2.7)	**0.018**
	24 m	105.8 (3.9)	105.7 (3.7)	106.2 (3.5)	105.3 (3.6)	105.1 (3.6)	0.094

P-values: chi-square test for trends or Kruskal-Wallis test where appropriate. SGA: small for gestational age (below P10 on Dutch Kloosterman growth curves). Maternal educational level: N = 1726. Low education: < 12 years of formal education; middle/high education: ≥ 12 years of formal education. Maternal ethnicity: N = 1701 (Dutch vs. non-Dutch). M = months.
*Excluded for the final results and figures because of too low numbers (all 13 children with a GA below 30 weeks with a motor assessment had an abnormal milestone score at one month of age).
Bold printed p-values indicate a significance < 0.05.

for binary variables or Kruskall-Wallis tests for continuous variables. Second, we assessed attainment rates of gross motor milestones for the GA categories, and differences between the PT categories and the reference FT group, using X^2 tests for all time-points. Third, we assessed the odds ratios (ORs) of failing gross motor milestones at different time-points, using univariable logistic regression. Thereafter we adjusted for gender, being born SGA, maternal educational level (low vs. middle/high) and maternal ethnicity (Dutch vs. non-Dutch). We have also compared gross motor milestone attainment for children with and without normal motor development at age 4, separately for MPT, EPT and FT children, and tested differences using chi square tests. All analyses were performed using SPSS version 23.0 (IBM, Chicago, Illinois, USA). P-values below 0.05 were considered to be statistically significant.

3. Results

Participant characteristics for the PT categories and FT children are shown in Table 2. Categories differed on almost all characteristics. Individual milestone data were available for 16–80% (mean 54.4%) of children in different GA categories across time-points. The mean age of the different PT categories was slightly higher than the mean age of FT children at the 1-, 3- and 15-month assessments.

3.1. Rates of motor milestone attainment and differences between PT and FT children

In the first six months of life all PT categories less frequently attained milestones within the set age ranges than did FT children (Fig. 1A). For FT children, gross motor milestone attainment rates varied between 55% and 96%. For PT categories, gross motor milestone attainment rates at the various time-points ranged from 16 to 96%. Differences in attainment rates between PT and FT children ranged from 9 to 60% (Fig. 1B). The lower the GA of the PT category, the more the attainment rates differed from those of FT children. Differences in attainment rates between FT and PT children decreased with calendar age for all categories of PT children. The PT category with the highest GA (34–35 weeks) had attainment rates equal to those of FT at age 12 months, whereas for the PT category < 30 weeks GA, rates remained 10% lower at 24 months of age compared with FT children (85 versus 95%, P < 0.01).

At 12 months, gross motor milestone attainment rates were lowest for all children, both PT categories and FT children. For the various PT categories, 61–83% were able to sit unaided, 62–79% were able to crawl and 35–72% were able to pull up to stand at that age. For FT children, attainment rates of these milestones ranged between 83 and 87%. Rates of attainment of the combination of all three milestones were lower than those for the separate milestones, but the pattern as observed in Fig. 1B remained consistent.

3.2. Risk of failing gross motor milestones per GA category

The higher the GA, the lower the ORs of failing milestones. With increasing calendar age, ORs gradually became lower for all PT categories. For children with a GA of 34/35 weeks, ORs became similar to ORs of FT children from 12 months onwards. For children with a GA of 32–33 weeks ORs became similar at 15 months and for children with a GA of 30–31 weeks at 24 months. For children with a GA < 30 weeks, the risk of failing gross motor milestones at 24 months was still threefold higher than for FT children (OR 3.36, CI 1.57–7.21 P = 0.002). Findings were very similar after adjustment for covariates (Table 3).

3.3. Difference between children with and without developmental delay at school entry

When comparing differences in gross motor milestone attainment among children with and without developmental delay at school entry, all children with motor delay tended to have a lower attainment rate for gross motor milestones (Table 4). For both MPT and EPT children with developmental delay at age 4 attainment rates were statistically significantly lower at 15 and 24 months.

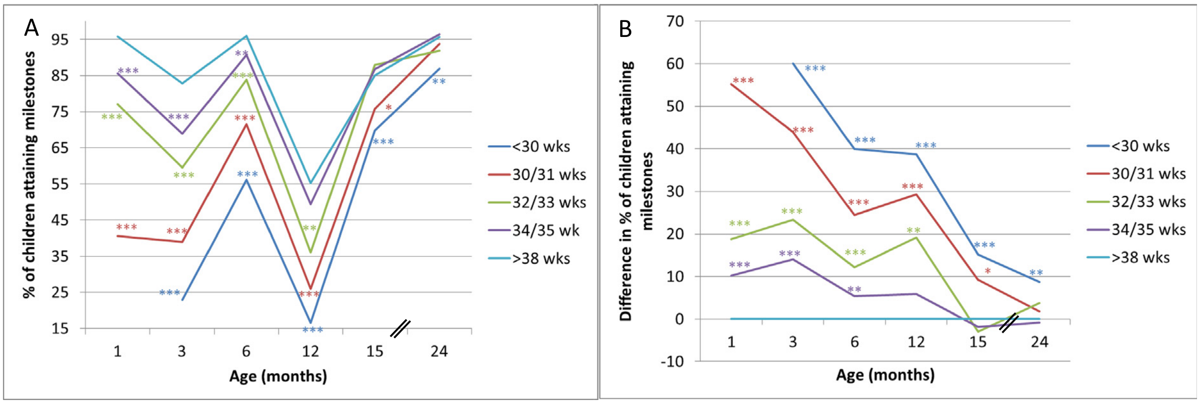

Fig. 1. Rates of children attaining developmental milestones at different time-points for children with a normal gross motor development at age four. A: absolute rates. B: differences in rates of attainment for preterm categories compared with fullterm children. * P < 0.05, ** P < 0.01, *** P < 0.001 for preterm categories compared with fullterm children.

Table 3
Odds ratios (OR), adjusted OR (aOR) and 95%-confidence intervals (CI) of the risk of failing developmental milestones for each gestational age category compared to fullterm children, per time-point.

Time-point	GA	OR	95%-CI	P-value	aOR[a]	95%-CI	P-value
1 m	< 30	–	–	–	–	–	–
	30/31	8.24	4.11–16.5	< **0.001**	8.40	4.16–17.0	< **0.001**
	32/33	4.90	2.35–10.2	< **0.001**	5.08	2.42–10.7	< **0.001**
	34/35	3.79	20.8–6.89	< **0.001**	3.83	2.10–6.99	< **0.001**
3 m	< 30	7.51	4.43–12.7	< **0.001**	7.31	4.29–12.5	< **0.001**
	30/31	3.98	2.50–6.34	< **0.001**	4.01	2.51–6.39	< **0.001**
	32/33	2.43	1.59–3.73	< **0.001**	2.48	1.61–3.81	< **0.001**
	34/35	1.99	1.41–2.82	< **0.001**	1.99	1.40–2.82	< **0.001**
6 m	< 30	15.0	7.85–28.8	< **0.001**	14.7	7.60–28.3	< **0.001**
	30/31	9.26	4.95–17.3	< **0.001**	9.33	4.98–17.5	< **0.001**
	32/33	3.93	2.01–7.69	< **0.001**	4.00	2.04–7.83	< **0.001**
	34/35	2.33	1.28–4.27	**0.006**	2.37	1.29–4.34	**0.005**
12 m	< 30	6.25	3.34–11.7	< **0.001**	5.85	3.11–11.0	< **0.001**
	30/31	3.27	1.99–5.39	< **0.001**	3.25	1.97–5.37	< **0.001**
	32/33	2.21	1.39–3.54	**0.001**	2.26	1.41–3.63	**0.001**
	34/35	1.23	0.84–1.18	0.30	1.26	0.86–1.86	0.24
15 m	< 30	2.49	1.55–3.98	< **0.001**	2.33	1.44–3.76	**0.001**
	30/31	1.74	1.08–2.80	**0.024**	1.70	1.05–2.75	**0.030**
	32/33	0.83	0.49–1.41	0.49	0.84	0.49–1.43	0.52
	34/35	0.85	0.55–1.31	0.45	0.88	0.57–1.36	0.56
24 m	< 30	3.59	1.70–7.58	**0.001**	3.36	1.57–7.21	**0.002**
	30/31	1.63	0.71–3.74	0.25	1.59	0.69–3.66	0.28
	32/33	2.00	0.94–4.30	0.07	2.01	0.93–4.32	0.07
	34/35	1.08	0.53–2.20	0.83	1.09	0.53–2.22	0.82

M = months.
Bold printed p-values indicate a significance < 0.05.
[a] Adjusted for gender (male vs. female), ethnicity (Dutch vs. non-Dutch), maternal educational level (middle/high vs. low) and being born small-for-gestational-age.

4. Discussion

In our study of PT and FT children with a normal development at age 4 years, rates of gross motor milestone attainment are highly dependent on the degree of prematurity in the first two years of life. Milestone attainment rates gradually increased during toddlerhood for all PT categories. For PT children with higher GA, differences in attainment rates compared with FT children were smaller and attainment rates became comparable to FT children at an earlier age. At 24 months, attainment rates were still lower for PT children with a GA < 30 weeks. Finally, milestone attainment rates were lowest for all children at age 12 months.

Our finding that the lower the GA the less likely children were to attain gross motor milestones between 1 and 24 months of age, is in line with other studies comparing motor skills of EPT children with those of FT children [10,11]. Our results contribute to previous research by incorporating many time points for a large GA-range. We believe that the increased risk of failing milestones for younger GA categories is due to a higher prevalence of perinatal complications, as well as a lower degree of maturation for children in various PT categories, compared with FT children [25]. We thus confirm, with a stronger design, that the risk of failing to reach milestones is strongly related to GA, largely independent of other covariates.

We found that motor milestone attainment rates become more similar for PT and FT children with advancing calendar age between 1 and 24 months of age. Our findings show that the lower the GA, the longer differences with FT children persist. This can be explained in two ways, based on different theories of development. First, the impact of being born preterm may decrease with advancing calendar age because the age ranges in which a developmental milestone should be mastered become wider with increasing age between birth and age 4 years. The chances for PT children to fit within the normal ranges of development

Table 4
Number (percentage) of gross motor milestone attainment per time-point, comparing children with normal (ASQ N) and abnormal (ASQ Abn) development at school entry, as measured by the Ages and Stages Questionnaire.

	FT children			MPT children			EPT children		
	ASQ N	ASQ Abn	P-value	ASQ N	ASQ Abn	P-value	ASQ N	ASQ Abn	P-value
1 m	344 (95.8)	13 (100)	0.45	337 (84.5)	27 (96.4)	0.084	–	–	–
3 m	295 (82.9)	9 (81.8)	0.93	308 (66.5)	10 (55.6)	0.34	42 (31.6)	11 (40.7)	0.36
6 m	339 (96.0)	12 (92.3)	0.51	461 (88.8)	17 (81.0)	0.27	129 (65.2)	16 (55.2)	0.30
12 m	101 (55.2)	5 (38.5)	0.24	162 (45.0)	8 (27.6)	0.069	45 (21.6)	5 (16.7)	0.53
15 m	250 (85.0)	10 (66.7)	0.057	498 (87.2)	27 (64.3)	< **0.001**	229 (72.7)	23 (52.3)	**0.006**
24 m	288 (95.7)	10 (90.9)	0.45	496 (96.2)	17 (58.6)	< **0.001**	215 (90.7)	21 (63.6)	< **0.001**

FT: fullterm, MPT: moderately preterm, EPT: early preterm, ASQ: Ages and Stages Questionnaire, N: normal, Abn: abnormal.
Bold printed p-values indicate a significance < 0.05.

will therefore increase as they get older [23]. This explanation postulates that development starts at conception and proceeds with a more or less fixed velocity of steps, and that thus the relative impact of prematurity decreases.

A second explanation for the decreasing differences in attainment rates with increasing calendar age for PT regards developmental catch-up, with PT children initially lagging behind but then attaining further milestones more quickly than FT children. This explanation postulates that the pattern of development of PT children differs from that of FT children, due to their different interplay between GA at birth, their brain plasticity, and the starting points of their interaction with the environment (nature versus nurture) [24].

With the available data, we cannot draw a definitive conclusion on which explanation for our findings is best. Discrimination between the two explanations requires additional data on attainment rates for PT children at corrected ages. We can, however, once more confirm that GA is a strong predictor of the risk of failing to reach milestones, while other risk factors hardly changed the effect size. This study might be a first step in unravelling the typical pattern of motor development for PT children, as we included only FT and PT children with development in the normal range upon school entry. Next, this study might lead to more understanding of development in other domains, as problems in motor function have also been linked to problems in other developmental domains later on [7–9].

We found attainment rates to be lowest at 12 months of age for all categories, including FT children. This could be an artefact, as at 12 months we assessed the highest number of milestones (three), making it computationally more likely to fail at this time-point. After only incorporating two out of the three milestones in various combinations, differences in gross motor attainment rates between PT and FT children remained greatest at this time-point. Another explanation might be that the 12-month milestones within the DDDS are more difficult to achieve within the set age range, or actually have a higher degree of variability in attainment age [11].

We have compared attainment rates of children with and without motor delay at school entry. Generally, all children with developmental delay at age 4 showed lower attainment rates of gross motor milestones throughout the first two years than the children without developmental delay, confirming the predictive validity of these milestones. However, these findings should be interpreted with some caution because of the relatively small numbers.

4.1. Strengths and limitations

The strengths of this study are its large, community-based cohort, including a large GA range of PT children and a large control group of FT children. Moreover, data were collected from the PCHCs in a standardized manner. Furthermore, we included many time-points to assess gross motor development longitudinally for the same group of children. Another strength is that we restricted our study to children with a normal gross motor development at age 4 years, to study the typical pattern of development of PT children. Finally, we limited potential confounding by excluding children with major congenital malformations and syndromes, often born PT.

This study also had some limitations. First, we used a parent-completed screening instrument (the ASQ), and not a validated gross motor test, to determine motor development status upon school entry. Nevertheless, the Dutch ASQ at 4 years is a valid screening tool for the assessment of motor development, with high sensitivity (89%) at acceptable specificity (80%) [18]. This suggests that the children that were included in our study most likely had normal gross motor development at school entry. Second, the mean gross motor milestone assessment rate was 55% across time points. Rates did not vary by GA in a major way, and neither by other major determinants of development, thus limiting the impact of bias, if any. Third, in our study, we did not have complete information on early interventions received by the participating children. These early interventions might have some impact on our results.

4.2. Implications

Our finding that calendar ages at which attainment rates of normally developing PT children became similar to those of FT children largely varied by GA, may imply that the period of adjustment should vary by GA too. Our finding that for MPT rates of attainment became similar before 12 months of age, whereas EPT still had lower rates of attainment at 24 months of age, might suggest that correction for GA could be applied for a shorter period of time for MPT children and that correction for GA until at least 24 months of age is appropriate for EPT children. Further research is needed to determine whether our findings are explained by a developmental catch-up or by a decrease of the impact of prematurity with advancing calendar age.

4.3. Conclusion

Rates of gross motor milestone attainment are highly dependent on the degree of prematurity in the first two years of life. The lower the GA, the longer differences in attainment of gross motor milestones between PT and FT children persist. At 24 months' calendar age, attainment rates of PT children with a GA < 30 weeks remain lower.

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