Stability of Developmental Problems after School Entry of Moderately-Late Preterm and Early Preterm-Born Children

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Objective To assess the stability of developmental problems in moderately-late preterm-born children compared with early preterm and full term-born children before school entry at age 4 years and 1 year after school entry at age 5 years.

Study design We included 376 early preterm, 688 born moderately-late preterm, and 403 full term-born children from the Longitudinal Preterm Outcome Project (LOLLIPOP) cohort study. Developmental problems were assessed by the total score and the 5 domain scores of the Ages and Stages Questionnaire at ages 4 (ASQ-4) and 5 (ASQ-5). From the combinations of normal and abnormal ASQ-4 and ASQ-5 scores we constructed 4 categories: consistently normal, emerging, resolving, and persistent problems.

Results The ASQ-4 total score was abnormal more frequently in moderately-late preterm (7.9%, $P = .016$) and early preterm-born children (13.0%, $P < .001$) than in full term-born children (4.1%). Compared with the ASQ-5 total score, moderately-late preterm-born children had persistence and change comparable with full term-born children, and early preterm-born children had significantly greater rates than full term-born children of persistent (8.4% vs 2.2%, $P < .001$) and emerging problems (7.8% vs 2.7% $P = .001$). On the underlying domains, both early preterm and moderately-late preterm-born children had mainly emerging motor problems and resolving communication problems, but the changing rates of moderately-late preterm-born children were lower.

Conclusions After school entry, the overall development of moderately-late preterm-born children had stability patterns comparable with full term-born children, whereas early preterm-born children had greater rates of persistent and emerging problems. On the underlying domains, moderately-late preterm-born children had patterns comparable with early preterm-born children but at lower rates. *(J Pediatr 2017;187:73-9).*

Preterm birth (<36 weeks' gestational age [GA]) has important consequences for further short-term and long-term development. Worldwide, 11% of the children are born preterm.[1] At preschool age, 15%-24% of early preterm-born children (<32 weeks' GA), and 8%-25% of moderately-late preterm-born children ($32^{0/7}$-$35^{6/7}$ weeks' GA) have developmental problems, in comparison with 4%-14% of full term-born children (38-41 weeks' gestational age).[2,3] After school entry, similar prevalence rates of developmental problems are reported among preterm-born children.[4,5] However, the preterm-born children with developmental problems at preschool age may not be the same children as those with developmental problems at early school age, as school entry stimulates development but also puts more demands on children's abilities.

Evidence on the stability of developmental problems of preterm-born children mainly concerns early preterm-born children and/or children with a low birth weight (<1500 g).[6,7] These early preterm-born children show, at age 4 years, greater rates of developmental problems on all domains,[8] which both emerge and resolve after school entry.[9-11] However, the evidence per developmental domain is inconsistent.[6,12] Moderately-late preterm-born children have at age 4 years problems with communication, fine motor function, and personal social skills.[8] After school entry, these preschool developmental problems of moderately-late preterm-born children are not good predictors for school problems and school readiness (predictive values 10.4%-17.1%).[13,14] However, studies that assess the association of developmental problems among moderately-late preterm-born children before and after school entry are lacking.

The aim of this study was to assess the stability patterns of developmental problems, overall and per domain, among moderately-late preterm-born children compared with early preterm-born children and full term-born children between the time before school entry and 1 year after school entry. We expected that

ASQ	Ages and Stages Questionnaire
ASQ-4	Ages and Stages Questionnaire appropriate for age 4
ASQ-5	Ages and Stages Questionnaire appropriate for age 5
GA	Gestational age
LOLLIPOP	Longitudinal Preterm Outcome Project

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developmental problems may both emerge and resolve after school entry, because this not only places greater demands on children's abilities but also provides them with more opportunities to practice these abilities by stimulating activities and by interacting with other children. In addition, we expected that problems might emerge more frequently in early preterm-born children and resolve more frequently in moderately-late preterm-born children, because moderately-late preterm-born children may have a less disrupted white matter maturation and more cortical plasticity than early preterm-born children.[15,16] These patterns may help to determine in advance of school entry which preterm-born children are likely to have the greatest risks of persistent and emerging problems after school entry and in which specific developmental domains. Such insight is important for the prevention and early identification of developmental problems in well-child care and neonatal follow-up and could facilitate early intervention, increasing the likelihood of normal development.

Methods

This study was part of the Longitudinal Preterm Outcome Project (LOLLIPOP) cohort study, which has its main focus on the growth and development of moderately-late preterm-born children compared with both early preterm and full term-born children (controlled-trials.com ISRCTN 80622320). The LOLLIPOP cohort is a community-based sample of early preterm and moderately-late preterm-born children and a random sample of full term-born children, born in 2002 and 2003 in the Netherlands. This community-based sample came from 13 preventive child health centers. These centers monitored a sample representative of 25% of the children born in 2002 and 2003 in The Netherlands. Children were included before their regular well-child visit at the age of 43-49 months. All children born before 36 weeks' GA without major congenital malformations, congenital infections, or syndromes were sampled. After each second preterm-born child which was sampled, the next full term-born child (38-41 weeks' GA), without the aforementioned exclusion criteria, was drawn from the same files to serve as a control. In addition, the early preterm-born sample was enriched with a sample of early preterm-born children, born in 2003, taken from 5 of the 10 neonatal intensive care units in The Netherlands. A detailed description of this study cohort can be found elsewhere.[8]

Measures

Developmental Problems: Ages and Stages Questionnaire (ASQ). Developmental problems were measured with the ASQ, which is, worldwide, the most commonly used parent-completed developmental screener.[17] We used the validated Dutch versions appropriate for ages 4 (ASQ-4) and 5 years (ASQ-5).[18-20] The ASQ contains 5 domains: communication, gross motor, fine motor, problem solving, and personal-social skills. Each domain is assessed by the use of 6 questions about reaching milestones. The response format is "yes" (10 points), "sometimes" (5 points), or "not yet" (0 points). The scores of the questions were summed into a score for each domain separately and overall, the ASQ total score. Subsequently, these scores were categorized into normal and abnormal scores, defined as abnormal if the score was more than 2 SDs below the mean of the Dutch reference population.[19,20]

We combined the dichotomous ASQ-4 and ASQ-5 outcomes on the 5 ASQ domains and the ASQ total score to form 4 stability categories for each ASQ outcome: stable normal, emerging problems, resolving problems, and persistent problems. The stable normal group had normal scores at both ages, the emerging problems group had a normal ASQ-4 score and an abnormal ASQ-5 score, the resolving problems group had an abnormal ASQ-4 and a normal ASQ-5, and the persistent problems group had 2 abnormal scores.

Gestational Age. The children in the preterm-born group were split into an early preterm-born category ($25^{0/7}$-$31^{6/7}$ weeks' GA) and an moderately-late preterm-born category ($32^{0/7}$-$35^{6/7}$ weeks' GA). GA was determined in completed weeks and was based on early ultrasound measurements in >95% of the cases. For the remaining cases, only clinical estimates based on last menstrual date were available; these were checked against clinical estimates of GA after birth.

Covariates. Covariates were selected based on previous studies of developmental problems in preterm-born children[6,7,21,22] and were divided into perinatal characteristics and family characteristics. Perinatal characteristics included sex, small for GA, and being part of a multiple pregnancy. Small for GA was determined as a birth weight below the 10th centile of the Dutch growth chart.[23] Family characteristics included low education of both mother and father, ethnicity (birth of parent and/or child outside the Netherlands), and single-parent family. Low education was defined as maximally primary education or low-level technical or vocational training.

Procedure

One month before the children's well-child visit at age 43-49 months, parents received information about the LOLLIPOP study, an informed consent form, the ASQ-4, and a questionnaire about family and perinatal characteristics. These were returned by the parents at their child's scheduled well-child visit. Following parental informed consent, we retrospectively recorded perinatal characteristics from discharge letters of mother and child, well-child care records, and information from linked national birth registers. Approximately 4-6 weeks before the child's fifth birthday, parents received the ASQ-5. The ASQ-5 was returned by mail.

The ASQ-4 and ASQ-5 were completed within the determined time windows[19,20] (43-49 months and 57-63 months after birth, respectively) for 1467 children, including 376 early preterm, 688 moderately-late preterm, and 403 full term-born children (**Figure 1**). The children with only an ASQ-4 (within the time window) but not an ASQ-5 (no ASQ-5 n = 484, outside time window n = 25) had more frequently an abnormal ASQ-4 total score than the children with completed ASQ's at both ages (11.1% vs 8.1%, $P = .048$), and their parents had more frequently a low education (28.6% vs 14.2%

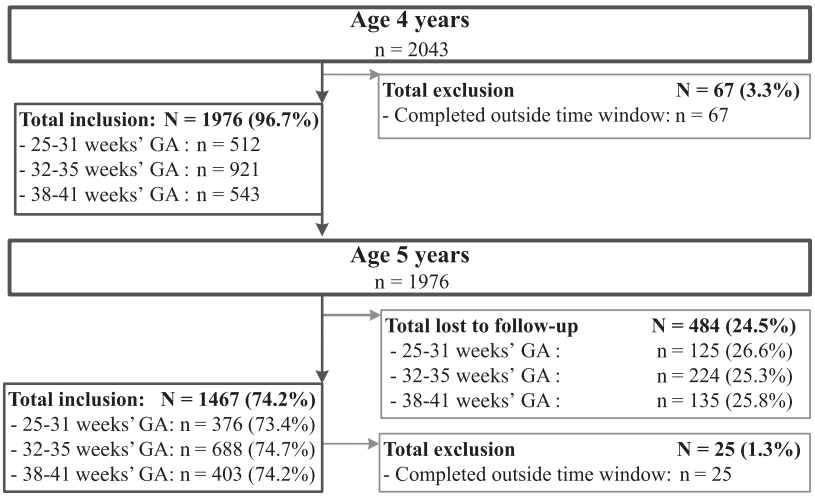

Figure 1. Overview of the children who were included in this study.

$P < .001$). Similar rates of preterm and full term-born children were lost to follow-up (25.8% vs 25.8%, $P = .988$).

Statistical Analyses

First, we compared characteristics between the GA groups (early preterm, moderately-late preterm, and full term). Second, we determined the overall stability per GA group by comparing rates of abnormal scores on the ASQ-4 and ASQ-5. Third, we assessed individual stability within the GA groups in 2 ways: by calculating the predictive values and by comparing prevalence rates of the 4 stability categories (consistently normal, resolving problems, emerging problems, persistent problems). The "predictive value of a normal ASQ-4" was defined as the proportion of children with a normal ASQ-5 out of the children with a normal ASQ-4, and the "predictive value of an abnormal ASQ-4" was defined as the proportion of children with an abnormal ASQ-5 out of the children with an abnormal ASQ-4. We performed the analyses on the 4 stability categories, both crude and adjusted for perinatal and family characteristics (sex, small for GA, being part of a multiple birth, low education level of the parents, non-Dutch birth country of parent or children, and single-parent family). All tests performed were 2-tailed and considered as significant when $P < .05$.

Results

Table I shows the main characteristics of the early preterm, moderately-late preterm, and full term-born children. The early preterm and moderately-late preterm-born children differed significantly from the full term-born children in characteristics associated with prematurity (small for GA, $P_{\text{early preterm}} < .001$; being a twin, $P_{\text{early preterm}}$ and $P_{\text{moderately-late preterm}} < .001$; male sex, $P_{\text{moderately-late preterm}} < .001$) and family composition (single-parent family, $P_{\text{early preterm}} = .011$, $P_{\text{moderately-late preterm}} = .002$; education level of parents, $P_{\text{moderately-late preterm}} = .012$; birth country of parents, $P_{\text{early preterm}} = .013$).

Stability of Developmental Problems per GA Group

Table II shows the rates of abnormal scores on the ASQ-4 and ASQ-5 per GA category. The total ASQ-4 score was abnormal more frequently in early preterm (13.0%, $P < .001$) and moderately-late preterm-born children (7.9%, $P = .004$) compared with full term-born children (4.1%) (Table II). However, the total ASQ-5 score was abnormal more frequently only in early preterm-born children (16.2%, $P < .001$) and not in moderately-late preterm-born children (7.3%, $P = .121$), compared with full term-born children (4.8%) (Table II). Concerning the ASQ domains, early preterm-born children had significantly more abnormal scores on all ASQ domains at both ages 4 and 5 than did full term-born children (P values $\leq .004$), except for communication on the ASQ-5 ($P = .067$). Moderately-late preterm-born children had significantly more abnormal scores than full term-born children on different domains on the ASQ-4 (communication, $P = .013$; fine motor, $P = .004$; and personal social, $P = .005$) than on the ASQ-5 (gross motor, $P < .001$; and personal social, $P = .003$), in which rates

Table I. Characteristics of children by GA category

Characteristics	Full term n = 403 n (%)	Moderately-late preterm n = 688 n (%)	Early preterm n = 376 n (%)
GA, median (25-75th percentile)	40 (39-40)	34 (33-35)*	30 (28-31)*
Boy	190 (47.1)	401 (58.3)*	191 (50.8)
Small for GA	28 (6.9)	64 (9.3)	81 (21.5)*
Twin	5 (1.2)	178 (25.9)*	113 (30.1)*
Single-parent family	8 (2.0)	44 (6.4)†	21 (5.6)‡
Low educational level			
Of both parents	43 (10.8)	111 (16.4)‡	51 (13.7)
Of mother	88 (21.9)	181 (26.5)	84 (22.4)
Of father	101 (25.6)	210 (31.1)‡	98 (26.4)
Non-Dutch birth country of parent and/or child	17 (4.3)	49 (7.2)	32 (8.7)‡

*$P < .001$, †$P < .01$, ‡$P < .05$; based on crude logistic regression analyses with full term as reference category.

Table II. Rates of abnormal ASQ scores and PVs of normal and abnormal ASQ-4 total and domain scores for the corresponding ASQ-5 scores, per GA category

Scores	Full term	Moderately-late preterm	Early preterm
Overall scores			
Total score			
Abnormal on ASQ-4, n (%)	16 (4.1)	**53 (7.9)**‡	**48 (13.0)***
Abnormal on ASQ-5, n (%)	18 (4.8)	47 (7.3)	**57 (16.2)***
PV normal ASQ-4	0.97	0.96	**0.91**†
PV abnormal ASQ-4	0.50	0.46	0.63
Scores per domain			
Communication			
Abnormal on ASQ-4, n (%)	22 (5.5)	**68 (10.0)**‡	**50 (13.4)***
Abnormal on ASQ-5, n (%)	11 (2.8)	26 (3.9)	20 (5.6)
PV normal ASQ-4	0.98	0.98	0.97
PV abnormal ASQ-4	0.09	0.25	0.20
Gross motor			
Abnormal on ASQ-4, n (%)	15 (3.7)	35 (5.1)	**47 (12.5)***
Abnormal on ASQ-5, n (%)	14 (3.5)	**70 (10.2)***	**68 (18.1)***
PV normal ASQ-4	0.98	**0.93**†	**0.88***
PV abnormal ASQ-4	0.40	0.59	0.64
Fine motor			
Abnormal on ASQ-4, n (%)	14 (3.5)	**55 (8.0)**†	**32 (8.5)**†
Abnormal on ASQ-5, n (%)	28 (7.1)	68 (10.0)	**63 (16.9)***
PV normal ASQ-4	0.94	0.93	**0.87**†
PV abnormal ASQ-4	0.50	0.47	0.59
Problem solving			
Abnormal on ASQ-4, n (%)	15 (3.8)	41 (6.0)	**34 (9.1)**†
Abnormal on ASQ-5, n (%)	18 (4.5)	34 (5.0)	**42 (11.3)**†
PV normal ASQ-4	0.97	0.97	**0.91**†
PV abnormal ASQ-4	0.40	0.34	0.39
Personal social			
Abnormal on ASQ-4, n (%)	9 (2.2)	**42 (6.1)**†	**31 (8.3)***
Abnormal on ASQ-5, n (%)	11 (2.8)	**49 (7.1)**†	**45 (12.1)***
PV normal ASQ-4	0.98	**0.94**‡	**0.93**†
PV abnormal ASQ-4	0.22	0.29	**0.65**‡

PV, predictive value.
Values in bold indicate statistical significance.
*$P < .001$, †$P < .01$, ‡$P < .05$; based on crude logistic regression analyses with full term as reference category.

of abnormal communication scores were lower on the ASQ-5 than the ASQ-4 (3.9%, $P = .349$, vs 10.0%, $P = .013$, respectively), but rates were greater on the ASQ-5 than on the ASQ-4 regarding abnormal gross motor scores (10.2%. $P < .001$, vs 5.1%, $P = .292$, respectively) and abnormal fine motor scores (10.0%, $P = .105$, vs 8.0%, $P = .004$, respectively).

Stability of Developmental Problems within the GA Groups

Table II also shows the individual persistence and change of developmental problems as measured by the predictive values of normal and abnormal ASQ-4 scores for the corresponding ASQ-5 scores. Regarding total scores of both preterm and full term-born children, the predictive values of a normal ASQ-4 were greater than the predictive values of an abnormal ASQ-4 (91%-97% and 50%-63%, respectively). The predictive value of a normal ASQ-4 was lowest for early preterm-born children (91% vs 97% for full term-born children, $P = .001$).

Figure 2 shows an overview of the individual persistence and change between the ASQ-4 and ASQ-5 for the 4 stability categories. The majority of the early preterm, moderately-late preterm, and full term-born children had consistently normal ASQ total scores (78.9%, 88.8%, and 92.9%, respectively). Compared with full term-born children, early preterm-born children had significantly more persistent (8.4% vs 2.2%, $P < .001$), emerging (7.8% vs 2.7%, $P = .001$), and resolving problems (4.9% vs 2.2%, $P = .026$) on the ASQ total score and on most ASQ domain scores. The stability of the ASQ total score of moderately-late preterm-born children was comparable with full term-born children ($P \geq .080$). However, on the underlying domains, stability patterns differed between moderately-late preterm and full term-born children. Rates of moderately-late preterm-born children in the stability categories were in between early preterm and full term-born children for the domains communication ($P_{persistent} = .036$), gross motor ($P_{emerging} = .001$), fine motor ($P_{resolving} = .034$), and personal social ($P_{emerging} = .015$, $P_{resolving} = .020$) but very comparable with full term-born children for problem solving ($P \geq .140$) and the total score ($P \geq .080$). Regarding both early preterm and moderately-late preterm-born children, communication problems mainly resolved (11.2%, $P = .003$, 7.5%, $P = .150$, respectively, vs 5.2%), and motor problems emerged (gross motor: 10.2%, $P < .001$, 7.1%, $P = .001$, respectively, vs 2.0%; fine motor: 11.8%, $P = .001$, 6.4%, $P = .388$, respectively, vs 5.3%). After adjustment for confounders, early preterm-born children still were more likely to have persistent (OR 3.02; 95% CI 1.28-7.10; $P = .012$) and emerging (OR 4.37; 95% CI 1.87-10.20; $P < .001$) problems on the ASQ total score in comparison with full term-born children, but not significantly more resolving problems (OR 1.55; 95% CI 0.061-3.94; $P = .359$).

Discussion

This study demonstrated that in the period after school entry, stability patterns of moderately-late preterm-born children were comparable with full term-born children, whereas early preterm-born children had greater rates of persistent and emerging developmental problems than full term-born children. With regard to the underlying domains, both moderately-late preterm- and early preterm-born children showed more emerging motor problems and more resolving communication problems.

Moderately-late preterm-born children had stability rates comparable with full term-born children regarding their overall development and problem solving, but the stability rates of moderately-late preterm-born children were in between the rates of early preterm and full term-born children for the other developmental domains. These results indicate that the relation between the GA in weeks of prematurity and the stability of developmental problems varies by developmental domain. The stability patterns of total developmental problems and problem-solving problems seem to be exponentially related to decreasing GA, with mainly the lowest GAs showing more persistent and changing problems. The stability patterns of the other underlying domains seem to be related linearly to decreasing GA, with persistent and changing problems gradually increasing with decreasing GA. These exponential and linear associations also were reported for developmental problems at a specific age.[2,24-26] In summary, the degree of prematurity

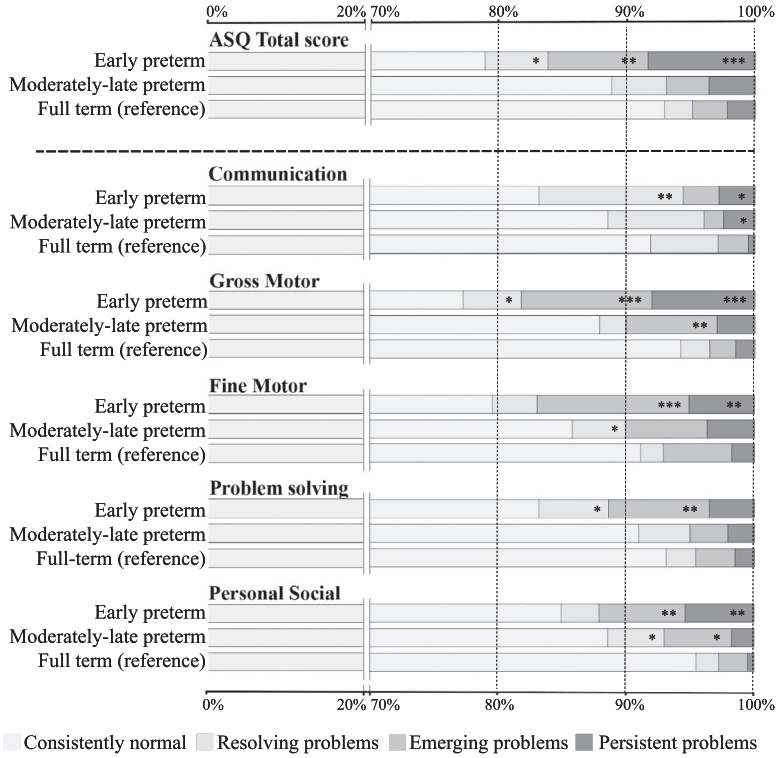

Figure 2. Rates of persistent and changing scores on the ASQ total score and the separate ASQ domains between ages 4 and 5 years among early preterm-born children, moderately-late preterm, and full term. *$P < .05$; **$P < .01$; ***$P < .001$, based on crude and adjusted multinomial logistic regression analyses with consistently normal full term as the reference category.

seems to have both exponential and linear relations with the stability patterns of developmental problems.

Both early preterm and moderately-late preterm-born children had greater rates of developmental problems than full term-born children before school entry, but 1 year after school entry only early preterm-born children had persistent and emerging problems more often. In a small cohort of preterm-born children at $34^{0/7}$-$36^{6/7}$ weeks' GA, rates of developmental problems also decreased between ages 4, 8, and 18 months. Studies regarding early preterm-born children reported the following as predictive values for persistent (mild-severe) developmental problems: 50%-71% for age 2/3 years and age 5/8 years; we found a comparable value of 63%.[9-11,27] Moderately-late preterm-born children may have more adaptation capacities than early preterm-born children, as moderately-late preterm-born children are born at a greater GA and have fewer postnatal complications.[24] Consequently, their brain's white matter maturation and cortical plasticity are less likely to be disrupted.[15,16] This may result in moderately-late preterm-born children having more abilities than early preterm-born children to improve their performance in a stimulating school environment.

Communication problems frequently resolved among both early preterm and moderately-late preterm-born children. We were surprised by these findings, because they contrast with studies among early preterm-born children <30 weeks' GA at comparable ages.[28,29] Howard et al[29] and Woods et al[28] found significant associations between communication problems and persistent language impairment from age 2-3 years to age 5 years. In addition, 71% of the early preterm-born children from the study by Woods et al[28] had persistent language impairment between ages 3 and 5 compared with 20% in our early preterm group. Different perspectives may shed light on our contradictory findings. First, clinimetric issues may explain our findings: for example, the questions on communication in the ASQ-4 could be relatively more difficult than those in the ASQ-5. However, this is unlikely, given the high validity of the ASQ-4 and ASQ-5 and the high reliabilities of the scores for the domain communication (Cronbach alphas 0.74 and 0.64, respectively).[19,20] Second, school entry may enhance a child's communication skills by the increased interaction with other children and the teacher and activities such as talking in group discussions, reading books, and singing songs.

The children from the studies by Howard et al[29] and Woods et al[28] did not attend, or had only very recently attended school, as the age of school entry in Australia is 5 years instead of 4 (as it is in The Netherlands). Therefore, unlike in our study, the stability of language skills of the children in these Australian studies could not be related to the event of school entry.

Gross and fine motor problems frequently emerged and persisted among early preterm and moderately-late preterm-born children after school entry. Greater rates of persistent and emerging fine and gross motor problems also were reported

previously in early preterm-born children ≤28 weeks' GA between age 2-3 years and age 5 years.[6,30] As with communication skills, we also expected school entry to have a positive influence because of stimulating activities such as sporting during gymnastic lessons, playing outside, and doing crafts. However, due to more demanding educational programs, schools allow less time for these motor activities. In addition, 5-year-old children become less physically active than 3- to 4-year-old children and spend more time behind a computer screen and television.[31] The combination of decreasing physical activity at home and limited time for motor activities at school may explain the emerging and persistent motor problems of preterm children after school entry.

The strengths of this study are its large community-based cohort, which included early preterm, moderately-late preterm as well as full term-born children. Furthermore, we used the same developmental screening tool at both ages. In addition, we were able to adjust our analyses for important confounders, such as the educational level of the parents and the child being small for GA. Our study also has some limitations. First, we used the parent-reported ASQ, which might be less valid than a clinical assessment. However, testing in the safety of a home situation may be more representative for a child's performance than in a consultation room. Second, we had no information about interventions between ages 4 and 5 years, which might have influenced persistence and change. Third, almost one quarter of the study sample was lost to follow-up between ages 4 and 5 years. This is probably due to the fact that at age 4 years parents filled out the questionnaires in advance of a well-child visit but at age 5 years had to return it by mail. In addition, children lost to follow-up had more frequently a low ASQ-4 total score than those with both ASQs. However, we do not expect that this loss to follow-up had a major influence on our findings, as similar rates of preterm and full term-born children were lost to follow-up.

Our study showed that developmental problems among preterm-born children are not always persistent but may emerge or resolve after school entry. Therefore, developmental surveillance of both early preterm and moderately-late preterm-born children should be continued at least until after school entry.

Future research should determine whether these trends continue during primary school ages among early preterm and moderately-late preterm-born children. Although we found different patterns for early preterm, moderately-late preterm, and full term-born children, the variation in individual persistence and change also was large within the GA categories. Therefore, future studies should determine the influence of other factors—such as physical activity, screen time, and educational programs—on the persistence and/or change of developmental problems of children born preterm.

In conclusion, after school entry, in overall development the moderately-late preterm-born children had stability patterns comparable with those of full term-born children, whereas early preterm-born children had greater rates of persistent and emerging problems. On most underlying domains, moderately-late preterm-born children had, although with lower rates, stability patterns comparable with those of early preterm-born children: motor problems mainly emerged and communication problems resolved. Given the great differences in the stability of developmental problems of individual preterm-born children, developmental surveillance of these children should be continued after school entry. ■

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