The association between gestational age, attainment of smiling and walking, and development at school entry

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Abstract

BACKGROUND: Developmental milestones, such as ‘smiling’ and ‘walking’, are used worldwide to monitor development of children. Preterm-born children reach developmental milestones later than term-born children. Exact attainment ages and predictive values for later neurocognitive functioning of these milestones for preterm-born children are still largely unknown.

AIM: First, to assess the association between gestational age (GA) and attainment ages of smiling and walking (smiling-age, walking-age). Second, to assess the predictive values of smiling-age and walking-age for developmental delay at age 4 years.

METHODS: Smiling-age was recorded for 201 term-born and 454 preterm-born children and walking-age for 425 term-born and 1,080 preterm-born children. Development was assessed at 4 years with the Ages and Stages Questionnaire (ASQ). We assessed the association between GA and attainment ages with Pearson correlation coefficients. Next, we assessed crude and adjusted odds for failing ASQ domains, with later smiling-age and walking-age.

RESULTS: GA was correlated with smiling-age (ρ -0.742, P<0.001), and walking-age (ρ -0.415, P<0.001). For every week a child smiled later, the adjusted odds for an abnormal ASQ-communication score increased with 16% (odds ratio [OR] 1.16, 95%-confidence interval [CI] 1.02-1.32). Smiling-age was not associated with other ASQ-domain scores. For every month a child walked later, the additional odds for an abnormal ASQ-total score was 14% (OR 1.14, CI 1.07-1.21). Walking-age was associated with failing on underlying gross motor, fine motor and problem solving ASQ domains.

CONCLUSIONS: Smiling-age is strongly associated with GA and predicts communication delay at age 4, independent of GA. The association of walking-age to GA is moderate, and predictive of developmental delay in several domains at age 4 years, independent of GA.

Nederlandse Samenvatting

INTRODUCTIE: De ontwikkeling van kinderen wordt wereldwijd gevolgd met behulp van ontwikkelingsmijlpalen, zoals teruglachen en loslopen. Voor prematuren is er weinig bekend over de leeftijd van het bereiken van deze mijlpalen en de voorspellende waarde hiervan voor latere neurocognitieve ontwikkeling.

DOEL: Vaststellen van de associatie tussen zwangerschapsduur en de leeftijd van bereiken van de mijlpalen ‘teruglachen’ en ‘loslopen’. Daarnaast vaststellen wat de voorspellende waarde van de leeftijd van behalen van deze mijlpalen is voor ontwikkeling op 4-jarige leeftijd.

METHODOLOGIE: Ouders uit het Pinkeltje cohort ('02-'03) benoemden bij het consultatiebureau de leeftijd waarop kinderen teruglachten (201 à termen en 454 prematuren) en losliepen (425 à termen en 1,080 prematuren). Op 4-jarige leeftijd werd de Ages and Stages Questionnaire (ASQ) ingevuld. We beoordeelden de associatie tussen zwangerschapsduur en leeftijd van bereiken van de mijlpalen met behulp van Pearson correlatiecoëfficiënten. De voorspellende waarde van behalen van mijlpalen voor de ontwikkeling op 4-jarige leeftijd bepaalden we met logistische regressie, waarin ook zwangerschapsduur werd meegenomen.

RESULTATEN: Zwangerschapsduur is negatief gecorreleerd met de leeftijd van teruglachen (ρ -0.742, P<0.001), en met de leeftijd van loslopen (ρ -0.415, P<0.001). Later teruglachen was alleen geassocieerd met een hogere kans op communicatieproblemen (odds ratio [OR] 1.16, 95%-betrouwbaarheidsinterval [BI] 1.02-1.32). Voor elke maand die een kind later losliep, steeg de kans op een afwijkende ASQ-totaal score met 14% (OR 1.14, BI 1.07-1.21). Ook voor de ASQ-domeinen grove en fijne motoriek en probleemoplossend vermogen steeg de kans op afwijkende scores bij later loslopen.

CONCLUSIE: De leeftijd van teruglachen is sterk gecorreleerd met zwangerschapsduur, en voorspelt communicatie op 4-jarige leeftijd, onafhankelijk van zwangerschapsduur. De leeftijd van loslopen is minder sterk geassocieerd met zwangerschapsduur, en voorspelt uitkomsten in meerdere ontwikkelingsdomeinen, onafhankelijk van zwangerschapsduur.
## List of Abbreviations

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<th>Full Form</th>
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<tbody>
<tr>
<td>GA</td>
<td>Gestational Age</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
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<td>ASQ</td>
<td>Ages and Stages Questionnaire</td>
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<tr>
<td>vWS</td>
<td>&quot;Van Wiechen Schema&quot;</td>
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<tr>
<td>PCHC</td>
<td>Preventive Child Healthcare Center</td>
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<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
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<tr>
<td>LOLLIPPO</td>
<td>Longitudinal Preterm-born Outcome Project</td>
</tr>
<tr>
<td>Pinkeltje</td>
<td>Preterm-born infants: knowledge on target height and outcome</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>SGA</td>
<td>Small for Gestational Age</td>
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Introduction

Worldwide, development of both preterm-born and term-born children is followed closely by means of monitoring attainment of developmental milestones, such as “smiling in response” and “walking independently”. The ultimate aim is to detect developmental delays early on, to be able to offer targeted early interventions. To detect possible developmental delays, both normal ranges of milestone attainment ages and predictive values of later milestone attainment are important.

For term-born children (born after a normal gestational age [GA] of 38 to 42 weeks), attainment ages of various developmental milestones have been firmly established. For this group, assessing developmental milestones has indeed proven to be useful in predicting developmental delay later in life. For example, reaching developmental milestones at an earlier age than other term-born children is associated with higher educational levels at ages 16 and 31 years. In addition, attainment ages of motor and cognitive milestones of term-born children have been associated with intelligence quotient (IQ) at ages 8, 26 and 53 years. In the same study, academic achievement was predicted by cognitive milestone attainment, but not by motor milestone attainment. For term-born children, age of attainment of combined motor and/or mental developmental milestones has also been linked to functional outcome in other developmental domains, illustrated by the association between personal-social development of term-born children and risk of Autism Spectrum Disorder.

For early preterm-born children (GA below 32 weeks), it is known that the attainment ages for most milestones in infancy and early toddlerhood are later than for term-born children, although exact age ranges are still largely unknown. In a large cohort study involving early preterm-born children, approximately 19% experienced severe developmental delay (i.e. being delayed in milestone attainment) from the early neonatal period onwards. At school age, these early preterm-born children showed poorer academic achievement in all subjects, with most problems in mathematics. An even larger group than the early preterm-born children, but gaining much less attention in international research, are the moderately preterm-born children (GA between 32 and 36 weeks). This group comprises approximately 85% of all preterm-born children. Moderately preterm-born children are also at increased risk of adverse developmental outcomes, albeit to a lesser extent than early preterm-born children. Moderately preterm-born children experience more motor, sensory and neurocognitive developmental delay, and more developmental delay at school age than term-born children as well. For the moderately preterm group, even less evidence exists on normal attainment ages of developmental milestones.

For both preterm groups, the delayed attainment of milestones is attributed to a shorter post conception age (less weeks in the womb before birth) and altered brain development outside the womb. As shown in Figure 1, the brain volume of a fetus still increases over 80% between the viability line of 22 to 24 weeks and term-age of 40 weeks. In addition, myelinated white matter increases fivefold between 35 weeks and term-age 40 weeks. In this time period
preterm-born children have to function outside the womb in an hostile environment with many unusual and stressful stimuli, such as septicemia, free oxygen radicals, restricted nutrient intake, pain, noise and light, which might very well interrupt and alter normal brain development in this critical period. Furthermore, preterm-born children more often experience additional pathological brain damage, both inside and outside the womb, due to antenatal problems, such as intrauterine growth restriction, and to complications during and after preterm-born birth, such as intra-ventricular haemorrhages and septicaemia. As a result of this altered brain development, caused by early birth itself and the altered, hostile environment after birth as well as perinatal complications, both early and moderately preterm-born children have increased risks of late milestone attainment and developmental delay on several developmental domains, such as cognition and motor skills.

One of the first important developmental milestones in life is “smiling in response” (hereafter: ‘smiling’). Smiling is a reflex dependant on facial movements of the forehead and eyes, and depends on the interaction between the child and the environment. With ageing, a child is more able in differentiating between positive and negative expressions of the person looking at the child and starts connecting emotions to the reflexes, such as smiling. For term-born children, this social, communicative and emotional developmental milestone is assumed to be related to cognitive development later in life. For preterm-born children, the association between attainment age of smiling and developmental delay later on has, to the best of our knowledge, not been reported.
Another important milestone, and one that is the most frequently researched, is “walking independently” (hereafter: ‘walking’). For term-born children, the age of attainment of this developmental milestone is associated with IQ in toddlerhood and at school age 6 to 11 years\textsuperscript{12,13}. In a recent study, both early and moderately preterm-born children were shown to walk at a later age than term-born children\textsuperscript{14}. To the best of our knowledge, the predictive value of the attainment age of walking for developmental delay at school-entry, for preterm-born children as well as term-born children, has never been investigated.

Smiling and walking are two examples of milestones in different developmental domains. Concerning these different developmental domains, variation in range of attainment ages of milestones might well differ for \textit{cognitive} versus \textit{motor} milestones for different preterm groups in comparison to term-born children. On the one hand, this might be attributed to the altered brain development outside of the womb\textsuperscript{9}. One example is having to overcome gravity outside the womb (instead of free-floating inside the womb), which alters the balance in flexor and extensor tonus, leading to the well-known over-extension of preterm-born children. On the other hand, due to their preterm birth, these children start interacting with the environment relatively earlier than term-born children, with might increase speed of achieving social-emotional and communicative milestones. For different preterm groups, the interaction with the environment therefore starts at varying time-points after conception, and during different stages of brain development. The result of this different nature versus nurture interaction could be that cognitive/social milestone attainment might be less delayed than motor milestone attainment in different preterm groups.

In conclusion, for preterm-born children, attainment ages of developmental milestones and the associations with neurocognitive functioning at later ages are largely unknown. Moreover, differences might exist between both attainment ages and predictive value for motor and cognitive milestones for different preterm groups.
Research Questions & Hypotheses

For this research project, we aimed to answer two research questions:

1. What is the association between GA and the attainment age of the milestones smiling and walking?
2. What is the association between the attainment age of the milestones smiling and walking, and development in different domains at school entry, crude and adjusted for covariates, including GA?

For the first research question, we hypothesized that the attainment age of both milestones would be inversely related to GA at birth. For the second research question, we expected an association between both the attainment ages of smiling and walking and development at age 4 years. We expected the association with different developmental domains to be varying. Hypotheses are visualized in Figure 2.

Figure 2. Hypotheses for the present study: (1) gestational age and attainment ages of smiling in response and walking independently are related, and (2) attainment age of smiling in response and walking independently are related to development at school entry, both associations will hold after correcting for socio-demographic factors. + = positive relationship (i.e. for example: longer gestation is positively related to better developmental scores at school entry. - = negative relationship (i.e. for example: later age of smiling or walking is negatively related to developmental scores at school entry.)
Materials & Methods

Setting and population
For the present study, we used data from the Longitudinal Preterm Outcome Project (LOLLIPOP study). LOLLIPOP, or Pinkeltje (Preterm Infants: Knowledge on Target Height and Outcome) in Dutch, is a community-based cohort of children born in 2002-2003, with data on growth and development of early and moderately preterm-born children with a control group of term-born children. From 13 Preventive Child Healthcare Centres (PCHCs) a cohort comprising of 45,446 children (roughly 25% of a Dutch year cohort) was screened. The study group sampled from within this cohort all preterm-born children (GA below 36 weeks) and a randomly selected reference group of term-born children (GA between 38 and 42 weeks). The cohort was enriched by selecting all early preterm-born children (GA < 32 weeks) also born in 2003, alive at discharge, from 5 Dutch neonatal intensive care units (NICUs). The study group excluded children with major congenital malformations and syndromes. Eventually 512 early preterm, 927 moderately preterm-born and 544 term-born children participated in the developmental part of LOLLIPOP (total inclusion 1983 children, 79%). For the first research question of the present study, we included all children from within this cohort for whom the attainment age of smiling and/or walking was recorded by PCHC physicians. For the second research question we included children with recorded attainment ages for one or both milestones and with developmental data at school entry, age 4 years.

Measures
Developmental milestones: ‘smiling’ and ‘walking’
In the Netherlands, development of all children is monitored by PCHCs, by means of attainment (ages) of developmental milestones within the van Wiechen scheme (vWS), the Dutch version of the Denver developmental screener. For most developmental milestones, the PCHC physician records whether or not the milestone is attained at a given time point, by actively inviting a child to perform a task and then actively observing these milestones during regular consults. Only for two developmental milestones, the exact attainment ages are recorded by the PCHC physician. These milestones are smiling and walking. The PCHC physician asks the parents retrospectively for the approximate age in weeks (smiling) or months (walking) of attaining these two milestones.

Gestational age and covariates
GA was calculated from the last day of menstruation, and was in over 95% of all cases verified by early ultrasound measurements during pregnancy. In all other cases, clinical estimates were used. Children where GA could not be reliably established were excluded. In addition, based upon the literature other risk factors that are known to be associated with risk of developmental delay, including being born small-for-gestational age (SGA), male gender, non-Dutch maternal ethnicity and lower maternal educational level, were added as covariates in the multivariable analyses. For the present study, we defined SGA as a birthweight below the 10th percentile of the Dutch Kloosterman growth curves. Maternal ethnicity was defined as Dutch versus non-Dutch based on the maternal birth country.
Maternal educational level was classified into low/middle (<16 years of formal education) and high (≥16 years of formal education).

**Ages and Stages Questionnaire**
Data on development at age 4 years was recorded by parents with the Dutch version of the Ages and Stages Questionnaire (ASQ). Originally, the ASQ is an American, parent-completed developmental questionnaire, which has been translated and validated for the Dutch setting, with proven internal consistency, content and construct validity. Furthermore, the ASQ has proven to be a reliable, cost-effective, fast and easy way to screen children for developmental delay. The ASQ 48 months’ form contains 30 questions in 5 developmental domains: communication, gross motor, fine motor, problem solving and personal-social functioning. All five domains add up to an ASQ-total score, indicating global developmental delay. A score below -2 SD for the reference group of Dutch term-born children was considered to be abnormal, both for the separate domains and for the combined ASQ-total score conform the official manual.

**Statistical analyses**
Background characteristics of the participating children (classified in three groups [early preterm-born, moderately preterm-born and term-born children] for the readability) were analysed with chi-square tests for trends when they were binary variables and Kruskall-Wallis tests when they were continuous variables, as the continuous variables were not normally distributed.

For the first research question, to assess the association between GA and attainment ages of both milestones, we first determined mean ages and ranges for early and moderately preterm-born children both compared to term-born children. Second, we determined mean ages and ranges per GA week. Next, we performed correlation analyses between GA and the attainment ages of the developmental milestones, using Pearson correlation coefficients. Finally, we performed partial correlation analyses, correcting for being born SGA, maternal ethnicity, maternal educational level and gender.

For the second research question, to assess the association between attainment ages of the two milestones and risk of developmental delay at age 4 years, we performed univariable logistic regression analyses with the developmental milestones as independent variables and dichotomous ASQ-domain scores and dichotomous ASQ-total score as outcome variables (model 1). Second, we corrected for the same covariates as mentioned above (model 2). Third, we included GA in the second model (model 3). The second and third model were performed with multivariable logistic regression analyses.

All analyses were conducted with SPSS version 23.0 (IBM, Chicago, Illinois, USA) and P-values below 0.05 were considered to be statistically significant.
Results

Background characteristics of the study population are summarized in Table 1. In total, the attainment age of smiling was recorded by PCHC physicians for 646 children. For term-born children, the attainment age of smiling was recorded more often than for moderately and early preterm-born children (chi-square test for trends P=0.001). Infants without a recorded value for smiling were more likely to have a non-Dutch mother (13.6% vs. 8.8%, P<0.001), but did not differ concerning gender, being born SGA or maternal educational level. For walking, 1,505 children had a recorded attainment age by PCHC physicians. PCHC physicians recorded walking for similar amounts of the three GA groups (chi-square test for trends P=0.07). Infants without a recorded value for walking were less likely to have a higher educated mother (61.4% vs. 66.8%; P=0.025), but did not differ regarding gender, being born SGA or maternal ethnicity.

<table>
<thead>
<tr>
<th></th>
<th>Early preterm (N=424)</th>
<th>Moderately preterm (N=769)</th>
<th>Term-born (N=472)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of smiling recorded, N (%)</td>
<td>132 (31.1)</td>
<td>313 (40.7)</td>
<td>201 (42.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age of walking recorded, N (%)</td>
<td>395 (93.2)</td>
<td>685 (89.1)</td>
<td>425 (90.0)</td>
<td>0.070</td>
</tr>
<tr>
<td>Gestational age (wks), mean (SD)</td>
<td>29.1 (1.96)</td>
<td>34.0 (1.04)</td>
<td>39.6 (1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight (g), mean (SD)</td>
<td>1294 (363)</td>
<td>2240 (469)</td>
<td>3543 (493)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGA, N (%)</td>
<td>93 (21.9)</td>
<td>65 (8.4)</td>
<td>32 (6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>227 (53.5)</td>
<td>448 (58.3)</td>
<td>222 (47.0)</td>
<td>0.001</td>
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<tr>
<td>Ethnicity (N=1420)</td>
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<tr>
<td>Dutch N (%)</td>
<td>328 (94.3)</td>
<td>630 (94.7)</td>
<td>387 (95.1)</td>
<td></td>
</tr>
<tr>
<td>Non Dutch N (%)</td>
<td>20(5.7)</td>
<td>35 (5.3)</td>
<td>20 (4.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>Maternal educational level (N=1438)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>High N (%)</td>
<td>96 (27.1)</td>
<td>171 (25.5)</td>
<td>120 (29.1)</td>
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</tr>
<tr>
<td>Low/middle N (%)</td>
<td>258 (72.9)</td>
<td>500 (74.5)</td>
<td>293 (70.9)</td>
<td>0.43</td>
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</table>

SGA <P10 on Dutch Kloosterman Curves.
Maternal educational level: Low <12 years formal education, Middle <16 years, High 16+ years. Bold printed P-values: <0.05; cursive printed P-values: <0.10.

Hereafter, the association between GA and the attainment age of smiling and walking (research question 1), and the association between the attainment ages of these milestones and ASQ outcome at age 4 years (research question 2) will be discussed.
1. Association between gestational age and attainment ages of milestones

1a. Attainment age of smiling

In Figure 2 and 3, the distribution of the attainment age of smiling among different GA groups (per GA group and in weeks) is shown. Classified into the three GA groups (term-born, moderately preterm-born and early preterm-born), the mean attainment ages of smiling were 5.6 weeks (range 2-15 weeks), 8.5 weeks (range 4-20 weeks) and 12.8 weeks (range 6-22 weeks) respectively.

Figure 2. Differences in attainment ages for smiling for term-born children, moderately preterm-born and early preterm-born children (N=646), tested by Mann-Whitney-U tests. *** P<0.001
A strong inverse correlation was found between GA and the attainment age of smiling (ρ = -0.742; P<0.001; **Figure 4**), with a seemingly cubic relationship (R² cubic=0.589). After correcting for confounding factors, the association remained statistically significant (ρ = -0.663; P<0.001).

**Figure 3.** The distribution attainment age of smiling among gestational age (N=646). ° = outlier, * = extreme outlier.

**Figure 4.** Correlation between attainment age of smiling and gestational age (N=646).
1b. Attainment age of walking

In Figure 5 and 6, we show the distribution of attainment ages per month for walking, distributed per GA group and per week. When classifying into the three groups (term-born children, moderately preterm-born and early preterm-born), for term-born children the mean was 13.9 months (range 7.5-24 months), whereas for moderately preterm-born children the mean was 15.4 months (range 10-30 months) and for early preterm-born children 17.1 months (range 11-26 months).

![Figure 5](image.png)

**Figure 5.** Differences in attainment ages for walking for term-born children, moderately preterm-born and early preterm-born children (N=1505), tested by Mann-Whitney-U tests. *** P<0.001
For the milestone walking, an inverse correlation was found between GA (as a continuous variable) and the attainment age per month ($\rho$ -0.415; $P<0.001$; Figure 7), with a linear association ($R^2$ linear=0.172). After correction for confounders, the association remained statistically significant ($\rho$ -0.382, $P<0.001$).

**Figure 6.** The distribution of the attainment age of walking for children with different gestational ages (N=1505). $\circ$ = outlier, $*$ = extreme outlier.

**Figure 7.** Correlation between attainment age of walking and gestational age (N=1505).
2. Association between age of attainment and development at age 4 years

2a. Smiling
Within the group of 646 children with a recorded attainment age for the milestone smiling, approximately 80% had parent-completed ASQ-domain and ASQ-total scores. In Table 2 the results of the regression analyses of the chance for abnormal ASQ-scores with later attainment of this milestone are shown. Univariable logistic regression analyses (model 1) showed that for each week a child smiled later, the odds of abnormal ASQ-domain scores and ASQ-total score increased on almost all domains. Risks for these domains were between 9 and 19% higher for every week lower GA at birth, with the highest OR for an abnormal ASQ-score in the gross motor domain (OR 1.19, P<0.001). After correcting for other factors but not for GA (model 2), the chance of having an abnormal ASQ score increased between 12 and 19% for every week a child smiled later. After adding GA to model 2 (model 3), only the risk of abnormal communication outcome remained associated with the attainment age of smiling. In model 3, for problem solving, gross motor skills and the ASQ-total score, the odds for abnormal scores were higher for every week lower GA. However, these findings were not statistically significant (P<0.06).

2b. Walking
Within the group of 1,505 children with a recorded attainment age for walking, approximately 80% had parent-completed ASQ-domain and ASQ-total scores. Table 3 shows the results of the regression analyses of the chance for abnormal ASQ-scores with later attainment of this milestone. In univariable logistic regression analyses (model 1) the chance of an abnormal ASQ-domain or ASQ-total score increased between 8 and 22% for each month that a child walked later. The highest OR was found for an abnormal score in the gross motor domain. When correcting for risk factors, but not for GA (model 2), the chance of having an abnormal score ranged between 9 and 21% for every month a child walked later. For all domains, the attainment age of walking proved to be associated with risk of abnormal scores, independently of other risk factors. The largest increase in risk of an abnormal score was seen for the gross motor domain. After adding GA to model 2 (model 3), attainment age of walking still predicted abnormal scores on the gross motor, fine motor and problem solving domains and the ASQ-total score. In model 3, odds for an abnormal score on the communication and personal social domains with later attainment of walking were also increased, although not statistically significant (P<0.09).
Table 2. Odds ratio for an abnormal ASQ-domain and total score for each week later smiling, unadjusted and adjusted for confounding factors.

<table>
<thead>
<tr>
<th>ASQ</th>
<th>Univariable analysis</th>
<th>Multivariable analyses</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
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<tr>
<td>Communication</td>
<td>1.14</td>
<td>1.05-1.23</td>
<td>0.002</td>
<td>1.13</td>
<td>1.04-1.22</td>
<td>0.004</td>
<td>1.16</td>
<td>1.02-1.32</td>
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<tr>
<td>Personal Social</td>
<td>1.09</td>
<td>0.99-1.20</td>
<td>0.072</td>
<td>1.07</td>
<td>0.97-1.18</td>
<td>0.19</td>
<td>1.10</td>
<td>0.94-1.29</td>
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<tr>
<td>Problem Solving</td>
<td>1.14</td>
<td>1.03-1.26</td>
<td>0.014</td>
<td>1.12</td>
<td>1.01-1.24</td>
<td>0.031</td>
<td>1.18</td>
<td>0.99-1.40</td>
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<td>Fine Motor</td>
<td>1.17</td>
<td>1.07-1.27</td>
<td>&lt;0.001</td>
<td>1.15</td>
<td>1.05-1.26</td>
<td>0.002</td>
<td>1.04</td>
<td>0.90-1.19</td>
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<tr>
<td>Gross Motor</td>
<td>1.19</td>
<td>1.09-1.29</td>
<td>&lt;0.001</td>
<td>1.19</td>
<td>1.09-1.30</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>1.00-1.31</td>
</tr>
<tr>
<td>Total Score</td>
<td>1.16</td>
<td>1.07-1.26</td>
<td>&lt;0.001</td>
<td>1.15</td>
<td>1.05-1.25</td>
<td>0.002</td>
<td>1.14</td>
<td>1.00-1.30</td>
</tr>
</tbody>
</table>

*Model 2: Adjusted for SGA, male gender, low/middle maternal educational level and non-Dutch ethnicity.  
*Model 3: Adjusted for SGA, male gender, low/middle maternal educational level, non-Dutch ethnicity and gestational age (as continuous variable). Bold printed P-values: <0.05, cursive printed P-values: <0.10.

Table 3. Odds ratio for an abnormal ASQ-domain and total score for each month later walking, unadjusted and adjusted for confounding factors.

<table>
<thead>
<tr>
<th>ASQ</th>
<th>Univariable analysis</th>
<th>Multivariable analyses</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Gross motor</td>
<td>1.22</td>
<td>1.14-1.30</td>
<td>&lt;0.001</td>
<td>1.21</td>
<td>1.13-1.29</td>
<td>&lt;0.001</td>
<td>1.19</td>
<td>1.11-1.27</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>1.15</td>
<td>1.08-1.22</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>1.08-1.22</td>
<td>&lt;0.001</td>
<td>1.12</td>
<td>1.05-1.19</td>
</tr>
<tr>
<td>Personal Social</td>
<td>1.13</td>
<td>1.07-1.21</td>
<td>&lt;0.001</td>
<td>1.13</td>
<td>1.06-1.20</td>
<td>&lt;0.001</td>
<td>1.06</td>
<td>0.99-1.14</td>
</tr>
<tr>
<td>Problem solving</td>
<td>1.08</td>
<td>1.02-1.15</td>
<td>0.012</td>
<td>1.09</td>
<td>1.02-1.16</td>
<td>0.007</td>
<td>1.11</td>
<td>1.04-1.19</td>
</tr>
<tr>
<td>Communication</td>
<td>1.08</td>
<td>1.03-1.14</td>
<td>0.003</td>
<td>1.08</td>
<td>1.03-1.14</td>
<td>0.003</td>
<td>1.06</td>
<td>1.00-1.12</td>
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<tr>
<td>Total score</td>
<td>1.18</td>
<td>1.11-1.25</td>
<td>&lt;0.001</td>
<td>1.17</td>
<td>1.10-1.25</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>1.07-1.21</td>
</tr>
</tbody>
</table>

*Model 2: Adjusted for SGA, male gender, low/middle maternal educational level and non-Dutch ethnicity.  
*Model 3: Adjusted for SGA, male gender, low/middle maternal educational level, non-Dutch ethnicity and gestational age as continuous variable. Bold printed P-values: <0.05, cursive printed P-values: <0.10.
**Discussion**

This study demonstrated that there is an inverse relationship between GA and attainment ages of smiling and walking. The association between GA and attainment age of smiling was strong. For walking, the association between GA and attainment age was medium. Attainment age of smiling was associated with risk of developmental problems on almost all developmental domains of the ASQ at age 4 years. After adjustment for GA, the association between the attainment age of smiling and developmental risk at 4 years was limited to the communication domain. Attainment age of walking was associated with risk of abnormal scores for both the ASQ-total score and all underlying ASQ-domains at age 4 years. After correction for covariates including GA, this association remained for the ASQ-total score and underlying scores in the gross motor, fine motor and problem solving ASQ-domains.

In this study, we found an inverse relationship between GA and the attainment age of smiling. Our results are in line with the study by di Rosa et al.\textsuperscript{14}, showing that the preterm-born children with the lowest GA were also latest in achieving smiling. Moreover, the attainment age of smiling of term-born children we determined in this study, is in agreement with the work by Flensborg and colleagues\textsuperscript{20}. This group found a mean attainment age for smiling of 5.5 weeks for term-born children. As far as we know, no data have been published on exact calendar attainment ages of smiling for a large group of children of different gestational ages. In the article of di Rosa, no gestational ages are given: groups were divided by birthweight. The lightest children (N=10) had a median birthweight of 1.22 kg, and were described as early preterm-born children. Their birthweight probably roughly corresponded to 29-31 weeks of gestation. Differences in attainment ages for smiling in varying gestational groups, is most likely explained by altered brain development\textsuperscript{9}, with preterm-born children outside the womb earlier when neuronal formation is not complete yet\textsuperscript{21}.

For walking, we also found an inverse relationship between the attainment age and GA. This result is in line with other studies, which showed that early preterm-born children attained walking later than term-born children\textsuperscript{3,22}. The study by Bucher et al\textsuperscript{3} used parental information on age of walking, whereas Restiffe et al\textsuperscript{22} used the Alberta Infant Motor Scale, which assesses gross motor milestones from birth onwards until independent walking is achieved. Thus, both results based on parental information and results based on professional observation, showed that early preterm-born children walked later than term-born children. In term-born children, we showed a later attainment age for walking than Chaibal et al\textsuperscript{23} (13.9 months versus 9.9 months). The mean difference of approximately 4 months might be due to the small number of children included by Chaibal et al. (N=10), as is also provided as a possible explanation by the researchers themselves. Furthermore, they defined this milestone as ‘walking 5 steps without support’, which is different than being able to really walk without support for longer stretches of time. In contrast, our median age of 13.9 months for term-born children was slightly lower than reported by Touwen\textsuperscript{24} who provided a range (minimum and maximum) of 13.5 months to 18 months as normal for typically developing term-born children. This difference could be explained by the fact that over the past decades, the pace of mastering milestones is known to have increased, so that the range of attainment age for typically
developing children has shifted leftwards, which is called the Flynn effect\textsuperscript{25}. Differences in attainment ages for walking in varying gestational groups, is most likely also explained by altered brain development of preterm-born children, and its interplay with the environment (i.e. preterm-born children having to work against gravity earlier).

We showed that smiling was related more strongly to GA than walking. Our results are once more contrast with the study by di Rosa et al\textsuperscript{14}, who found regression coefficients for GA in relation to smiling and walking of the same magnitude, although their study included only a small sample per gestational group. The difference between the dependence of the attainment ages of the milestones on GA, might be explained by the fact that smiling is achieved very early in life, whereas walking is achieved later. For walking, not only brain development, but also perinatal factors including as intraventricular hemorrhages, muscle development, social skills and stimulation from the environment (i.e. preterm-born children having to work against gravity earlier)

Regarding the predictive value of the milestones, the study results showed that -after correction for covariates, including GA- later attainment of smiling predicted developmental delay at age 4 years in the communication domain only. For attainment of smiling, limited evidence exists on the predictive value for later development, although an association with the communication domain later on indeed seems to be the most logical one, conform our hypothesis. To the best of our knowledge, no other studies exist that examined the relationship between smiling and communication. However, one study provided evidence that attainment of smiling is predictive of IQ at age 34 for term-born children\textsuperscript{20}. This finding is different from our findings, but this difference might be explained by the outcome measure used. We examined the association to developmental delay in the communication domain at school entry, which is at the age of 4 years, whereas the other study examined IQ at age 34, many years later in life and encompassing a much broader domain.

For walking, our results showed that later attainment predicts abnormal ASQ-total scores, and underlying abnormal gross motor, fine motor and problem solving ASQ-domain scores. This effect remained after correction for covariates including GA. In the same study mentioned earlier, attainment of walking has been shown to be predictive of IQ at age 34 for term-born children\textsuperscript{20}. Moreover, achieving walking earlier than peers has been associated with higher educational levels in adolescence and adulthood for term-borns as well\textsuperscript{2}. Therefore, our results are in line with these studies. As far as we know, no other studies have been performed examining the predictive value of attainment of walking for preterm-born children. In conclusion, our results show that also for preterm-born children, attainment of walking is a predictive factor for developmental delay at school entry.
An explanation for the differences in predictive value of different milestones is provided by Murray et al\(^3\), who speculate that the difference in association between motor and cognitive milestones and developmental outcome at a later age, are due to different neuronal pathways at varying stages of development. In addition, maturation of these neuronal pathways that might be involved in the attainment of developmental milestones, could have its influence on the development of other brain regions that are associated with cognitive or motor development later in life. Another explanation is posed by Flensborg and colleagues\(^{20}\), who stated that the attainment ages of milestones might be markers for underlying factors that influence both motor and cognitive development. We suggest that a combination of both explanations could be possible: an interaction between nature and nurture. Different neuronal pathways could be influenced by an interaction with the environment, and underlying biological factors, such as prematurity or intraventricular hemorrhages. These underlying factors might in turn influence milestone attainment.

**Strengths and limitations**

To our knowledge, this study is the first to assess the relationship between the attainment age of two different developmental milestones as well as their predictive value for developmental delay at school entry for a large range of preterm gestational ages compared to term-born children. Moreover, this study has been based on a large community-based prospective cohort, with an oversampling of early preterm-born children. For moderately preterm-born children, the community-based character of the LOLLIPPO study provides that not only the moderately preterm-born children with problems right after birth are included, but also the relatively “healthy” moderately preterm-born children. This study had also some limitations. First, a parent-completed screening tool (the ASQ) was used to evaluate development at school entry, instead of a standardized diagnostic test, such as the Bayleys Scales of Infant and Toddler Development\(^{26}\). Nonetheless, the ASQ has proven to be a reliable screening tool to identify children at high risk for developmental problems\(^{17,18,27,28}\). Second, infants without a recorded attainment age for smiling more often had a non-Dutch mother. This could possibly have influenced our results, as cultural differences in interaction with the child might exist. Moreover, children without a recorded attainment age for walking more often had a lower educated mother. This could also possibly have influenced our results, as social economic status is associated with risk of developmental delay\(^{29}\). Finally, the quality of the milestones has not been assessed methodologically in this study. In this study, walking did not provide information on the fluency of walking gait. Qualitative assessment of milestones might also contribute to assessing whether or not a child deviates from the normal developmental trajectory\(^{30-32}\).
Implications
The finding that independently of GA, attainment age of smiling is predictive of abnormal communication ASQ-scores at school entry, implies that this milestone can serve as a red flag in the monitoring of both term-born and preterm-born children. Moreover, the finding that attainment age of walking is predictive of abnormal scores on multiple ASQ-domains at age 4 years, implies that this milestone also deserves a place in the follow-up of both term-born and preterm-born children. When PCHC physicians underline this implication, extra follow-up and/or offering early targeted intervention to the children attaining these milestones later than peers might be considered in order to improve developmental outcomes during the golden window of opportunity during the first years of life. Further research might focus on the predictive value of (a combination of (other)) developmental milestones. To further clarify the predictive role of the milestones, other outcome measures, such as development at school-age or IQ could be used. In addition, future research might focus on underlying mechanisms to further clarify differences between cognitive and motor milestone attainment, and factors that are associated with later milestone attainment.

Conclusions
Attainment age of smiling is strongly associated with GA and predicts communication delay at age 4, independent of GA. The association of the attainment age of walking with GA is moderate, and predictive of developmental delay in multiple developmental domains at age 4, independent of GA.
References


