# Predictors of persistent and changing developmental problems of preterm children

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# Early Human Development

# Predictors of persistent and changing developmental problems of preterm children

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## ARTICLE INFO

## ABSTRACT

*Background:* Accurate prediction of persistent and emerging developmental problems in preterm-born children may lead to targeted interventions.
*Aims:* To determine whether specific perinatal and social factors were associated with persistent, emerging, and resolving developmental problems of early-preterm (EPs) and moderately-and-late-preterm children (MLPs) from before to after school entry.
*Study design:* Observational longitudinal cohort study, part of the LOLLIPOP cohort-study.
*Subjects:* 341 EPs and 565 MLPs.
*Outcome measures:* Developmental problems using the Ages and Stages Questionnaire at ages 4 and 5. We collected data on perinatal and social factors from medical records. Using logistic regression analyses we assessed associations between 48 factors and persistent, emerging, and resolving problems.
*Results:* Of EPs, 8.7% had persistent and 5.1% emerging problems; this was 4.3% and 1.9% for MLPs, respectively. Predictors for persistent problems included chronic mental illness of the mother, odds ratio (95% confidence interval) 8.01 (1.85–34.60), male sex 4.96 (2.28–10.82), being born small-for-gestational age (SGA) 2.39 (1.15–4.99), and multiparity 3.56 (1.87–6.76). Predictors for emerging problems included MLP birth with prolonged premature rupture of membranes (PPROM) 5.01 (1.38–18.14). Including all predictors in a single prediction model, the explained variance (Nagelkerke $R^2$) was 21.9%, whereas this was 3.0% with only EP/MLP birth as predictor.
*Conclusions:* Only few perinatal and social factors had associations with persistent and emerging developmental problems for both EPs and MLPs. For children with specific neonatal conditions such as SGA, and PPROM in MLPs, problems may persist. Insight in risk factors largely improved the prediction of developmental problems among preterm children.

## 1. Introduction

Worldwide, 11% of all children are born before 37 weeks' gestational age (GA) [1]. More than 80% of these children are born moderately-and-late preterm (MLP), with GA between 32 and 36 weeks; the remainder are born early-preterm (EP), with GA less than 32 weeks. Although most preterm children have normal developmental outcomes, still around 8% of the MLPs and 15% to 24% of the EPs have developmental problems at preschool and school ages in comparison with 4% of full-term children [2,3]. The prevalences of developmental problems among preterm children at preschool age and school age [4–6] are quite similar, suggesting persistence of developmental problems at group level. That is different, however, on an individual level. Within the preterm group problems emerge in some individuals, resolve in others, and are

persistent in a minority during the period from before to after school entry [6–8]. In almost half of the preterm children who had developmental problems at preschool age (29 to 50% of the EPs and 54% of the MLPs) problems resolved after school entry, but they also emerged in 4 to 51% of the EPs who have no developmental problems at preschool age [7,8]. This great variation within the preterm group makes it hard to predict which preterm children will have persistent, or emerging, developmental problems.

Although maternal, perinatal and neonatal (all three referred to as 'perinatal' in the remaining of this manuscript), and social factors contribute to the risk of developmental problems among preterm children [9–12], the influence of these factors seems to vary over time. For instance, a systematic review by Linsell et al. showed among EPs and preterm children <1250 g various perinatal and social factors to be associated with global cognitive impairment before the age of 5y. However, only the association with parental education persisted after that age [11]. To our knowledge neither this study nor other studies determined the influence of perinatal and social factors on the stability of developmental problems among individual preterm children, or compared the influence of these factors between EPs and MLPs.

The aim of our study was, therefore, to determine which perinatal and social factors are associated with persistent, emerging and/or resolving developmental problems among EPs and MLPs from before to after school entry. Such knowledge can help us during the neonatal and preschool periods to determine which children have the highest risk of developing persistent or emerging developmental problems after school entry. This can support the counseling of parents and the identification of those preterm children who will most benefit from early interventions, thereby ameliorating the future perspectives of these children.

## 2. Patients and methods

### 2.1. Study design and participants

For this study we used data from the Longitudinal Preterm Outcome Project (LOLLIPOP). LOLLIPOP is a community-based cohort of preterm and full-term children born in the Netherlands in 2002 and 2003. A detailed description of this study cohort can be found elsewhere [12]. In short, we included preterm children from 13 preventive child healthcare centers (PCHC) before their regular well-child visit at the age of 43 to 49 months. After every two preterm-born children one fullterm born child was included as control. In addition, we enriched the preterm sample with EPs born in 2003 in five of the ten neonatal intensive care units in the Netherlands. We did not include children with major congenital malformations, congenital infections, and syndromes. The LOLLIPOP study was approved by our local institutional review board and written informed consent was provided by all parents.

For the analyses in the present study we included only the preterm children from the LOLLIPOP sample and not the fullterm children.

### 2.2. Measures

#### 2.2.1. Developmental problems: Ages and Stages Questionnaire (ASQ)

We measured developmental problems using the Ages and Stages Questionnaire (ASQ), worldwide the most commonly used parent-completed developmental screener [13]. We asked the parents to fill out the validated Dutch versions appropriate for ages 4 and 5 years, around the children's 4th and 5th birthday, and return it at the scheduled visit and by mail, respectively [14–16]. The ASQ contains age-specific questions about milestones on the domains Communication, Gross motor, Fine motor, Problem solving, and Personal-social skills. These questions can be answered with 'yes' (10 points)/'sometimes' (5 points)/'not yet' (0 points). We categorized the overall score (with a maximum of 300) per questionnaire, into normal and abnormal scores, defining abnormal scores as >2 standard deviations (SD) below the

mean of the Dutch reference population (<183 on the ASQ for age 4 and < 219 on the ASQ for age 5) [15,16].

We combined the dichotomized overall scores of the ASQ's at ages 4 and 5 to construct four stability categories: 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 at age 4 and an abnormal ASQ at age 5; the resolving problems group had an abnormal ASQ at age 4 and a normal ASQ at age 5; and the persistent problems group had abnormal scores at both ages.

#### 2.2.2. Maternal, neonatal, and social factors

We included a total of 48 maternal, neonatal and social factors in our analyses, as shown in Table 1. We selected these factors because they were common in the preterm population during pregnancy and the neonatal period, or reported to be associated with developmental problems at follow-up in previous studies [7–12,17,18]. We collected the data of pre-existing maternal conditions, pregnancy-related factors, and neonatal factors from the hospital records of both mothers and children, and crosschecked these data with PCHC charts, and a parental general questionnaire filled out at the age of 4 years. Sociodemographic and lifestyle factors were collected from the general questionnaire, and also crosschecked with medical data.

### 2.3. Procedure

One month before the routine children's PCHC visit at 43 to 49 months of age, the parents received information about the LOLLIPOP study, including an informed consent form, the ASQ for age 4, and a questionnaire about social and pregnancy-related characteristics. Parents returned these at their child's scheduled PCHC visit. Following informed parental consent, we retrospectively recorded maternal, perinatal, and neonatal characteristics from discharge letters of mother and child, PCHC reports, and information from linked national birth registers. Approximately 4–6 weeks before the child's fifth birthday, parents received the ASQ for age 5, which they returned by mail upon completion.

Data on both ASQs (for ages 4 and 5) were available for 1064 preterm children. For 927 of them (93.1%), both ASQs were filled out completely (answers on all domains on both questionnaires). Twenty children were excluded because they were categorized in the resolving or emerging category, but with small differences between the ASQs at ages 4 and 5, i. e. less than 1 SD. Data on perinatal and social factors were available for 906 of the remaining 907 children, 341 EPs and 565 MLPs.

### 2.4. Analysis

First, we compared background characteristics between the EP and MLP groups, using Chi-Square tests and Mann-Whitney *U* tests. Second, we assessed which perinatal and social factors were associated with the outcomes persistent, emerging, and resolving developmental problems in crude analyses, using logistic regression. The consistently normal category was used as reference category. For the variables associated with an outcome at $P < .20$, we assessed whether these associations were still below $P < .20$ after adjustment for EP/MLP-status (using logistic regression) and we determined if the association was modified by EP/MLP-status (interaction terms).

Third, we constructed three multivariable logistic regression models for each outcome (persistent, emerging and resolving problems versus consistently normal). We included, from the second step of the analyses, all independent variables which sufficed $P < .20$ and independent variables that were involved in significant ($P < .20$) interaction terms to a model already containing EP/MLP-status. We then reduced the number of independent variables in these models using stepwise backward selection procedures, with $P < .10$ as selection cut-off. The variables that remained from the stepwise selection procedure, EP/MLP birth, and the

**Table 1**

Description of the perinatal and social factors included in this study, categorized as maternal and pregnancy-related, neonatal and fetal, and social.

| Variable | Definition | Missing N (% of 906) |
|---|---|---|
| **Maternal and pregnancy-related factors** | | |
| Chronic somatic illness | Chronic somatic illness in the mother (autoimmune, renal, cardiac, lung, other) | 14 (1.5) |
| Chronic mental illness | Preexisting mental illness in the mother (depression, psychosis, other) | 14 (1.5) |
| Maternal obesity | Pregnancy obesity, body mass index greater than 30 kg/m2 | 22 (2.4) |
| HELLP | Hemolysis, Elevated Liver enzymes, and Low Platelet count syndrome, or (pre)-eclampsia | 7 (0.8) |
| Diabetes | Preexisting or gestational diabetes treated with diet or insulin | 9 (1.0) |
| Alcohol during pregnancy | Alcohol, more than 1 unit per week during pregnancy | 7 (2.9) |
| Smoking during pregnancy | Any smoking during pregnancy | 3 (0.3) |
| In vitro fertilization | In vitro fertilization or intracytoplasmic sperm injection | 6 (0.7) |
| Antepartum hemorrhage | Abruptio, placenta previa, placental bleeding, or all in the second or third trimester or both | 11 (1.2) |
| Antenatal steroids | Full course antenatal steroids (two shots, and greater than 48 h after first shot) | 24 (2.6) |
| Infection | Clinical infection of mother, child or both, perinatally, or proven placental infection. | 9 (1.0) |
| PPROM | Prolonged premature rupture of membranes (greater than 24 h before delivery) | 9 (1.0) |
| Breech presentation | Breech presentation during delivery | 8 (0.9) |
| Induced birth | Indication for preterm birth: spontaneous, fetal, maternal, both, elective | 16 (1.8) |
| Cesarean delivery | Primary or secondary cesarean delivery | 8 (0.9) |
| Assisted delivery | Forceps and or vacuum | 12 (1.3) |
| Meconium amniotic fluid | Meconium containing amniotic fluid | 21 (2.3) |
| **Neonatal factors** | | |
| Male sex | Male sex | 0 (0.0) |
| Multiple | Being part of a multiple birth | 0 (0.0) |
| Apgar <5 | 5-min Apgar score below 7 | 11 (1.2) |
| SGA | Small for gestational age; less than P10 according to Dutch growth charts [44] | 0 (0.0) |
| GA | Gestational age at birth. Determined in completed weeks, based on early ultrasound measurements (>95%) or clinical estimates on basis of last menstrual date in combination with clinical estimates of GA after birth. | 0 (0.0) |
| Asphyxia | Asphyxia documented in the conclusion of the discharge letter | 9 (1.0) |
| NICU admission | Admission to a tertiary NICU | 15 (1.7) |
| Length of NICU stay | Days on NICU in comparison with the median of that GA week. The median was 0 days for all MLPs, and 7, 10, 17, 24, 37, 50, 63, 76 days, respectively, for children born at 32, 31, 30, 29, 28, 27, 26, 25, 24 weeks GA. The median of 25 weeks and 24 weeks GA was estimated on basis of the trends of the medians of the older EPs because only few EPs were born at 24 and 25 weeks GA. | 25 (2.8) |
| NICU Transportation | Transfer from a regional hospital to a tertiary NICU within 72 h after birth | 15 (1.7) |
| Circulatory insufficiency | Inotropics, including dopamine, dobutamine, or (nor)adrenaline | 21 (2.3) |
| CPAP | Continuous positive airway pressure for longer than initial stabilization in the delivery room only | 18 (2.0) |
| Mechanical ventilation | Mechanical ventilation for a longer duration than initial stabilization in the delivery room only | 18 (2.0) |
| Mechanical ventilation duration | Days of mechanical ventilation | 22 (2.4) |
| CPAP/ mechanical ventilation | CPAP and/or mechanical ventilation with same definitions as described above | 15 (1.7) |
| Apnea | Apnea in discharge letter or documented on bedside charts | 29 (3.2) |
| Caffeine | Treatment with caffeine for apnea | 34 (3.8) |
| Septicemia | Both clinical symptoms and at least 1 positive blood culture result | 49 (5.4) |
| Hypoglycemia | At least 1 plasma glucose value,1.7 mmol/L (30 mg/dL), within first 72 h of life or hypoglycemia without reported value | 37 (4.1) |
| Hyperbilirubinemia | Peak bilirubin value of >340 μmol/L (20 mg/dL) for MLPs or >255 for EPs and/or any value requiring phototherapy | 20 (2.2) |
| Phototherapy | Phototherapy treatment and/or exchange transfusion | 26 (2.9) |
| Necrotizing enterocolitis[a] | Proven necrotizing enterocolitis | 13 (1.4) |
| Surfactant[a] | Surfactant treatment | 23 (2.5) |
| Bronchopulmonary dysplasia[a] | Bronchopulmonary dysplasia: additional O2 needed after >36 weeks postpartum or bronchopulmonary dysplasia with unknown duration | 29 (3.2) |
| Cerebral bleeding[a] | At least degree 3 bleeding or venous infection. | 24 (2.6) |
| Cerebral white matter abnormalities[a] | Periventricular echodensities (PVE) of periventricular leukomalacia (PVL) | 24 (2.6) |
| **Social factors** | | |
| Multiparity | Mother who has gone through a previous pregnancy | 0 (0.0) |
| Socio-economic status | Low/medium/high socioeconomic status Based on education level of both parents, family income, and occupation level of both parents. Measures were standardized to a z-score. Scores below the 25th percentile were considered as low socioeconomic status and above the 75th percentile as high socioeconomic status [17]. | 1 (0.1) |
| Non-Dutch background | Non-Dutch birth country of child, mother or father | 11 (1.2) |
| One parent family | One parent family | 64 (7.1) |

[a] This mainly occurs in EPs, all MLPs have been rated as "not present". GA: Gestational age, NICU: neonatal intensive care unit.

independent variables that were involved in significant interaction terms were entered into the final model. If for example CPAP x EP/MLP was significant, CPAP was included in the final model. We also determined the relative risks (RRs) of these variables that were entered into the final model. From the adjusted odds ratios (OR), we calculated the adjusted RRs based on the method by Zhang and Yu [19], using the formula: adjusted RR = (adjusted OR/[(1-p0) + (adjusted OR*p0)], p0 being the incidence among the nonexposed regarding the variable in question.

Fourth, we evaluated the accuracy of the separate final prediction models for persistent, emerging and resolving problems based on the area under the curve (AUC), the Hosmer-Lemeshow test, and the Nagelkerke $R^2$. Additionally, we included all predictors from the final models in a single prediction model, and used multivariable multinomial logistic regression to evaluate the overall Nagelkerke $R^2$. The AUC scores were classified as: 0.50–0.69 poor, 0.70–0.79 fair, 0.80–0.89 good, and 0.90–1.0 excellent. The model was considered to fit well if the Hosmer-Lemeshow test was not significant ($P \geq .05$). We performed all analyses

in IBM SPSS version 23.

## 3. Results

In Table 2 we present the characteristics of the study sample of EPs and MLPs. In comparison with MLPs, the EPs' problems were more often persistent (8.7% versus 4.3%) and emerging (5.1% versus 1.9%). Most differences between EPs and MLPs were related to the neonatal period.

In Table 3 we present the perinatal and social factors which were in the final model associated with $P < .20$ with persistent, emerging, and/or resolving problems after adjustment for EP/MLP birth. We also show in Table 3 the ORs for combined pairs of variables in case of statistically significant interactions of factors with EP/MLP birth.

Factors that remained in the final model associated with persistent or emerging problems included chronic mental illness of the mother, male sex, being born small-for-gestational age (SGA), and multiparity. Antepartum hemorrhage and smoking during pregnancy remained in the models at $P < .10$. Regarding resolving problems, maternal obesity, transportation to a NICU, and again being born SGA remained in the final models.

For EPs and MLPs the effect of perinatal factors was not always the same. Prolonged premature rupture of membranes (PPROM) was associated with emerging problems in MLPS, but not in EPs. Male sex was associated with resolving problems in MLPs and not in EPs. Finally, treatment with CPAP was associated with persistent problems in EPs at $P < .10$ in the univariate analysis, but the association disappeared in the multivariable analysis. We provide the RRs of all factors remaining in the final models in Table 4. The RRs are in the same range as the ORs, and significance was similar.

The accuracy of the final models is shown in Table 5. In comparison with only the inclusion of the factor EP/MLP birth, the accuracy improved from poor to fair, and a greater part of the variance was predicted by the model, with Nagelkerke $R^2$ for the overall model increasing from 3.0% to 21.9%. Although this model largely improved the prediction, the majority of the variance remained unexplained. Concerning the separate final models, prediction of emerging problems was the poorest (Nagelkerke $R^2$ 9.6%).

## 4. Discussion

This study demonstrated that only few perinatal and social factors were associated with persistent or emerging developmental problems in preterm-born children. The ones we did find, however, largely improved the prediction of persistent, emerging and resolving developmental problems at age 5 more than 7-fold. The risk increased if they grew up in a social context with less optimal social and maternal factors, including maternal chronic mental illness, maternal smoking and multiparity. Additionally, being born SGA was associated with persistent developmental problems. Between EPs and MLPs the influence of perinatal factors differed, and was limited to some specific factors. PPROM increased the risk of persistent problems for MLPs, whereas male sex of MLPs was associated with resolving problems.

Factors related to a less optimal social context were associated with persistent and emerging developmental problems, a finding in line with previous reports [11,17,20–22]. In our final model, persisting and emerging problems were associated with living in a family with a mother with chronic mental illness, having siblings (multiparity), and having a mother who smoked during pregnancy. Many studies reported that, for preterm children, a less optimal social context increases the risk of developmental problems at a specific age [11,17,20–22]. However, studies on the effect of siblings on development reported both negative and positive effects [23–25], but these did not focus on the stability of development, nor on the influence of siblings among MLPs. A less optimal social context may increase the risk of developmental problems, because brain development highly depends on external stimulation [26]. In families with a less optimal social context parents frequently

**Table 2**
Comparison of the characteristics of the early preterm (EPs) and moderately-and-late-preterm children (MLPs).

| Variable | EPs N(%) | MLPs N(%) | Total | P-value |
|---|---|---|---|---|
| Total group | 341 | 565 | 906 | |
| Persistent problems | 27 (7.9) | 23 (4.1) | 50 (5.5) | **.009** |
| Emerging problems (diff >1 SD) | 15 (4.4) | 10 (1.8) | 25 (2.8) | **.013** |
| Resolving problems (diff>1 SD) | 17 (5.0) | 25 (4.4) | 42 (4.6) | .533 |
| Consistently normal | 282 (82.7) | 507 (89.7) | 789 (87.1) | |
| **Maternal and pregnancy-related factors** | | | | |
| Chronic somatic illness | 33 (10.1) | 30 (5.3) | 63 (7.1) | **.007** |
| Chronic mental illness | 4 (1.2) | 9 (1.6) | 13 (1.5) | .657 |
| Maternal obesity | 26 (7.8) | 65 (11.8) | 91 (10.3) | .053 |
| HELLP | 89 (26.6) | 111 (19.6) | 200 (22.2) | **.015** |
| Diabetes | 8 (2.4) | 13 (2.3) | 21 (2.3) | .917 |
| Alcohol during pregnancy | 8 (2.4) | 23 (4.1) | 31 (3.4) | .183 |
| Smoking during pregnancy | 65 (19.1) | 109 (19.4) | 174 (19.3) | .929 |
| In vitro fertilization | 24 (7.2) | 42 (7.4) | 66 (7.3) | .881 |
| Antepartum hemorrhage | 45 (13.6) | 60 (10.6) | 105 (11.7) | .176 |
| Antenatal steroids | 178 (54.6) | 114 (20.2) | 287 (32.5) | **<.001** |
| Infection | 56 (16.9) | 77 (13.6) | 133 (14.8) | .187 |
| PPROM | 59 (17.8) | 131 (23.3) | 190 (21.2) | .055 |
| Breech presentation | 95 (28.5) | 84 (14.9) | 179 (19.9) | **<.001** |
| Indication birth: | | | | |
| - Spontaneous | 175 (53.8) | 407 (72.0) | 582 (65.4) | **<.001** |
| - Fetal indication | 75 (23.1) | 51 (9.0) | 126 (14.2) | |
| - Maternal indication | 34 (10.5) | 48 (8.5) | 82 (9.2) | |
| - Fetal and maternal | 11 (3.4) | 33 (5.8) | 44 (4.9) | |
| - Elective | 30 (9.2) | 26 (4.6) | 56 (6.3) | |
| Cesarean delivery | 182 (54.7) | 193 (34.2) | 375 (41.8) | **<.001** |
| Assisted delivery | 7 (2.1) | 53 (9.4) | 60 (6.7) | **<.001** |
| Meconium amniotic fluid | 12 (3.6) | 14 (2.5) | 26 (2.9) | .362 |
| **Neonatal factors** | | | | |
| Male sex | 173 (50.7) | 325 (57.5) | 498 (55.0) | **.047** |
| Multiple | 106 (31.1) | 154 (27.3) | 260 (28.7) | .217 |
| Apgar <5 | 25 (7.5) | 14 (2.5) | 39 (4.4) | **<.001** |
| SGA | 73 (21.4) | 56 (9.9) | 129 (14.2) | **<.001** |
| GA (weeks) *median(range)* | 30 (25–31) | 34 (32–35) | 33 (25–35) | |
| Asphyxia | 14 (4.2) | 9 (1.6) | 23 (2.6) | **.018** |
| NICU admission | 318 (97.0) | 89 (15.8) | 407 (45.7) | **<.001** |
| Length of NICU stay (d) *median(range)* | 12 (0-143) | 0 (0–60) | 0 (0-143) ( | **<.001** |
| NICU Transportation | 29 (8.8) | 25 (4.4) | 54 (6.1) | **.008** |
| Circulatory insufficiency | 53 (16.5) | 16 (2.8) | 69 (7.8) | **<.001** |
| CPAP | 273 (84.0) | 95 (16.9) | 368 (41.4) | **<.001** |
| Mechanical ventilation | 177 (54.5) | 43 (7.6) | 220 (24.8) | **<.001** |
| Mechanical ventilation duration (d) *median(range)* | 1 (0–84) | 2 (0–12) | 1 (0–84) | **.015** |
| CPAP / mechanical ventilation | 286 (87.2) | 103 (18.3) | 389 (43.7) | **<.001** |
| Apnea | 291 (91.8) | 126 (22.5) | 417 (47.5) | **<.001** |
| Caffeine | 280 (89.5) | 66 (11.8) | 346 (39.7) | **<.001** |
| Septicemia | 88 (29.8) | 18 (3.2) | 106 (12.4) | **<.001** |
| Hypoglycemia | 51 (16.3) | 42 (7.6) | 93 (10.7) | **<.001** |

**Table 2** (*continued*)

| Variable | EPs N(%) | MLPs N(%) | Total | *P*-value |
|---|---|---|---|---|
| Hyperbilirubinemia | 65 (20.1) | 256 (45.6) | 321 (36.2) | **<.001** |
| Phototherapy | 268 (84.3) | 255 (45.4) | 523 (59.4) | **<.001** |
| Necrotizing enterocolitis | 10 (3.0) | 0[a] | 10 (1.1) | |
| Surfactant | 117 (36.8) | 0[a] | 117 (13.3) | |
| Bronchopulmonary dysplasia | 94 (30.1) | 0[a] | 94 (10.7) | |
| Cerebral bleeding | 12 (3.8) | 0[a] | 12 (1.4) | |
| Cerebral white matter abnormalities | 148 (46.7) | 0[a] | 148 (16.8) | |
| **Social factors** | | | | |
| Multiparity | 83 (24.3) | 195 (34.5) | 278 (30.7) | **.001** |
| Socio-economic status | | | | |
| - High | 97 (28.5) | 153 (27.1) | 250 (27.6) | .880 |
| - Low | 73 (21.5) | 121 (21.4) | 194 (21.4) | |
| - Middle | 170 (50.0) | 291 (51.5) | 461 (50.9) | |
| Non-Dutch background | 32 (9.5) | 40 (7.2) | 72 (8.0) | .207 |
| One parent family | 17 (5.2) | 28 (5.5) | 45 (5.3) | .855 |

All included variables in univariable are described in Table 1.

[a] This mainly occurs in EPs, all MLPs have been rated as "not present". SD: standard deviation; HELLP: Hemolysis, elevated liver enzymes, and low platelet count syndrome, or (pre)-eclampsia; PPROM: prolonged premature rupture of membranes; GA: gestational age; NICU: neonatal intensive care unit; CPAP: continuous positive airway pressure; SGA: small-for-gestational age.

have less time, abilities and money to stimulate their children's development than in families with a better social conext [27]. In the context of having siblings, parents have to divide their attention and resources between the children. Siblings also spend time with each other, but this may not reach the quality of stimulation that can be provided by the parents [28], particularly if sibling are younger [29]. Moreover, families with a less optimal social context experience more stressful events, which also may influence development [27]. Particularly children who are more vulnerable to developmental problems, such as preterm children, may benefit from a more optimal social context and may have a greater need for external stimulation to improve their development. We speculate that children with a less optimal social context have fewer abilities and opportunities to improve their development, resulting in emerging and persistent problems at school age.

Perinatal factors that were predictive of the stability of developmental problems were partially different between EPs and MLPs. All preterm children who were SGA were at increased risk of persistent, but also resolving developmental problems. Many cross-sectional studies reported a negative influence on development of being born SGA [11,12,22]. Intrauterine growth restriction due to placental insufficiency is a major cause of being born SGA, although constitutional and genetic causes add to a small but considerable minority of cases [30]. One can expect that with limited supply of nutrients and oxygen through the placenta, those children are born less mature and with more brain alterations [31]. Our findings may be interpreted as that these effects become more visible after school entry.

Another partial difference between EPs and MLPs concerns PPROM, this only being associated with more often emerging problems in MLPs. Some previous studies [32,33] also reported a negative influence of PPROM on development, whereas other studies reported no difference [34,35]. Children born after PPROM have an increased vulnerability to white matter lesions and intraventricular hemorrhage, due to higher risks of inflammation, infections and hemodynamic instability [36–38]. MLPs born after PPROM may be more vulnerable to emerging developmental problems because between 30 and 34 weeks' GA white matter

is more sensitive to inflammation [39]. Apparently these white matter lesions are subtle, as they give rise to observable developmental problems after school entry, and not before.

Male preterm children had higher risks than females of persistent developmental problems. The problems among male MLPs were also more likely to resolve. In line with our findings, most other studies also reported higher risks of developmental problems at a specific age among male preterm children [10–12,22]. In a review based on cross-sectional studies, Linsell et al. reported that studies focusing on children after the age of 5 found a smaller influence of sex than studies focusing on neurodevelopment before the age of 5 [11]. In contrast, Leversen et al. showed that male EPs had more persistent problems than female EPs between ages 2 and 5 [8], whereas Roberts et al. reported that female EPs had more emerging cognitive problems than male EPs between ages 2 and 8 [7]. Boys differ from girls in every level of organization of their brain –morphological, neurochemical, and functional - and have a higher vulnerability to pro-inflammatory responses [40,41]. Consequently, EP boys have higher risks than EP girls of preterm birth, neonatal mortality, severe intraventricular hemorrhage, sepsis, major surgery, and developmental problems [42–44]. Despite these higher initial risks, male sex influences stability patterns of development not in a single direction, but varying.

We found persistent or emerging developmental problems to be more associated with social context factors than with factors related to the pregnancy and neonatal period. Our findings contrast with those of other studies on the association between pregnancy-related and neonatal factors and developmental problems at a specific age [8–10,12,18]. However, those studies mainly determined developmental problems at ages younger than 5 years, and did not assess the effects of the combination of social ánd perinatal factors in a single model. Particularly the less severe neonatal conditions may have a decreasing influence on development as age increases, as also shown in the systematic review by Linsell et al. on EPs and preterm children <1250 g [11]. Our findings suggest that with increasing age the social context becomes more important, whereas the influence of pregnancy-related and neonatal factors decreases. The problems of most preterm children may resolve as a result of the stimulation of a more optimal social context, but for some children with specific neonatal conditions such as PPROM and SGA problems may persist.

Our final overall model predicted nearly 22% of the variation of persistent, emerging and resolving developmental problems among preterm children. This is a large predictive power as compared with predictions based only on being born EP or MLP (3% of the variance explained). As comparison, Roberts et al. were able to explain 8.9% of the variance in cognitive outcomes between ages 2 and 8 by including the sociodemographic variables gender and mothers from a non-English speaking country [7]. Perinatal and social factors are thus very important for the prediction of persistent and changing developmental problems among preterm children, even though the greater part of the variance remained unexplained.

The strengths of our study are the large, longitudinally followed community-based cohort, with a great variety of maternal, pregnancy-related, neonatal, and social factors for both EPs and MLPs. Furthermore, we used the same measure of developmental problems at different ages, and determined individual changes between these measures. Our study also had some limitations. First, although we had a large study population, the low incidence of persistent and emerging developmental problems in combination with the low incidence of some risk factors may have caused exclusions from the models due to low power. However, the more common factors have the greatest impact at group level. Second, we used the parent-reported ASQ, which might be considered less valid than a clinical assessment. Nevertheless, the ASQ is very well validated [13–16], and is based on the home situation, being more representative of a child's performance in daily life than a consultation room. Third, we only determined associations with overall developmental problems (ASQ total score), and not with the underlying

**Table 3**

Perinatal and social factors associated with persistent, emerging and resolving problems in preterm children (overall) in backward multivariable logistic regression analyses (with $P < .10$). Only univariable and multivariable results of factors present in the final models are shown. The consistently normal category was used as reference ($n = 789$) in all analyses. If there was significant interaction (i.a.), the combined OR was shown of the combined variable (e.g. PPROM for MLP and PPROM for EP).

| Variable | N (%) | Persistent problems N persistent = 50 | | Emerging problems N emerging = 25 | | Resolving N resolving = 42 | |
|---|---|---|---|---|---|---|---|
| | | Univariable | Multivariable [a] | Univariable | Multivariable [b] | Univariable | Multivariable [c] |
| | | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| **Maternal and pregnancy-related factors** | | | | | | | |
| Chronic mental illness | 13 (1.4) | 5.57 (1.46–21.28)* | 8.01 (1.85–34.60)** | | | | |
| Maternal obesity | 64 (11.7) | | | | | 2.74 (1.25–5.96)* | 2.41 (1.06–5.48)* |
| Smoking during pregnancy | 180 (19.5) | | | 2.13 (0.90–5.07)# | 2.14 (0.89–5.17)# | | |
| Antepartum hemorrhage | 107 (11.7) | 2.02 (0.97–4.19)# | 2.11 (0.97–4.61)# | | | | |
| PPROM | 192 (20.9) | | | Significant i.a. | Significant i.a. | | |
| *PPROM and MLP* | | | | 5.17 (1.44–18.64)* | 5.01 (1.38–18.14)* | | |
| *PPROM and EP* | | | | 2.34 (0.77–7.01) | 0.82 (0.18–3.82) | | |
| **Neonatal factors** | | | | | | | |
| Male sex | 513 (55.3) | 3.85 (1.90–7.79)*** | 4.96 (2.28–10.82)*** | 1.99 (0.85–4.68) | 2.42 (0.98–5.97)# | Significant i.a. | Significant i.a. |
| *Male sex and MLP* | | | | | | 19.93 (2.68–148)** | 16.81 (2.24–126)** |
| *Male sex and EP* | | | | | | 1.32 (0.49–3.51) | 1.31 (0.45–3.82) |
| SGA | 129 (14.2) | 2.63 (1.38–5.05)** | 2.39 (1.15–4.99)* | | | 3.12 (1.57–6.21)** | 2.92 (1.41–6.05)** |
| NICU Transportation | 56 (6.1) | | | | | 4.16 (1.81–9.56)** | 4.21 (1.75–10.14)** |
| CPAP | 379 (41.7) | Significant i.a. | Significant i.a. | | | | |
| *CPAP and MLP* | | 0.45 (0.10–1.96) | 0.44 (0.10–1.98) | | | | |
| *CPAP and EP* | | 5.53 (0.73–41.76)# | 4.94 (0.63–38.70) | | | | |
| **Social factors** | | | | | | | |
| Multiparity | 278 (30.7) | 2.31(1.31–4.08)** | 3.56 (1.87–6.76)*** | | | | |
| **Confounders** | | | | | | | |
| EP versus MLP | | 2.19 (1.24–3.87)** | 1.69 (0.21–13.40)[d] | 2.70 (1.20–6.08)* | 5.60 (1.77–17.66)** | 1.22 (0.65–2.30) | 7.93 (0.95–66.06)# |

All included variables in univariable analyses are described in Table 1.

[a] Included variables: maternal chronic mental illness, in vitro fertilization, antepartum hemorrhage, sex, sex*EP/MLP, SGA, asphyxia, length of NICU stay, circulatory insufficiency, CPAP, CPAP*EP/MLP, mechanical ventilation, bronchopulmonary dysplasia, multiparity, socioeconomic status, non-Dutch background, one parent family, EP/MLP. $N_{included} = 814$.

[b] Included variables: smoking during pregnancy, smoking during pregnancy*EP/MLP, PPROM, PPROM*EP/MLP, sex, Apgar $< 5$, length of NICU stay, EP/MLP. $N_{included} = 805$.

[c] Included variables: maternal obesity, maternal obesity*EP/MLP, sex, sex*EP/MLP, SGA, NICU admission, NICU transportation, mechanical ventilation duration, EP/MLP. $N_{included} = 801$.

[d] Manually added to final model to correct for confounding of being EP/MLP, and if the interaction variable was significant in the final model.

\# $P < .10$.

\* $P < .05$.

\*\* $P < .01$.

\*\*\* $P < .001$; i.a. = interaction.

domains. Consequently, factors related to a specific developmental domain or more subtle problems may not have been detected. Finally, we were not informed on possible constitutional or genetic aspects that may be related to persistent and emerging problems in preterm-born children at school age. Apart from a less optimal social context, constitutional and genetic aspects may play a role in why some infants with exposure to particular maternal or neonatal factors develop poor, while others do not.

This study demonstrated that mainly factors related to the social context predicted persistent and emerging developmental outcomes of preterm children. Our results suggest that whereas preterm birth and perinatal factors increase a child's vulnerability to developmental problems, a more optimal social context may prevent these problems from emerging or persisting. The preterm child's social context should therefore be an important target for prevention and treatment. In addition, in perinatal and neonatal care, health care professionals should be aware of the risks of PPROM for later developmental problems, particularly in MLPs. The perinatal and social factors in our final model may help to determine which preterm children are at greatest risk of persistent and emerging developmental problems after school entry.

## 5. Conclusion

Only few perinatal and social factors had associations with persistent and emerging developmental problems for both EPs and MLPs. These included maternal mental illness, maternal smoking, multiparity, and being born small-for-gestational age. Prolonged premature rupture of membranes was associated with developmental problems, but only among moderate-late preterm children. Identifying these risk factors greatly improved prediction of persistent and emerging developmental problems among preterm children.

**Table 4**

Relative risk (RR) for persistent, emerging and resolving problems in preterm children (overall) of various perinatal and social factors. Only univariable and multi-variable results of factors present in the final models are shown.

| Variable | N (%) | Persistent problems N persistent = 50 | | Emerging problems N emerging = 25 | | Resolving N resolving = 42 | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | Univariable | Multivariable[a] | Univariable | Multivariable[b] | Univariable | Multivariable[c] |
| | | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
| **Maternal and pregnancy-related factors** | | | | | | | |
| Chronic mental illness | 13 (1.4) | 4.43 (1.60–12.28)* | 5.75 (1.33–24.85)** | | | | |
| Maternal obesity | 64 (11.7) | | | | | 2.55 (1.26–5.16)* | 2.27 (1.00–5.17)# |
| Smoking during pregnancy | 180 (19.5) | | | 2.07 (0.90–4.76)# | 2.08 (0.87–5.03)# | | |
| Antepartum hemorrhage | 107 (11.7) | 1.92 (0.99–3.71)# | 1.99 (0.92–4.35)# | | | | |
| PPROM | 192 (20.9) | | | Significant i.a. | Significant i.a. | | |
| *PPROM and MLP* | | | | 4.96 (1.42–17.30)* | 4.82 (1.33–17.44)* | | |
| *PPROM and EP* | | | | 1.36 (0.32–5.84) | 0.83 (0.18–3.85) | | |
| **Neonatal factors** | | | | | | | |
| Male sex | 513 (55.3) | 3.98 (1.96–8.08)*** | 4.55 (2.09–9.92)*** | 1.96 (0.85–4.48) | 2.35 (0.95–5.80)# | Significant i.a. | Significant i.a. |
| *Male sex and MLP* | | | | | | 18.42 (2.51–135)** | 15.84 (2.11–119)** |
| *Male sex and EP* | | | | | | 1.30 (0.51–3.27) | 1.29 (0.44–3.77) |
| SGA | 129 (14.2) | 2.28 (1.25–4.16)** | 2.23 (1.07–4.66)* | | | 2.88 (1.54–5.37)** | 2.71 (1.31–5.62)** |
| NICU Transportation | 56 (6.1) | | | | | 3.67 (1.78–7.56)** | 3.71 (1.54–8.94)** |
| CPAP | 379 (41.7) | Significant i.a. | Significant i.a. | | | | |
| *CPAP and MLP* | | 0.46 (0.11–1.94) | 0.45 (0.10–2.03) | | | | |
| *CPAP and EP* | | 5.05 (0.70–36.35)# | 4.56 (0.58–35.74) | | | | |
| **Social factors** | | | | | | | |
| Multiparity **Confounders** | 278 (30.7) | 2.27(1.33–3.87)** | 3.21 (1.68–6.09)*** | | | | |
| EP versus MLP | | 2.01 (1.18–3.45)** | 1.64 (0.20–13.01)d | 2.61 (1.19–5.74)* | 5.14 (1.63–16.24)** | 1.21 (0.66–2.20) | 5.98 (0.72–49.83)# |

All included variables in univariable analyses are described in Table 1.

<sup>a</sup> Included variables: maternal chronic mental illness, in vitro fertilization, antepartum hemorrhage, sex, sex*EP/MLP, SGA, asphyxia, length of NICU stay, circulatory insufficiency, CPAP, CPAP*EP/MLP, mechanical ventilation, bronchopulmonary dysplasia, multiparity, socioeconomic status, non-Dutch background, one parent family, EP/MLP. $N_{included}$ = 814.

<sup>b</sup> Included variables: smoking during pregnancy, smoking during pregnancy*EP/MLP, PPROM, PPROM*EP/MLP, sex, Apgar < 5, length of NICU stay, EP/MLP. $N_{included}$ = 805.

<sup>c</sup> Included variables: maternal obesity, maternal obesity*EP/MLP, sex, sex*EP/MLP, SGA, NICU admission, NICU transportation, mechanical ventilation duration, EP/MLP. $N_{included}$ = 801.

<sup>d</sup> Manually added to final model to correct for confounding of being EP/MLP, and if the interaction variable was significant in the final model.

# P < .10.
* P < .05.
** P < .01.
*** P < .001; i.a. = interaction.

**Table 5**

Accuracy (Area under the curve), fit (P Hosmer Lemeshow), and explained variance (Nagelkerke $R^2$) of final models in comparison with prediction based solely on being early-preterm (EP) or moderately-and-late-preterm born (MLP).

| Included factors | Persistent problems | | Emerging problems | | Resolving problems | | Overall model | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | EP/MLP | Final model[a] | EP/MLP | Final model[b] | EP/MLP | Final model[c] | EP/MLP | Final model[a,b,c] |
| Area under the curve | 0.596 (poor) | 0.794 (fair) | 0.621 (poor) | 0.745 (fair) | 0.524 (poor) | 0.755 (fair) | | |
| P Hosmer-Lemeshow | | 0.322 | | 0.137 | | 0.463 | | |
| Nagelkerke $R^2$ | 0.023 | 0.191 | 0.030 | 0.096 | 0.001 | 0.156 | 0.030 | 0.219 |

<sup>a</sup> Final model for persistent problems contains: chronic mental illness of mother, antepartum hemorrhage, male sex, SGA, CPAP*EP/MLP, CPAP (manually added), multiparity, EP/MLP (manually added).

<sup>b</sup> Final model for emerging problems contains: smoking during pregnancy, PPROM*EP/MLP, PPROM, EP/MLP.

<sup>c</sup> Final model for resolving problems contains: maternal obesity, sex*EP/MLP, sex, SGA, NICU transportation, EP/MLP.

## CRediT authorship contribution statement

Prof. Arend F. Bos made substantial contributions to the conception of this study, supervised the data curation and analyses, interpreted the data, drafted the final manuscript, and approved the final manuscript as submitted. Together with prof. SA Reijneveld he acquired funding for the LOLLIPOP study.

Ms. Jorijn Hornman made substantial contributions to the conception of this study, conceptualized and carried out the analysis, interpreted the data, drafted an initial version of the manuscript, and approved the final manuscript as submitted.

Prof. Sijmen A. Reijneveld and Dr. Andrea F. de Winter made substantial contributions to the conception and analysis of this study, interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

## Declaration of competing interest

All authors have indicated they have no financial relationships relevant to this article to disclose.

The authors have no conflicts of interest relevant to this article to disclose.

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