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Predictors of early motor trajectories from birth to 5 years in neonatal at-risk and control children

Running head: Predictors of motor trajectories in children

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Abbreviations: CP – Cerebral Palsy; DCD - Developmental Coordination Disorder; Bavarian-Finnish Longitudinal Study (BFLS); BLS – Bavarian Longitudinal Study; AYLS – Arvo Ylppö Longitudinal Study; GA – Gestational age; SGA - Small for gestational age; INTI - Intensity of Neonatal Treatment Index; SES – Socio-economic status; FAI - Family Adversity Index; PIRI - Parent-Infant Relationship Index; PSI – Psychosocial Stress Index; LCGA – Latent Class Growth Analysis; BIC -Bayesian Information Criterion; BLRT - Bootstrapped Likelihood Ratio Test; LMR - Lo-Mendel-Rubin Likelihood Ratio Test; VLMR - Vuong-Lo-Mendell-Rubin Likelihood Ratio Test.

Abstract

Aims. To describe early motor development in at-risk and control children, to identify perinatal and neonatal risk factors, and early social environmental factors of poor motor development, and to replicate results in a second cohort.

Methods. Two prospective whole-population samples in Germany (Bavarian Longitudinal Study, BLS; primary cohort) and Finland (Arvo Ylppö Longitudinal Study, AYLS; replication cohort) assessed 4741 and 1423 children from birth to 56 months, respectively. Identical measures were used. Motor functioning was evaluated at birth, and 5, 20 and 56 months. Perinatal, neonatal and social environmental information was collected at birth and 5 months.

Results. Latent class growth analysis identified two distinct trajectories of early motor functioning: low (BLS: N=4,486 (94.6%), AYLS: N=1,391 (97.8%)) and high (BLS: N=255 (5.4%), AYLS: N=32 (2.2%)) degree of motor difficulties. In the BLS, high degree of motor difficulties was predicted by neonatal complications, abnormal neonatal neurological status, duration of hospitalisation, and poor parent-infant relationships. Although neonatal complications and poor parent-infant relationships did not significantly predict high degree of motor difficulties in the AYLS, the trends identified were similar to those obtained from the BLS.

Conclusion. Early identification of children at-risk of a trajectory of high degree of motor difficulties across infancy and toddlerhood may help referring those children to interventions at an earlier age. Modifiable environmental risk factors, such as parent-infant relationships, may be addressed by intervention strategies to prevent children from developing motor problems.

Key Terms: cohort studies; motor development; population at-risk; risk factors; trajectories of motor functioning

Key Notes:

- Two distinct trajectories of motor functioning from birth to 56 months were identified in two samples in two countries.
- Poor motor development was predicted by neonatal complications, abnormal neonatal neurological status, duration of hospitalisation, and poor parent-infant relationships.
- As a possible implication, children with motor problems may benefit from interventions that focus on parent-infant interactions.

INTRODUCTION

The spectrum of motor impairment can range in severity and form, and has significant implications for sensorimotor learning, cognition and social development (1). However, even in the absence of a clinical diagnosis (i.e., cerebral palsy (CP) or developmental coordination disorder (DCD)), motor deficits may have an adverse impact on children's development (2).

Most children do not outgrow their motor problems (2, 3) and these may negatively impact on mental health, academic achievement, health-related quality of life and social functioning into adolescence and adulthood (4-6). Therefore it is important to identify children who are at-risk for developing any motor deficits (7) to enable early support or referral for intervention that may help improve motor functioning or ameliorate developmental problems.

Although recent findings have shown that most treatment or intervention programmes for improving motor skills of children with neurodevelopmental disorders are limited (8, 9), there is evidence that parent training or interventions involving parents may have positive effects on early motor development (9, 10). This is not surprising as motor development is affected by the physical environment, as well as by social and cultural influences. As such, parents may largely influence their child's motor development (11). However, few observational studies have tested the effects of early social environmental factors on child motor development (12, 13). The results of these studies suggest that in addition to biological and medical risk factors (i.e., pre- and perinatal complications), psychosocial risk factors, such as family adversity and poor parent-infant relationships, can have a detrimental effect on later motor, cognitive and social-emotional development in children born at-risk (e.g., preterm birth).

The present study assessed two large samples of children born across the full gestation spectrum in Germany or Finland who received the same standardised physical and neurological assessments from birth to age 56 months. Identical data on perinatal and neonatal risk factors, and early social environment measures, such as family adversity or early parent-infant-relationships, were collected.

The study aims were: (1) to identify trajectories of motor functioning over the first 5 years of life in neonatal at-risk and control children; (2) to investigate whether parent-infant-relationships influence motor development (i.e., early motor trajectories), in addition to known perinatal, neonatal and other early social environmental risk factors in the Bavarian Longitudinal Study (BLS) in Germany; and (3) to test whether findings are replicated in a second cohort, the Arvo Ylppö Longitudinal Study (AYLS) in Finland.

METHODS

Participants and Procedures

Data were collected as part of the prospective Bavarian-Finnish Longitudinal Study (BFLS) (14). The BFLS includes two geographically defined, whole population samples of neonatal at-risk children born in 1985 and 1986 in Southern Bavaria, Germany and in the county of Uusimaa, Finland, who required admission to a children's hospital within the first 10 days after birth (BLS: N=7,505; AYLS: N=1,536). Healthy infants born at term in the same hospitals were recruited as controls (BLS: N=916; AYLS: N=658).

Parents were approached within 48 hours of the infant's hospital admission and asked to give written informed consent to participate. Ethical permissions were granted by the ethics committees of the University of Munich Children's Hospital and the Bavarian Health Council (Landesärztekammer Bayern) in Germany, and of the Helsinki City Maternity Hospital, Helsinki University Central Hospital, and Jorvi Hospital in Finland.

Children and their parents were assessed at birth and followed up at 5 and 20 months corrected age, and at 56 months chronological age, by an interdisciplinary team for an entire day, including neurological and physical assessments, parent interviews, cognitive assessments and observations of behaviour.

In Germany, 415 families declined to participate, and 390 children died during hospitalisation or between discharge and 56 months. In Finland, 5 families declined participation, and 67 children died during hospitalisation or between discharge and 56 months. In total N=7,616 and N=2,122 children were eligible for follow up at age 5 months in Germany and Finland, respectively (Figure 1).

The current study used the BLS as the primary sample and the AYLS as the replication sample.

Measures

Motor Functioning. At birth, 5, 20 and 56 months, an extensive and detailed standardised neurological and physical examination based on Precht's neurological examination method (15, 16), was carried out by specially trained developmental paediatricians. Examinations at 5, 20 and 56 months were adapted to include extended and age-related items. All paediatricians attended retraining sessions every two months and were blinded to the child's birth status and medical history. To compute a motor problem score from the data obtained through this examination, items on neurological and motor functioning, such as fine and gross motor skills, oculomotor function, muscle tone, and reflexes were combined and categorised into 'within' and 'outside the normal range' of motor function. Missing motor data on item-level were low across all assessment time points. For details on motor items including missing data see Tables S1 to S4 (online supporting information). However, cases with the majority of motor functioning items missing were

deemed as lacking sufficient information and not suited for missing data imputation (17). As this criterion pertained only to a small number of cases relative to the respective sample size, they were excluded (cases with more than half of motor functioning items missing: BLS N=12 at birth, N=1 at 5 months, N=4 at 20 months, N=361 at 56 months; AYLS: N=1 at birth, N=0 at 5 months, N=0 at 20 months, N=72 at 56 months). All remaining missing data were imputed by simple imputation using the two-way imputation method (17). Subsequently, a motor problem score was computed based on the sum of motor functioning ‘outside the normal range’ (i.e., a higher score indicates more motor problems). As the number of items varied across time, scores were standardised to a mean of 0 and a standard deviation of 1 (z-scores) to allow comparability across ages (Table S5, online supporting information).

In total, longitudinal data on motor functioning were available for 4,741 (62.3% of eligible children at 5-month follow up) and 1,423 (67.1% of eligible children at 5-month follow up) at-risk and term control children in the BLS and AYLS, respectively (Figure 1).

Predictive measures

Pre-pregnancy, pregnancy and perinatal complications were assessed from standard perinatal survey medical records within 10 days of admission. Data on neonatal characteristics and health (i.e., gestational age, birth weight, head circumference, child sex, smallness for gestational age, and neonatal complications), neonatal course (i.e., neonatal neurological problems, and duration of initial hospitalisation), and early social environment (i.e., family socioeconomic status, family adversity, parent-infant relationships, psychosocial stress, and breastfeeding) were collected prospectively during hospitalisation and at 5 months after the child’s birth using information from maternal interview, medical records, and standard research nurse observations. For a detailed description of all predictive measures see Table S6 (online supporting information).

Statistical Analysis

All statistical analyses were performed using SPSS Version 22 (IBM SPSS Statistics, IBM Corporation) and Mplus 7.31 (Muthén and Muthén, Los Angeles, California).

Sample characteristics and attrition analysis (i.e., comparisons with participants who were lost to follow-up or missing/uncomplete motor data) were conducted using t-tests for interval scaled variables or chi-square tests for dichotomous variables.

To identify groups of children with similar development of motor functioning over time (motor trajectories), latent class growth analysis (LCGA), a person-centred statistical approach, was performed using Mplus. Within the LCGA, the number of latent classes were estimated, compared, and decided upon according to standard conventions (18, 19). The optimal number of classes was determined by assessing the Bayesian Information Criterion (BIC), the adjusted BIC, the Parametric Bootstrapped Likelihood Ratio Test (BLRT), the Lo-Mendel-Rubin Likelihood Ratio Test (LMR), and the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR) (18). Further, the rule of parsimony and the substantive relevance of a class were taken into account (19). Subsequently, each participant was assigned to the class with the highest probability of membership.

To investigate the relationship between latent classes of motor trajectories and perinatal and neonatal risk factors, logistic regressions were performed using SPSS. First, univariate regressions were run with all predictors. Next, multivariate regressions were applied using all significant predictors from univariate regressions. Analyses were performed in a stepwise fashion: pre-pregnancy, pregnancy and perinatal complication factors (Model 1), neonatal characteristics and health (Model 2), neonatal course (Model 3), and early social environment factors (Model 4).

All analyses were applied to BLS data first. To test whether results would be replicated, LCGA, univariate regressions, and the final multivariate regression model (Model 4) were repeated with AYLS data.

Additionally, to assess retrospectively whether severe neurological impairments diagnosed at 56 months are associated with the identified motor trajectories, chi-square tests were performed (Table S8, online supporting information). To rule out that motor trajectories had been influenced by severe neurological impairments (BLS N=95 (2.0%), AYLS N=15 (1.1%)), regression models were repeated without these children in both cohorts (see Appendix, online supporting information).

RESULTS

Sample characteristics and dropouts

Sample characteristics (i.e., antenatal, perinatal and neonatal variables) and comparisons with dropouts (i.e., lost to follow-up or missing/incomplete motor data) are provided in Table S7 (online supporting information).

BLS. Compared with dropouts, participants had higher perinatal but lower neonatal complication rates. Dropouts were more often male, received more neonatal treatment and on average stayed longer in hospital in comparison to participants. Overall, dropouts were more often born into families with a low socioeconomic status, higher family adversity, and higher psychosocial stress. Further, they had poorer early parent-infant relationships and were less often breastfed.

AYLS. Dropouts received more neonatal treatment and were born into families with a lower socioeconomic status. In addition, they more frequently had poor early parent-infant relationships and were less often breastfed.

Trajectories of Motor Problems

BLS. LCGA modelling estimated one, two, and three latent classes (trajectories) within motor functioning from birth to 56 months. Model fits BIC, and adjusted BIC decreased gradually with the number of classes, indicating improved model fits (Table S9, online supporting information). BLRT, LMR, and VLMR were all significant for a 2-class model, while only BLRT continued to be significant for a 3-class model. Considering that not all statistical indicators improved, and the size of classes, the more parsimonious 2-class model was deemed optimal.

AYLS. Following the same statistical indicators, the 2-class model was deemed to offer the best results.

The selected LCGA model identified two motor trajectories within both cohorts (Figure 2): low (BLS: N=4,486 (94.6%); AYLS: N=1,391 (97.8%)), and high (BLS: N=255 (5.4%); AYLS: N=32 (2.2%)) degree of motor difficulties. In both cohorts, motor problem scores differed between trajectories with a large effect size across all four time points (Table S10, online supporting information).

Predictors of Motor Trajectories: Unadjusted Models

Table 1 shows the descriptive values and unadjusted estimates of all predictors of motor problems.

BLS. Mothers of children with high degree of motor difficulties were more likely to have more complications before and during pregnancy, and around birth. Children with high degree of motor difficulties were more often born preterm, with low birth weight, and had a smaller head circumference. Further, they were more often small for gestational age and had more neonatal complications. Children with high degree of motor difficulties were rated with higher intensity of neonatal treatment scores and stayed in hospital for longer. They were also

less often breastfed, more likely to have a family experiencing high adversity, and had poorer parent-infant relationships.

AYLS. Mothers of children with high degree of motor difficulties were more likely to have pre-pregnancy and pregnancy complications. Children with high degree of motor difficulties were more likely to be born preterm and with low birth weight, and had more often a smaller head circumference and neonatal complications. Moreover, they were more likely to have higher intensity of neonatal treatment scores and were hospitalized for longer. Additionally, they were more likely to have a family of low socioeconomic status, and a family experiencing more psychosocial stress, and they had poorer parent-infant relationships

Predictors of Motor Trajectories: Adjusted Models

Adjusted estimates of significant predictors of high degree of motor difficulties in multivariate models are shown in Table 2.

BLS. The results of adjusted stepwise models showed that when pre-pregnancy, pregnancy and perinatal complications were combined into one model (Model 1), all three predictors were associated with motor problems. However, when neonatal health predictors were added (Model 2), only head circumference and neonatal complications remained as significant predictors. In Model 3, neonatal complications, abnormal neonatal neurological status and longer hospitalisation were associated with high degree of motor difficulties. The final model (Model 4), showed the same associations as in Model 3, with poor parent-infant relationships also predicting high degree of motor difficulties. All predictors explained 17.4% of the variance in the final model.

AYLS. The final adjusted model (Model 4) with AYLS data showed the same pattern of results as with BLS data. However, only abnormal neonatal neurological status and longer hospitalisation were significantly associated with high degree of motor difficulties whereas

neonatal complications and poor parent-infant relationship ceased to be significant predictors. All predictors explained 19.4% of the variance in Model 4. Results of all stepwise models are shown in Table S11 (online supporting information).

Figure 3 illustrates all four risk factors associated with high degree of motor difficulties in the final adjusted model for both cohorts: neonatal complications (BLS: OR 1.11, CI 1.03-1.20; AYLS: OR 1.11, CI 0.90-1.37), abnormal neonatal neurological status (BLS: OR 1.17, CI 1.08-1.26; AYLS: OR 1.85, CI 1.38-2.48), duration in hospital (10 days) (BLS: OR 1.17, CI 1.11-1.24; AYLS: OR 1.19, CI 1.02-1.39), and poor parent-infant-relationship (BLS: OR 1.55, CI 1.16-2.08; AYLS: OR 1.13, CI 0.40-3.15).

DISCUSSION

We identified two distinct motor trajectories in this longitudinal study of two samples of at-risk and control children in two countries. These two motor trajectories across the first 5 years of life are described as low and high degree of motor difficulties. Significant independent predictors of children with high degree of motor difficulties were neonatal complications, abnormal neonatal neurological status, duration of hospitalisation, and poorer parent-infant relationships in the BLS. The same predictors were identified in the AYLS, however, estimates of neonatal complications and poor parent-infant relationship were not significant at the 0.05 level in multivariate analyses. Nevertheless, the trends were similar to findings obtained from the BLS data, as shown in Figure 3. The differences are likely due to the smaller AYLS sample and smaller group of children with poor motor development, resulting in lower statistical power compared to the larger BLS sample (i.e., the low number of children with poor parent-infant relationships in the AYLS sample; see Table 1). However, there are important differences between the BLS and AYLS sample that may have been contributed to the differences in findings. The AYLS children were more advantaged in terms of neonatal health and neonatal course, compared to BLS children. They were less often born

premature, had lower neonatal complication and abnormal neonatal neurological status scores, and stayed in hospital for a shorter period of time (see Table S7).

Results of LCGA show that children's development of motor functioning either followed a low or a high degree of motor difficulties trajectory across early childhood. Most children in both samples consistently had no or low degree of motor difficulties from birth to 56 months, while children in the group with high degree of motor difficulties demonstrated problems at all four assessments.

Three recent longitudinal studies (20-22) have used LCGA to identify different groups of children with distinct early motor trajectories. Even though more than two groups were identified in these studies, the trajectories represented stable and declining/delayed motor development, with most children exhibiting stable motor development, i.e. average or typically developing motor performance. This is comparable to the two trajectories ascertained in the present study, with the majority of children exhibiting no or low degree of motor difficulties across early childhood. Thus, despite methodological differences, such as the inclusion of very low birth weight infants (20) or children born after assisted reproductive techniques (22), and the reliance on parental information to assess motor function (21), our findings are broadly in keeping with previous research.

Interestingly, perinatal risk factors previously identified to predict motor impairment or delayed motor development, i.e. prematurity, low birth weight, smallness for gestational age, male sex (2, 20, 23, 24), were only found to be related to poor motor development in univariate but not in multivariate models. Instead, clinical neonatal factors, i.e., complications, abnormal neurological status, duration of hospitalisation, and poor parent-infant relationships emerged as unique predictors of poor motor development. The number and type of risk factors included in previous studies varies considerably. Further, most of these studies have included preterm children only and had smaller sample sizes compared to

the present study. Our finding thus may be explained by a more inclusive approach with broader preconditions, i.e. the inclusion of more comprehensive clinical and early motor-related predictors as well as early social environment factors, the large sample size of both cohorts and the inclusion of children born across the whole gestation spectrum in our analyses.

The data suggest that a higher number of neonatal complications (including seizures, cerebral haemorrhage, and ventilation), ratings of abnormal neonatal neurological status (i.e., increased or decreased mobility, muscle tone or activity/reactivity to hyper-/hypokinesia, hyper-/hypotonia, apathy, coma or hyperexcitability), and longer stay in hospital negatively affect motor outcomes (24-26). These early predictors highlight the importance of infants' health and neurological status during the neonatal period. One explanation may be that due to infants' poor health and treatment being paramount, and the stressors that those infants are being exposed to in the NICU environment, normal early movements, motor control and motor learning are impeded or delayed (27, 28). Other factors, such as decreased or delayed weight gain and body growth, as well as a constrained environment in the NICU and parental support could play a role (27). Further, processes in brain development (e.g., myelination and synaptogenesis), which are important for motor coordination and functioning, and the integrity of the central nervous system may also be affected by the infant's level of morbidity (29). Overall, neonatal complications, abnormal neonatal neurological status, and duration of hospitalisation are useful early medical markers of poor motor development and can be monitored regularly in the neonatal care unit. Importantly, this knowledge would make it possible to inform parents in a timely manner about their child's risk of developing motor problems or delay and enable early referral to interventions.

Most notable, poor early parent-infant relationships increased the infants' risk of early motor problems. As to the reasons and specific mechanisms behind the association between

parent-infant relationships and motor development, we can only speculate. Parents are important facilitators of infants' motor learning and development (11). Not only do they provide an appropriate environment (e.g., high chairs to support sitting or crawling tunnels to practice arm and leg movements) (30), they also support and guide their infant verbally and non-verbally (31), and help develop muscle strength and gross motor skills (e.g., making noises to encourage the infant to lift its head). As a result, parents influence and determine their child's development. This raises the question, how and why the quality of parent-infant relationships may alter parents' behaviour and perception of their child in regard to how they implement support and guidance for their infants' motor learning and development. Poor parent-infant relationships in the current study were defined by parents not seeing or visiting their child often during the day, and by parents showing little pleasure or confidence in interacting with their infant. This indicates that parents' confidence and belief in their competence to take care and interact with their infant, especially if the infant is perceived as too fragile, may be an important factor in their ability to create opportunities for their child's motor learning and motor skill practice (10). Parents whose child had been referred to the NICU may even feel less confident and have little opportunity to support and encourage their infant's motor development and learning due to their child's medical condition and care provided through NICU personnel, and the associated stress and anxiety (32). However, integrating parents while their child is in the NICU and encouraging them to hold their infant, may positively influence motor outcomes (27). A recent meta-analysis found that parenting interventions can positively affect children's motor abilities (10). The authors suggest that such an intervention may alter parents' perception of their preterm born child as being too fragile and may increase parental feelings of competence and self-confidence resulting in positive parent-infant interactions (13). These findings are important as early parent-infant relationships represent a potentially modifiable factor that can be addressed by support

services and in early intervention programmes. Further, previous findings have shown that early parent-infant relationships predict long-term cognitive outcomes (33).

Our findings support future research to investigate whether targeted intervention programmes to improve early parent-infant relationships and to provide parent support in the NICU can lead to significant and long-term improvements in children's motor development. Given the evidence from previous studies that early motor deficits do not diminish over time (34), and that poor motor skills in adulthood are associated with mental health problems and lower health-related quality of life (35), the early motor trajectories identified in this current study may help to predict whether children with high degree of motor difficulties over the first 5 years of life are more likely to have additional problems in other developmental domains across the life span.

The strengths of this study are its prospective longitudinal design, large sample size, the inclusion of children born across the whole gestation spectrum, the assessment of motor functioning via extensive and detailed physical and neurological examinations at four time points, and the uniquely built-in replication with identical data from a second large longitudinal study from a different country. Further, even after excluding children with severe neurological impairments diagnosed at 56 months (sensitivity analysis), the results were similar to our main results. There are also limitations. Although more than 60% of eligible children could be assessed in both cohorts, the dropout was not random. Children who had a poorer health status and a socially disadvantaged family were less likely to continue participation. This may suggest that identified early predictors have an even larger effect on early motor development than reported here. Attrition is a problem in many longitudinal studies. However, simulations have shown that predictions only marginally change even when dropout is selective or correlated with the outcome (36). Further, the participants of both cohorts were born in the mid-80s. Over the last three decades, changes in reproductive

medicine and improvements in neonatal practices and care have led to increased survival rates of smaller infants. However, despite these changes, recent findings indicate that the prevalence of neurodevelopmental sequelae, including motor impairments, has not improved (37, 38). Thus, although our results should be cautiously interpreted, they provide a baseline for newer cohorts to investigate whether findings differ for children born after our cohorts.

Conclusion

Our results show distinct pathways of early motor functioning, with a subgroup of children developing major motor problems in early childhood. In addition to known risk factors, such as neonatal complications, abnormal neonatal neurological status, and duration of hospitalisation, our findings confirm the importance of parent-infant relationships in motor development and should be considered in intervention studies to prevent or ameliorate possible secondary issues in other developmental domains and continued developmental problems in motor functioning.

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Figure legends**Legend Figure 1**

Flow chart BLS and AYLS

Legend Figure 2

Trajectories of early childhood motor difficulties: 2-class solution (BLS and AYLS)

Legend Figure 3

Unique neonatal and early environment predictors of high degree of motor difficulties trajectory in the BLS and AYLS (adjusted estimates of multivariate binomial logistic regression analyses (Odds Ratio and 95% Confidence Interval)).

Table 1. Descriptives and unadjusted estimates^a of potential predictors of early childhood motor trajectories in the BLS and AYLS

BLS				AYLS					
Low degree of motor difficulties trajectory	High degree of motor difficulties trajectory	Reference: Low <i>degree of motor difficulties trajectory</i>	Low degree of motor difficulties trajectory	High degree of motor difficulties trajectory	Reference: Low <i>degree of motor difficulties trajectory</i>	OR (95% CI)	p-value	OR (95% CI)	p-value
<i>Pre-/pregnancy and perinatal complications</i>									
Pre-pregnancy, mean (SD)	1.10 (0.78)	1.28 (0.98)	1.30 (1.12, 1.51)	<.001	1.24 (0.88)	1.72 (1.17)	1.67 (1.19, 2.33)	.003	
Pregnancy, mean (SD)	1.34 (1.22)	1.72 (1.32)	1.25 (1.14, 1.38)	<.001	1.22 (1.16)	1.53 (1.16)	1.23 (0.94, 1.62)	.139	
Perinatal, mean (SD)	3.07 (1.74)	3.81 (1.68)	1.27 (1.18, 1.36)	<.001	2.86 (1.52)	3.25 (1.55)	1.17 (0.94, 1.45)	.151	
<i>Neonatal characteristics and health</i>									
Prematurity (<37 weeks GA), n (%)	1,434 (32.0)	143 (56.1)	2.72 (2.11, 3.51)	<.001	282 (20.3)	11 (34.4)	2.06 (0.98, 4.32)	.056	
Low birth weight (<2500g), n (%)	1,499 (33.4)	158 (62.0)	3.25 (2.50, 4.21)	<.001	221 (15.9)	11 (34.4)	2.77 (1.32, 5.83)	.007	
Head circumference, mean (SD)	33.31 (2.42)	31.37 (3.79)	0.79 (0.75, 0.82)	<.001	34.55 (2.27)	32.75 (4.21)	0.81 (0.73, 0.90)	<.001	
Male sex, n (%)	2,339 (52.1)	148 (58.0)	1.27 (0.98, 1.64)	.067	746 (53.6)	19 (59.4)	1.26 (0.62, 2.58)	.520	

SGA, n (%)	1,057 (23.6)	95 (37.3)	1.93 (1.48, 2.51)	<.001	187 (13.4)	5 (15.6)	1.19 (0.45, 3.14)	.721
Neonatal complications, mean (SD)	3.84 (2.87)	6.62 (3.82)	1.30 (1.25, 1.35)	<.001	2.12 (2.43)	4.63 (4.41)	1.26 (1.16, 1.38)	<.001
<i>Neonatal course</i>								
INTI - Clinical course, mean (SD)	2.27 (2.15)	4.03 (2.89)	1.33 (1.27, 1.40)	<.001	1.67 (1.94)	3.19 (2.29)	1.37 (1.18, 1.59)	<.001
INTI - Neurological status, mean (SD)	2.31 (2.28)	4.32 (2.64)	1.40 (1.32, 1.47)	<.001	1.17 (1.56)	2.98 (2.14)	1.67 (1.40, 1.99)	<.001
Duration in hospital (10 days), mean (SD)	2.01 (2.04)	4.89 (4.67)	1.32 (1.27, 1.37)	<.001	0.83 (1.51)	2.74 (4.04)	1.25 (1.14, 1.37)	<.001
<i>Early social environment</i>								
Low SES, n (%)	1,686 (37.6)	118 (46.3)	1.30 (0.98, 1.71)	.066	282 (20.5)	8 (26.7)	2.01 (0.77, 5.26)	.156
High SES, n (%)	999 (22.3)	40 (15.7)	0.74 (0.51, 1.08)	.119	456 (33.2)	13 (43.3)	2.02 (0.86, 4.76)	.109
Low FAI, n (%)	1,342 (30.1)	52 (20.4)	0.74 (0.52, 1.05)	.086	173 (12.4)	5 (15.6)	1.33 (0.46, 3.89)	.600
High FAI, n (%)	1,482 (33.3)	117 (45.9)	1.50 (1.12, 2.00)	.006	711 (51.1)	16 (50.0)	1.04 (0.48, 2.25)	.926
Poor PIRI, n (%)	1,425 (33.6)	129 (52.7)	2.19 (1.69, 2.84)	<.001	167 (12.1)	7 (22.6)	2.13 (0.90, 5.01)	.085
High PSI, n (%)	1,231 (27.9)	69 (27.8)	1.00 (0.75, 1.32)	.975	407 (29.4)	14 (46.7)	2.11 (1.02, 4.35)	.045
No breastfeeding, n (%)	1,986 (46.0)	176 (69.9)	2.73 (2.07, 3.61)	<.001	102 (7.5)	4 (13.3)	1.88 (0.65, 5.50)	.247

^a Unadjusted estimates of univariate binomial logistic regression analyses; OR=Odds Ratio, CI=Confidence Interval.

GA=gestational age; SGA=small for gestational age; INTI = Intensity of Neonatal Treatment Index; SES=socioeconomic status; FAI=Family Adversity Index; PIRI=Parent-Infant Relationship Index; PSI=Psychosocial Stress Index.

Table 2. Adjusted estimates^a of significant predictors of a high degree of motor difficulties trajectory in the BLS and the AYLS^b

	BLS				AYLS
	Model 1	Model 2	Model 3	Model 4	Model 4
<i>Pre-/pregnancy, perinatal complications</i>					
Pre-pregnancy	1.20 (1.03, 1.40)	1.13 (0.97, 1.32)	1.14 (0.97, 1.33)	1.15 (0.98, 1.36)	1.28 (0.84, 1.96)
Pregnancy	1.15 (1.04, 1.27)	0.97 (0.87, 1.09)	0.97 (0.87, 1.10)	0.92 (0.81, 1.05)	1.04 (0.72, 1.51)
Perinatal	1.22 (1.13, 1.31)	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	1.04 (0.95, 1.14)	0.97 (0.72, 1.29)
<i>Neonatal characteristics and health</i>					
Prematurity (<37 weeks GA)		0.83 (0.55, 1.26)	0.82 (0.53, 1.27)	0.84 (0.53, 1.33)	0.44 (0.11, 1.70)
Low birth weight (<2500g)		1.23 (0.79, 1.91)	1.24 (0.78, 1.97)	1.18 (0.73, 1.91)	1.95 (0.44, 8.68)
Head circumference	0.92 (0.86, 0.99)	1.00 (0.93, 1.08)	0.99 (0.91, 1.07)	0.96 (0.78, 1.19)	
SGA		1.13 (0.82, 1.56)	1.17 (0.84, 1.62)	1.07 (0.75, 1.51)	0.64 (0.18, 2.24)
Neonatal complications	1.23 (1.17, 1.29)	1.11 (1.03, 1.19)	1.11 (1.03, 1.20)	1.11 (0.90, 1.37)	
<i>Neonatal course</i>					
INTI – Clinical course		0.92 (0.83, 1.00)	0.92 (0.83, 1.01)	0.77 (0.54, 1.10)	
INTI – Neurological status		1.21 (1.12, 1.29)	1.17 (1.08, 1.26)	1.85 (1.38, 2.48)	
Duration in hospital (10 days)		1.19 (1.13, 1.26)	1.17 (1.11, 1.24)	1.19 (1.02, 1.39)	

<i>Early social environment</i>		
Low FAI	0.94 (0.64, 1.39)	2.22 (0.68, 7.26)
High FAI	1.34 (0.97, 1.86)	1.19 (0.47, 2.99)
Poor PIRI	1.55 (1.16, 2.08)	1.13 (0.40, 3.15)
No breastfeeding	1.34 (0.97, 1.84)	0.40 (0.10, 1.62)

^a Adjusted estimates of multivariate binomial logistic regression analyses (Odds Ratio and 95% Confidence Interval), predictors adjusted for all other variables in the prediction model; ^b Replication: The same multivariate regression analysis (Model 4) established for BLS data was applied to AYLS data; GA=gestational age; SGA=small for gestational age; INTI = Intensity of Neonatal Treatment Index; FAI=Family Adversity Index; PIRI=Parent-Infant Relationship Index.