Neurodevelopment and the effects of a neurobehavioral intervention in very preterm-born children
van Hus, J.W.P.

Citation for published version (APA):

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Chapter 6

Longitudinal developmental effects of the IBAIP in very preterm-born infants

Janeline W.P. Van Hus, Martine Jeukens-Visser, Karen Koldewijn, Rebecca Holman, Joke H. Kok, Frans Nollet, Aleid G. Van Wassenaer-Leemhuis

Submitted
Abstract

**Background and aim:** Very preterm-born and very low birth weight (VLBW) infants are at risk of developmental problems. Therefore, early interventions are needed. The Infant Behavioral Assessment and Intervention Program® (IBAIP) improved development in VLBW infants at separate time-points. Our objective was to investigate longitudinal intervention effects of the IBAIP in VLBW infants on neurodevelopment up to and including 5.5 years of corrected age (CA).

**Methods:** In a randomized controlled trial, 86 VLBW infants received the IBAIP and 90 VLBW infants received standard care. At 6, 12, and 24 months CA, cognitive and motor development was assessed with the Bayley Scales of Infant Development. At 5.5 years CA the Wechsler Preschool and Primary Scale of Intelligence and the Movement Assessment Battery for Children were used. Longitudinal data were analyzed with linear mixed models in the total group and three subgroups, using Z-scores generated from raw cognitive and motor scores.

**Results:** A significant longitudinal intervention effect (0.4SD) on motor development was found \( (P = 0.006) \), but not on cognitive development \( (P = 0.063) \). In the subgroup “VLBW children with bronchopulmonary dysplasia (BPD)” significant longitudinal intervention effects were found for both cognitive \( (0.75SD; P = 0.019) \) and motor \( (0.95SD; P = 0.026) \) outcome. Maternal education hardly influenced intervention effects over time, but in children with combined biological and social risks an intervention effect of 0.8SD was found on cognitive development \( (P = 0.044) \).

**Conclusion:** The IBAIP leads to long-term improvements on motor development in VLBW infants. Particularly VLBW children with BPD benefit from the intervention, both on the cognitive and motor domains.
Introduction

Improved and technologically more advanced care increased the survival rate of premature and sick neonates\(^1\) and decreased the incidence of severe handicaps like cerebral palsy\(^2\). However, mild cognitive, motor and behavioral problems, with prevalence's of up to 50 to 75%, are the dominant developmental deficits reported in infants born before 32 weeks’ gestation and/or birth weight less than 1500 gram. These deficits tend to co-occur and persist throughout childhood.\(^3,4,5\) Biological risk factors, such as brain injuries, bronchopulmonary dysplasia (BPD), and social risk factors, such as low level of parental education, and poor parent-infant relationships, have been associated with poor neurodevelopmental outcome.\(^5,7\)

In response to these outcomes, focus of outcome research in NICU-graduates has shifted from mortality and morbidity to healthy survival, and inspired health care professionals to develop evidence-based early intervention programs. A recent meta-analysis concluded that programs focusing on sensitive and responsive parenting, along with infant development, have the greatest impact on improvement in developmental outcomes.\(^8\)

In a randomized controlled trial (RTC), we have evaluated the effects of an early intervention program, the Infant Behavioral Assessment and Intervention Program\(^9\) (IBAIP) on neurodevelopment in infants with a gestational age <32 weeks and/or birth weight <1500 gram, in short, very low birth weight (VLBW) infants. Cross-sectional data-analyses revealed significant and clinically relevant intervention effects on cognitive development at 6 months and 5.5 years corrected age (CA), and on motor development at 6, 12 and 24 months and 5.5 years CA.\(^10-13\) Moreover, subgroup analyses indicated improved developmental outcomes in extra vulnerable VLBW infants, such as infants with BPD.\(^13\)

Effects of RCTs involving early intervention in VLBW infants are generally described for each follow-up age without studying longitudinal effects over time. As this approach is insensitive to individual developmental changes over time, mean outcomes of the study groups may not be representative for the patterns of individual outcomes.\(^14,15\) To our knowledge no longitudinal data-analysis of early intervention studies, based on individual developmental outcomes over time, has been described. Therefore, our aim in this study is to evaluate the effects of the IBAIP in VLBW infants on cognitive and motor development from 6 months up to and including 5.5 years CA, using longitudinal data-analysis. Also, we present longitudinal intervention effects on subgroups of VLBW infants with BPD, with low maternal education (LME) and with multiple biological and social risks (MR).
Methods

Participants
The original RCT\textsuperscript{10} evaluated the effectiveness of the IBAIP in VLBW infants at 6, 12 and 24 months CA between 2004 and 2007. Two level-III hospitals with neonatal intensive care unit facilities and 5 general hospitals in Amsterdam, the Netherlands, participated in the study. The Medical Ethics Committees of all hospitals involved approved the study design. A follow-up study was performed at 5.5 years CA between 2009 and 2011 and was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam.

All infants with a gestational age <32 weeks and/or birth weight <1500 gram, were eligible for the trial. We excluded infants with severe congenital abnormalities, infants whose mother had severe physical or mental illness, infants from non-Dutch-speaking families for whom an interpreter could not be arranged, and infants participating in other post discharge trials. Infants were randomized to IBAIP or control groups using a computer based procedure, which stratified for gestational age (< and ≥30 weeks) and recruitment site. The infants and parents in the IBAIP group received 1 intervention session shortly before discharge and 6 to 8 sessions at home from an IBAIP-trained pediatric physical therapist up to 6 months CA. The control group received standard care.

Early intervention program
The IBAIP is a preventive neurobehavioral intervention program which addresses the infant and parents. It is primarily based on the synactive model of neonatal behavioral organization.\textsuperscript{17} The IBAIP, focusing on environmental, behavioral and early developmental factors, aims to support the infant's self-regulatory competence and multiple developmental functions via responsive parent-infant interactions. The interventionist supports the parents to interact sensitively and responsively with their infant, by observing the infant's behavior. The intervention is guided by the Infant Behavioral Assessment© (IBA).\textsuperscript{18} The IBA is an observational tool that systematically observes and interprets 113 infant communicative behaviors that are categorized according to four subsystems: the autonomic, motor, state and attention/interaction system. Within each subsystem, the behaviors are interpreted as approach (stable/engagement), self-regulation, or stress (unstable/disengagement) behaviors. Facilitation strategies may be offered to best support the infant's neurodevelopmental progression and self-regulation, within the context of the environment. Thus, the IBAIP aims to provide ample opportunities for the infant to actively process and explore information, while at the same time maintaining stable physiological and behavioral functioning.
Assessment Procedure

The neurodevelopmental assessments took place between 2004 and 2011, at 6, 12, 24 and 5.5 years CA. The assessors were blinded to study group assignment. Perinatal factors were extracted from the children’s medical records at discharge. Cranial ultrasound abnormalities were defined as the existence of intraventricular hemorrhage (grade III to IV), periventricular leukomalacia (grade I to IV), or ventricular dilation for which treatment was needed. BPD was defined as oxygen dependency at ≥28 days. A multiple risk (MR) factor was composed to explore potential effects of biological and social risk factors, including low maternal education as social risk and abnormal cranial ultrasound or BPD as biological risks.

Mothers were defined as having a low level of education if they had received less than four years of post-elementary schooling.

Assessment Instruments

At 6, 12 and 24 months CA, cognitive and motor development were assessed using the mental and psychomotor scale of the Bayley Scales of Infant Development, Dutch second edition (BSID-II-NL). The mental scale consists of 178 items with regards to visual and additive information processing, eye-hand coordination, imitation, language development, memory, and problem resolution. The 111 items of the psychomotor scale measure fine and gross motor skills.

Cognitive development at 5.5 years CA was assessed using the Wechsler Preschool and Primary Scale of Intelligence, Dutch third edition (WPPSI-III-NL). All core subtests were administered. The sum of all composite scores and full scale intelligence quotient were calculated.

Motor development at 5.5 years CA was assessed using the Movement Assessment Battery for Children; second edition (MABC-2). Within the 3 to 6 years age band, 8 tasks are grouped under 3 components: manual dexterity, aiming and catching and balance.

In order to facilitate comparison among cognitive and motor developmental assessments across time-points and instruments, we performed our analyses using age standardized Z-scores generated from the total raw scores of the above mentioned assessment instruments.

Statistical Analyses

Univariate analyses (t-tests and χ² tests) were performed to compare the perinatal and sociodemographic characteristics of the IBAIP and control group. A propensity score approach was used to adjust for group differences. For each infant, the propensity score was calculated using a binary logistic regression analysis with dependent variable group allocation (IBAIP or control). The independent variables in this analysis
were: gender; gestational age less than ≤28 weeks; small for gestational age; use of Indomethacin; Surfactant; continuous positive airway pressure; septic periods; abnormal cranial ultrasound; and mother’s first language (Dutch, not Dutch). The variables BPD, LME and MR were not included in the propensity score, as we assessed longitudinal outcome according to these three risk factors separately.

Univariate analyses of variance (ANOVA) were performed to obtain adjusted means for the cognitive and motor raw and z-scores for the IBAIP and control groups at each time point.

Two linear mixed models were built to evaluate the longitudinal effects of the intervention on cognitive and motor development separately, adjusted for the propensity score, BPD, LME, and MR. Each model consisted of 6 steps. In Step 1, an empty model was fitted with all the infants and a repeated measures covariance matrix of the type Toeplitz to the cognitive or motor data. In Step 2, the time-point (6, 12, 24 months or 5.5 years) was added as a categorical fixed effect. In Step 3, the propensity score was added as a fixed effect. In Step 4, three variables: BPD; LME; and MR were added as fixed effects simultaneously. In Step 5, we entered the study group (IBAIP or control) into the model. In Step 6, an interaction term between study group and time was added.

To evaluate the effect of the IBAIP in subgroups, we used the same modeling strategy but with stratification according to BPD, LME and MR factors and omitting Step 4. The fit of the model in the different steps was assessed using Akaike’s Information Criterion (AIC) in the smaller-is-better form. A P value of less than 0.05 was considered as statistically significant and effect sizes between 0.2 and 0.5 as small, between 0.5 and 0.8 as moderate and above 0.8 as large.23 All statistical analysis were carried out using SPSS computer program, version 20.0 (SPSS Inc, Chicago, Illinois).

Results

Of the 315 VLBW infants born during the inclusion period, 176 infants were included in the study: 86 infants in the IBAIP group and 90 infants in the control group. The study flow diagram shows the course in time of the number of participants, the reasons for not participating, and assessment instruments used at each time point (Figure 1). The response rate at 6, 12, 24 months and 5.5 years CA was respectively 100%, 98%, 97% and 80% in the IBAIP group and in the control group respectively 94%, 88%, 87% and 74%. Despite random assignment, there were some significant differences in perinatal characteristics at baseline between the IBAIP and control group (Table 1). More infants in the IBAIP group than in the control group received indomethacin and had a gestational age <28 weeks. In addition, the infants in the IBAIP group had more septic episodes, were oxygen dependent for a longer period and were longer hospitalized.
Figure 1. Study flow diagram

315 eligible participants

176 randomized

139 excluded
Refused to participate (38)
Died (11)
Language reasons (11)
Child factors (12)
Parental factors (12)
Older brother/sister in trial (3)
Participation in other trial (52)

86 intervention infants

Follow-up 6 months: 86
BSID-II: MDI 86, PDI 86

Follow-up 12 months: 84
Withdrawn (1), living abroad (1)
BSID-II: MDI 83, PDI 83

Follow-up 24 months: 83
Withdrawn (1), living abroad (2)
BSID-II: MDI 81, PDI 76

Follow-up 5.5 years: 69
Withdrawn (5), moved abroad (2), lost to follow-up (10)
WPPSI-III: 67, MABC-2: 69

90 control infants
Died before discharge (1)

Follow-up 6 months: 85
Died (1), withdrawn (1), lost to follow-up (3)
BSID-II: MDI 83, PDI 83

Follow-up 12 months: 79
Died (2), withdrawn (3), living abroad (2), lost to follow-up (4)
BSID-II: MDI 76, PDI 77

Follow-up 24 months: 78
Died (2), withdrawn (3), living abroad (2), lost to follow-up (5)
BSID-II: MDI 77, PDI 75

Follow-up 5.5 years: 67
Died (2), withdrawn (10), moved abroad (1), lost to follow-up (10)
WPPSI-III: 66, MABC-2: 67

315 eligible participants

176 randomized

139 excluded
Refused to participate (38)
Died (11)
Language reasons (11)
Child factors (12)
Parental factors (12)
Older brother/sister in trial (3)
Participation in other trial (52)
Table 1. Perinatal and sociodemographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>IBAIP (n=86)</th>
<th>Control (n=90)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perinatal factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male / female, n (%)</td>
<td>50 (58.1) / 36 (41.9)</td>
<td>41 (45.6) / 49 (54.4)</td>
<td>.095</td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>27 (31.4)</td>
<td>26 (28.9)</td>
<td>.750</td>
</tr>
<tr>
<td>Birth weight in g, mean (SD)</td>
<td>1242 (332)</td>
<td>1306 (318)</td>
<td>.200</td>
</tr>
<tr>
<td>Gestational age in weeks, mean (SD)</td>
<td>29.6 (2.2)</td>
<td>30.0 (2.2)</td>
<td>.300</td>
</tr>
<tr>
<td>Gestational age &lt;28 weeks, n (%)</td>
<td>21 (24.4)</td>
<td>11 (12.2)</td>
<td>.040*</td>
</tr>
<tr>
<td>Small for gestational age**, n (%)</td>
<td>23 (26.7)</td>
<td>17 (18.9)</td>
<td>.229</td>
</tr>
<tr>
<td>Artificial ventilation, n (%)</td>
<td>43 (50.0)</td>
<td>32 (35.6)</td>
<td>.060</td>
</tr>
<tr>
<td>Surfactant, n(%)</td>
<td>34 (39.5)</td>
<td>16 (17.7)</td>
<td>.005*</td>
</tr>
<tr>
<td>CPAP, n (%)</td>
<td>75(87.2)</td>
<td>65 (72.2)</td>
<td>.008*</td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>34 (39.5)</td>
<td>18 (20.0)</td>
<td>.005*</td>
</tr>
<tr>
<td>Septic periods before discharge, n (%)</td>
<td>52 (60.0)</td>
<td>35 (38.9)</td>
<td>.030*</td>
</tr>
<tr>
<td>Necrotizing enterocolitis, %</td>
<td>4 (4.7)</td>
<td>1 (1.1)</td>
<td>.160</td>
</tr>
<tr>
<td>IVH grade 1-4***, n (%)</td>
<td>21 (24.4)</td>
<td>14 (15.6)</td>
<td>.890</td>
</tr>
<tr>
<td>PVL grade 1-3****, n (%)</td>
<td>12 (14.0)</td>
<td>10 (11.1)</td>
<td>.430</td>
</tr>
<tr>
<td>Ventricular dilatation, n (%)</td>
<td>3 (34.9)</td>
<td>4 (44.4)</td>
<td>.750</td>
</tr>
<tr>
<td>Abnormal ultrasound, n (%)*****</td>
<td>31(36.0)</td>
<td>26 (28.9)</td>
<td>.390</td>
</tr>
<tr>
<td>Indomethacin use, n (%)</td>
<td>18 (20.9)</td>
<td>7 (7.8)</td>
<td>.014*</td>
</tr>
<tr>
<td>ROP grade ≥3, n (%)</td>
<td>4 (4.7)</td>
<td>1 (1.1)</td>
<td>.160</td>
</tr>
<tr>
<td>Length stay hospital in days, mean (SD)</td>
<td>55.4 (25.9)</td>
<td>47.6 (21.7)</td>
<td>.030*</td>
</tr>
<tr>
<td><strong>Sociodemographic factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age in y, mean (SD)</td>
<td>32.4 (5.4)</td>
<td>32.0 (5.2)</td>
<td>.790</td>
</tr>
<tr>
<td>Family status of 2 parents, n (%)</td>
<td>70 (81.4)</td>
<td>82 (91.1)</td>
<td>.060</td>
</tr>
<tr>
<td>First language not Dutch, n (%)</td>
<td>28 (32.6)</td>
<td>39 (43.3)</td>
<td>.110</td>
</tr>
<tr>
<td>Mother with job, n (%)</td>
<td>63 (73.3)</td>
<td>53 (61)</td>
<td>.840</td>
</tr>
<tr>
<td>Low maternal education, n (%)</td>
<td>30 (34.9)</td>
<td>38 (40.2)</td>
<td>.318</td>
</tr>
<tr>
<td>Multiple risk, n (%)*****</td>
<td>25 (14.2)</td>
<td>14 (8.0)</td>
<td>.072</td>
</tr>
<tr>
<td><strong>Mean age assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months, mean (SD) in days</td>
<td>183 (8.0)</td>
<td>185 (8.5)</td>
<td>.416</td>
</tr>
<tr>
<td>12 months, mean (SD) in days</td>
<td>372 (14.4)</td>
<td>372 (11.6)</td>
<td>.901</td>
</tr>
<tr>
<td>24 months, mean (SD) in days</td>
<td>738 (18.1)</td>
<td>740 (17.9)</td>
<td>.436</td>
</tr>
<tr>
<td>5.5 years, mean (SD) in years</td>
<td>5.5 (0.1)</td>
<td>5.5 (0.1)</td>
<td>.320</td>
</tr>
</tbody>
</table>

Differences in mean scores and proportions between the groups are analyzed using t-tests or χ² tests. * p < .05.

** Small for gestational age was defined as >1 SD below mean Dutch reference data.

***IVH = Intraventricular haemorrhage, grade defined according to Papile.

**** PVL = Periventricular leucomalacie defined according to de Vries.

*****Multiple risk was defined as children with low maternal education and BPD/abnormal ultrasound.

******Abnormal ultrasound was defined as IVH grade 3-4, PVL and ventricular dilatation.

ROP = Retinopathy for prematurity.
Outcomes on cognitive development
Outcomes on cognitive development at 6, 12, and 24 months and 5.5 years CA and over time are reported in Table 2. Adjusted mean cognitive outcomes of the raw and Z-scores are presented in Table 2A. At all time-points, the IBAIP group had higher scores than the control group. Linear mixed models for repeated measures analyses (Table 2B) showed a non-significant intervention effect on cognitive development in the total group over time ($P = 0.063$). A non-significant and small difference in adjusted Z-scores of 0.2 SD in favor of the IBAIP group was found. The intervention-time interaction was not significant ($P = 0.142$), which implies that the intervention effect on cognitive development did not increase or decrease over time (Figure 2A). Linear mixed models analyses in the subgroups (Table 2B) showed a significant intervention effect in infants with BPD ($P = 0.019$) and with MR ($P = 0.044$), with a moderate difference in adjusted Z-scores of respectively 0.7 SD and 0.8 SD (Figure 2B, 2D). No significant intervention effect was found in the subgroup LME (Figure 2C).

Outcomes on motor development
Adjusted mean motor outcomes of the raw and Z-scores are presented in Table 2A. At all time-points the IBAIP group scored higher than the control group. Linear mixed models for repeated measures analyses showed a significant intervention effect on motor development over time ($P = 0.006$) (Table 2B). The moderate difference in adjusted Z-scores was 0.4 SD in favor of the IBAIP group. The intervention-time interaction was not significant ($P = 0.484$) which implies that the intervention effect on motor development did not increase or decrease over time (Figure 2E). Linear mixed models analyses in the subgroups (Table 2B) showed a significant intervention effect in infants with BPD (large effect size of 0.9SD, $P = 0.014$) (Figure 2F) and with high maternal education (small effect size of 0.45SD, $P = 0.012$) (Figure 2G). In the groups with or without MR, similar small effect sizes (0.369) were found but the effect was only significant in the group without MR (Figure 2H).
Figure 2. Linear mixed model comparisons

2A. Cognition total group

2B. Cognition subgroup BPD

2C. Cognition subgroup Low maternal education (LME)

2D. Cognition subgroup Multiple risk (MR)

2E. Motor total group

2F. Motor subgroup BPD

2G. Motor subgroup Low maternal education (LME)

2H. Motor subgroup Multiple risk (MR)

Linear mixed models were built to assess longitudinal cognitive (2A,B,C,D) and motor (2E,F,G,H) developmental outcome in total group (2A,E) and in the subgroups.

Intervention = children who received the IBAIP intervention. Control = children who received standard care.

Subgroup BPD = children with or without (= no) bronchopulmonary dysplasia.

Subgroup LME = children with or without (= no) mothers with low education.

Subgroup MR = children with or without (= no) multiple risk.
Table 2 Longitudinal comparison of cognitive and motor development

2A Cognitive and motor outcomes per time-point

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>5.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj. mean ± SE</td>
<td>Adj. mean ± SE</td>
<td>Adj. mean ± SE</td>
<td>Adj. mean ± SE</td>
</tr>
<tr>
<td><strong>Cognitive raw scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBAIP</td>
<td>59.49 ±0.61</td>
<td>83.90 ±0.68</td>
<td>126.5 ±1.44</td>
<td>97.04 ±2.00</td>
</tr>
<tr>
<td>Control</td>
<td>57.43 ±0.63</td>
<td>83.30 ±0.71</td>
<td>125.9 ±1.50</td>
<td>94.90 ±2.00</td>
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<tr>
<td><strong>Motor raw scores</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBAIP</td>
<td>35.60 ±0.46</td>
<td>60.00 ±0.61</td>
<td>82.00 ±0.61</td>
<td>73.30 ±2.3</td>
</tr>
<tr>
<td>Control</td>
<td>33.40 ±0.47</td>
<td>58.70 ±0.64</td>
<td>80.20 ±0.62</td>
<td>68.90 ±2.3</td>
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<tr>
<td><strong>Cognitive Z-scores</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBAIP</td>
<td>0.18 ±0.11</td>
<td>0.05 ±0.11</td>
<td>0.02 ±0.12</td>
<td>0.07 ±0.13</td>
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<tr>
<td>Control</td>
<td>-0.19 ±0.11</td>
<td>-0.05 ±0.12</td>
<td>-0.02 ±0.12</td>
<td>-0.07 ±0.13</td>
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<tr>
<td><strong>Motor Z-scores</strong></td>
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<tr>
<td>IBAIP</td>
<td>0.24 ±0.11</td>
<td>0.12 ±0.11</td>
<td>0.15 ±0.13</td>
<td>0.12 ±0.12</td>
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<tr>
<td>Control</td>
<td>-0.25 ±0.11</td>
<td>-0.12 ±0.11</td>
<td>-0.28 ±0.13</td>
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2B Linear Mixed Model comparisons

<table>
<thead>
<tr>
<th></th>
<th>Group n=176</th>
<th>Time Group</th>
<th>BPD n=52</th>
<th>No BPD n=124</th>
<th>LME n=68</th>
<th>No LME n=108</th>
<th>MR n=39</th>
<th>No MR n=137</th>
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<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Estimate</td>
<td>0.223</td>
<td>-</td>
<td>0.681</td>
<td>0.071</td>
<td>0.095</td>
<td>0.265</td>
<td>0.770</td>
<td>0.106</td>
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<tr>
<td>Effect size</td>
<td>0.063</td>
<td>0.142</td>
<td>0.019</td>
<td>0.584</td>
<td>0.650</td>
<td>0.092</td>
<td>0.044</td>
<td>0.390</td>
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<tr>
<td>Effect size</td>
<td>0.355</td>
<td>-</td>
<td>0.896</td>
<td>0.142</td>
<td>0.213</td>
<td>0.419</td>
<td>0.369</td>
<td>0.369</td>
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<tr>
<td>Effect size</td>
<td>0.006</td>
<td>0.484</td>
<td>0.014</td>
<td>0.195</td>
<td>0.470</td>
<td>0.012</td>
<td>0.268</td>
<td>0.009</td>
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</table>

Univariate Analysis of Variance were used for adjusted (Adj.) mean ± standard error (SE) cognitive and motor developmental raw and Z-score (Table 2A), Adjusted for propensity score and O2≥28days, maternal low education and multiple risk factors. Linear mixed models were built to assess longitudinal cognitive and motor developmental outcome in total group and in the subgroups (Table 2B). BPD = bronchopulmonary dysplasia, LME = low maternal education, MR = multiple risk.

Discussion

The present paper describes the longitudinal intervention effects of the IBAIP on development of VLBW infants from 6 months up to and including 5.5 years of corrected age. This longitudinal data-analysis study demonstrates that the IBAIP leads to stable improvements of motor development over 5.5 years. Contrary to this clear effect on
motor development, the longitudinal intervention effect on cognitive development was non-significant and had a small effect size. But in the subgroup of VLBW infants with BPD both cognitive and motor development was improved over time in IBAIP children. The VLBW infants with BPD benefitted most from the early intervention.

The motor gains acquired at 6 months CA, when the intervention ended, were preserved over at least 5 years’ time. This stable main effect on motor outcome over time seems to confirm that early experiences during sensitive periods of brain development play an important role in shaping the capacities of the brain and affect long-term development.24

Despite literature suggesting that cognitive and motor development are interrelated and improved motor development may lead to improved cognitive development,25 no longitudinal effect on cognitive development was found. Neither was any interaction with time found. At 5.5 years performance IQ was improved in the IBAIP group13 and not total IQ and thus a cognitive gain might have been missed because only total cognitive scores were used in our mixed models. At the age of 6, 12 and 24 months, the BSID-II cognitive assessment does not have a verbal or performance separation. These cognitive abilities may not be present before age 3, when aspects of cognitive function start maturing. Alternatively, an age specific intervention aiming at both verbal and performance abilities of cognitive development, may be necessary during the sensitive period of the brain for cognitive development.26 Another possibility is that improvements of overall IQ are not yet present and will be in due time.

By adding the perinatal factors into the models and especially studying the most prominent biological (we chose BPD), social (LME) and combined biological and social risk (MR) factors in three subgroups, we hypothesized, based on an earlier study,13 to find significant intervention effects in high risk subgroups. Indeed infants with BPD benefitted from the intervention, both on cognitive and motor development. BPD affects as much as 35% of the VLBW infants27 and is associated with white matter abnormalities in the brain which have a negative influence on self-regulation and neurodevelopment in these infants.28,29 Also difficulties in gaining homeostatic, postural and state control due to the breathing problems may play a role. These problems makes them particularly vulnerable to stress and obtaining a responsive parent-infant relationship is more difficult which, in return, may hinder their environmental explorations. The focus of the IBAIP to support responsive parent-infant interactions and infants’ self-regulation may be especially helpful for infants with BPD, as it may facilitate their postural control and exploratory activities without stress.

LME is associated with worse developmental, especially cognitive outcome.30 We did not find intervention effects in this subgroup, however. Few studies have investigated the association between maternal education, parenting stress and responsive mother-
infant interactions. Mothers with low education are known to experience more stress and the stress decrease over time. They may be less available, and may have a lower quality of interactions with their child. The intervention effect on motor outcome which we found in VLBW infants with high educated mothers and the failure to do so in infants with LME, demonstrates how important it is to design interventions, focusing especially on supporting parent-infant interaction in social risk groups and its influence on effectiveness of early intervention and child development. Recently researchers stressed the need to strengthen the resources and self-regulatory capabilities of the parents, so that they can better support their children.

A large intervention effect was found in VLBW infants with MR on cognitive development. The effects in this subgroup should however be interpreted with caution, because the parameter estimates were similar in both groups with or without MR and did not differ from the total group and therefore were attributed to low power.

As far as we know, no longitudinal data-analyses in early intervention studies in VLBW infants have been published. The mixed model approach has several advantages over cross sectional analyses repeated at different time-points. Taylor et al describes that this approach incorporates estimates of intra-individual relations across repeated assessments and, thus, is a sensitive method for assessing alterations. Additional advantages are that assessments do not have to be equally spaced in time, and that maximum likelihood methods allow incomplete longitudinal data to be considered in estimating model effects. Further, risk factors can be included, allowing assessment of the concurrent influences of these factors on outcomes, like we did in our subgroups.

There are no comprehensive cognitive or motor developmental tests that can be applied from infancy to childhood and therefore different instruments had to be combined in this longitudinal data analysis. The BSID is considered as the best measure for the assessment for infants from the age of 1 to 42 months. For children beyond age 42 months, the WPPSI and MABC-2 are the most common and extensively used measurements to assess cognitive or motor development respectively. In order to facilitate comparison among the different tests we used standardized Z-scores generated from the raw scores. An increase or decrease of the infant’s development can therefore not be read from our graphs. However, the effect of the intervention on cognitive and motor development is obvious and remained stable over time.

Strengths of this study included the relatively large sample size of VLBW infants, high response rate over time, the use of multiple standardized, norm-referenced method measurements approach to the assessment of cognitive and motor development and the use of repeated measures over time.
Conclusion

This longitudinal data analysis study demonstrates that the IBAIP leads to improvements on motor development in VLBW children over time. Particularly VLBW children with BPD benefit from the intervention, both on the cognitive and motor domains. Strengthening the parental sensitive-responsiveness and the child’s self-regulation in an early and sensitive period of brain development, possibly underlie the sustained neurodevelopmental improvements.
References


