Neonatal Predictors of Cognitive Ability in Adults Born Very Preterm: A Prospective Cohort Study

Linda D. Breeman[a], PhD., Julia Jaekel[b], PhD., Nicole Baumann[c], BSc., Peter Bartmann[d], MD. Dr rer nat, Dieter Wolke[c], PhD Dr rer nat h.c.

Corresponding author: Dieter Wolke, Department of Psychology, University of Warwick, Coventry CV4 7AL, United Kingdom, +442476573217, D.Wolke@warwick.ac.uk

Affiliations
[a]Department of Youth and Family, Utrecht University, The Netherlands
[b]Department of Child and Family Studies, University of Tennessee, Knoxville, USA
[c]Department of Psychology, University of Warwick, United Kingdom
[d]Department of Neonatology, University Hospital Bonn, Germany

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ABSTRACT

Aim To identify neonatal predictors to allow a developmental prognosis of very preterm / very-low birthweight (VP/VLBW) survivors' cognitive abilities into adult life.

Method The Bavarian Longitudinal Study is a prospective whole population study that followed 260 VP/VLBW infants from birth to adulthood. Regression analyses were performed to examine which neonatal factors predicted adult IQ.

Results VP/VLBW infants' neonatal morbidity, neonatal treatment, and early social environment explained 37.6% of the variance in adult IQ. Seven unique early life predictors of lower adulthood IQ were found: Respiratory distress syndrome, intraventricular hemorrhage, problems with mobility, mechanical ventilation, less parenteral nutrition, low/middle SES, and poor early parent-infant relationships. Specifically, modifiable factors such as mechanical ventilation predicted a drop of 0.43 IQ points for each day of treatment, adjusted for initial respiratory problems. Good early parent-infant relationships predicted an approximately 5-points increase in adult IQ, adjusted for other significant predictors such as SES.

Interpretation Mechanical ventilation, parenteral feeding, and early parenting were identified as significant modifiable factors that were strongly related to adulthood IQ. Mechanical ventilation policies have changed but there is scope for early interventions that focus on positive parenting which may reduce the adverse effects of VP/VLBW birth on cognitive abilities.

Keywords: premature; low birth weight; cohort study; risk factors; intelligence

Running head: Predicting IQ in preterm born adults

What this paper adds

- A specific combination of early life characteristics strongly predict adult IQ.
- Among the most important predictors were modifiable factors such as parent-infant relationships and neonatal treatments such as mechanical ventilation.
- The findings aid early identification of preterms at highest risk of cognitive impairment.
- Modifiable factors provide potential avenues for intervention.

The most common neurodevelopmental sequelae of very preterm (VP) or very low birth weight (VLBW) birth is cognitive impairment. VP/VLBW children's IQ is about 12 points lower than that of term-born children[1] and these differences in cognitive abilities persist into adulthood.[2] VP/VLBW birth and impaired cognitive abilities are related to real life implications such as lower academic achievements and less job success and wealth.[3] Thus, parents of VP/VLBW survivors often worry how early complications and treatment may have affected their child's future chances.

VP/VLBW infants are often exposed to pregnancy complications such as raised blood pressure (e.g., preeclampsia) and infections[4] which may adversely impact cognitive development.[5] The same is true for neonatal complications such as bronchopulmonary dysplasia[6] that are associated with an increased risk of brain injury.[7] Treatments such as mechanical ventilation may adversely affect cognitive development,[8] while nutritional support may help improve neurodevelopmental outcomes.[9] In contrast, a favorable early social environment including responsive parenting may stimulate cognitive development[10] and VP/VLBW infants are more affected by both favorable and unfavorable environments than term-born infants.[11]

Unknown is which prenatal, perinatal, and neonatal factors most strongly predict adult cognitive abilities, thus the goal of this study was to investigate the combined and separate risks of pregnancy complications, neonatal morbidity, neonatal treatment, and early social environment on adult cognitive abilities in a large prospective sample of VP/VLBW individuals.

METHODS

Design and participants

The Bavarian Longitudinal Study is a prospective population study of children born in a geographically-defined area of Southern Bavaria (Germany) between January 1985 and March 1986 who required admission to one of 16 hospitals in the first ten days of life. In total, 682 individuals were born VP (<32 weeks of gestation) and/or VLBW (<1500 grams). In Figure S1 (online supporting information) it can be seen that of this cohort, 411 individuals were presumed alive and eligible for inclusion at 26 years of age and 260 (63.3%) participated in the present study. The study design and dropout analyses have been described in detail elsewhere.[12] In short, the 260 participants had older mothers, better pregnancy health, and were more often socially advantaged than the 151 dropouts.[12] Ethical approval was obtained from University of Munich Children's Hospital, Landesärztekammer Bayern, and University Hospital Bonn (reference 159/09). Informed written consent was provided by parents within 48 hours of their child's birth and all participants gave fully informed written consent for the adulthood assessments.

Measures

Parents were approached within 48 hours of their infant's hospital admission. Pregnancy complications were assessed from medical records within 10 days of admission. Data on neonatal morbidity, neonatal treatment, and early social environment were collected prospectively up to 5 months after the child's birth. Data on adulthood cognitive abilities were assessed at 26 years (mean age: 26 years, 4 months; SD = 0.76). Of the 260 participants, 15 could not participate in the cognitive assessment due to severe cognitive impairment and 43 adults chose to only participate in partial assessments involving telephone interviews / questionnaires instead of a day-long assessment visit.

Cognitive ability. A short German version of the Wechsler Adult Intelligence Scale (WAIS-III) was used including 6 subtests: Vocabulary, similarities, letter-number-sequence, block design, matrix reasoning, and digit symbol coding.[13] Subtest scores were converted into

age-normed full scale IQ scores (FSIQ). Research has shown that even with only two WAIS-III subtests, correlations with FSIQ are high (≥.90).[14] For the 15 participants who did not participate due to severe cognitive impairment, IQ scores were set at 39.

Pregnancy complications. Maternal age (years), multiple births (twins/other multiples), oedema proteinuria and hypertension (EPH-gestosis), severe pregnancy illness (e.g., hyperemesis), oligohydramnios, amnion infection syndrome, fetal lie (i.e., transverse lie/breech presentation), and rapid/prolonged delivery (i.e., dilatation in early labor <3or>12 hours or bearing-down pains <10or>60 min) were coded from the Bavarian Perinatal Survey and cross checked with medical notes. Maternal smoking was coded (0) never smoked and (1) smoked during pregnancy.

Neonatal morbidity. Gestational age (days), body weight (grams), body length and head circumference (centimeters) and sex were assessed at birth. Measures were standardized according to their gestational age using the Fenton preterm growth chart.[15] A diagnosis of bronchopulmonary dysplasia (BPD) was assessed using the criterion of needing oxygen ≥28 days and x-ray diagnosis. Intraventricular hemorrhage (IVH) was assessed with ultrasound examination graded 1-4[6] and coded into (0) no IVH or IVH grade 1-2 and (1) IVH grade 3-4. Respiratory distress syndrome (RDS) was diagnosed by the attending physician based on clinical parameters (e.g., oxygen demand >60%, peak inspiratory pressure >22-28 cm H_2O) and the need for respiratory support. The manifestation of hypothermia (<36°C), hyperbilirubinemia, apnea-bradycardia syndrome, sepsis, and neonatal seizures were recorded daily by specially employed research nurses. The quantity and quality of mobility (slightly/greatly reduced/increased), muscle tone, and neurological excitability were recorded daily by research nurses according the method of Casaer and Eggermont.[16] All research nurses were trained in advance, but inter-rater agreement was not assessed. Mobility, muscle tone, and excitability were assessed and included as indicators as movements may be an excellent marker for early brain impairment and dysfunction.[17]

Neonatal treatment. Volume substitution was assessed as performed in the delivery room. Surgical intervention (e.g., operation for patent ductus arteriosus) was recorded during the neonatal hospitalization period. Duration (days) of oxygen supplementation (>21% oxygen), continuous positive airway pressure (CPAP), mechanical ventilation, parenteral nutrition, and gavage nutrition were recorded daily by research nurses.[16]

Early social environment. Detailed information on these measures can be found in Supplement 1 online. Socioeconomic status (SES) was assessed by parents' education and occupation and grouped as low/middle/high. Family Adversity Index (FAI) covered potential developmental risk factors grouped as low/middle/high. The Psychosocial Stress Index (PSI) covered family-related problems coded (0) no psychological stress and (1) some degree of psychosocial stress. The Parent–Infant Relationship Index (PIRI) assessed attachment-related parental concerns, feelings, and behavior coded into (0) no concerns and (1) some degree of concern for the parent–infant relationship. Breast milk was assessed at 5 months and coded (0) has been/is breastfeeding/provided breast milk and (1) never breastfed/provided breast milk.

Statistical analysis

All analyses were conducted using SPSS version 22.0. Statistical significance was set at p <.05 and all tests were two-tailed. For adults with missing IQ scores at 26 years (n=43; 16.5%), their latest available childhood IQ score was used as a proxy for adult IQ (number of imputed cases and range correlations between childhood and adulthood IQ scores: 8 years: n=39, r=.84; 4 years: n=2, r=.75; 20 months: n=1, r=.73; 5 months: n=1, r=0.51). Missing values on the predictor variables were imputed in SPSS specifying 10 datasets to be created.

Imputed values were based on all predictors and adult IQ. Table 1 reports on the predictors' descriptives.

First, simple linear regression analyses were performed for each of the 39 factors separately to yield unadjusted estimates of impact on adult IQ (Table 2). Second, all significant predictors from the previous step were analyzed together using one multiple linear regression analysis, thus with multiple predictors to correct all findings for the other predictors and identify the most important unique predictors of adult IQ (Table 3). Multicollinearity between predictors was assessed by examining tolerance statistics with small values (threshold <0.1) indicating multicollinearity problems. A regression function ($\hat{Y} = \beta_0 + (\beta_1 * factor1) + (\beta_2 * factor2)\ etc.$) was used to indicate the relative importance of each unique predictor. Third, cognitive impairment was calculated as having an IQ score <2 SD of a recruited healthy term-born control group, born in the same hospitals and matched on variables such as sex and SES).[12] All analyses were repeated using logistic regression analyses to predict cognitive impairment including the construction of a receiver operating characteristic curve (ROC) to analyze whether combining information on the most important predictors would distinguish between VP/VLBW individuals with and without cognitive impairment in adulthood. As these results were comparable to predicting continuous IQ scores, they are only reported in online Supplement 2.

RESULTS

VP/VLBW adults' mean IQ was 86.58 (95%CI: 84.24-88.92). Table 1 shows the predictors' descriptive values. Table 2 shows the predictors' unadjusted estimated impact on adult IQ. With regard to pregnancy complications, only increasing maternal age predicted increased adult IQ (0.55 IQ-points higher for each maternal year). With regard to neonatal morbidity, increasing gestational age (1.68 IQ-points/week) and head circumference (1.73 IQ-points for each SD of larger head circumference corrected for gestational age) predicted increased IQ, while apnea-bradycardia syndrome (-5.60 IQ-points), RDS (-9.01 IQ-points), BPD (-7.09 IQ-points), neonatal seizures (-16.00 IQ-points), IVH (-16.89 IQ-points), and abnormalities of mobility (-0.27 IQ-points/day of observed problems), muscle tone (-0.20 IQ-points/day), and neurological excitability (-0.23 IQ-points/day) predicted decreased adult IQ. Yet, corrected for the other statistically significant predictors in the model, the only three neonatal morbidity factors uniquely related to IQ were the presence of RDS, IVH, and abnormal mobility (Table 3).

Concerning treatment, longer duration of oxygen supplementation (-0.39 IQ-points/day of treatment), mechanical ventilation (-0.39 IQ-points/day), gavage nutrition (-0.24 IQ-points/day), and parenteral nutrition (-0.25 IQ-points/day) predicted decreased adult IQ. With all statistically significant predictors in the model – and thus corrected for infants' initial neonatal morbidity – longer parenteral feeding predicted higher adult IQ while longer mechanical ventilation decreased adult IQ.

With regard to early social environment, coming from a family of high SES was associated with an increase of adult IQ (9.11 IQ-points) compared to a family of middle SES. Family adversity (-6.02 IQ-points for a family of low versus middle adversity), poor parent-infant relationships (-8.92 IQ-points), and not having had breast milk (-6.66 IQ-points) were significantly related to decreased adult IQ. Yet family adversity and breast milk were not significant predictors anymore when SES and poor parent-infant relationships were added to the model.

Seven factors significantly and uniquely added to the prediction of adult IQ – explaining 30.8% of the variance in adult IQ – according to the following formula: $\hat{Y} = 96.17 + (-4.11 * RDS) + (-9.55 * IVH) + (-0.14 * mobility) + (-0.36 * ventilation) + (0.21 * parenteral\ feeding) + (11.47 * SES) + (-5.81 * PIRI)$. In

comparison, all 39 factors together explained 37.6% of the variance in adult IQ. The relative importance of each of these seven predictors – expressed as the percentage of explained variance in adult IQ – can be seen in Figure 1.

DISCUSSION

This is the first study to identify a large variety of early-life predictors of cognitive abilities in VP/VLBW adults 26 years later. Our results indicate that as much as 37.6% of the variance in VP/VLBW adults' cognitive abilities is explained by morbidity, treatment, and social environmental factors identified and measured in the first 5 months of life. In comparison, VP/VLBW cognitive abilities measured as developmental quotient (DQ) in infancy may explain around 21% of VP/VLBW adult IQ.[12] Especially the presence of RDS, IVH, problems with mobility during the neonatal period, days of mechanical ventilation, less parenteral feeding, low/middle SES, and poor parent-infant relationship in the NICU and shortly after discharge were significant and unique predictors of adult cognitive abilities. These predictors can be routinely assessed in NICU's to identify VP/VLBW at risk of long-term adverse cognitive development. This knowledge will help inform parents on their child's chances of normal cognitive development and help provide adequate and tailored support. In particular, early parent-infant relationships have a significant relationship with adult IQ, not simply accounted for by SES and provide an important window and opportunity for intervention.[18]

We found generally no effects of pregnancy complications on the infants' adult IQ consistent with previous findings.[19] With regard to neonatal morbidity, lung diseases such as RDS (which may lead to BPD) was a common complication in VP/VLBW infants before surfactant treatment was available and predictive of adult IQ. The data indicate that CPAP was only rarely used as first respiratory support. Hospital staff preferred to apply mechanical ventilation which has been widely reported to decrease cognitive development[8], either directly or indirectly through adverse events related to mechanical ventilation such as pain and stress involved, drugs used, hyper/hypoventilation, or hyper/hypoxemia. Mechanical ventilation was recorded as treatment in 74% of the VP/VLBW infants and this study suggests that the adverse effect on early brain development persist into adulthood. IVH grade 3-4 involves significant dilatation of the ventricles and bleeding into the brain's white matter tissue[20] which has important long-term implications for adult cognitive abilities. Systematic daily observation of the quantity and quality of mobility (i.e., the infant's general movements) as an indicator of neurological intactness[17] additionally – beyond IVH – predicted adult IQ. Because infants' movements involve the whole body, occur frequently, and are long lasting, they are easy to observe by clinicians for diagnostic purposes. Finally, the significant negative effect of parenteral nutrition (i.e., more days of parenteral nutrition was related to lower IQ) in the simple liner regression analyses indicated that this treatment was a good marker of the infant's level of morbidity with infants in worse physical shape needing more parenteral feeding and having lower adulthood cognitive abilities. As could be expected, this effect of parenteral nutrition became positive once corrected for the infant's health, indicating a protective role of parenteral nutrition on the infant's health and brain development.[9] Nutrition is clearly a modifiable risk factor as undernutrition/malnutrition is still very common in VP/VLBW infants and early optimal nutrition may thus improve developmental outcomes.[21]

To evaluate the risks related to preterm birth, long-term follow-up is necessary. However, an inevitable problem is that neonatal treatments may have changed by the time highly important outcomes such as adult IQ can be assessed. German NICU's used to give VP/VLBW infants more intensive medical treatment compared to other European countries in the 1980s. More advanced neonatal procedures such as surfactant treatment have resulted

in reduced usage of invasive therapies such as mechanical ventilation and higher survival of very premature infants without increased rates of cognitive handicap.[22] In addition, the ventilators used in the 1980s were less advanced than nowadays and the abilities to optimally monitor the ventilation process were limited compared to today's standards. Future research must demonstrate whether the reduction in prevalence of neonatal risks may have led to better long-term outcomes into adulthood or whether any gains may have been nullified by more infants of smaller gestation surviving.

Of the social factors, SES was uniquely related to adult IQ, with a large effect size, comparable to previous findings.[10] However, as SES was also used as a proxy for parent IQ, it is possible that part of this relationship is actually accounted for by genetic factors.[23] Most notable is the additional risk afforded by poor early parent-infant relationships. Infants who had parents who visited little, showed little pleasure in the infant, or were not confident in their caring practices, scored about 9 IQ-points less as adults than those with good parent-infant relationships, an effect larger than found previously in studies with premature infants of higher gestational age.[10] Thus, a critical factor in caring for a VP child may be parental self-efficacy, i.e. parents' believe in their competence and effectiveness and the supported opportunity to take good care of their premature infant. This may be especially true for parents of VP infants born in the NICU whose self-efficacy may be diminished in this very stressful period with the infant medically at risk and partially cared for by others such as nurses. Although parents of VP/VLBW infants may not be overall less sensitive than those of term-born infants,[24] VP/VLBW infants may require a higher quality of parenting for favorable cognitive development.[18]

Strengths and limitations

Strengths of this study are the large geographically-defined birth cohort of VP/VLBW infants that were followed-up into adulthood and the fact that neonatal factors were recorded daily by trained research nurses. This prospective gathering of data from the 80's enables to examine predictors and possible underlying mechanisms of relevant outcomes in adulthood. There were also limitations. As in most longitudinal cohort studies, there was selective loss to follow-up with low SES families having a higher chance of dropout. Our predictions are thus based on a group of higher SES and less handicapped participants, while SES was also one of the strongest predictors of adult IQ. However, selective loss to follow-up may affect prevalence rates, but is less likely to affect prediction.[25] There was also missing data. For 43 participants, adulthood IQ data was not available and imputed with the latest available childhood IQ score. Additional analyses showed that for the 217 participants with available adulthood IQ scores, results only marginally changed. Hyperbilirubinemia had 24% missing values, likely because hyperbilirubinemia levels were only determined if there was a clinical indication and missing data may thus suggest that phototherapy was not necessary. Body length and head circumference had 16% missing values as for infants who required emergency transport to intensive care units, no measures were taken as getting them admitted to intensive care was paramount. In addition, we did not find pregnancy complications to be a risk factor for adult IQ, which may be partly due to the fact that pregnancy complications were recorded retrospectively from standard obstetric hospital survey forms and/or partly due to more severe pregnancy complications resulting in premature death and thus no IQ measurement in adulthood. Finally, we were not able to measure parent IQ which may be an important confounder of child IQ.[23] We have, however, measures of SES, FAI, and parent-infant relationship that are correlated with parental IQ and provide information on mechanisms of how parental IQ may affect their offspring's IQ. Additionally, it is important to note that in contrast to term-born infants, VP/VLBW infants' genetic effects on cognitive development may be overpowered by their preterm birth and associated complications.[26]

Conclusions

Early risk factors predicted over a third of unique variance in cognitive abilities of VP/VLBW adults, indicating the importance of early social environment, nurture, and medical care for these infants at high risk for cognitive impairment. The results of this study may be used to inform clinicians and identify VP/VLBW infants at risk for poor cognitive development who may benefit from early interventions to reach their full cognitive potential. Specifically, our findings show that the most important modifiable factors to address were medical treatment and parent-infant relationships. Our results regarding parent-infant relationships provide evidence for the importance of family-centered care, a philosophy now central in increasing numbers of NICU's. Improving the quality of care can be accomplished by addressing parent involvement, supporting sensitive parenting in the NICU and at home, and to provide more opportunities for appropriate stimulation.[27]

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Table 1. Descriptives of predictors before and after data imputation

	n complete cases	% missing data	Complete cases M / %	Multiple imputation[1] M / %
Pregnancy Complications				
Maternal age (years)	260	0.0%	28.87	28.87
Multiples	260	0.0%	26.5%	26.5%
Smoking during pregnancy	250	3.8%	16.8%	16.9%
EPH gestosis	234	10.0%	7.7%	11.8%
Severe pregnancy illness	259	0.3%	24.3%	24.3%
Oligohydramnios	259	0.3%	5.8%	5.8%
Amnion infection syndrome	260	0.0%	26.9%	26.9%
Complicated fetal lie	234	10.0%	29.9%	30.2%
Rapid or prolonged delivery	260	0.0%	28.1%	28.1%
Neonatal Morbidity				
Gestational age (weeks)	260	0.0%	30.59	30.59
Weight (z-score)	260	0.0%	-0.71	-0.71
Length (z-score)	218	16.2%	-0.37	-0.37
Head circumference (z-score)	219	15.8%	-0.36	-0.36
Sex (female)	260	0.0%	46.9%	46.9%
Hypothermia	260	0.0%	39.6%	39.6%
Hyperbilirubinemia	197	24.2%	21.8%	22.6%
Apnea-bradycardia syndrome	259	0.3%	51.4%	51.2%
RDS	260	0.0%	64.2%	64.2%
BPD	260	0.0%	52.7%	52.7%
Sepsis	260	0.0%	46.5%	46.5%
Neonatal seizures	260	0.0%	18.5%	18.5%
IVH	259	0.3%	7.7%	7.7%
Abnormal mobility (days)	259	0.3%	36.26	36.15
Abnormal muscle tone (days)	259	0.3%	43.03	42.93
Abnormal excitability (days)	259	0.3%	28.92	28.89
Neonatal Treatment				
Volume substitution	234	10.0%	16.7%	16.6%
Surgical intervention	260	0.0%	17.3%	17.3%
Oxygen supplementation (days)	260	0.0%	7.50	7.50
CPAP (days)	260	0.0%	2.36	2.36
Mechanical ventilation (days)	260	0.0%	14.67	14.67
Gavage nutrition (days)	260	0.0%	39.08	39.08
Parenteral nutrition (days)	260	0.0%	22.75	22.75
Early Social Environment				
High SES	259	0.3%	20.5%	20.5%
Low SES	259	0.3%	32.4%	32.4%
High FAI	254	2.3%	36.2%	36.0%
Low FAI	254	2.3%	24.0%	24.7%
High PSI	240	7.7%	35.0%	35.3%
Poor PIRI	248	4.6%	48.0%	48.0%
No breast milk	246	5.4%	73.2%	72.9%

Note. [1] = pooled results after multiple imputation (n = 260); RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; CPAP = continuous positive airway pressure; SES = socioeconomic status; FAI = family adversity index; PSI = psychosocial stress index; PIRI = parent-infant relationship index.

Table 2. Predictors' unadjusted estimates of their relationship with IQ in adulthood

		b	*95% CI*		*p*
Pregnancy Complications					
Maternal age (years)		0.55	0.05	1.04	**.031**
Multiples		4.46	-0.83	9.74	.098
Smoking during pregnancy		-0.25	-6.61	6.10	.938
EPH gestosis		-2.74	-10.30	4.83	.478
Severe pregnancy illness		-1.01	-6.35	4.34	.718
Oligohydramnios		-0.86	-10.92	9.20	.867
Amnion infection syndrome		-0.39	-5.68	4.90	.886
Complicated fetal lie		2.03	-3.22	7.28	.448
Rapid or prolonged delivery		-3.97	-9.17	1.23	.135
Neonatal Morbidity					
Gestational age (weeks)		1.68	0.65	2.72	**.001**
Weight (z-score)		0.37	-1.49	2.23	.696
Length (z-score)		0.71	-0.99	2.40	.414
Head circumference (z-score)		1.73	0.06	3.40	**.042**
Sex (female)		-4.00	-8.67	0.68	.094
Hypothermia		-3.39	-8.17	1.39	.164
Hyperbilirubinemia		2.42	-3.52	8.37	.424
Apnea-bradycardia syndrome		-5.60	-10.00	-1.20	**.018**
RDS		-9.01	-13.78	-4.24	**<.001**
BPD		-7.09	-11.71	-2.47	**.003**
Sepsis		-3.23	-7.91	1.46	.177
Neonatal seizures		-16.00	-21.72	-10.27	**<.001**
IVH		-16.89	-25.45	-8.33	**<.001**
Abnormal mobility (days)		-0.27	-0.35	-0.19	**<.001**
Abnormal muscle tone (days)		-0.20	-0.27	-0.13	**<.001**
Abnormal excitability (days)		-0.23	-0.31	-0.14	**<.001**
Neonatal Treatment					
Volume substitution		-4.99	-11.47	1.48	.131
Surgical intervention		-1.03	-7.23	5.17	.745
Oxygen supplementation (days)		-0.39	-0.63	-0.14	**.002**
CPAP (days)		-0.06	-0.45	0.34	.783
Mechanical ventilation (days)		-0.39	-0.50	-0.28	**<.001**
Gavage nutrition (days)		-0.24	-0.33	-0.14	**<.001**
Parenteral nutrition (days)		-0.25	-0.37	-0.13	**<.001**
Early Social Environment					
SES	High SES	9.11	3.05	15.17	**.003**
	Low SES	-2.91	-8.14	2.32	.275
FAI	High FAI	-0.16	-5.51	5.19	.955
	Low FAI	6.02	0.04	12.00	**.048**
High PSI		-0.96	-5.90	3.98	.703
Poor PIRI		-8.92	-13.54	-4.30	**<.001**
No breast milk		-6.66	-12.04	-1.27	**.015**

Note. Unadjusted estimate = simple linear regressions based on imputed data; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; CPAP = continuous positive airway pressure; SES = socioeconomic status; FAI = family adversity index; PSI = psychosocial stress index; PIRI = parent-infant relationship index.

Table 3. Adjusted estimates of significant predictors relationship with IQ in adulthood

		b	*95% CI*		*beta*	*p*	*tolerance*
Pregnancy Complications							
Maternal age (years)		0.27	-0.19	0.72	.07	.247	0.87
Neonatal Health							
Gestational age (weeks)		0.13	-1.29	1.54	.01	.862	0.41
Head circumference (z-score)		1.47	-0.29	3.23	.11	.102	0.66
Apnea-bradycardia syndrome		-1.09	-5.62	3.43	-.03	.636	0.77
RDS		-5.86	-11.67	-0.05	-.15	**.048**	0.51
BPD		1.90	-4.14	7.93	.05	.538	0.43
Neonatal seizures		-2.30	-8.48	3.88	-.05	.466	0.69
IVH		-8.92	-17.03	-0.81	-.12	**.031**	0.84
Abnormal mobility (days)		-0.19	-0.34	-0.04	-.27	**.014**	0.23
Abnormal muscle tone (days)		0.04	-0.09	0.17	.07	.512	0.24
Abnormal excitability (days)		0.04	-0.08	0.16	.06	.506	0.37
Neonatal Treatment							
Oxygen supplementation (days)		-0.00	-0.28	0.27	-.00	.982	0.59
Mechanical ventilation (days)		-0.43	-0.64	-0.22	-.43	**<.001**	0.24
Gavage nutrition (days)		0.07	-0.08	0.21	.08	.362	0.35
Parenteral nutrition (days)		0.19	0.01	0.37	.19	**.039**	0.33
Early Social Environment							
SES	High SES	9.40	3.65	15.14	.20	**.001**	0.73
	Low SES	-2.15	-6.82	2.53	-.05	.368	0.82
FAI	High FAI	3.65	-1.19	8.49	.09	.139	0.74
	Low FAI	2.06	-3.41	7.53	.05	.460	0.73
Poor PIRI		-5.13	-9.55	-0.70	-.13	**.023**	0.81
No breast milk		-2.24	-7.29	2.82	-.05	.385	0.83

Note. Adjusted estimates = multiple linear regression including all significant predictors of adult IQ from Table 2, based on imputed data; tolerance <.01 indicate multicollinearity problems; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; SES = socioeconomic status; FAI = family adversity index; PIRI = parent-infant relationship index.

Figure Caption and Legend

Title Figure 1
Explained Variance of the Significant, Unique, Early Risk Predictors in Adult IQ-Scores Adjusted for Other Predictors

Legend Figure 1
Note. RDS = respiratory distress syndrome; IVH = intraventricular hemorrhage; SES = socioeconomic status; PIRI = parent-infant relationship index.

Supplement Captions

Title Figure S1
Flowchart of Participants through the Study

Title Supplement 1
Measures of Early Social Environment

Title Supplement 2
Predicting Moderate to Severe Cognitive Impairment