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REGULAR ARTICLE

Long-term cognitive outcomes of extremely low-birth-weight infants: the influence of the maternal educational background

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ABSTRACT
Aim: The purpose of the present contribution is to analyse the relationships between perinatal risk factors, social parameters and neurodevelopmental outcomes in extremely low-birth-weight (ELBW) children up to the age of 10–13 years.
Methods: Of 200 live-born ELBW infants, 148 were enrolled in the high-risk infant follow-up programme. Each follow-up visit included a neurodevelopmental examination and an interview with the infant's parents. Multivariate analyses using SPSS (version 17.0, Chicago, IL, USA) were conducted, and a p-value of <0.05 indicated a statistically significant result.
Results: The results of the logistic regression analysis of the biological and sociodemographic risk factors illustrated that a low maternal educational background is the most important factor (OR, 21.9) associated with a decreased composite intelligence quotient (IQ) in children between 10 and 13 years old. A Grade III or Grade IV intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL) were also associated with decreased IQ at the age of 10–13 years (OR, 6.9). These results were confirmed by ANOVAs with repeated measurements.
Conclusion: Maternal educational background is the strongest predictor of long-term neurodevelopment in ELBW children. The findings emphasize the need for special support and follow-up care services for poorly educated parents.

INTRODUCTION
Because of improvements in obstetric and neonatal care in the last decades, the survival rate of extremely low-birth-weight (ELBW) infants has risen to 70%, and their developmental outcomes have become more promising (1–3). However, cognitive deficits are the most prevalent disability in the population of extremely preterm children: intelligence quotient (IQ) scores <70 are twice as frequent as cerebral palsy (4). The most significant neonatal risk factors for neurological and developmental morbidity are severe intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), neonatal seizures, necrotizing enterocolitis and long-term ventilation after preterm birth (5,6).

The influence of sociodemographic factors (e.g. maternal education and immigrant background) on the development of children born at term is well established (7). Previous research has shown that the long-term outcomes of very low-birth-weight (VLBW) infants are dependent on gestational age and/or perinatal complications and mitigated by the level of maternal or parental education (8–10). According to the Bavarian Longitudinal Study (11), the level of maternal education exerted a significant influence on cognitive development at 8 years of age only in children born after 32 weeks of gestation, but it did not in children born before or at 32 weeks of gestation. The authors concluded that limited plasticity in brain development hinders compensational environmental effects on neurodevelopment in extremely premature infants.

More recent European studies, as the EPIPAGE prospective cohort study, concluded that social and biological risk factors are strong predictors of poor cognitive outcome in very preterm infants. Whereas social factors, for example, low social status, lack of breastfeeding and having a high

Key notes
- Socio-economic status is the best predictor of long-term cognitive development in extremely low-birth-weight (ELBW) children, followed by the presence of brain lesion. Irrespective of brain compromises, the neurodevelopmental trajectories between 6 and 10–13 years of age are more promising in children from mothers with high educational background compared with those from less-educated mothers. Possible explanations may be quality of cognitive stimulation, the parenting style, both associated with educational background or genetics.

number of siblings predicted mild as well as severe cognitive deficiencies, medical factors, for example, presence of cerebral lesions on ultrasound scan and being born small for gestational age predicted mostly severe cognitive deficiencies (12).

Because the association between perinatal and sociodemographic factors and long-term neurodevelopmental outcomes in ELBW infants is still unknown, the purpose of this study was to examine these relationships.

PATIENTS AND METHODS

Study population

The participants included in the study were the survivors of a cohort of 200 consecutive, live-born ELBW infants. They were treated at our level-III neonatal intensive care unit at the Children's Hospital 'Auf der Bult'. Of the 200 ELBW infants born between January 1993 and December 1998, 171 (86%) survived. Details regarding the neonatal care of the participants are described elsewhere (5,13). Twenty-three children (13%) were lost during follow-up. The remaining 148 (87%) children were retrospectively assessed at our outpatient clinic at regular intervals up to the ages of 10–13 years. There were no significant differences in the perinatal characteristics of the study group and the ELBW infants who were lost during follow-up.

Follow-up assessments

All of the surviving children were enrolled in a high-risk infant follow-up programme. In the present study, the results from the 6-year assessment and the final assessment, which was conducted when the children were between 10 and 13 years old, are reported. Each follow-up visit included an interview with the infant's parents and an examination that included measurements of the child's weight, height and head circumference.

The following neurodevelopmental outcomes were considered:

Neurological outcomes

An abnormal outcome classification was assigned to infants with cerebral palsy or significant abnormalities in motor coordination that caused functional impairments. Children with bilateral blindness or hearing deficits that required hearing aids were classified as having abnormal neurosensory outcomes.

Cognitive outcomes

The child's intelligence quotient (IQ) was assessed using the Kaufman Assessment Battery for Children (14) at the age of 6 years and the Hamburg-Wechsler Intelligence Test for Children (HAWIK-III) (15) between the ages of 10 and 13 years. All of the scores were standardized to a mean of 100 and a standard deviation of 15 (normal range: 85–115). Scores that fell between 1 and 2 standard deviations below the mean were considered borderline (70–84), and scores below 70 indicated a significant delay.

Table 1 Criteria used for the overall outcome classification

Normal development	Participants met all of the following conditions: • a normal neurological evaluation • IQ >84 • no neurodevelopmental deficits
Minor impairment	Participants had one or more of the following problems: • subnormal cognitive abilities (IQ 70–84) • gross and fine motor activity deficits • language development disorders • visual and auditory deficiencies
Major impairment	Participants had one or more of the following problems: • cerebral palsy (CP) • intellectual disability (US: mental retardation) with an IQ < 70 • blindness, deafness • intractable epilepsy

IQ, Intelligence quotient.

As summarized in Table 1, each child was classified as normal or as having a minor or major impairment, depending on the overall results of these assessments. Children whose intelligence was unable to be measured because of severe impairments were assigned a score of 39, because a score of 40 is the lowest possible HAWIK-III composite IQ score.

Sociodemographic variables

Data regarding immigration and the maternal educational background were retrospectively collected in interviews at the time of the final assessment. Three professionals independently rated maternal education according to the International Standard Classification of Education (ISCED) (16). The mothers were classified into two groups. The mothers in Group H (H = high) had achieved qualifications for either higher education or post-secondary education (ISCED Levels 4–6). The mothers in Group N (N = normal or low) had normal or low levels of education (ISCED Levels 1–3). The inter-rater reliability was 0.95. The few discrepancies were discussed, and the raters achieved a consensus.

Statistics

SPSS for Windows (version 17.0, SPSS Inc.) was used as database and for statistical analyses. *T*-tests and chi-squared tests were conducted to test for significant differences in the obstetric and neonatal variables as well as neurodevelopmental and school outcomes of ELBW children from mothers with high vs. low educational backgrounds. Logistic regression analyses were performed to identify the most important social and medical risk factors that affect neurodevelopment. Analyses of variance (ANOVAs) with repeated measurements were conducted using the social and medical risk factors that had been shown to be most important for neurodevelopment as independent variables and the composite IQ score as the dependent variable. All tests of significance were two-tailed, and the level of significance was set at $p < 0.05$ in all of the analyses. The data are presented as means and standard deviations (in brackets), unless stated otherwise.

RESULTS

Patient cohort

A total of 148 children, comprising 87% of the surviving ELBW cohort, were evaluated at a mean age of 10.8 years (range: 10–13 years). The obstetric and neonatal variables of the former ELBW infants are summarized in Table S1. IVH occurred in 33.2% of the infants. Patent ductus arteriosus and culture-proven septicaemia were frequent complications that affected more than 40% of the ELBW infants.

When children of Group H mothers were compared with children of Group N mothers, only minor differences in the obstetric and neonatal variables were found. However, these groups differed significantly in their rates of smoking during pregnancy. Only 2.3% of the Group H women smoked, whereas 25.6% of the women in Group N reported nicotine consumption during pregnancy ($p < 0.05$).

Neurodevelopmental outcomes at 10–13 years of age

At the time of the final assessment, 48.1% of the children exhibited normal neurodevelopment (Table S2). Minor impairments were observed in 36.5%, and major problems were evident in 15.5%. The most frequent finding was an IQ of <85 (42.6%), followed by gross (24.3%) and fine (20.9%) motor problems.

The children of the Group H mothers exhibited significantly better cognitive, school and overall outcomes. Significant differences in the composite IQ scores and the verbal and non-verbal IQ scores were observed between the groups. Only 7.4% of the children of Group H mothers attended a special school, compared with 34.0% of the children of Group N mothers.

In contrast, no significant differences with respect to cerebral palsy, fine or gross motor achievements, blindness or hearing loss were observed between children from the two groups of mothers. Weight and height were also comparable between the two groups. There were no group-dependent differences in head circumference at birth, at the time of discharge from the hospital, and at 1 year of age. However, the mean head circumference was significantly larger in children of Group H mothers at the time of the final assessment, and a smaller proportion of children of Group H mothers had a head circumference below the 10th percentile.

Risk factors for a decreased IQ (<85) at 10–13 years of age

Figure 1 illustrates the results of a logistic regression analysis on child's overall intelligence, with biological and sociodemographic risk factors.

The most important factor for a decreased IQ at the final assessment was the maternal educational background, with an odds ratio of 21.9 ($n = 76$, $p < 0.001$). This was followed by the biological risk factors of Grade III- or Grade IV-IVH or PVL (OR 6.9, $n = 18$, $p < 0.05$). Additionally, an increase in head circumference of <6 mm per week was associated

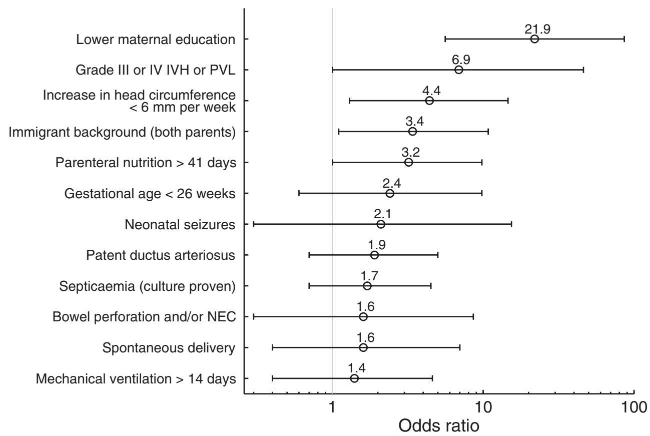

Figure 1 The results of a logistic regression analysis on composite intelligence quotient (HAWIK-III), with biological and sociodemographic risk factors.

with lower overall intelligence (OR 4.4, $n = 36$, $p < 0.05$). Additional significant factors in the regression were immigrant backgrounds in both parents (OR 3.4, $n = 27$, $p < 0.05$) and parenteral nutrition >41 days (OR 3.2, $n = 55$, $p < 0.05$).

Longitudinal analyses of cognitive outcomes

An ANOVA with repeated measurements was conducted using the composite IQ as the dependent variable. Because they were the most important factors in the logistic regression, the maternal educational background (Group H/Group N) and occurrence of IVH (yes/no) were entered as the independent variables. Complete datasets were available at both assessment times for 115 of the 148 children. There were no significant differences in the perinatal characteristics of these 115 children and the 33 children without complete datasets.

Although the 'time × maternal education' interaction effect failed to reach statistical significance ($F_{(1;\ 111)} = 3.455$, $p = 0.066$), ELBW children from highly educated mothers with or without IVH exhibited more promising cognitive development over time, as Figure 2 illustrates.

As expected, the results revealed a significant main effect of maternal educational background ($F_{(1;111)} = 26.267$, $p < 0.001$) on composite IQ development. Six-year-old ELBW children of Group H mothers without IVH had IQ scores that were 9.6 points higher than those of ELBW children of Group N mothers. Four years later, the difference between these groups was even more pronounced, and the IQ scores of the children of Group H mothers were 13.4 points higher than those of the children of Group N mothers. In ELBW children with IVH, this effect was even more pronounced; a difference of 16.2 points was observed at 6 years of age, and a difference of 21.8 points was evident in children at 10-13 years of age. Furthermore, there was a significant main effect of IVH ($F_{(1;111)} = 15.042$, $p < 0.001$) on composite IQ development. The longitudinal results confirmed the results of the logistic regression analysis.

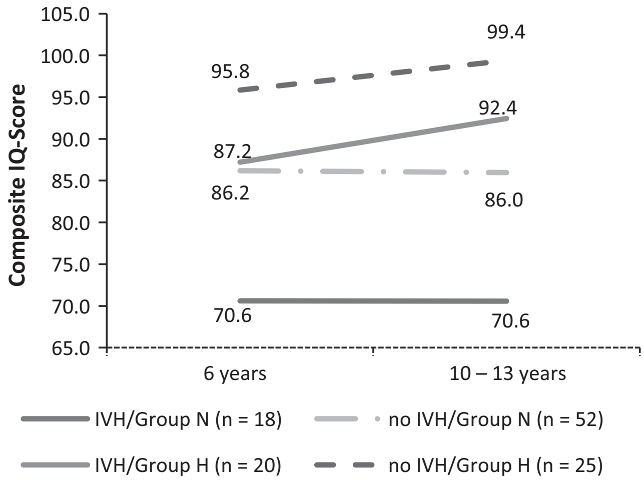

Figure 2 Developmental trajectories of composite intelligence quotient in extremely low-birth-weight children (intraventricular haemorrhage (IVH) vs. no IVH) from highly (Group H) vs. poorly educated mothers (Group N).

DISCUSSION

In the present study, the relationships between the perinatal risk factors, social parameters and neurodevelopmental outcomes of ELBW children at the age of 10–13 years were analysed for the first time. Consistent with previous research, biological risk factors, including IVH, PVL and long-term ventilation, were found to be important factors in long-term neurodevelopment.

The impact of social factors on cognitive development has generally been well proven in children born at term (7). To date, only a few studies have addressed this research question using large cohorts of VLBW (12,17) and ELBW infants (18,19). Research studies conducted in the 1990s (11) have highlighted the combined effects of biological and social factors on the development of preterm infants, and research has shown that the influences of biological factors outweigh the influences of social factors on ELBW infants.

The strengths of this study are follow-up assessments of a large cohort of ELBW infants and the measurements of a wealth of perinatal and social family data. In contrast to previous studies, we chose the ISCED (16) to rate maternal educational background. Designed by the UNESCO in the early 1970s and revised in 1997, this instrument is outstanding in its coverage of all deliberate and systematic activities designed to meet learning needs under the term of 'education'. It assesses two cross-classification variables: levels and fields of education, and general, vocational, prevocational orientation and educational/labour market destination, instead of considering education and occupation separately. We found that maternal educational background is the strongest predictor of intelligence in children at 10–13 years of age (odds ratio, 21.9), followed by IVH or PVL (odds ratio, 6.9). As mentioned earlier, the results of an ANOVA with repeated measurements indicate that maternal educational background has a significant positive effect on neurodevelopmental trajectories between 6 and 10–13 years after birth, especially in ELBW infants with IVH. We cannot address the important question of when these differences initially emerge during development, as comparable assessments of IQ at children's younger ages are not available. To answer this important research question, further studies are needed.

Explanations for the more promising cognitive outcomes in children of more highly educated mothers at school age may be a better health behaviour, a higher quality of child care, as well as the superior utilization of support and follow-up care services. Further, IQ differences in children may be genetically caused by differences in the maternal IQ. But we can only speculate about this, because we did not assess maternal IQ to test for this hypothesis. Later in development, differences in the learning opportunities offered to children by mothers from varying educational backgrounds may explain the differences in developmental achievement. Specifically, the importance of the goodness of fit between a child's predispositions and maternal responsiveness has been well proven (20). Because the primary intent of this study was not to test this hypothesis, we did not assess the quality of the learning opportunities or the quality of mother–child interaction in play and subsequent learning situations.

Along with differences in the cognitive development, we found significant differences in head circumference between ELBW children of Group H and Group N mothers at the age of 10–13 years. Both cannot be explained by maternal prenatal smoking and/or nutritional factors. Although Group N mothers smoke significantly more often during pregnancy than Group H mothers, head circumference differed between the maternal educational background groups neither at birth nor at the expected delivery date, but it emerged later. This finding makes smoking an unlikely candidate for influencing head growth. Studies explicitly addressing the association between maternal smoking during pregnancy and low intellectual performance in the offspring show that the effects of smoking are hard to separate from confounding genetic and environmental factors (21–23). As far as nutrition-related factors are concerned, it would be expected that differences in nutrition would have affected anthropometric variables other than head circumference (e.g. weight and height), but these additional group differences were not apparent. Instead, it is well known from other studies (24) that more highly educated mothers tend to have children with increased postnatal head growth and better intellectual outcomes. The extent to which this reflects the quality of cognitive stimulation, the parenting style or genetic influences warrants further investigation.

In conclusion, it is not the intent of the present contribution to depreciate perinatal risk factors. Rather, the important influence of social factors on the neurodevelopment of ELBW children is highlighted, particularly for those with biologically damaged brains. The results of our research illustrate that special support and follow-up care services are needed for less-educated parents because existing services are seldom attended. Furthermore, these services are often only symptom oriented. Our results underscore the importance of integrating components that aim towards improved quality of parent–child interaction in play and subsequent learning situations. Services must be systematically evaluated for their effectiveness and monitored for their appropriateness for this target group.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Obstetric and neonatal parameters of ELBW infants.
Table S2 Neurodevelopmental outcomes at last assessment (10–13 years of age).

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