

Biological and Social Influences on Outcomes of Extreme-Preterm/Low-Birth Weight Adolescents

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abstract

BACKGROUND AND OBJECTIVES: The importance of biological versus social influences on long-term outcomes of extremely preterm children is debatable. The goal of this study was to determine the relative contributions of biological and social exposures to outcomes into adolescence in extremely preterm survivors, hypothesizing that biological exposures would be more important early, but social exposures would dominate later.

METHODS: The study included 298 consecutive survivors born at <28 weeks' gestation or weighing <1000 g in Victoria, Australia (during 1991–1992), and 262 normal birth weight (>2499 g) control subjects who were used to standardize outcomes for the preterm group. Cognitive ability was assessed at 2, 5, 8, and 18 years of age. Academic achievement was assessed at 8 and 18 years of age.

RESULTS: The differences between the preterm and control groups for cognitive and academic scores remained relatively constant over time. The biological variables most associated with worse outcomes within the extremely preterm group were intraventricular hemorrhage and postnatal corticosteroid therapy. Of the social variables, being reared in a multilingual household was disadvantageous early, with social class and maternal education becoming more important for later outcomes. The strength of the biological associations mostly equaled or exceeded those of social exposures, even in late adolescence.

CONCLUSIONS: Contrary to expectations, several perinatal biological exposures had large and persistent adverse associations with cognitive and academic outcomes among extremely preterm survivors. As expected, some social variables assumed increasing importance in later years but mostly did not diminish or exceed the important biological associations.



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Dr Doyle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; he obtained funding, conceptualized and designed the study, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Cheong obtained funding, conceptualized and designed the study, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Burnett and Roberts contributed to data collection and reviewed and revised the manuscript; Dr Lee contributed to data analysis and reviewed and revised the manuscript; and Dr Anderson obtained funding, conceptualized and designed the study, contributed to data collection, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Cognitive scores of children born preterm are reported to improve over time. Biological associations with adverse cognitive outcomes are assumed to wane over time, as the influence of social variables increases.

WHAT THIS STUDY ADDS: Cognitive scores of children born extremely preterm were consistently lower than those of control subjects from ages 2 to 18 years. Biological associations with adverse cognitive outcomes in preterm children persisted adolescence, as the influence of social variables increased.

Survival rates for infants born extremely preterm (EP; <28 weeks' gestational age) or extremely low birth weight (ELBW; <1000 g) increased with the introduction of exogenous surfactant into clinical practice in the early 1990s.¹ However, EP/ELBW survivors since that time continue to have worse cognitive and academic outcomes compared with term (37–42 weeks' gestational age) or normal birth weight (>2499 g) control infants.²

Outcomes vary for EP/ELBW survivors related to the occurrence of various perinatal biological events, many of which culminate in brain injury or maldevelopment.³ Social risk is also related to child development and long-term outcomes. In a recent review,⁴ maternal education less than high school completion compared with completion of high school, nonprivate health insurance status compared with private health insurance status, and a manual parental occupation rather than a more skilled occupation were each associated with an increased odds for cognitive delay. However, these social variables are interrelated and their independent effects (ie, adjusting for the influence of each other) were not assessed.

It has been suggested that cognitive outcomes for preterm survivors may improve through childhood,⁵ but whether this improvement occurs relative to term peers, and the relative contributions of biological and social variables to change in cognitive outcomes throughout childhood, must be determined. Moreover, the contributions of biological and social variables to academic achievement over time have been less well studied.

The aims of the present study were to determine whether differences in cognitive and academic outcomes between EP/ELBW and control groups changed over time and to determine the relative contributions of perinatal biological variables and

childhood social variables to cognitive performance and academic achievement. It was hypothesized that the gap in cognitive and academic outcomes between EP/ELBW and control groups would be stable over time and that biological variables would be more important in predicting early childhood outcomes but social variables would be more predictive of later childhood outcomes.

METHODS

Participants were enrolled in a geographical birth cohort comprising 298 consecutive survivors born EP/ELBW in the state of Victoria, Australia, over the 2-year study period (1991–1992) and a contemporaneously recruited control group of 262 normal birth weight infants. Control subjects were randomly selected from eligible births on the day an EP/ELBW survivor was due to be born, matched for gender, maternal country of origin (primarily English-speaking or not), and maternal health insurance status (as a proxy for social class). Control subjects were essential to provide a basis for comparison with EP/ELBW children who were being assessed with tests derived from other settings.

All participants were recruited at birth, and the majority were assessed at 2 years,⁶ 5 years,⁷ 8 years,⁸ and 18 years^{9–11} of age, corrected for prematurity. Age correction eliminates an important bias in cognitive test scores, which occurs even after the first few years of life in EP children.¹²

Exposures

Perinatal Biological Variables

From the 5-year assessment of this study cohort,⁷ we reported that severe intraventricular hemorrhage (IVH; grade 3 or 4), cystic periventricular leukomalacia, surgery requiring an anesthetic during the primary hospitalization, or being

treated with postnatal corticosteroids for ventilator dependence were each independently associated with worse neurosensory outcome; hence, it seemed appropriate to explore these variables among our biological exposures. Gestational age and growth restriction at birth were not independently associated with adverse outcomes at age 5 years, but they were included because smaller and more immature infants are more prone to all of the preceding biological complications. Birth weight SD scores were computed for age and sex relative to the British Growth Reference.¹³ We also included bronchopulmonary dysplasia (BPD), defined as having respiratory distress and requiring oxygen at 36 weeks' postmenstrual age, and the sex of the child; both of these factors are reportedly associated with worse neurosensory outcome at 5 years of age.¹⁴

Social Variables

Of the possible social variables that could potentially influence outcome, we considered mother's years of schooling, dichotomized at the median (<12 vs ≥12 years), and social class, based on employment of the major income earner in the family, dichotomized into lower (unskilled occupations or unemployed) and higher (semi-skilled, skilled, or professional occupations). These variables were chosen because of their influence on cognitive outcomes in a previous systematic review.⁴ Because all tests are English-based, we also included whether the family was multilingual (spoke languages other than English at home). We also determined whether both biological parents were living in the family home from birth, as we were interested in the potential effects of family disruption on childhood functioning. Similar social data were collected at all ages, but data from the 8-year assessment were used to reflect exposures in early life, including the first few years of the

child's schooling, and because the social data were most complete at that age.

Outcomes

Children were assessed at each age by research psychologists who were unaware of the perinatal findings or the details of assessments earlier in childhood.

Cognitive Measures

The mental development index of the Bayley Scales of Infant Development¹⁵ was assessed at 2 years. IQ was determined at age 5 years by using the Wechsler Preschool and Primary Scale of Intelligence–Revised,¹⁶ at age 8 years with the Wechsler Intelligence Scale for Children–Third Edition,¹⁷ and at age 18 years with a 2-subtest version of the Wechsler Abbreviated Scale of Intelligence.¹⁸ At each age, some subjects were untestable because of severe cognitive delay; these subjects were allocated a score equivalent to 4 SDs below the normative mean (eg, IQ = 40).

Academic Achievement

At 8 years of age, subjects' basic educational skills of reading, spelling, and arithmetic were assessed by using the Wide Range Achievement Test–Third Edition.¹⁹ At 18 years of age, subjects' word reading (single word decoding), spelling, and math computation skills were assessed by using the Wide Range Achievement Test–Fourth Edition.²⁰ All scales were age-standardized with a mean of 100 and an SD of 15.

At each assessment age, scores for cognitive and academic tests were restandardized relative to the mean \pm SD of the scores obtained from the control group. A few subjects at each age were tested with alternative cognitive tests, either because they were assessed with only part of the appropriate test (eg, the verbal or performance scales of 1 of the Wechsler tests) or because they were assessed at sites where the primary test was unavailable but a

suitable alternative was available. For these subjects, standardized mean scores were calculated based on the mean \pm SD of the test used.

The most recent assessment of the cohort was at ~18 years of age, when participants completed a comprehensive cognitive, medical, and psychological assessment.^{9–11} The human research ethics committees of the participating sites (Royal Women's Hospital, Mercy Hospital for Women, Monash Medical Centre, and Royal Children's Hospital, Melbourne, Australia) approved the original and follow-up studies. All participants provided written informed consent for the 18-year follow-up. If participants were aged <18 years, consent was also obtained from their parents.

Data Analysis

Data were analyzed by using Stata version 13 (Stata Corp, College Station, TX).²¹ Differences in characteristics and outcomes between the birth groups were analyzed by using χ^2 tests (categorical data) or 2-tailed *t* tests (continuous data). Within the EP/ELBW group, the influences of biological and social exposures on the standardized cognitive and academic scores at each age were assessed by using univariable and multivariable linear regression. Separate models were fitted to each outcome measure at each time point by using generalized estimating equations to allow for multiple births in the 1 family. We also tested for possible interactions between statistically significant biological and social variables.

Results are reported as regression coefficients, representing the mean difference in outcome between those with and without the exposure of interest and their 95% confidence intervals. To avoid problems of co-linearity between postnatal corticosteroids (which are used to treat or prevent BPD) and BPD itself,

we computed a new variable of BPD not treated with postnatal corticosteroids (which was used for analyses) rather than BPD alone.

RESULTS

There were expected differences in gestational age between the EP/ELBW and control groups, but the proportion of male subjects was equal (Table 1). The mean \pm SD birth weight score for control subjects was close to the expected value of zero but was substantially lower in the EP/ELBW group because ~20% of the cohort was >27 weeks' gestation but had birth weights <1000 g. Rates of severe IVH and cystic periventricular leukomalacia were relatively low in the EP/ELBW group, but 33% had been treated with corticosteroids after birth, 37% had BPD (68 of 111 with BPD were treated with postnatal corticosteroids), and 26% required surgery in the newborn period. None of the control subjects had any of these biological exposures. Compared with the control subjects, the EP/ELBW group was disadvantaged on all social variables except for multilingual status.

The cognitive and academic achievement scores of EP/ELBW subjects were substantially lower than those for control subjects at each age (Table 2). There were similar differences in the standardized cognitive scores between groups from ages 2 to 18 years, as well as in the standardized academic achievement scores from ages 8 to 18 years. Adjustment for sociodemographic variables reduced the mean differences between the EP/ELBW and control groups by 12% for developmental quotient scores at 2 years and up to 22% for IQ scores at 18 years; all differences between groups remained highly statistically significant.

Follow-up rates were high up to 8 years of age but were lower at 18 years (Table 2). Within the

TABLE 1 Summary of Biological and Social Exposures According to Birth Group

Exposure	EP/ELBW (n = 298)	Control (n = 262)
Biological		
Gestational age (completed wks), mean ± SD	26.7 ± 1.9	39.2 ± 1.4
Birth weight score, mean ± SD	−0.73 ± 1.19	−0.03 ± 0.89
Male	138 (46)	126 (48)
Severe IVH	18 (6)	0
Cystic periventricular leukomalacia	18 (6)	0
Postnatal corticosteroids	98 (33)	0
BPD	111 (37)	0
BPD, not treated with postnatal corticosteroids	43 (14)	0
Surgery during the primary hospitalization	77 (26)	0
Social		
Lower maternal education	140/269 (52)	86/221 (39)
Lower social class	117/269 (43)	67/224 (30)
Multilingual family	50/283 (18)	34/235 (14)
Not having both biological parents at home from birth	60/274 (22)	32/223 (14)

Unless otherwise specified, data are n (%).

EP/ELBW group, there was little difference in the sociodemographic variables between those assessed at 8 years of age but not subsequently at 18 years (not assessed versus assessed at 18 years, respectively;

lower maternal education, 58% vs 51%; lower social class, 53% vs 41%; multilingual family; 24% vs 16%; both parents not at home from birth, 25% vs 21%) or in full-scale IQ at 8 years (mean ± SD of 94 ± 12 not

assessed at 18 years vs mean 96 ± 16 assessed at 18 years).

Many biological exposures were associated on univariable analysis with lower cognitive scores in early childhood; these associations persisted to 18 years of age (Supplemental Appendix Table 3). Higher gestational age was associated with better cognitive scores at all ages, but the relationship at age 8 years was weaker than at other ages. Of the social variables, lower social class and maternal education were associated with worse outcomes from 5 years of age onward; living in a multilingual household had persistent negative associations from 2 to 8 years of age but not at 18 years of age.

On multivariable analysis, the magnitude of associations for most variables with cognitive scores was reduced when simultaneously adjusting for all other variables. Of the biological variables, evidence remained that higher birth weight SD scores were associated with higher cognitive scores at 2 and 8 years of age. Being male was associated with lower cognitive scores at 2 years of age only. IVH was associated with lower cognitive scores at all ages after 2 years, as was postnatal corticosteroid treatment at age 5 and 18 years (Fig 1, Appendix Table 3). Having BPD but not receiving corticosteroids and having surgery in the newborn period had little effect on outcomes at any age. Of the social variables, living in a multilingual household was associated with lower cognitive test scores at early ages, but the association attenuated as the children aged and was negligible by 18 years of age. Lower maternal education and lower social class had little effect on cognitive outcome at 2 years of age but were increasingly associated with lower cognitive scores in later years. Living without both biological parents in the household from birth had little effect on cognitive test scores. The

TABLE 2 Cognitive and Academic Achievement Scores Contrasted Between Birth Groups at Each Outcome Assessment

Age	EP/ELBW (n = 298)	Control (n = 262)	Mean Difference (95% CI)	Standardized Mean Difference ^a (95% CI)
Cognitive				
2 y	98.4 (22.7) n = 285	113.7 (21.1) n = 236	−15.3 (−19.1 to −11.5)	−0.80 (−1.00 to −0.60)
5 y	96.7 (15.4) n = 253	105.7 (13.9) n = 221	−9.0 (−11.6 to −6.3)	−0.78 (−0.99 to −0.58)
8 y	95.5 (16.0) n = 258	104.9 (14.1) n = 220	−9.4 (−12.1 to −6.7)	−0.80 (−1.00 to −0.60)
18 y	95.3 (16.3) n = 224	106.4 (13.7) n = 160	−11.1 (−14.3 to −8.0)	−0.82 (−1.04 to −0.59)
Academic achievement				
Reading				
8 y	96.6 (16.0) n = 259	103.3 (14.7) n = 219	−6.7 (−9.5 to −3.9)	−0.46 (−0.65 to −0.27)
18 y	95.1 (14.1) n = 223	101.2 (14.3) n = 160	−6.2 (−9.1 to −3.3)	−0.43 (−0.63 to −0.23)
Spelling				
8 y	94.4 (12.6) n = 258	100.0 (13.3) n = 218	−5.6 (−8.0 to −3.3)	−0.42 (−0.60 to −0.25)
18 y	98.0 (15.7) n = 222	104.6 (14.1) n = 160	−6.5 (−9.6 to −3.5)	−0.46 (−0.68 to −0.25)
Arithmetic/math computation				
8 y ^b	89.2 (14.3) n = 256	98.0 (13.4) n = 219	−8.7 (−11.3 to −6.2)	−0.65 (−0.84 to −0.47)
18 y ^c	85.4 (14.7) n = 223	94.8 (15.1) n = 160	−9.5 (−12.5 to −6.5)	−0.63 (−0.83 to −0.43)

Unless otherwise indicated, data are mean ± SD. CI, confidence interval.

^a Standardized relative to the mean ± SD scores obtained for the control group.

^b Arithmetic at 8 years of age.

^c Math computation at 18 years of age.

magnitudes of the negative associations of cognitive scores with IVH and postnatal corticosteroids were relatively constant over time, and they mostly exceeded the magnitudes of relationships with social variables in the school-aged years. The amount of variance (adjusted R^2) explained by the models with all variables entered was 20.5% at 2 years of age, 17.9% at 5 years, 17.3% at 8 years, and 18.6% at 18 years. The biological variables contributed more to the amount of variance explained at younger ages but not at 18 years of age (biological only versus social only: age 2 years, 17.3% vs 5.3%; age 5 years, 12.4% vs 8.2%; age 8 years, 11.0% vs 7.4%; and age 18 years, 8.9% vs 11.2%).

On univariable analysis, of the biological variables, gestational age was positively associated with some academic scores at both 8 and 18 years of age, whereas postnatal corticosteroid treatment and surgery were associated with lower performance on academic outcomes. Lower maternal education and lower social class were the social variables associated with lower performance on academic achievement on

univariable analysis (Supplemental Appendix Table 4).

On multivariable analysis, gestational age and birth weight SD score were positively associated with some academic scores at age 8 years only, whereas postnatal corticosteroid treatment was associated with poorer performance on all of the academic achievement tasks at age 18 years only (Fig 2, Supplemental Appendix Table 4). Surgery was also associated with lower scores for reading at 8 years of age and math computation at 18 years of age. Of the social variables, both lower maternal education and lower social class were associated with reductions in performance on all of the academic achievement tasks at both 8 and 18 years of age. Interestingly, there was some evidence that living in a multilingual household was associated with increased spelling scores at 8 and 18 years of age. The magnitudes of the negative associations with postnatal corticosteroids on academic achievement at age 18 years were similar to those of lower maternal education and lower social class at that age.

There were no significant interactions between statistically significant biological and social variables (all $P > .05$).

DISCUSSION

The present contemporary cohort study included EP/ELBW survivors born in the era after surfactant was introduced into clinical care. As shown in this study, the disadvantage in cognitive and academic test scores in preterm participants compared with control participants was relatively constant throughout childhood and into adolescence, as hypothesized. This finding is contrary to the suggestion that cognitive outcomes for preterm survivors may improve through childhood.⁵ Of the biological variables known to be associated with adverse outcomes, severe IVH, although uncommon, was associated with worse cognitive outcome from 5 years of age onward; postnatal corticosteroids had some adverse associations with cognitive outcomes in childhood but particularly with cognitive and academic outcomes at 18 years of age. Contrary to expectations, the associations between these 2 biological variables and cognitive and academic scores did not diminish substantially over time, and the magnitudes of their independent effects were mostly greater than or equal to those of the various social exposures studied. In line with this finding, gestational age and birth weight SD scores were also positively associated with some cognitive and academic outcomes in early childhood but not at age 18 years. Of the social variables, being raised in a multilingual household was associated with lower performance on cognitive assessments until 8 years of age, but this effect had attenuated by late adolescence. In contrast, lower maternal education and lower social class had little

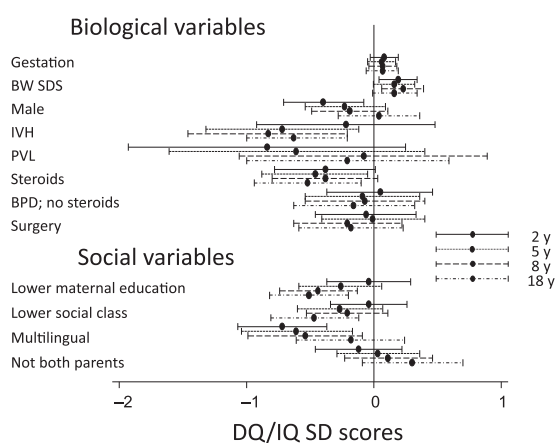


FIGURE 1

Relationship of biological and social variables with cognitive test scores at each age standardized relative to the control group. Results are regression coefficients (and 95% confidence intervals) from a single multivariable model for each outcome and represent the mean difference in cognitive scores (SD units) between those with and without the exposure of interest or per-unit increase in continuous variables. The results for each variable are adjusted for the presence of all other variables. Steroids refer to postnatal corticosteroids. BW SDS, birth weight SD score; DQ, developmental quotient; PVL, periventricular leukomalacia.

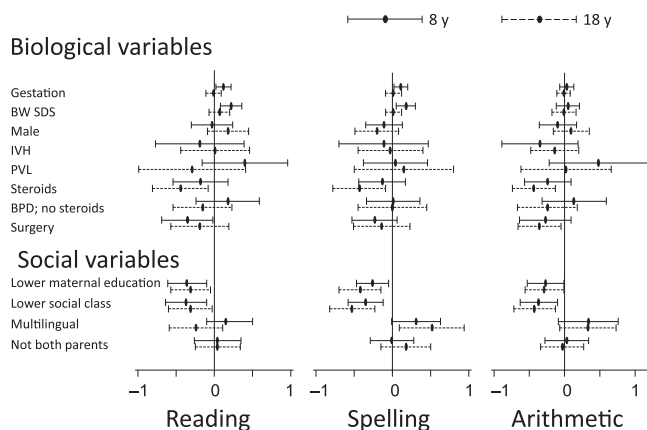


FIGURE 2

Relationships of biological and social variables with academic achievement test scores at 8 and 18 years of age standardized relative to the control group. Results are regression coefficients (and 95% confidence intervals) from a single multivariable model for each outcome, and they represent the mean difference in academic scores (SD units) between those with and without the variable of interest or per-unit increase in continuous variables. The results for each variable are adjusted for the presence of all other variables. Arithmetic refers to arithmetic skills at 8 years of age and math computation skills at 18 years of age; steroids refer to postnatal corticosteroids. BW SDS, birth weight SD score; PVL, periventricular leukomalacia.

influence on cognitive functioning in early life, but associations increased with both cognitive function and academic achievement at school-age and adolescence. In our cohort, the effects of the biological and social variables were only additive, rather than multiplicative.

Although it is believed that the influence of biological variables diminishes and that of social factors increases with age,²² no studies have explicitly addressed the issue longitudinally in EP/ELBW survivors. Most studies have observed preterm children over short periods or have reported adolescent outcomes from children born before the 1990s, when survival rates for EP/ELBW infants were considerably lower than in the present study. Greater degrees of prematurity and more medical complications have been associated with lower cognitive growth trajectories from 12 to 36 months of age, irrespective of socioeconomic status, compared with lower risk preterm and term children.²³ However, in a small sample of lower risk preterm children, birth status and medical complications were not predictive of language development

by 36 months of age.²² Importantly, data comparing the magnitude of social and biological influences in adolescence are limited. Among 12-year-olds, family income and maternal education accounted for at least as much variance in IQ as did being very low birth weight in 1 study from the early 1980s of very low birth weight survivors and control subjects.²⁴ Whitaker et al²⁵ reported persistent and independent effects of some infant biological variables (including major brain injury detected by cranial ultrasound) on IQ in teenagers with a birth weight <2000 g born in the 1980s. Swedish register data from births in the 1970s also emphasized the importance of socioeconomic factors in predicting cognitive ability in the teenage years, but the investigators could not simultaneously assess the influence of biological variables.²⁶ Among other methodologic differences from the present study, none of these previous studies reported serial data throughout childhood and into late adolescence.

The results of our study should not be interpreted as evidence to stop using postnatal corticosteroids in

ventilator-dependent infants; the risks and benefits of these agents, including their effects on mortality, are more properly considered in randomized trials of postnatal corticosteroids, rather than observational studies, and are discussed elsewhere.^{27–29} The importance of the associations with postnatal corticosteroids depends more on identifying survivors at risk for potentially lifelong impairments, which applies to one-third of the current cohort.

The major strengths of the present study are its regional cohort, which avoids selection bias; the blinded assessments at each age; the high follow-up rates, particularly for the 2-, 5-, and 8-year assessments; the selection of an appropriate normal birth weight control group from birth; and the ability to reassess the cohorts throughout childhood and into late adolescence. Limitations of the study include the lower follow-up rate at 18 years, the inability to study other possible biological variables (eg, genetic or epigenetic factors), and the fact that only distal rather than proximal social variables were studied.³⁰

CONCLUSIONS

Specific perinatal biological exposures, particularly postnatal corticosteroids and IVH, have strong and persistent influences on cognitive and academic outcomes in EP/ELBW survivors. The magnitude of the biological associations mostly equals or exceeds those of social exposures, even in late adolescence. The relative importance of biological versus social exposures on outcomes later in adulthood, and the influence of other biological and proximal social variables, requires further evaluation.

ACKNOWLEDGMENTS

Victorian Infant Collaborative Study Group Members who contributed

through planning the study or through data collection are as follows. Convenor: Lex W. Doyle, MD, FRACP (Premature Infant Follow-up Program at the Royal Women's Hospital, Departments of Obstetrics and Gynaecology and Paediatrics at the University of Melbourne, and Murdoch Childrens Research Institute, Melbourne, Australia). Collaborators (in alphabetical order): Peter J. Anderson, PhD (Department of Paediatrics at the University of Melbourne and Murdoch Childrens Research Institute, Melbourne, Australia); Alice Burnett, PhD (Murdoch Childrens Research Institute, Melbourne, Australia); Catherine Callanan, RN (Premature Infant Follow-up Program at the Royal Women's Hospital, Melbourne, Australia); Elizabeth Carse, FRACP, and Margaret P. Charlton, MEd Psych (Monash Medical Centre, Melbourne, Australia); Jeanie Cheong, MD, FRACP (Premature Infant Follow-up Program at the Royal Women's Hospital, Department of Obstetrics and Gynaecology at the University of Melbourne, and Murdoch Childrens Research Institute, Melbourne, Australia); Cinzia R. De Luca, BSc,

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
ELBW: extremely low birth weight
EP: extremely preterm
IVH: intraventricular hemorrhage

The funders did not have any role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; decision to publish; or in the preparation, review, or approval of the manuscript.

www.pediatrics.org/cgi/doi/10.1542/peds.2015-2006

DOI: 10.1542/peds.2015-2006

Accepted for publication Sep 2, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the National Health and Medical Research Council of Australia, through a Centre of Research Excellence Grant (ID 1060733), a project grant (ID 491246), and fellowship support (Dr Anderson, ID 628371; Dr Lee, ID 1053609; and Dr Cheong, ID 1053787). The following were successful applicants for the Project Grant (ID 491246): Dr Doyle, Dr Anderson, Dr Stephen J. Wood, Dr Colin Robertson, Dr Sarah Hope, Dr Doug Hacking, and Dr Cheong. Support was also provided by the Victorian Government's Operational Infrastructure Support Program.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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