School-age Outcomes of Extremely Preterm or Extremely Low Birth Weight Children

AUTHORS: Esther A. Hutchinson, DpsychClinNeuro,[a,b,c] Cinzia R. De Luca, PhD,[a,c,d] Lex W. Doyle, MD,[a,c,d] Gehan Roberts, PhD,[a,b,c,d] and Peter J. Anderson,[c,d] for the Victorian Infant Collaborative Study Group

[a]Royal Women's Hospital, [b]Royal Children's Hospital, [c]The University of Melbourne; and [d]Murdoch Childrens Research Institute, Melbourne, Australia

KEY WORDS

academic achievement, IQ, low birth weight, neurobehavior, preterm

ABBREVIATIONS

CI—confidence interval
ELBW—extremely low birth weight
EP—extremely preterm
FSIQ—full-scale IQ
GA—gestational age
PRI—Perceptual Reasoning Index
SDQ—Strengths and Difficulties Questionnaire
T/NBW—term/normal birth weight
VCI—Verbal Comprehension Index
WISC-IV—Wechsler Intelligence Scale for Children, Fourth Edition
WRAT3—Wide Range Achievement Test, Third Edition

Dr Hutchinson drafted the initial manuscript, conducted the analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr De Luca contributed to the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Roberts critically reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Doyle conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted; and Dr Anderson conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-2311

doi:10.1542/peds.2012-2311

Accepted for publication Dec 19, 2012

Address correspondence to Peter J. Anderson, PhD, Victorian Infant Brain Studies, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, VIC, 3052, Australia. E-mail: peter.anderson@mcri.edu.au

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

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

FUNDING: Supported in part by Australia's National Health and Medical Research Council Senior Research Fellowship (Dr Anderson, 628371) and Victorian Government's Operational Infrastructure Support Program.

WHAT'S KNOWN ON THIS SUBJECT: Although it is known that extremely preterm children are at increased risk for cognitive deficits, academic underachievement, and behavioral problems, the frequency and severity of these impairments may decline with advances in neonatal care.

WHAT THIS STUDY ADDS: Despite recent changes in obstetric and neonatal management of extremely preterm infants, the rate of neurobehavioral impairments at school age is still too high.

abstract

FREE

OBJECTIVE: Research is required to monitor changes in the nature of neurobehavioral deficits in extremely preterm (EP) or extremely low birth weight (ELBW) survivors. This study examines cognitive, academic, and behavioral outcomes at age 8 years for a regional cohort of EP/ELBW children born in 1997.

METHODS: The EP/ELBW cohort comprised all live births with a gestational age <28 weeks (EP) or birth weight <1000 g (ELBW) born in the state of Victoria, Australia, in 1997. Of 317 live births, 201 (63.4%) survived to 2 years of age. A term/normal birth weight (T/NBW) cohort was recruited comprising 199 infants with birth weights <2500 g or gestational age <37 weeks. Measures of intellectual ability, educational achievement, and behavior were administered at age 8.

RESULTS: Retention was 94% for the EP/ELBW group and 87% for the T/NBW group. The EP/ELBW group performed poorer than the T/NBW group on measures of IQ, educational achievement, and certain behavioral domains, even after adjustment for sociodemographic factors and exclusion of children with neurosensory impairment. The rate of any neurobehavioral impairment was elevated in the EP/ELBW group (71% vs 42%), and one-half of subjects had multiple impairments. The outcomes for those with <750 g birth weight or <26 weeks' gestational age were similar to those with a birth weight of 750 to 999 g or a gestational age of 26 to 27 weeks, respectively.

CONCLUSIONS: Despite ongoing improvements in the management of EP/ELBW infants, the rate of neurobehavioral impairment at school-age remains too high relative to controls. *Pediatrics* 2013;131:e1053–e1061

In the past, cognitive deficits, academic underachievement, and behavioral problems have occurred more frequently in school-aged children born extremely preterm (EP; <28 weeks' gestational age [GA]) and/or extremely low birth weight (ELBW; <1000 g) compared with children born at term or of normal birth weight.[1–5] Changes in obstetric and neonatal management of high-risk pregnancies and infants occur constantly, with reductions in mortality and short-term morbidity, especially for infants at the edge of viability. Treatments associated with short-term neurologic benefits include antenatal administration of magnesium sulfate,[1] caffeine for the treatment of apnea of prematurity,[6] and high-dose docosahexaenoic acid supplementation,[7] the first 2 of which are now routine treatments in Australia and the third is used in some units. There is also growing evidence that early-intervention programs enhance the development of preterm infants.[4,8] Accordingly, the frequency, nature, and severity of neurobehavioral deficits observed in contemporary cohorts of EP/ELBW children may differ from those of earlier eras.

The aim of the current study was to investigate cognitive, academic, and behavioral outcomes at age 8 years for a cohort of children born EP or ELBW in 1997. In contrast to most previous published reports of long-term outcome, not only is our study more contemporaneous, it also reports on a geographic cohort, includes a matched term/normal birth weight (T/NBW) group, and achieves high retention.

METHODS

The EP/ELBW cohort comprised all live births with either a GA <28 weeks or birth weight <1000 g born in the state of Victoria, Australia, in 1997. Survivors received neonatal care in 1 of the 4 NICU nurseries in the state and were enrolled in this longitudinal study in the newborn period. Of 317 eligible live births, 201 (63.4%) survived to 2 years of age.

The T/NBW cohort, recruited in the same time period, comprised 199 infants with a GA ≥37 weeks or birth weight ≥2500 g, all of whom survived to age 2 years. These children were randomly selected from births on the expected date of birth for each EP/ELBW child and matched for gender, mother's country of birth (English speaking or not), and health insurance status (private health insurance or not). Written informed consent was obtained.

The study was approved by the Human Research Ethics Committees at the Royal Women's Hospital, Mercy Hospital for Women, and Monash Medical Centre, Victoria, Australia. Psychologists performing assessments were unaware of the history and group status of the children. Outcome data at 2 years have previously been reported.[9–11]

General Intellectual Ability

General intellectual ability was assessed by using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV).[12] Full-scale IQ (FSIQ) was used as a measure of general intelligence, and the 4 index scores provide information on more specific cognitive domains. The Verbal Comprehension Index (VCI) measures knowledge of word meanings and verbal reasoning abilities, the Perceptual Reasoning Index (PRI) measures visuoconstructional skills and visual reasoning abilities, the Working Memory Index measures immediate and working memory, and the Processing Speed Index measures speed and accuracy of information processing. Each index score is age standardized, with a mean of 100 and an SD of 15. Cognitive impairment was classified according to both test norms and the T/NBW distribution.

Children unable to attempt the WISC-IV due to severe disability (n = 3) were assigned FSIQ and index scores of 40 (–4 SDs). Children with severe visual impairment who could not be administered subtests with visual stimuli (n = 2) were assigned an FSIQ based on their VCI score. One child with significant hearing impairment was not administered subtests with significant language demands, and an FSIQ was assigned according to their PRI score. All these children were in the EP/ELBW cohort.

Academic Skills

Academic abilities were assessed by using the Wide Range Achievement Test, Third Edition (WRAT3).[13] The WRAT3 comprises reading (single word decoding), spelling, and arithmetic subtests. Each scale has a mean of 100 and an SD of 15, and impairment was classified according to both test norms and the T/NBW distribution.

Children with either WISC-IV or WRAT3 standard scores from –1 to –2 SDs relative to the normative mean or the T/NBW mean were classified as mildly impaired, whereas those with scores –2 or lower SDs relative to the normative mean or the T/NBW mean were considered to have a major impairment.

Behavioral Outcomes

Behavioral outcomes were assessed by using the Strengths and Difficulties Questionnaire (SDQ).[14,15] This 25-item, parent-rated questionnaire has 5 scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. Twenty of the items are combined to generate a "total difficulties" score, and an "impact" score is produced from items that ask about the effect of these difficulties on the child (level of distress; impact on home, friendships, classroom, and leisure).

Normative data for children (www.sdqinfo.org) were used to determine those in the clinical range. Children with scores above the 90th percentile were classified as being in the "abnormal" range, those between the 80th and 90th percentile were classified as "borderline," and those below the 80th percentile were classified as "normal." Children were also classified into these clinical categories according to cutoffs based on the T/NBW distribution.

Sociodemographic Factors

Sociodemographic information was collected at 8 years, including marital status of mother (married or single), language spoken at home (English only or other), maternal and paternal education (≥12 years of education or <12 years of education), family structure (intact or other), and occupation of the primary income earner (skilled/semiskilled or unskilled/unemployed).

Statistical Analyses

Group differences were contrasted by using *t* tests for continuous data, χ^2 analysis for dichotomous data, and χ^2 tests for linear trends for ordered dichotomous variables. The magnitude of group differences on WISC-IV and WRAT3 indices was calculated by dividing the group difference by the published normative SD for those indices. Analyses were repeated excluding children with neurosensory impairment (eg, cerebral palsy, deafness, blindness). Analysis of covariance was then undertaken to control for the potential impact of sociodemographic factors (gender, marital status, language spoken at home, mother's and father's educational level, family structure, and occupation of primary income earner) on cognitive, academic, and behavioral outcomes. Subgroup analyses were performed comparing the smallest (birth weight, <750 g) and most preterm (<26 weeks' GA) children and the slightly heavier (750–999 g) and older (26–27 weeks' GA) children. An α level was set at .05 for all analyses, and no adjustment was made for multiple comparisons because the outcomes parameters are not independent.[16]

RESULTS

Follow-up rates were 94% (189 of 201) for the EP/ELBW group and 87% (173 of 199) for the T/NBW group. Of the 12 EP/ELBW children not seen, 10 were assessed at 2 years' corrected age. EP/ELBW participants and nonparticipants at 8 years did not differ on the Mental Development Index of the Bayley Scales of Infant Development (BSID-II) at 2 years (mean difference, –4.2 [95% confidence interval [CI], –18.0 to 9.7], P = .55). Eighteen of the 26 T/NBW children not seen were assessed at 2 years of age. No difference was found between T/NBW participants and nonparticipants on the Mental Development Index (mean difference, –0.2 [95% CI, –7.9 to 7.6], P = .97).

Table 1 displays perinatal and sociodemographic characteristics of the groups. Of the EP/ELBW cohort, 61 children (32%) were born <26 weeks' GA and 62 (33%) weighed <750 g. Antenatal corticosteroids were administered for the majority of EP/ELBW infants, and approximately one-third received postnatal corticosteroids. Cystic periventricular leukomalacia or grade 3/4 intraventricular hemorrhage were observed in a small number. The gender and age-at-assessment distributions for the EP/ELBW and T/NBW groups were similar. Although no child in the T/NBW group was small for gestational age (birth weight less than –2 SDs), 18% of the EP/ELBW group fell within this category (χ^2 = 34.3, P < .001). Family structure, maternal marital status, and language spoken at home did not differ between groups. In contrast, parents of EP/ELBW children were less likely to have completed 12 years of schooling than parents of T/NBW children (mothers, χ^2 = 11.6, P = .001; fathers, χ^2 = 14.4, P < .001), and the primary income earner in EP/ELBW families was more likely to be unskilled (χ^2 = 17.5, P < .001).

When seen at age 8 years, 29 (15%) children in the EP/ELBW cohort had neurosensory impairment; 3 were blind, 4 required hearing aids, and 24 had cerebral palsy (1 child with cerebral palsy was also blind and another child was also deaf). In the T/NBW cohort, no child had a neurosensory impairment.

TABLE 1 Perinatal and Sociodemographic Characteristics of the EP/EBLW and T/NBW Groups

Characteristic	EP/ELBW (n = 189)	T/NBW (n = 173)	P
Perinatal characteristics			
Male	100 (52.9)	92 (53.2)	.96
GA, mean ± SD, completed wk	26.5 ± 2.0	39.3 ± 1.1	<.001
Birth weight, mean ± SD, g	833 ± 164	3506 ± 1455	<.001
Birth weight less than –2 SDs	34 (18.0)	0 (0)	<.001
Age at evaluation, mean ± SD, y	8.45 ± 0.41)	8.50 ± 0.39)	.10
Antenatal corticosteroids	166 (87.8)	2 (1.2)	<.001
Surfactant	154 (81.5)	1 (0.6)	<.001
Postnatal corticosteroids	70 (37.0)	0 (0)	<.001
Oxygen dependency at 36 wk	72 (38.1)	0 (0)	.<.001
Cystic periventricular leukomalacia	6 (3.2)	0 (0)	.02
Grade 3/4 intraventricular hemorrhage	7 (3.7)	0 (0)	.03
Sociodemographic characteristics			
English only spoken at home	150/186 (80.6)	147/171 (86.0)	.18
Intact family structure	131/169 (77.5)	139/165 (84.2)	.12
Married mother	136/169 (80.5)	128/159 (80.5)	.99
Primary income earner skilled/semiskilled	96/171 (56.1)	125/161 (77.6)	<.001
Maternal education (≥12 y of schooling)	94/189 (49.7)	116/172 (67.4)	.001
Paternal education (≥12 y of schooling)	71/177 (40.1)	99/163 (60.7)	<.001

Data are presented as number (percent) unless otherwise indicated.

General Intellectual Ability

The mean FSIQ for the EP/ELBW group was significantly below that of the T/NBW cohort, with the magnitude of the group difference exceeding 0.8 SD (t = –8.2, $P < .001$). The same pattern was evident for the index scores, with EP/ELBW children performing between 0.4 to 0.8 SD below the T/NBW group (Table 2): verbal comprehension (t = –7.1, $P < .001$), perceptual reasoning (t = –7.7, $P < .001$), working memory ($t = -5.5$, $P < .001$) and processing speed ($t = -4.3$, $P < .001$).

Controlling for sociodemographic variables marginally reduced the mean group difference on these WISC-IV scales, and all comparisons remained highly significant. Statistical conclusions also remained unchanged when children with neurosensory disabilities were excluded.

Academic Progress

The EP/ELBW group performed significantly below the T/NBW group on tests of reading (t = –4.71, $P < .001$), spelling (t = –4.69, $P < .001$), and arithmetic (t = –5.40, $P < .001$). The magnitude of the group differences was 0.5 SD for reading and spelling but slightly higher for arithmetic (0.6 SD). Mean differences between the groups on academic tests remained significant after adjusting for sociodemographic variables and excluding those with neurosensory impairment.

Behavioral Problems (SDQ)

Parents of children in the EP/ELBW group reported more behavioral problems than those of the T/NBW group (t = 25.5, $P < .001$), with these difficulties having greater impact (t = 2.5, P = .013). EP/ELBW parents reported that their children were displaying more hyperactivity/inattention (t = 3.9, $P < .001$), emotional problems (t = 5.42, $P < .001$), and peer relationship problems (t = 2.85, P = .005) compared with control children. Results were robust, with group differences remaining stable after adjusting for sociodemographic variables and excluding those with neurosensory impairment.

Birth Weight and GA

For the EP/ELBW sample, the <750-g subgroup displayed lower performances on all cognitive scales than the ≥750- to 999-g subgroup, but only differences in VCI and PRI reached significance (Table 3). Significant differences were also demonstrated across all academic measures. However, when comparisons were adjusted for neurosensory impairment, significant differences were lost for spelling and arithmetic. No differences were seen on any of the SDQ behavior scales.

The <26-week GA subgroup achieved lower scores on cognitive and academic scales than the 26- to 27-week GA subgroup, although only performance on the PRI reached significance. When comparisons were adjusted for neurosensory impairment, the significant difference between groups on the PRI was lost. In relation to the behavioral outcomes, parents of children in the

TABLE 2 Cognitive and Academic Outcomes (Mean ± SD) for the EP/ELBW and T/NBW Cohorts at 8 Years of Age, Including Adjustment for Sociodemographic Variables and Neurosensory Impairment

Outcome	EP/ELBW (n = 189)	Controls (n = 173)	Mean Difference (95% CI)	Adjusted Mean Difference 95% CI)[a]	Adjusted Mean Difference 95% CI)[b]
WISC-IV					
FSIQ	93.1 ± 16.1	105.6 ± 12.4	−12.5 (–15.5 to –9.5)*	−10.2 (–13.7 to –6.6)*	−8.8 (–12.2 to –5.3)*
Verbal comprehension	93.1 ± 14.3	103.2 ± 12.6	−10.2 (–13.0 to –7.4)*	−7.8 (–11.1 to –4.5)*	−7.0 (–10.2 to –3.9)*
Perceptual reasoning	95.9 ± 16.8	108.2 ± 12.8	−12.3 (–15.4 to –9.2)*	−10.1 (–13.9 to –6.4)*	−8.0 (–11.5 to –4.7)*
Working memory	94.0 ± 16.3	102.4 ± 12.9	−8.5 (–11.6 to –5.4)*	−7.1 (–10.9 to –3.4)*	−6.1 (–9.7 to –2.6)**
Processing speed	94.7 ± 15.9	101.1 ± 11.9	−6.4 (–9.4 to –3.5)*	−5.7 (–9.3 to –2.3)***	−4.3 (–7.7 to –1.0)***
WRAT3					
Reading	98.0 ± 16.1	105.5 ± 13.8	−7.6 (–10.7 to –4.4)*	−6.7 (–10.4 to –3)*	−6.7 (–10.4 to –3)*
Spelling	96.8 ± 15.2	104.2 ± 14.4	−7.5 (–10.6 to –4.3)*	−7.4 (–11.1 to –3.6)*	−7.7 (–11.5 to –4)*
Arithmetic	90.0 ± 16.9	99.1 ± 14.5	−9.2 (–12.5 to –5.8)*	−6.9 (–11 to –2.9)**	−6.8 (–10.9 to –2.8)**
SDQ					
Total	11.0 ± 6.3	7.9 ± 5.4	3.1 (1.9 to 4.4)*	3.3 (2.0 to 4.6)*	3.4 (2.0 to 4.7)*
Emotional symptoms	2.9 ± 2.4	1.7 ± 1.7	1.2 (0.8 to 1.6)*	1.2 (0.7 to 1.7)*	1.2 (0.7 to 1.7)*
Conduct problems	1.7 ± 1.7	1.4 ± 1.5	0.3 (–0.1 to 0.6)	0.3 (–0.1 to 0.6)	0.3 (–0.1 to 0.7)
Hyperactivity/inattention	4.3 ± 2.7	3.2 ± 2.5	1.1 (0.5 to 1.6)*	1.3 (0.7 to 1.9)*	1.3 (0.7 to 1.9)*
Peer relationships	2.1 ± 2.1	1.5 ± 1.8	0.6 (0.2 to 1.0)**	0.7 (0.2 to 1.1)***	0.6 (0.2 to 1.1)**
Prosocial behavior	8.3 ± 1.9	8.6 ± 1.7	–0.3 (–0.7 to –0.0)	–0.3 (–0.7 to –0.1)	–0.4 (–0.8 to 0.1)
Impact	1.1 ± 1.9	0.6 ± 1.4	0.5 (0.1 to 0.8)***	0.4 (0.1 to 0.8)***	0.3 (–0.1 to 0.7)

a Adjusted for demographic variables.

b Adjusted for demographic variables, with children with neurosensory impairment excluded.

* $P < .001$.

** $P < .01$.

*** $P < .05$.

TABLE 3 Comparisons of Outcomes Between Birth Weight and GA Subgroups

Outcome	Mean ± SD Birth Weight		Mean Difference (95% CI)
	<750 g(*n* = 60)	750–999 g(*n* = 96)	
WISC-IV			
FSIQ	91.3 (12.9)[a]	95.5 (15.2)	−4.2 (−9.0 to −0.6), *P* = .09
Verbal comprehension	90.2 (12.2)[b]	95.7 (12.6)	−5.5 (−9.6 to −1.4), *P* = .009
Perceptual reasoning	93.4 (14.9)[c]	99.0 (14.8)[b]	−5.6 (−10.5 to − 0.7), *P* = .025
Working memory	92.3 (15.5)[b]	96.6 (14.8)	−4.3 (−9.3 to 0.7), *P* = .09
Processing speed	92.3 (15.4)[d]	96.8 (13.6)[b]	−4.6 (−9.3 to −0.2), *P* = .06
WRAT3			
Reading	93.7 (16.5)[c]	100.8 (14.8)[a]	−7.1 (−12.2 to −2.0), *P* = .007
Spelling	93.3 (15.9)[c]	99.5 (14.3)[d]	−6.2 (−11.1 to − 1.3), *P* = .014
Arithmetic	85.3 (17.0)[d]	92.2 (15.9)[a]	−6.9 (−12.4 to −1.4), *P* = .014
SDQ			
Total	11.2 (6.6)	10.6 (6.3)	0.5 (−1.6 to 2.6), *P* = .62
Emotional symptoms	3.0 (2.5)	2.8 (2.3)	0.2 (−0.5 to 1.0), *P* = .56
Conduct problems	1.6 (1.6)	1.7 (1.9)	−0.1 (−0.7 to 0.5), *P* = .67
Hyperactivity/inattention	4.3 (2.8)	4.1 (2.6)	0.2 (−0.7 to 1.1), *P* = .68
Peer relationships	2.3 (2.2)	2.0 (2.0)	0.3 (−0.4 to 1.0), *P* = .43
Prosocial behavior	8.3 (2.0)	8.3 (1.8)	0.0 (−0.6 to 0.6), *P* = .93
Impact	1.4 (2.5)	0.9 (1.7)	0.5 (−0.2 to 1.1), *P* = .15
	Mean ± SD GA		
Outcome	23–25 wk (*n* = 59)	26–27 wk (*n* = 79)	Mean Difference (95% CI)
WISC-IV			
FSIQ	93.5 (14.8)[d]	95.3 (12.3)[a]	−1.7 (−6.4 to 3.0), *P* = .46
Verbal comprehension	93.7 (12.2)	93.7 (11.0)[a]	−0.0 (−4.0 to 4.0), *P* = .99
Perceptual reasoning	94.6 (16.2)[c]	99.7 (12.5)[a]	−5.1 (−10.0 to − 0.2), *P* = .04
Working memory	94.5 (16.6)	95.0 (12.2)[a]	−0.5 (−5.4 to 4.4), *P* = .84
Processing speed	93.7 (16.0)[d]	97.9 (12.3)[e]	−4.2 (−9.1 to 0.7), *P* = .09
WRAT3			
Reading	95.3 (15.5)[d]	98.7 (17.5)[d]	−3.4 (−9.2 to 2.4), *P* = .25
Spelling	95.9 (14.0)[d]	97.1 (17.2)[b]	−1.2 (−6.7 to 4.4), *P* = .67
Arithmetic	87.4 (15.8)[e]	92.3 (17.8)[d]	−4.8 (−10.8 to 1.2), *P* = .11
SDQ			
Total	10.1 (6.8)	11.3 (6.1)	−1.2 (−3.4 to 1.0), *P* = .29
Emotional symptoms	2.3 (2.2)	3.3 (2.4)	−0.9 (−1.7 to −0.1), *P* = .02
Conduct problems	1.7 (1.8)	1.7 (1.7)	0.1 (−0.5 to 0.7), *P* = .78
Hyperactivity/inattention	4.2 (2.9)	4.4 (2.7)	−0.2 (−1.1 to 0.8), *P* = .74
Peer relationships	1.9 (2.2)	2.0 (1.8)	−0.1 (−0.8 to 0.6), *P* = .70
Prosocial behavior	8.3 (2.0)	8.4 (1.8)	−0.1 (−0.7 to 0.6), *P* = .80
Impact	1.1 (2.2)	1.2 (1.9)	−0.1 (−0.8 to 0.6), *P* = .81

a *n* = 4 with missing data.
b *n* = 2 with missing data.
c *n* = 1 with missing data.
d *n* = 3 with missing data.
e *n* = 5 with missing data.

26- to 27-week GA subgroup reported more emotional problems compared with the <26-week GA subgroup, but there were no other significant differences.

Rates of Neurobehavioral Impairment

Rates of cognitive, academic, or behavioral impairment were significantly elevated in the EP/ELBW group when judged according to either test norms or the T/NBW distribution (Table 4).

Based on the T/NBW group distribution, 71% of EP/ELBW children had at least 1 mild to severe neurobehavioral impairment, with 47% exhibiting ≥2 impairments (Table 5). In contrast, 42% of the T/NBW group had at least 1 neurobehavioral impairment, with only 16% exhibiting ≥2 impairments.

The actual rates of impairment were lower when based on test norms, but again the EP/ELBW group had higher impairment rates than the T/NBW group.

Discussion

Our EP/ELBW cohort performed significantly below T/NBW peers on all cognitive and academic domains assessed and were elevated on most behavioral scales (reflective of greater difficulties), consistent with previous research.[2] Our findings were robust and remained significant after adjusting for sociodemographic factors and excluding children with neurosensory impairment. In accordance with these results, the EP/ELBW cohort exhibited higher rates of impairments across all domains than the T/NBW cohort. We report impairment rates according to both the T/NBW distribution as well as test norms due to the secular shift in test norms for measures of general intelligence.[17] Our group and others have previously demonstrated that the rate of impairment may be significantly underestimated when determined according to test norms in contrast to local controls,[3,18,19] and, as expected, we found the overall impairment rate to be substantially higher when judged according to the local control group's distribution. Alarmingly, 71% of the EP/ELBW group had at least 1 mild to severe neurobehavioral impairment, with 47% having multiple impairments. However, this rate needs to be interpreted in context, with 42% of the T/NBW group exhibiting at least 1 impairment and 16% displaying multiple problems.

The IQ of our EP/ELBW cohort was 0.8 SD below the T/NBW cohort (adjusted, −0.6 SD). For a cohort born in 1991–1992 in the identical geographic region and assessed by using similar recruitment and follow-up procedures, the group difference in IQ at age 8 years was

TABLE 4 Rates of Cognitive, Academic, and Behavioral Impairment in the EP/ELBW and T/NBW Cohorts According to T/NBW and WISC-IV Normative Distributions

Outcome	EP/ELBW (n = 189)	T/NBW (n = 173)	Test for Trend
General cognitive impairment			
T/NBW distribution (106 ± 12)			
No impairment	49.2	87.1	χ^2 = 52.9, P < .0001
Mild impairment	35.8	10.0	
Major impairment	15.0	2.9	
WISC-IV distribution (100 ± 15)			
No impairment	75.9	94.1	χ^2 = 22.7, P < .0001
Mild impairment	17.6	5.3	
Major impairment	6.4	0.6	
Reading impairment			
T/NBW distribution (106 ± 14)			
No impairment	71.7	85.5	χ^2 = 14.5, P < .001
Mild impairment	19.6	14.0	
Major impairment	8.7	0.6	
WRAT3 distribution (100 ± 15)			
No impairment	81.0	91.9	χ^2 = 10.3, P = .001
Mild impairment	14.7	7.6	
Major impairment	4.3	0.6	
Spelling impairment			
T/NBW distribution (104 ± 14)			
No impairment	73.5	89.5	χ^2 = 16.9, P < .001
Mild impairment	22.9	9.9	
Major impairment	4.3	0.6	
WRAT3 distribution (100 ± 15)			
No impairment	82.7	94.8	Cannot be calculated
Mild impairment	15.1	5.2	
Major impairment	2.2	0	
Arithmetic impairment			
T/NBW distribution (99 ± 14)			
No impairment	72.0	87.2	χ^2 = 14.8, P < .001
Mild impairment	18.1	10.5	
Major impairment	9.9	2.3	
WRAT3 distribution (100 ± 15)			
No impairment	72.0	87.2	χ^2 = 14.8, P < .001
Mild impairment	18.1	10.5	
Major impairment	9.9	2.3	
Behavioral problem			
T/NBW distribution			
Normal	59.6	77.3	χ^2 = 12.3, P < .001
Borderline (80th percentile)	17.5	11.0	
Abnormal (90th percentile)	23.0	11.6	
SDQ norms			
Normal	71.0	86.9	χ^2 = 12.4, P < .001
Borderline (80th percentile)	10.9	6.4	
Abnormal (90th percentile)	18.0	7.6	

Data are presented as %, unless otherwise specified. Distribution values are presented as mean ± SD. Mild impairment for cognitive and academic scales refers to standard scores from −1 to −2 SDs relative to the normative or T/NBW distribution. Major impairment for cognitive and academic scales refers to standard scores less than −2 SDs relative to the normative or T/NBW distribution.

slightly lower (unadjusted, −0.6 SD; adjusted, −0.5).[2] Thus, no improvement in IQ is obvious between the early and late 1990s in the state of Victoria, although it should be noted that the survival rate for the 1997 cohort was higher (63% vs 53%) and included more children born at <26 weeks' GA (34% vs 27%) and with birth weights <750 g (33% vs 20%). The findings from the current study are consistent with a meta-analysis of studies of subjects born before the 1990s, which reported an IQ deficit in the preterm/LBW population of 11 points (0.7 SD),[20] and a more recent review of VP/VLBW population-based studies, which found that in most cases, the mean IQ deficit ranged from 9 to 13 points.[21] A gradient effect has been described in very preterm populations, with IQs declining by 1.7 to 2.5 points with each week's decrease in GA.[20,21] In the current study, the <750-g subgroup had a significantly lower IQ than their heavier EP/ELBW peers, and although failing to reach statistical significance, the <26-week GA subgroup had a lower IQ than the 26- to 27-week GA subgroup.

With regard to WISC-IV indices, the EP/ELBW cohort scored significantly lower than the T/NBW cohort across all domains, suggesting a global cognitive deficit rather than impairments in selective domains, and this result is consistent with our findings in the Victorian Infant Collaborative Study Group (VICS) 1991–1992 cohort.[2] More refined neuropsychological testing may reveal cognitive domains of greater vulnerability; however, current research supports the notion of a global cognitive deficit, with impairments reported in motor skills,[22] processing speed,[23] attention,[24] memory and learning,[25] language,[26] and executive function.[27]

Academic difficulties are consistently reported in EP and VLBW (<1500 g) cohorts.[28,29] The rates of reading and spelling impairment in our EP/ELBW cohort were approximately double the rate observed in the T/NBW cohort. Literacy skills do not seem to be improving in more contemporary EP/ELBW cohorts: the group differences and rates of impairment were marginally lower in the VICS 1991–1992 cohort.[2] As reported previously,[2,29,30] concerns were even greater for the EP/ELBW cohort with regard to arithmetic, as this group scored 0.6 SD below their T/NBW peers. Given the difficulties EP/ELBW children have acquiring rudimentary academic skills, further research is needed to determine the basis for these learning deficits. If

TABLE 5 Distribution of Neurobehavioral Impairments in the EP/ELBW and T/NBW Cohorts Judged According to the T/NBW and Test Normative Distributions

Outcome	EP/ELBW (n = 175)	T/NBW (n = 169)
T/NBW distribution[a]		
No impairment	29.1 (51)	58.6 (99)
1 impairment	24.0 (42)	25.4 (43)
2 impairments	18.3 (32)	7.7 (13)
3 impairments	16.0 (28)	4.7 (8)
4 impairments	7.4 (13)	1.8 (3)
5 impairments	5.1 (9)	1.8 (3)
Test norms[b]		
No impairment	44.6 (78)	69.8 (118)
1 impairment	22.8 (40)	21.3 (36)
2 impairments	16.6 (29)	4.7 (8)
3 impairments	6.8 (12)	1.8 (3)
4 impairments	6.3 (11)	1.2 (2)
5 impairments	2.9 (5)	1.2 (2)

Data are presented as % (n).
[a] χ^2 (linear trend) = 38.4, $P < .0001$.
[b] χ^2 (linear trend) = 37.7, $P < .0001$.

working memory deficits and reduced processing speed underlie academic problems in this population, as has been proposed,[31] adaptive cognitive training interventions for working memory, such as Cogmed,[32] may be effective in reducing educational morbidity. We should be attempting to prevent problems, and this goal may be achieved by introducing programs to ensure these children are school-ready.[33]

It is also accepted that children born EP/ELBW exhibit more behavioral problems.[20,28] The most commonly reported behavioral disorders are inattention, including a diagnosis of attention-deficit/hyperactivity disorder, anxiety, and autism; this cluster of disorders has been proposed to be the "preterm behavior phenotype."[34] Our study supports this behavior phenotype, with problems identified in attention, hyperactivity, and emotional symptoms. Furthermore, our EP/ELBW group displayed more difficulties with peers, reflecting the potential ramifications of cognitive and behavioral problems with forming friendships and more general social functioning. However, notably, there was no group difference in prosocial behavior, indicating that not all areas of social functioning are affected. Finally, within the EP/ELBW cohort, the 26- to 27-week GA subgroup was reported to exhibit more emotional problems by their parents than the <26-week GA subgroup. This finding was unexpected, the only significant difference in this direction, and most likely reflects a chance finding.

Few outcome studies of EP/ELBW children report on large geographic cohorts or achieve follow-up rates in middle childhood of >90%; as such, our results are more generalizable than most of the published research. Furthermore, many outcome studies lack an appropriate control group, without which interpretation of results for EP/ELBW children is impossible. Our study also has limitations. The T/NBW group was matched to the EP/ELBW group in terms of date of birth, gender, mother's country of birth, and health insurance status, yet the control group was more educated and the primary income earner was more likely to have a skilled occupation. In addition, the follow-up rate of the T/NBW group was 87% in contrast to 94% for the EP/ELBW group. To deal with these issues, we adjusted for relevant social demographic factors in secondary analyses, but this action failed to alter any of the statistical conclusions.

CONCLUSIONS

EP/ELBW children born in the late 1990s continue to be significantly disadvantaged compared with T/NBW peers. Approximately 70% of EP/ELBW children experience a cognitive, educational, or behavioral impairment at 8 years of age, and, alarmingly, nearly 50% exhibit multiple areas of concern. The outcomes for those of <750 g birth weight or <26 weeks' GA were similar to those with birth weights of 750 to 999 g or 26 to 27 weeks' GA, respectively. Efforts to reduce this level of morbidity, such as neuroprotective and neurorecovery interventions, need to be encouraged and supported.

ACKNOWLEDGMENTS

This study was conducted by members of the Victorian Infant Collaborative Study Group, including Lex W Doyle, MD, FRACP (Convenor), Royal Women's Hospital, Murdoch Childrens Research Institute and University of Melbourne (Melbourne, Australia); Peter J Anderson, PhD, Murdoch Childrens Research Institute and University of Melbourne (Melbourne, Australia); Catherine Callanan, RN, Royal Women's Hospital (Melbourne, Australia); Elizabeth Carse, FRACP, Monash Medical Centre (Melbourne, Australia); Margaret P Charlton, M Ed Psych, PhD, Monash Medical Centre (Melbourne, Australia); Noni Davis, FRACP, Royal Women's Hospital (Melbourne, Australia); Julieanne Duff, FRACP, Royal Women's Hospital (Melbourne, Australia); Cinzia R De Luca, PhD, Royal Women's Hospital, Murdoch Childrens Research Institute, and University of Melbourne (Melbourne, Australia); Marie Hayes, RN, Monash Medical Centre (Melbourne, Australia); Esther A Hutchinson, DPsychClinNeuro,

Royal Women's Hospital, Royal Children's Hospital, and University of Melbourne (Melbourne, Australia); Elaine Kelly, MA, Royal Women's Hospital and Mercy Hospital for Women (Melbourne, Australia); Marion McDonald, RN Royal Women's Hospital (Melbourne, Australia); Gillian Opie, FRACP, Mercy Hospital for Women (Melbourne, Australia); Gehan Roberts, PhD, FRACP, Royal Women's Hospital and Royal Children's Hospital (Melbourne, Australia); Andrew Watkins, FRACP Mercy Hospital for Women (Melbourne, Australia); Amanda Williamson, MA Mercy Hospital for Women (Melbourne, Australia); Heather Woods, RN Mercy Hospital for Women (Melbourne, Australia).

REFERENCES

1. Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA*. 2003;290(20):2669–2676
2. Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. *JAMA*. 2003;289(24):3264–3272
3. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med*. 2005;352(1):9–19
4. Spittle AJ, Anderson PJ, Lee KJ, et al. Preventive care at home for very preterm infants improves infant and caregiver outcomes at 2 years. *Pediatrics*. 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e171
5. Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risks of <1000-g birth weight for neuropsychological skills, achievement, and adaptive functioning. *J Dev Behav Pediatr*. 2006;27(6):459–469
6. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893–1902
7. Makrides M, Gibson RA, McPhee AJ, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. *JAMA*. 2009;301(2):175–182
8. Orton J, Spittle AJ, Doyle LW, Anderson PJ, Boyd RN. Do early intervention programmes improve cognitive and motor outcomes for preterm infants after discharge? A systematic review. *Dev Med Child Neurol*. 2009;51(11):851–859
9. Doyle LW; Victorian Infant Collaborative Study Group. Evaluation of neonatal intensive care for extremely low birth weight infants in Victoria over two decades: I. Effectiveness. *Pediatrics*. 2004;113(3 pt 1):505–509
10. Doyle LW; Victorian Infant Collaborative Study Group. Evaluation of neonatal intensive care for extremely low birth weight infants in Victoria over two decades: II. Efficiency. *Pediatrics*. 2004;113(3 pt 1):510–514
11. Doyle LW; Victorian Infant Collaborative Study Group. Neonatal intensive care at borderline viability—is it worth it? *Early Hum Dev*. 2004;80(2):103–113
12. Wechsler D. *Wechsler Intelligence Scale for Children—Fourth Version (WISC-IV): Manual*. San Antonio, TX: The Psychological Corporation; 2003
13. Wilkinson, G. *The Wide Range Achievement Test–1993 Edition (WRAT3): Administration Manual*. Wilmington, DE: Wide Range; 1993
14. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38(5):581–586
15. Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatry*. 1999;40(5):791–799
16. Tabachnick B, Fiddell LS. *Using Multivariate Statistics*. 5th ed. Needham Heights, MA: Pearson/Allyn and Bacon; 2007
17. Flynn J. Searching for justice: the discovery of IQ gains over time. *Am Psychol*. 1999;54(1):5–20
18. Wolke D. The cognitive outcome of very preterm infants may be poorer than often reported: an empirical investigation of how methodological issues make a big difference. *Eur J Pediatr*. 1994;153(12):903–915
19. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW; Victorian Infant Collaborative Group. Underestimation of developmental delay by the new Bayley-III Scale. *Arch Pediatr Adolesc Med*. 2010;164(4):352–356
20. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA*. 2002;288(6):728–737
21. Johnson S. Cognitive and behavioural outcomes following very preterm birth. *Semin Fetal Neonatal Med*. 2007;12(5):363–373
22. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2010;52(3):232–237
23. Strang-Karlsson S, Andersson S, Paile-Hyvärinen M, et al. Slower reaction times and impaired learning in young adults with birth weight <1500 g. *Pediatrics*. 2010;125(1). Available at: www.pediatrics.org/cgi/content/full/125/1/e74
24. Anderson PJ, De Luca CR, Hutchinson E, Spencer-Smith MM, Roberts G, Doyle LW; Victorian Infant Collaborative Study Group. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. *Dev Neuropsychol*. 2011;36(1):57–73
25. Taylor GH, Klein NM, Minich NM, Hack M. Verbal memory deficits in children with less than 750 g birth weight. *Child Neuropsychol*. 2000;6(1):49–63
26. Barre N, Morgan A, Doyle LW, Anderson PJ. Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. *J Pediatr*. 2011;158(5):766–774, e1
27. Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics*. 2004;114(1):50–57
28. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics*. 2009;124(2):717–728
29. Johnson S, Hennessy E, Smith R, Trikic R, Wolke D, Marlow N. Academic attainment and special educational needs in extremely preterm children at 11 years of age: the

EPICure study. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(4):F283–F289

30. Taylor HG, Espy KA, Anderson PJ. Mathematics deficiencies in children with very low birth weight or very preterm birth. *Dev Disabil Res Rev*. 2009;15(1):52–59
31. Mulder H, Pitchford NJ, Marlow N. Processing speed and working memory underlie academic attainment in very preterm children. *Arch Dis Child Fetal Neonatal Ed*. 2010; 95(4):F267–F272
32. Klingberg T, Fernell E, Olesen PJ, et al. Computerized training of working memory in children with ADHD—a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2005;44(2):177–186
33. Roberts G, Lim J, Doyle LW, Anderson PJ. High rates of school readiness difficulties at 5 years of age in very preterm infants compared with term controls. *J Dev Behav Pediatr*. 2011;32(2):117–124
34. Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. *Pediatr Res*. 2011;69(5 pt 2):11R–18R

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

School-age Outcomes of Extremely Preterm or Extremely Low Birth Weight Children

Esther A. Hutchinson, Cinzia R. De Luca, Lex W. Doyle, Gehan Roberts, Peter J. Anderson and for the Victorian Infant Collaborative Study Group

Pediatrics 2013;131;e1053
DOI: 10.1542/peds.2012-2311 originally published online March 18, 2013;