Trends in Executive Functioning in Extremely Preterm Children Across 3 Birth Eras

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BACKGROUND AND OBJECTIVES: To determine if executive functioning outcomes at school age are different for extremely preterm (EP; <28 weeks’ gestation) or extremely low birth weight (ELBW; <1000 g birth weight) children born in 1991 to 1992, 1997, and 2005 relative to their term-born peers.

METHODS: Population-based cohorts of all EP/ELBW survivors born in the state of Victoria, Australia, in 1991 to 1992, 1997, and 2005, and contemporaneous controls (matched for expected date of birth, sex, mother’s country of birth [English speaking or not], and health insurance status) were recruited at birth. At 7 to 8 years of age, parents of 613 children who were EP/ELBW and 564 children who were controls rated their children’s executive functioning on the Behavior Rating Inventory of Executive Function (BRIEF). The proportion of children with elevated BRIEF scores (in the clinically significant range) in each birth group and era was compared by using logistic regression. Sensitivity analyses explored these associations after excluding children with intellectual impairment.

RESULTS: Across the eras, EP/ELBW children had higher rates of elevated scores than controls in almost all BRIEF domains. The 2005 EP/ELBW cohort had increased executive dysfunction compared with earlier cohorts, particularly in working memory and planning and organization. This effect persisted after accounting for demographic factors and weakened slightly when those with intellectual impairment were excluded.

CONCLUSIONS: These results indicate a concerning trend of increasing executive dysfunction for EP/ELBW children who were born more recently. This may have adverse implications for other functional domains, such as academic achievement and social-emotional well-being.

WHAT’S KNOWN ON THIS SUBJECT: Extremely preterm children are at risk for difficulties in complex reasoning and goal-oriented skills, or executive functioning (EF). It is unknown whether EF outcomes are improving for preterm children born recently compared with those who were born in the 1990s.

WHAT THIS STUDY ADDS: Extremely preterm children born in 2005 had similar or increased rates of EF problems in everyday life compared with those born in the 1990s. This pattern was not accounted for by medical or demographic differences across the eras.

Dr Burnett contributed to the design of the study, data collection, interpretation of data, drafting of manuscript, and critical revisions of the manuscript; Drs Anderson, Lee, Roberts, Boyle, and Cheong contributed to the design of the study, interpretation of data, manuscript preparation, and critical revisions of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Children born extremely preterm (EP; <28 weeks’ gestation) or with extremely low birth weight (ELBW; <1000 g) are at high risk of cognitive, behavioral, and medical challenges. A gestational age (GA) gradient is recognized, with the most preterm and smallest children at the greatest risk of poor outcomes compared with those born at higher gestations or birth weights (BW). Executive functioning (EF) is an umbrella term referring to a range of high-level cognitive skills needed for goal-directed and adaptive problem-solving and behavior. We have previously described how parents report greater symptoms of everyday EF difficulties in EP/ELBW children than controls in cohorts born in the 1990s. As neonatal care advances and survival of EP/ELBW infants improves, it is critical to monitor the changes in long-term outcomes for this vulnerable population. We have previously identified an encouraging trend in outcomes at age 2 years for infants born in 2005 compared with those born in the early 1990s, with lower rates of severe disability in infants born more recently. Despite these positive early signs, intellectual outcomes do not appear to be improving over time as these children progress further into childhood; indeed, there may be deterioration in academic performance. Importantly, it is unknown whether the lack of improvement in later childhood in preterm children born more recently is restricted to intellectual ability or if it is observed in EF skills such as attention, self-regulation, and planning, which are related to but dissociable from intellectual functioning. EF skills such as working memory are strong, independent predictors of academic achievement, even after accounting for IQ. Furthermore, EF skills emerge across development and cannot be fully assessed in the early years, meaning it is vital to monitor EP/ELBW infants into school age and beyond.

Here, we aimed to compare the prevalence of EF difficulties at school age (ages 7–8 years) relative to matched control groups of children who were term-born and had a normal BW in 3 geographical cohorts of EP/ELBW children born in 1991 to 1992, 1997, and 2005. Because we have observed a deterioration in academic performance in EP survivors from these cohorts, we hypothesized that EP/ELBW children born more recently would have higher rates of executive function problems than those born in earlier eras.

**METHODS**

**Participants**

The EP/ELBW cohorts comprised all survivors with either GA <28 weeks or a BW of <1000 g born in the state of Victoria, Australia, in 3 eras: 1991 to 1992, 1997, and 2005. Survivors received neonatal care in 1 of the 4 neonatal intensive care nurseries in the state and were recruited into these longitudinal studies in the newborn period. For each era, controls were also recruited and comprised infants born with GA ≥28 weeks and/or a BW of ≥2500 g randomly selected from births on the expected date of birth for each EP/ELBW child and matched for sex, the mother’s country of birth (English-speaking or not), and health insurance status (private health insurance or not). All children were invited for follow-up at ages 2 and 7 to 8 years, the outcomes of which have been reported elsewhere. In the current study, we focus on outcomes at the 7- to 8-year assessment. Written informed consent was obtained from parents of all controls and for the 2005 EP/ELBW cohort; follow-up was considered routine clinical care for EP/ELBW children in the earlier cohorts. The studies were approved by the Human Research Ethics Committees at the Royal Women’s Hospital (Melbourne, Australia), Mercy Hospital for Women (Melbourne, Australia), and Monash Medical Centre (Clayton, Australia).

**Measures**

**Background Variables**

Background information during the neonatal period was collected from medical records and included maternal age, antenatal corticosteroid administration, multiple pregnancy, inborn status (ie, birth within a tertiary hospital or not), GA, BW, sex, BW SD score relative to the British Growth Reference, days of assisted ventilation, patent ductus arteriosus (PDA), necrotizing enterocolitis, bronchopulmonary dysplasia (BPD; requiring oxygen or assisted ventilation at 36 weeks’ postmenstrual age), postnatal corticosteroids, major brain injury on cranial ultrasound (grade 3 or 4 intraventricular hemorrhage or cystic periventricular leukomalacia), neonatal surgery, and duration of the primary hospitalization. At each follow-up, children were assessed by using standardized methods by psychologists and pediatricians unaware of the child’s earlier history or results, and parents completed a range of questionnaires. Age was corrected for prematurity to avoid a known bias in cognitive test scores. At age 2 years, moderate to severe disability was identified as any blindness, deafness, moderate to severe cerebral palsy (CP), or delayed development (score ≤−2 SD below the control group’s mean [SD] on the Mental Development.
Index on the Bayley Scales of Infant Development\textsuperscript{20} (1991–1992 and 1997 cohorts)\textsuperscript{21} or on the Cognitive or Language Composite Scales of the Bayley Scales of Infant and Toddler Development, Third Edition (2005 cohort).\textsuperscript{22}

At age 7 to 8 years, psychosocial variables were captured from caregiver interviews, including the level of maternal education, coded as lower relative to the median of the control group within that era (<12 years: 1991–1992 and 1997 cohorts; ≤12 years: 2005 cohort) or higher, language spoken at home (multilingual versus English only), and social class (based on the main income earner’s occupation, categorized as lower [unskilled or unemployed] or higher [semiskilled, skilled, or professional]). Moderate to severe disability at 7 to 8 years was defined as blindness, deafness, moderate or severe CP, or low IQ (score ≥2 SD below the control group mean). IQ measures were full-scale IQ from the Wechsler Intelligence Scale for Children, Third Edition\textsuperscript{23} (1991–1992 cohort) and Fourth Edition\textsuperscript{24} (1997 cohort), and the general conceptual ability score from the Differential Ability Scales, Second Edition\textsuperscript{25} (2005 cohort). IQ is reported as z scores standardized against each era’s control group because the tests differed across eras; control means were weighted to match the distribution of social risk factors in the EP/ELBW groups.

Outcome: EF in Everyday Settings

EF in everyday life was assessed in all cohorts at the 7 to 8 year follow-up by using the parent-completed Behavior Rating Inventory of Executive Function (BRIEF) questionnaire.\textsuperscript{26} The BRIEF comprises 8 scales: inhibit (inhibiting behavior and impulse control), shift (moving between activities or aspects of a problem), emotional control (regulating emotions), initiate (starting tasks and/or activities and independently generating ideas or strategies), working memory (focusing on and holding information in his or her mind to achieve a goal), plan/organize (coordinating and planning current and future task requirements), organization of materials (keeping belongings neat and organized), and monitor (self-monitoring behavior and activity to achieve goals). Three scales (inhibit, shift, and emotional control) form the Behavioral Regulation Index (BRI), and 5 scales (initiate, working memory, plan/organize, organization of materials, and monitor) form the Metacognition Index (MI). The BRI and MI can be summed to create the Global Executive Composite (GEC). Indices and scales are age- and sex-normed to $T$-scores (mean of 50, SD of 10). Potentially clinically significant difficulties are indicated by scores ≥65.\textsuperscript{26}

Data Analysis

Logistic regression models were applied separately to each index and scale to participants with available data at the 7- to 8-year follow-up, including a group (EP/ELBW versus control) by era (1991–1992 vs 1997 vs 2005) interaction term. The 2005 cohort was the reference group. Models were fitted by using generalized estimating equations with an exchangeable correlation structure and are reported with robust SEs to account for the nonindependence of multiple births within families.\textsuperscript{27} Secondary analyses were adjusted for social factors (lower maternal education, lower social class, and multilingual status) because these factors have been associated with outcomes.\textsuperscript{28} Maternal age and child’s corrected age at follow-up were included as covariates in the adjusted models because these differed across eras, as well as multiple birth, antenatal corticosteroid exposure, sex, and BPD as potential confounders. Regression results are presented from the adjusted models. As a sensitivity analysis, models were also run excluding children with IQ scores >2 SD less than the (weighted) control group mean. Because we conducted a number of statistical analyses, we focused our interpretation on the direction and magnitude of effects rather than specific $P$ values.

RESULTS

Sample Characteristics

Retention at ages 7 to 8 years exceeded 80% in all 3 cohorts. EP/ELBW children with and without BRIEF data were similar in most perinatal variables for all 3 cohorts (Supplemental Table 3). In all cohorts, the children in the EP/ELBW groups and the children in the control groups without data tended to have younger mothers than those with data (Supplemental Tables 3 and 4). The EP/ELBW children without data also more often had cranial ultrasound abnormalities and higher rates of moderate to severe disability at 2 years than those with data, with a similar pattern across eras. In Supplemental Table 3, we also show the perinatal characteristics of EP/ELBW participants with BRIEF data across cohorts. Antenatal corticosteroid administration increased in the later cohorts, whereas postnatal corticosteroid use was less frequent in 2005 than earlier. Across the cohorts, maternal age at birth increased and multiple pregnancies decreased in frequency. PDA was more common in 2005 than in 1991 to 1992, but other perinatal and sociodemographic variables were similar across cohorts. The EP/ELBW groups had consistently lower maternal education than controls in each era, although overall maternal education was higher in 2005 than 1991 to 1992 (Table 1). The 2 birth groups had a similar frequency of multilingual households, which was consistent across eras. The
proportion of girls was similar across eras and in both groups. Lower social class was less frequent in 2005 than 1991 to 1992 among controls, but similar across eras in the EP/ELBW groups. The 2005 participants were assessed at a younger average age than the other cohorts, but age at assessment was similar between the EP/ELBW groups and the control groups within each cohort.

Effects of Prematurity on Behavioral EF Across the 3 Eras

In Table 2, we show the percentage of the EP/ELBW groups and the control groups with elevated scores for the BRIEF indices and scales in each era. The proportions with elevated scores were similar across eras for the control groups. More EF problems were shown in the preterm groups compared with controls for all eras for the 3 BRIEF indices (GEC, BRI, and particularly M1; Fig 1A). The group difference was similar in the 1997 and 2005 cohorts, and although the evidence for group difference was stronger in the 2005 cohort, interactions did not reach significance (all P > .05). At the scale level, there was evidence that the preterm groups had more EF problems than controls in most scales, and again, the evidence for the group difference was often stronger in the 2005 cohort than the earlier cohorts. Particularly, there was evidence for a greater difference in the odds of elevated working memory scores between the EP/ELBW groups and the control groups in the 2005 cohort compared with the 1991 to 1992 cohort (unadjusted interaction: P = .07; adjusted interaction: P = .04) and the 1997 cohort (unadjusted interaction: P = .057), although this weakened after adjustment (P = .14). There was evidence that group effects in the plan/organize scale also differed in the 2005 compared with 1991 to 1992 and 1997 cohorts (unadjusted interaction: P = .02 and P = .03, respectively; adjusted interaction: P = .04 and P = .052, respectively). In Fig 1B, we show results of sensitivity analyses excluding children with intellectual impairment. In these analyses, evidence for the group-by-era interaction terms was reduced only slightly for working memory (1991–1992 vs 2005: P = .055) and weakened for the plan/organize scale (1991–1992 vs 2005: P = .16; 1997 vs 2005: P = .16). Overall, however, EP/ELBW children without intellectual impairment had increased odds of elevated scores compared with controls across various BRIEF scales across all eras (Fig 1B).

DISCUSSION

For the first time, we indicate that not only do contemporary EP/ELBW children have greater parent-reported behavioral EF problems compared with their term-born peers, but difficulties in some EF domains may be increasing in EP/ELBW children born in 2005 compared with those born in the 1990s. Specific areas of increasing vulnerability across the eras included working memory and planning and organization. These findings are consistent with our recent report of greater academic difficulties in the 2005 cohort compared with earlier cohorts.12

EF has been identified as an area of vulnerability for preterm children, with a meta-analysis indicating that very preterm (<32 weeks) children perform 0.3 to 0.7 SD below term-born controls on EF tests, which tap shifting, working memory, verbal fluency, inhibitory control, planning, and cognitive flexibility.8,29 Direct assessment and parental ratings of EF do not always concur, however, and both assessment approaches may provide valid but different information about EF in different contexts.30 Parent-rated questionnaires such as the BRIEF capture information about children’s functioning in everyday life, thus providing clinically important data that may not be accessible through direct neuropsychological testing situations.31 Our findings of persistently increased EF difficulties in EP/ELBW children are consistent with another report of school-aged EP children born since 2000, which
also indicated high rates of EF deficits on direct testing.\(^3\)\(^2\)

In the current study, we found a greater difference between EP/ELBW children and children in the control group in working memory problems between the 1991 to 1992 and 2005 cohorts and a greater group difference in rates of planning and organization deficits in the 2005 children compared with both earlier cohorts. Importantly, the 2005 preterm cohort had similar or higher rates of difficulties in all domains of behavioral EF compared with those born in earlier eras. These findings were robust to adjustment for demographic factors known to be associated with neuropsychological outcomes and key biological confounders, such as antenatal corticosteroids, BPD, multiple birth, and sex. However, the reasons for these findings remain unclear; survival was steady from 1997 to 2005, and the 2005 cohort experienced advances in neonatal care that might have positive neurodevelopmental consequences (eg, less postnatal corticosteroid use, less invasive ventilation). Social and biological variables that differed across eras did not account for the era findings, and there have been no dramatic changes to the Australian primary schooling system across the period of interest. Thus, the finding that the most recent EP/ELBW cohort does not have improved EF outcomes and, indeed, appears at higher risk of some specific EF difficulties than those born before deserves further study.

We recently reported that the rate of major disability at school age (predominantly comprising intellectual impairment) is not improving in the 2005 EP group.

### TABLE 2 Rates of Elevated Scores on BRIEF Indices and Scales by Era and Birth Group

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<tr>
<td></td>
<td>EP/ELBW</td>
<td>Control</td>
<td>EP/ELBW</td>
</tr>
<tr>
<td></td>
<td>n = 246 (%)</td>
<td>n = 208 (%)</td>
<td>n = 184 (%)</td>
</tr>
<tr>
<td>GEC</td>
<td>32 (13)</td>
<td>17 (8)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>BRI</td>
<td>32 (13)</td>
<td>17 (8)</td>
<td>23 (13)</td>
</tr>
<tr>
<td>MI</td>
<td>37 (15)</td>
<td>14 (7)</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Inhibit</td>
<td>26 (11)</td>
<td>16 (8)</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Shift</td>
<td>28 (11)</td>
<td>11 (5)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Emotional control</td>
<td>34 (14)</td>
<td>16 (8)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Initiate</td>
<td>37 (15)</td>
<td>16 (8)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Working memory</td>
<td>50 (20)</td>
<td>18 (9)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>Plan and organize</td>
<td>35 (14)</td>
<td>24 (12)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Organization of materials</td>
<td>32 (13)</td>
<td>26 (13)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Monitor</td>
<td>23 (9)</td>
<td>7 (3)</td>
<td>13 (7)</td>
</tr>
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Data are n (%).

### FIGURE 1

Adjusted odds (95% confidence interval) of elevated scores on BRIEF indices and scales by era for EP/ELBW groups compared with controls. A, All participants. B, Excluding children with IQs < −2 SD. Note, x-axis is in log scale. These models covary for antenatal corticosteroids, multiple birth, sex, BPD, lower maternal education (relative to within-era controls), lower social class, maternal age, language spoken at home, and child’s corrected age at follow-up.
compared with previous eras, and some aspects of academic performance are poorer in the 2005 EP group.12 Those findings were not accounted for by postnatal corticosteroids, brain injury, neonatal surgery, or demographic factors. With the present findings, we may provide insights into the cognitive substrates of this decline in academic performance, although we do not yet understand the deeper mechanisms driving these findings. Our results are also concerning because we have recently shown that EP/ELBW children exhibit poorer EF than controls into at least late adolescence,23 and although poor childhood EF resolves for some, persistent EF difficulties are associated with reduced academic achievement in adolescence.24 With this finding, we suggest that longer-term EF and academic outcomes in our most recent preterm survivors may also be worse than in those from earlier eras.

EF represents complex cognitive skills that rely on other cognitive domains to operate optimally. For instance, some have found that executive difficulties in preterm children occur secondarily to reduced information processing speed,35 whereas others report persistent executive difficulties after controlling for processing speed and IQ.7 In our sensitivity analyses, the evidence for a worsening effect of prematurity in the most recent era weakened somewhat after excluding those with intellectual impairment, suggesting that more global cognitive difficulties may be contributing to planning and organization difficulties. However, the 2005 cohort appears to be more vulnerable to working memory difficulties relative to the 1991 to 1992 cohort, even after excluding those with low IQ, with increased rates of difficulties observed in preterm children within eras for various BRIEF scales. Further research is required to determine the contribution of other cognitive domains to the EF difficulties parents reported in EP/ELBW children in this study.

Strengths of the current study include the fact that we are the first to examine EF across 3 distinct eras in complete geographical cohorts of EP/ELBW group and control group children recruited and assessed with identical methods. Retention rates were high across all cohorts, and we were able to characterize those lost to follow-up and include important potential confounders in analysis. We employed the same questionnaire in all cohorts to examine EF in everyday life, allowing direct comparison of birth eras. We also acknowledge some potential limitations. The 2005 cohort was seen at a slightly younger age than the other cohorts. Although EF develops into young adulthood,36 the BRIEF T-scores are age-normed, the 2005 EP/ELBW group and the control group had similar ages at follow-up, and covarying for age did not substantially alter the pattern of findings. With this finding, we suggest that the stable or increasing difficulties in the 2005 cohort were not an artifact of their younger age at assessment. Nonetheless, future follow-up is essential given the protracted development of EF and the potential for at least some EF skills, such as inhibitory control, to “catch up” in preterm children.7,37 In terms of demographic characteristics, the 2005 control group tended to be of higher social class than earlier control groups, and the duration of maternal education increased over time, although it did so similarly in the preterm and control groups, and adjusting for these factors did not substantially alter the findings. Finally, we have focused on parental ratings of EF in everyday settings rather than objective EF assessments, and these 2 paradigms may provide distinct information about children’s abilities.31 Future studies would benefit from including both parent-report and direct testing of EF and other aspects of behavior to holistically assess functioning.

CONCLUSIONS

In this study, we have revealed a concerning trend for a decline in some EF outcomes for EP/ELBW survivors compared with term-born peers, which has implications for clinical and research practice. Close monitoring of this and other contemporary EP/ELBW cohorts is essential to determine if these findings represent delay or deviation in the maturation of executive skills, whether currently unknown clinical features account for the trend observed, and whether EF difficulties are a primary or secondary cognitive deficit in preterm children. These findings also have implications for academic and psychosocial functioning in preterm children. Clinically, EP/ELBW children should be engaged in follow-up services beyond toddlerhood, as complex cognitive skills continue to emerge and mature.

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The collaborators were convened by Jeanie Cheong, MD, Royal Women’s Hospital (Melbourne, Australia), Murdoch Children’s Research Institute (Melbourne, Australia), and University of Melbourne (Melbourne, Australia).

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