School-aged neurodevelopmental outcomes for children born extremely preterm

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Jeanie Ling Yoong Cheong 1,2

ABSTRACT
As survival rates for children born extremely preterm (EP, <28 weeks’ gestation) have increased with advances in perinatal and neonatal care, their long-term functioning and quality of life assume more importance. Outcomes in early childhood provide some information, but outcomes at school-age are more informative of lifelong functioning. Children born EP at school-age have substantially higher rates of intellectual impairment, poorer executive, academic and motor function, more neurodevelopmental disability, and poorer health-related quality of life than do contemporaneous term-born controls. Because the rates of adverse outcomes remain unacceptably high, and particularly since some outcomes may be deteriorating rather than improving over time, new strategies to ameliorate these problems, targeting periods before, during and after birth, and throughout the lifespan, are a priority.

Survival rates for children born extremely preterm (EP, <28 weeks’ gestation) have improved dramatically, from <10% fifty years ago, before the advent of modern neonatal intensive care, to close to 90% for those offered intensive care today. Consequently, their long-term health and functioning assume increasing importance. Studies in the first few years after birth provide critical information on early development, but do not relate well to functioning at school-age and beyond because important outcomes such as general intelligence (IQ), executive function and motor coordination cannot be reliably assessed. Moreover, it is important to determine long-term outcomes to understand whether delays in early childhood evolve into long-term neurodevelopmental impairments, or the children ultimately improve and ‘catch-up’ with their peers.

Our aim in this article is to review data on important functional outcomes at school-age, including IQ, executive function, academic achievement, motor performance, neurodevelopmental disability, and health-related quality of life of children born EP since 1990, the post-surfactant era. In particular, we want to document if these outcomes are changing over time, in parallel with advances in neonatal intensive care and improving survival rates for children born EP. We will focus only on some major neurodevelopmental outcomes, but acknowledge that other outcomes such as behaviour, respiratory function, growth or general health are important, but outside the scope of the present review; however, their effects will indirectly be reflected in quality of life measures, which are included in this narrative review.

METHODODOLOGICAL ISSUES
The most accurate data on school-age outcomes for populations of children born EP will come from complete cohorts from defined geographical regions that capture all births. More selective cohorts, such as those derived from single hospitals or networks of hospitals, or from randomised controlled trials of specific interventions during pregnancy or after birth, have selection filters which can result in bias by excluding individuals or subgroups from whole populations who have systematically different outcomes.

Other desirable methodological issues include recruitment of contemporaneous term-born controls to compare outcomes with those born EP to allow for different versions of test instruments and to avoid the known drift in test scores over time, known as the ‘Flynn effect’. Participants should be assessed blind to knowledge of birth group. Follow-up needs to be long enough (i.e., past early childhood) to determine important outcomes, and as complete as possible because those who are not followed will have higher rates of cognitive problems than those who are otherwise assessed.

What is already known?
► There are many individual studies that have reported on neurodevelopmental outcomes in school-aged children who were born extremely preterm.
► Most have reported single outcomes and have come from disparate sources.

What this study adds?
► This study synthetises data from multiple sources on multiple neurodevelopmental outcomes in school-aged children who were born extremely preterm.
► The review focuses on studies from complete geographical cohorts.
► It also address the issue of whether multiple neurodevelopmental outcomes in school-aged children who were born extremely preterm are improving or not over time.
The Victorian Infant Collaborative Study (VICS) Group has recruited three cohorts of children born EP in the state of Victoria from three discrete eras since surfactant was introduced into clinical practice in 1991. These cohorts were born in 1991–1992, 1997 and 2005, and they have all been assessed at school-age (around 8 years of age). Each cohort has a contemporaneous control group born at term who have been assessed simultaneously by trained personnel, blinded to group allocation. We will use data from these cohorts to illustrate the extent of problems faced by children born EP when they reach school-age, and to address the issue of whether outcomes are improving or deteriorating over time. For comparable data from other regions, we will focus on studies with geographically defined cohorts who have been compared with contemporaneous controls born at term.

For individual outcomes of interest, we will also rely on recently completed systematic reviews, as identified in PubMed, rather than repeating systematic reviews ourselves, which are beyond the scope of this review.

**GENERAL INTELLIGENCE (IQ)**

Numerous test batteries of general intelligence or general cognitive ability can provide an estimate of IQ. In a systematic review and meta-analysis of 71 studies of children born after 1990, Twilhaar et al. recently reported that children born either <32 weeks’ gestation or <1500 g birth weight had a standardised IQ score at 5 or more years of age of −0.86 SD (95% CI −0.94 to −0.78, p < 0.001) compared with children born at term. With an SD of 15, this translates into a mean IQ difference of −12.9 (95% CI −14.1 to −11.7). Another systematic review published in the same year comprising 44 individual studies concluded that children aged between 4 and 17 years who had been born <32 weeks’ gestational age had an IQ of −0.82 SD (95% CI −0.90 to −0.74) compared with controls. Although the latter systematic review explicitly excluded studies that selected on birth weight alone, the two reviews included many of the same studies, and hence the results are similar. Neither systematic review reported results for EP subgroups alone. Another systematic review of cognitive scores in children born preterm reported a Full Scale IQ standardised mean difference (SMD) of −0.78 (95% CI −0.85 to −0.72) in a subgroup of 2136 children born EP compared with 1829 children born at term, which translates to a mean IQ difference of −11.7 (95% CI −12.8 to −10.8). The latter review included a wide age range, but the mean differences were not substantially different between preterm and control groups across subgroups 2–4 years, 4–11 years, 11–18 years and >18 years.

Data have been reported from six geographical cohort studies of children born EP or more immature after 1990 where cognitive scores at 5 or more years of age have been compared with term-born controls (table 1). The mean differences between EP and control groups from these studies are either similar to or wider than those in the systematic reviews, described previously. Moreover, proportions with intellectual impairment (IQ < −2 SD) were much higher in those born EP (10%–41%) compared with controls (0%–3%).

The differences between EP and control groups in table 1 look wider in studies outside of Australia compared with the Australian studies. This is likely due in part to the UK and Swedish EP cohorts being less mature; IQ is lower in more immature infants compared with more mature infants within the <28-week gestational age range. Also, the non-Australian studies, unlike the Australian studies, did not correct age for prematurity. Adjusting for prematurity reduces a known bias in cognitive test scores. For a 6-year-old child born at 23 weeks, not adjusting for prematurity would lower a corrected IQ of 100 by approximately 8 points. Adjustment for prematurity is not mentioned in any systematic review but was probably rare among the pooled studies.

From Victorian data over three discrete eras, the mean differences in IQ between children born EP and controls within each era were similar (table 1).

**EXECUTIVE FUNCTION**

While children born EP have been reported to have poorer functioning than children born at term across most domains of cognition, executive function (EF) has been a particular focus of research. EF refers to higher-order cognitive skills necessary for completing goal-oriented activities, and includes attentional control, cognitive flexibility, reasoning ability, and planning and organisation.

A 2009 systematic review of 12 studies containing EF data obtained at ages 7–23 years reported that working memory, cognitive flexibility and verbal fluency were all lower by 0.36 to 0.57 SD in children born either <34 weeks or <1501 g compared with controls. Data were not separately reported for the EP subgroup or at school-age only. In a subsequent systematic review and meta-analysis of 34 studies of EF at ages 4–17 years in 3701 children born <32 weeks’ gestation, mean scores on various tests of EF were lower by −0.51 SD (95% CI −0.58 to −0.44) compared with 2921 controls.

The VICS group has reported the results of executive functioning rated by parents on the Behavior Rating Inventory of Executive Function at 8 years of age for 613 children born EP or extremely low birth weight (<1000 g) in Victoria in 1991–1992, 1997 and 2005, and 564 contemporaneous matched controls. Children born EP/extremely low birth weight (ELBW; <1000 g) had higher rates of executive function impairments.

### Table 1: Cognitive scores of children born EP compared with controls from geographically defined cohorts from different countries

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Years of birth</th>
<th>GA (weeks)</th>
<th>Age assessed (years)</th>
<th>IQ Mean (SD)</th>
<th>Control</th>
<th>Mean difference (95% CI)</th>
<th>&lt;−2 SD</th>
<th>(%)</th>
<th>Control (%)</th>
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<tbody>
<tr>
<td>Australia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1991–1992</td>
<td>23–27</td>
<td>8.7</td>
<td>94.9 (16.5) n=198</td>
<td>104.7 (14.1) n=212</td>
<td>−8.0 (−10.9 to −5.1)*</td>
<td>14.3</td>
<td>2.7</td>
<td></td>
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<tr>
<td>1997</td>
<td>22–27</td>
<td>8.4</td>
<td>93.8 (14.7) n=133</td>
<td>105.6 (12.4) n=170</td>
<td>−10.5 (−13.8 to −7.1)*</td>
<td>9.9</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>22–27</td>
<td>7.7</td>
<td>94.7 (15.7) n=137</td>
<td>107.2 (10.9) n=189</td>
<td>−10.2 (−13.3 to −7.1)*</td>
<td>13.6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK and Ireland&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1995</td>
<td>22–25</td>
<td>6.3&lt;sup&gt;t&lt;/sup&gt;</td>
<td>82.1 (19.2) n=241</td>
<td>105.7 (11.8) n=160</td>
<td>−24.0 (−27 to −20)</td>
<td>40.7</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>France&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1997</td>
<td>24–27</td>
<td>5&lt;sup&gt;t&lt;/sup&gt;</td>
<td>90.0 (18.7) n=223</td>
<td>106.4 (17.8) n=320</td>
<td>−16.4 (−17.9 to −14.8)</td>
<td>17.9</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Sweden&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2004–2007</td>
<td>22–26</td>
<td>6.6&lt;sup&gt;t&lt;/sup&gt;</td>
<td>83.4 (14.8) n=371</td>
<td>100.3 (11.7) n=367</td>
<td>−14.2 (−16.3 to −12.1)*</td>
<td>32.1</td>
<td>2.2</td>
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</table>

<sup>a</sup>Adjusted for sociodemographic variables.

<sup>t</sup>Age not corrected for prematurity.

<sup>EP</sup>, extremely preterm; <sup>Gs</sup> gestational age.


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problems compared with controls, but the differences were greatest between EP/ELBW and control groups for the 2005 cohort. Within specific domains, the 2005 cohort had particular problems with working memory, and planning and organisation. Poorer EF in children born EP/ELBW persisted into adolescence (mean age 17 years) for the those born in 1991–1992 compared with controls; at 17 years, they had worse functioning in verbal processing speed, attentional control, cognitive flexibility and goal-setting (effect sizes, −0.7 to −0.2 SD). In the same cohort, persistence of EF difficulties from early school-age to adolescence in children born EP/ELBW was associated with poorer academic achievement in adolescence.22

ACADEMIC ACHIEVEMENT
In a systematic review of 17 studies comparing 2390 children born preterm with 1549 controls where children were at least 5 years of age, preterm children had lower scores for arithmetic (SMD −0.71), reading (SMD −0.44) and spelling (SMD −0.52), but results were not reported for children born EP alone.23 With a SD of 15, these differences convert to −10.6 for arithmetic, −6.6 for reading and −7.8 for spelling.

The VICS group have reported academic achievement at 8 years of the three discrete cohorts of children born EP and controls, described previously. Not only do children born EP have poorer performance on tests of academic achievement than do controls born at term, the gap is widening over time (table 2). Moreover, the mean differences for the Victorian cohort born in 2005 well exceed those in the systematic review. For example, the Victorian children born EP in 2005 performed −0.8 SD lower than term controls on tests of reading, spelling and mathematics, with rates of specific learning difficulties (<−2 SD) ranging from 14% for spelling to 23% for mathematics. Not surprisingly, children born EP are more likely to need educational remediation and repeat grades in school.20

Table 2 Academic achievement at 8 years for extremely preterm and control groups born in the state of Victoria, contrasted over different eras

<table>
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<tr>
<td></td>
<td>EP</td>
<td>Control</td>
<td>EP</td>
</tr>
<tr>
<td>Word reading</td>
<td>96.2 (16.4) n=200 103.1 (14.6) n=211</td>
<td>97.1 (16.9) n=133 105.5 (13.8) n=168</td>
<td>94.1 (17.1) n=140 109.4 (14.2) n=189</td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>−5.5 (−8.5 to −2.4)</td>
<td>−8.1 (−11.8 to −4.5)</td>
<td>−12.3 (−16.0 to −8.5)</td>
</tr>
<tr>
<td>Spelling</td>
<td>93.8 (12.9) n=199 99.7 (13.2) n=210</td>
<td>96.4 (16.0) n=134 104.2 (14.5) n=168</td>
<td>93.9 (17.6) n=138 108.6 (15.2) n=188</td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>−4.8 (−7.3 to −2.3)</td>
<td>−7.7 (−11.3 to −4.1)</td>
<td>−12.0 (−15.9 to −8.2)</td>
</tr>
<tr>
<td>Mathematics</td>
<td>88.8 (14.3) n=197 97.9 (13.6) n=211</td>
<td>89.9 (17.5) n=131 99.0 (14.5) n=168</td>
<td>89.4 (18.9) n=140 105.1 (13.4) n=188</td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>−8.3 (−10.9 to −5.6)</td>
<td>−9.1 (−12.9 to −5.3)</td>
<td>−13.1 (−16.9 to −9.2)</td>
</tr>
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*Allowing for clustering for multiple births, and adjusted for age of the child at assessment, mother’s age at birth of the child and sociodemographic variables.

Non-CP motor impairment
Non-CP motor impairment in very preterm children has been systematically reviewed on several occasions. De Kieviet et al22 reported that mean scores on standardised motor tests were up to 0.65 SD lower in children born <33 weeks’ gestation or <1501 g birth weight at school age compared with controls. Williams et al24 reported a pooled estimate for mild–moderate non-CP motor impairment in children born preterm of 40%, and for moderate motor impairment a rate of 19%. Neither systematic review reported results for children born EP only.

For the Victorian cohorts of births in 1991–1992, 1997 and 2005, Spittle et al24 reported that motor impairment at school-age for children born EP/ELBW was substantially worse than in contemporaneous controls, and that the gap was widening over time between cohorts. Since the rates of CP were relatively stable over time, as described previously, the deterioration in motor function resulted from an increase in non-CP motor impairment in survivors born EP/ELBW, from 13% in 1991–1992, to 15% in 1997, and to 26% in 2005. While the reasons for this increase in so-called ‘milder’ motor impairments are unknown, motor competence of children is decreasing globally as a result of increased sedentary behaviour and reductions in physical activity over time.25

MAJOR NEURODEVELOPMENTAL DISABILITY
Combining some of the previous outcomes, the overall rates of major neurodevelopmental disability at school-age, generally defined as any of an IQ <−2 SD, CP that is more than just mild, blindness or deafness in six geographical cohorts are shown in table 3.7–10 To parents, these outcomes translate into substantial problems for their child with thinking, walking, talking, seeing or hearing, and range from approximately 1-in-5 to 2-in-5. These rates cannot be interpreted fully without understanding that 1-in-5 to 2-in-5 controls born at term also have these problems.

HEALTH-RELATED QUALITY OF LIFE
Zwicker and Harris26 systematically reviewed studies reporting health-related quality of life (HRQOL) from infancy to early adulthood, reporting that HRQOL was worse in children born preterm or very low birth weight than controls when they were younger, but differences between the groups diminished with age. The review contained only one study when children were 8 years of age, and four studies of teenagers between 12 and 16 years. The median QoL score for controls was −0.49 (IQR −0.79 to −0.19) in the systematic review, which was substantially lower than what VICS reported for births in 2005.
years of age; the other studies included in the review were either preschool-age (<5 years) or young adults (18 or more years of age). They did not report differences specifically for children born EP at school-age compared with controls.

In the first school-age report of quality of life, Saigal et al27 studied 136 8-year-olds who were born between 1977 and 1982 weighing <1001 g, and 145 controls. Utilities were obtained from community preference values for various health states. Children born <1001 g had lower overall utility scores as well as more limitations in cognition, sensation, mobility and self-care than did controls, but not in emotion or pain. Gire et al28 reported that HRQOL of 301 8-year-old children born <28 weeks’ gestation in 2004–2007 and free of major disabilities was worse than that in the French population as a whole. Interestingly, children born EP identified more problems with relationships with friends, self-esteem and leisure than did control children, whereas parents of children born EP identified more problems with psychological well-being, schoolwork and vitality than did parents of controls.

HRQOL at 8 years of age in 475 children born EP in the state of Victoria was compared with 570 contemporaneous term controls over the three eras 1991–1992, 1997 and 2005.29 In all eras, parent-reported median utilities were lower by more than 0.05 for children born EP compared with controls, a clinically important difference on a scale that ranges from 1 for perfect health to 0 for death. Mean differences (MDs) between EP children and matched controls within each era were lower in the 2005 cohort compared with both the 1991–1992 cohort (MD −0.054, 95% CI −0.097 to −0.010) and the 1997 cohort (MD −0.053, 95% CI −0.097 to −0.009), which suggests that parent-reported HRQOL may be deteriorating over time.

Findings are more variable when assessing HRQOL in adolescents and young adults born preterm or low birth weight; results have been synthesised in several different reviews.30 31 At these older ages, most studies report no substantial differences in HRQOL between those born preterm or low birth weight and controls, particularly if the participant was reporting on their own HRQOL. Although the Victorian cohort born EP in 1991–1992 cohort had lower utility scores than controls at 8 years on parental report, when they were 18 years of age their HRQOL on self-report was similar to controls.31

### CLINICAL IMPLICATIONS

An understanding of the range of outcomes at school-age for children born EP will help clinicians and families when making decisions about care at critical timepoints. An early timepoint is typically around the time of birth, when knowledge of long-term problems may influence a decision to not embark on intensive care for an infant born EP. There may be other potentially life-changing events that occur during the newborn hospital stay where decisions to cease intensive care might arise. Organising the transition to home, including providing early intervention both in the nursery and after discharge home is informed by knowledge of the various school-age outcomes that are possible.

Although CP may be decreasing in infants born EP,1 it is important for clinicians to be aware that other motor impairments can have a substantial impact on a child at school age and on their family’s function. Children with milder challenges at school age are the ones who are often missed, or who have diagnoses delayed, and hence struggle to access assistance. Clinicians need to remember that the school-age problems that they would like to avoid most for the child, such as CP or intellectual impairment, may not be the problems that might concern the parents or the child themselves; the latter groups might be more concerned with future happiness and peer relationships, for example, rather than more specific medically-defined impairments.

Understanding a range of important school-age outcomes can help to target interventions more specifically. They are also important endpoints to consider for monitoring the effectiveness of interventions, particularly from randomised controlled trials. However, obtaining funding for school-age outcomes for perinatal trials is difficult because of the long time frame involved. Increasingly, the importance of choosing the most important outcomes for the child and their family is being recognised. Rather than using traditional measures of cognitive and motor development such as rates of intellectual impairment and CP as end points of trials, outcomes such as quality of life and well-being may be considered. Many interventions may not be able to change a diagnosis, such as CP or autism spectrum disorder, but can still improve the functional outcomes for these children, resulting in better peer-friendships or increased participation in physical activity. Involving consumers, both children born EP and their families, in the design of research trials from the beginning will ensure research is focused on improving outcomes that are meaningful for both clinicians and the families and children themselves.

Because the rates of adverse outcomes at school-age are too high in children born EP, and particularly since some outcomes may be deteriorating rather than improving over time,7 16 24 strategies before, during and after birth, including after discharge home, through infancy and into school-age to ameliorate these problems must be developed. Financial support for new trials may require separate grant applications, but we must persist to optimise the outcomes for our most vulnerable children and their families.
Correction notice  This article has been amended since it was published online. In the previous version, in table 1, the upper confidence intervals for mean differences all lost their minus signs. The article has since been corrected.

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