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# Have outcomes following extremely preterm birth improved over time?

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ABSTRACT

Increased survival of infants born preterm, especially those born extremely preterm (< 28 weeks' gestation), has meant that more are reaching later childhood and adulthood. As preterm birth is associated with a higher risk of neurodevelopmental deficits, the aim of this review was to determine whether or not the advances in perinatal care that led to improved survival have also had a positive impact on long-term neurodevelopment. Studies examining temporal changes in neurodevelopment are limited, and only from high-income countries. However, based on available published data, there is no definite trend of improved neurodevelopment at school age for neurosensory, cognitive, academic achievement, motor or executive function with time. Cerebral palsy rates, however, may be decreasing. More research is needed into the potential contributors for the trends observed, and also for other outcomes such as mental health and behavior.

## 1. Introduction

The rates of preterm birth (< 37 completed weeks' gestation) have risen worldwide. Time trends from 65 countries over the period from 1990 to 2010 reported that overall preterm birth rates had increased from 7.5% to 8.5%, a relative rise of 14.7% [1]. The largest increase in preterm birth rates was noted in the Caribbean, followed by many high-income countries and Latin America [1]. A more recent report from the World Health Organisation (WHO) estimated preterm birth rates worldwide to be as high as 10.6% of live births [2]. In Australia, preterm birth rates have increased from 6.8% in 1991 [3] to 8.7% in 2017 [4]. With advances in neonatal intensive care, survival of infants born extremely preterm (EP; < 28 weeks' gestation) has increased substantially in the last few decades [5–8]. As EP survivors have a higher risk of health and developmental problems compared with those born full term [9], it is imperative to understand whether or not the advances in neonatal intensive care have also led to improved long-term health and neurodevelopment. Unfortunately few randomized-controlled trials of new perinatal interventions examine health and developmental outcomes beyond early childhood, resulting in many interventions being integrated into clinical practice with little or no evidence of the long-term developmental effects. It is therefore critical to appraise long-term neurodevelopmental data from cohort studies that have repeatedly assessed these outcomes to assess the effects of changing perinatal care on whole populations.

We start this review with a brief historical summary highlighting the critical advances in modern perinatal care. This will be followed by appraising whether different domains of neurodevelopment in those born preterm have changed over time.

## 2. Advances in perinatal intensive care

Long-term survival rates of EP or extremely low birth weight (ELBW, < 1000 g birthweight) infants prior to the 1970s were typically less than 10% in whole populations, but rose from around 1-in-4 in the late 1970s to 3-in-4 by the late 1990s[10]. The most important cause of mortality for EP/ELBW infants before the 1970s was respiratory failure related to respiratory distress syndrome, which is primarily caused by surfactant deficiency. Then came several innovations that led to a reduction in mortality associated with respiratory distress syndrome.

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Continuous positive airway pressure and mechanical ventilation were introduced in the late 1960s to early 1970s [11]. Antenatal corticosteroids, first reported to be of benefit in reducing respiratory distress syndrome in a randomized controlled trial in humans in 1972 [12], have subsequently been proven to reduce some of the most serious adverse outcomes related to preterm birth, including mortality, severe respiratory distress syndrome, intraventricular haemorrhage and necrotizing enterocolitis [13]. The early 1990s saw another major advance with the introduction into clinical practice of exogenous surfactant to treat respiratory distress syndrome [14]. Coupled with the increased willingness of neonatologists to offer intensive care to EP/ELBW babies, survival rates soared, as described above.

Since the 1990s, there have been additional refinements to practice, which have resulted in further improvements in survival, although not of the magnitude seen with the earlier innovations in care. Avoidance of the liberal use of postnatal corticosteroids to treat or prevent bronchopulmonary dysplasia came about in the early 2000s following evidence of associations with increased rates of cerebral palsy [15,16]. Oxygen targeting was revised following results of several large international randomized-controlled trials, with higher oxygen saturation targets associated with a better survival than lower oxygen saturation targets, although at a cost of increased retinopathy of prematurity [17]. The long-term consequences relating to the wide adoption of newer modes of respiratory support, the increasing use of non-invasive respiratory support, and caffeine to treat apnea of prematurity are yet to be evaluated outside of randomized-controlled trials. Antenatal magnesium sulphate has been shown to be effective for fetal neuroprotection [18], but its uptake has been variable worldwide, with non-receipt rates ranging from 22.5% to 40% [19–21]. Thus its impact on long-term neurodevelopment at a population level is still unknown.

## 3. Survival

Survival of infants born EP/ELBW worldwide has increased. In Victoria, Australia, the survival rates to 8 years for the Victorian Infant Collaborative Study (VICS) cohorts of EP newborns rose from 53% in 1991–92 to 70% in the 1997 cohort, but fell to 63% for the 2005 birth cohort [5]. The EPICure study in the United Kingdom assessed two cohorts of infants born almost 10 years apart; the first comprised infants born between 22 and 25 completed weeks' gestation in the birth year of 1995, and subsequently EPICure 2 for births in 2006 of infants born between 22 and 26 completed weeks' of gestation. They reported an increase in survival from 39% (95% confidence interval [CI] 35%, 43%) in 1995 to 52% (95% CI 49%, 55%) in 2006, an absolute increase of 13% (95% CI 8%, 18%) [22]. However it is interesting to note that variation exists within regions in the United Kingdom. A recent report from the National Neonatal Research Database comparing infants born 22–31 completed weeks' of gestation from 2008 to 2014 reported an overall increase in survival from 88.0% to 91.3%, with the best improvements noted in the London and South of England regions [23].

The National Institute of Child Health and Human Development Neonatal Research Network in the USA compared survival and neurodevelopmental outcomes at 18–22 months' corrected age in infants born 22 to 24 completed weeks' gestation across three birth year epochs: 2000–2003 (epoch 1), 2004–2007 (epoch 2), 2008–2011 (epoch 3). Survival increased between epochs from 30% in epoch 1–36% in epoch 3, with the greatest difference seen in the infants born at 24 weeks compared with the more immature infants [24]. The authors attributed these changes to improvements in obstetric and neonatal care, which included proactive perinatal management.

The EPIPAGE study in France also recruited 2 cohorts over time, EPIPAGE (1997 births) and EPIPAGE-2 (2011 births). The inclusion was different between cohorts; in the original EPIPAGE study, only 9 French regions were included compared with 25 (of the 26) regions in EPIPAGE-2 [25]. Survival to 2 years' corrected age for livebirths born 22–31 weeks' gestational age in the 9 regions that participated in both EPIPAGE and EPIPAGE-2 increased from a mean of 79.4%–84.1% (adjusted mean difference 6.0%; 95% CI 3.5%, 8.5%; $p < 0.001$) [25].

In Sweden, the one-year survival among *all liveborn* infants at 22–26 weeks' gestational age had increased from 70% in 2004–2007 to 77% in 2014–2016 [6]. However, when considering survival amongst infants who were admitted to the neonatal intensive care unit, the rise did not reach statistical significance (from 78% to 82%, $p = 0.07$) [6]. The authors of the study attributed the rise in survival between epochs to a change in national recommendations for more active management of extremely preterm infants between the study periods [6]. In fact, the increased willingness to offer intensive care to extremely preterm newborns is an important contributing factor to the rise in survival rates in high-income countries.

There are less data available from other countries. A population-based study collected by the Israel Neonatal Network reported an increase in survival to hospital discharge in infants born very low birthweight (≤1500 g) from 79.8% in 1995–2000 to 86.2%% in 2006–2010 [26].

## 4. Neurodevelopmental outcomes

Neurodevelopmental outcomes include cerebral palsy, vision, hearing, and general cognition. This section will focus on studies that have reported composite neurodevelopmental outcomes, whereas subsequent sections will detail the individual outcomes of cerebral palsy and cognitive development. Younge et al. [24] reported outcomes at 18–22 months of infants born 22–24 completed weeks who were cared for at 11 tertiary academic neonatal centres in the USA. Survival without *neurosensory* impairment increased to a mean of 29% (95% CI 27%, 32%) in the most recent epoch (2008–2011) compared with the first epoch (2000–2003, mean 25% [95% CI 22%, 27%]) [24]. Neurosensory impairment was defined as moderate-to-severe cerebral palsy (Gross Motor Function Classification Scale of 2 or greater), profound hearing loss (requiring amplification), or profound visual impairment (less than 20/200 in both eyes). In addition, the study also reported outcomes of survival without *neurodevelopmental* impairment, which was defined as *neurosensory* impairment and/or cognitive impairment, the latter defined as a Mental Developmental Index score of < 70 (< 2 standard deviations [SD] on the Bayley-II) or a Cognitive Composite score of < 85 (< 1 SD on the Bayley-III). The conclusions were similar in that survival without neurodevelopmental impairment increased over the three epochs.

The VICS study in Australia also reported outcomes at 2 years' corrected age for 3 cohorts from the early 1990s. Rates of *any* neurosensory disability were similar across eras but the latest cohort of 2005 births had significantly lower rates of *severe* developmental delay and *severe* neurologic disability than earlier cohorts of 1997 and 1991–92 (Rates of *severe* developmental delay: 7.3% (1991–92), 14.8% (1997), 3.7% (2005); rates of *severe* disability: 7.8% (1991–92), 15.4% (1997), 3.7% (2005)) [27]. In that study, *severe* developmental delay was defined as a score of < 3 SD on the Mental Development Index on the Bayley-II [28] (1991–92, 1997 cohorts) or a score of < 3 SD on either the cognitive or language scale on the Bayley-III (2005 cohort) relative to scores for controls [29]. The definition of *severe* disability comprised severe cerebral palsy (unlikely to walk, Gross Motor Function Classification Scale [30] level 4 or 5), blindness, or severe developmental delay [27].

The EPICure study in the United Kingdom also reported neurodevelopmental outcomes for both of their cohorts in the birth years of 1995 and 2006. The rates of severe disability at 2½ to 3 years, which comprised non-ambulant cerebral palsy, deafness not improved with amplification, blindness, or a developmental quotient < 3 SD, were similar between the 2 epochs (18% and 19% respectively) [22]. When individual domains of disability (cognition, motor, communication, vision, and hearing) were compared between epochs, no significant differences were noted [22]. Possible explanations for the different

conclusions of the EPICure study and the NICHD study include different gestational age ranges, differences between geographic and neonatal network hospital populations, varying sociodemographic characteristics, or differing care practices.

The EPIPAGE cohorts of births in 1997 and 2011 also reported 2 year outcomes for the 9 regions in France that participated in both cohorts [25]. Cerebral palsy, blindness and deafness were determined by questionnaires completed by the referring doctor, and development was assessed using the Ages and Stages Questionnaire completed by parents. Survival without neuromotor or sensory disabilities at 2 years' corrected age for infants born 22–31 weeks' gestational age increased from 74.5% in 1997 to 80.5% in 2011 (adjusted mean difference 7.2%; 95% CI 4.7%, 9.8%; $p < 0.001$). Cerebral palsy rates in survivors born 24–31 weeks' gestational age decreased from a mean of 9.0%–5.4%, with the largest differences seen in the subgroup of 25–26 week infants [25].

There are, however, other studies that have reported worsening outcomes over time for children assessed at older ages. Data from the VICS cohorts of children born EP in 1991–92, 1997 and 2005 did not show any significant improvement in the composite outcome of major neurodevelopmental disability (i.e. cerebral palsy, blindness, deafness or IQ z-score relative to controls < 2 SD) at 8 years of age; with rates ranging from 15 to 18% across the three eras [5]. When considering individual impairments contributing to neurosensory disability in that study, rates were unchanged across eras for all components; any cerebral palsy ranged between 11 and 14%, blindness (defined as visual acuity worse than 6/60 in the better eye) and deafness (hearing impairment requiring amplification, or cochlear implant) were present in < 3%, and 10–14% of children had an IQ z-score < 2 SD [5]. It is therefore interesting that the early improvement in outcomes in the 2005 cohort at age 2 years [27] did not persist at 8 years, which highlights the importance of longer term assessments of neurodevelopment beyond the first few years after birth as they are more reflective of the true long-term outcomes for the child. Moreover, some of the apparent improvement in cognitive scores at two years of age in the cohort born in 2005 might have been related to the different developmental assessment used between eras. The 1991–92 and 1997 cohorts were assessed with the Bayley-II, whereas the 2005 cohort was assessed with the Bayley-III; which is well known to overestimate developmental progress, and hence underdiagnose developmental delay [31]. At both 2 and 8 years, classification of developmental delay in each of the eras (1991–92, 1997, and 2005) was relative to the corresponding control group of that era.

In summary, there are conflicting reports as to whether or not rates of neurodevelopmental impairment in late infancy or early childhood have improved in high-income countries from the mid-1990s. The only study that has reported outcomes to school age has shown no demonstrable improvement in neurosensory disability for EP cohorts. There are no published long-term outcome data over time from middle-to low-income nations.

## 5. Cognitive function

Cognitive function is most commonly assessed using measures of general intelligence (IQ). Consistent with the stability in the rates of intellectual impairment, as detailed above, mean IQ scores appear to be broadly stable in children born since 1990. For instance, in the VICS 1991–92, 1997, and 2005 cohorts, the mean IQ z-score relative to matched controls was stable across birth eras and ranged from −0.70 to −0.80. A meta-regression of IQ in children born either very preterm (< 32 weeks) or EP between 1990 and 2008 reported a mean difference in IQ z-score of −0.86 (95% CI -0.94, −0.78) compared with term-born controls, which was not influenced by the participants' years of birth [32], providing further support for stability in IQ across eras.

IQ is a composite measure of cognitive functioning, and specific neuropsychological measures are needed to determine the cognitive domains most affected by preterm birth. While there is extensive literature documenting greater difficulties across all cognitive domains relative to term-born controls, the domain that has attracted considerable interest is executive functioning. Executive function is an umbrella term referring to interrelated abilities that are essential for goal-directed and adaptive behavior [33], including impulse control, working memory, cognitive flexibility, conceptual reasoning, and planning and organisation. Few reports have systematically examined differences in executive functioning across birth eras. Van Houdt and colleagues recently conducted a meta-regression of studies reporting children's performance on various measures of two aspects of executive functioning: working memory and inhibitory control [34]. They found no association between participants' year of birth (1991–2011) and working memory and inhibitory control, suggesting these outcomes are not improving for children during this epoch. However, it should be noted that this meta-regression included a wide range of gestational ages at birth with some studies having a mean gestation at birth of 35 weeks.

A distinction may be drawn between the use of executive functions in the highly-structured neuropsychological assessment environment and how these skills are manifested in real-life settings. In the VICS cohorts of 1991–92, 1997, and 2005, parents provided ratings of various aspects of their children's executive functioning at 8 years using the Behavior Rating Inventory of Executive Function (BRIEF) [35,36]. This study revealed similar or increasing prevalences of potentially clinically important executive functioning difficulties in the 2005 cohort compared with those born in earlier cohorts (Fig. 1). Increasing difficulties were identified in the 2005 cohort in the subdomains of working memory, and planning and organisation, with 37% and 29% of the 2005 cohort being rated in the potentially clinically important ranges, respectively, compared with rates of 20% and 14%, respectively, for the 1991–92 cohort, and 15% and 11%, respectively, for the 1997 cohort. This pattern of stable or increasing executive functioning problems was not attributable to antenatal corticosteroids, bronchopulmonary dysplasia, multiple birth, or sex. Based on the limited body of evidence to date, it appears that executive functioning is not improving for children born since 1991, and the potential for deteriorating outcomes in executive function skills merits further investigation.

## 6. Academic performance

Little data exist as to how academic performance in children born preterm has changed over time. The VICS cohorts from 1991–92, 1997 and 2005 were assessed at 8 years of age for academic achievement

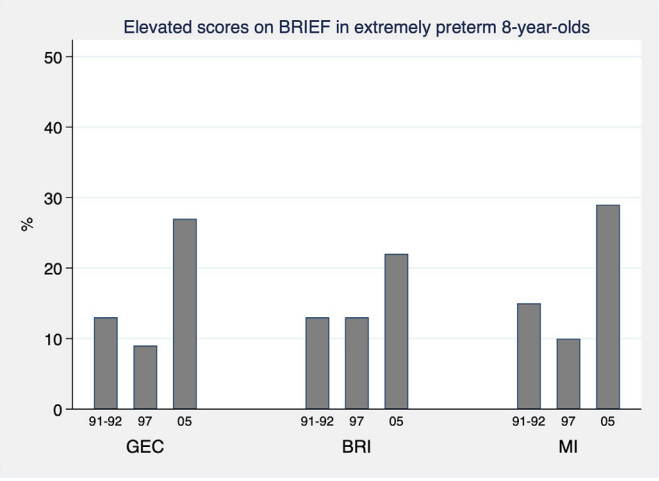


**Fig. 1.** Impairments in executive function at 8 years of age for children born extremely preterm from 1991 to 2005 [47]. BRIEF – Behavior Rating Inventory of Executive Function; GEC – Global Executive Composite; BRI – Behavioral Regulation Index; MI – Metacognition Index. Elevated scores ≥ 65.

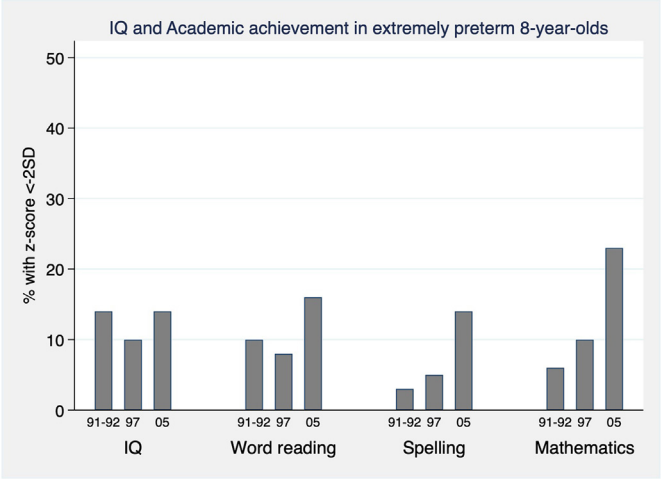


**Fig. 2.** Impairments in general cognition (IQ) and academic achievement at 8 years of age for children born extremely preterm from 1991 to 2005 [5].

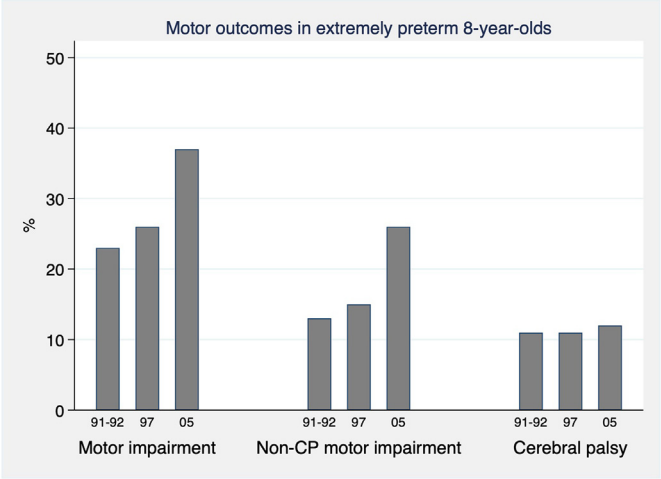


**Fig. 3.** Impairments in motor function at 8 years of age for children born extremely preterm from 1991 to 2005 [43]. CP – cerebral palsy.

using different versions of the Wide Range Assessment Test (WRAT) [5]. In Victoria, Australia, 8 years of age usually coincides with the 3rd formal year of schooling. Outcomes for word reading, spelling and mathematics were compared with contemporaneous term controls and z-scores generated to enable comparisons over time. For all three outcomes, rates of poor academic performance (z-scores < 2 SD) worsened over time, whereas rates of low IQ remained unchanged (Fig. 2), even after adjustment for age at assessment, maternal age, sociodemographic variables and perinatal variables. The trend of worsening academic achievement could not be easily explained by major changes in clinical practice at the time. Caffeine to treat apnea of prematurity was commonly prescribed in the 2005 cohort. In a large, multicenter randomized controlled trial, caffeine in infants born < 1250 g birthweight improved neurosensory outcomes at 18 months [37], which was not sustained at 5 years with the exception of improved motor performance [38,39]. Postnatal corticosteroid use in the 2005 cohort had diminished significantly to 23%, down from 35% in 1991–92 and 37% in 1997 [5]. Other factors that may influence academic outcomes such as parenting practices, parental mental health, nutrition, and child behavior need to be explored in future studies.

## 7. Motor outcomes

Motor outcomes include both cerebral palsy and non-cerebral palsy motor impairment, which is often referred to as developmental coordination disorder. Rates of cerebral palsy, along with the severity of cerebral palsy have been reported to be reducing in some high-income countries over the past decades, including the US, Europe and Australia [40–42]. Data from cerebral palsy registers shows that the reduction in rates of CP was partly due to reduced rates of CP in infants born EP, however, this is not a consistent trend. For example, data from the Australian Cerebral Palsy Register (ACPR) showed that rates of CP in infants born EP have dropped consistently in the state of Victoria; from 9.9% for births in 1995–1997, to 9.5% in 1998–2000, 8.7% in 2001–2003, 6.8% in 2004–2006 and to 5.9% in 2007–2009. In contrast, the same trend has not been noted in the state of Western Australia with rates varying from 8.3% for births in 1995–1997, to 12.8% in 1998–2000, 11.0% in 2001–2003, 8.0% in 2004–2006 and to 6.2% in 2007–2009 [40]. In the same data from the ACPR, severity of cerebral palsy has been shown to be decreasing for infants born weighing < 1000 g, with the percentage of children with bilateral compared with unilateral cerebral palsy decreasing from 72.2% for births in 1995–1997, to 64.7% in 1998–2000, 64.2% in 2001–2003, 62.5% in 2004–2006 and to 55.8% in 2007–2009. Almost all children with unilateral cerebral palsy (99%) can walk compared with around half of children with bilateral cerebral palsy (98% with diplegia vs 23% for quadriplegia). The reasons for the decrease in rates and severity of cerebral palsy in EP children are likely to be multifactorial.

Whilst rates of cerebral palsy appear to be reducing or at least stabilizing for children born EP, rates of non-CP motor impairments are on the increase. In the VICS cohorts of 1991–92, 1997, and 2005 motor impairment was assessed using the Movement Assessment Battery for Children (MABC) at 8 years of age, with children classified as having a motor impairment if they scored < 5th centile (1991–1992; 1997) or ≤5th centile (2005 – 2nd edition of MABC) [43]. Rates of children with motor impairment increased over time from 23% in 1991–92, to 26% in 1997 to 37% in 2005. This increase in motor impairment across eras was due to an increase in motor impairment not due to cerebral palsy, which increased from 13% in 1991–92, to 15% in 1997 and to 26% in 2005, with rates of cerebral palsy remaining relatively constant (Fig. 3). The increase in cerebral palsy was not explained by differences in perinatal characteristics between the cohorts, with poorer fetal growth, postnatal corticosteroids, grade III/IV intraventricular haemorrhage and neonatal surgery all independently associated with motor impairment across all time points. A control group of healthy term born children who were matched for expected date of birth, sex and socio demographic variables, also demonstrated an increase in impairment not due to cerebral palsy over time, although to a lesser extent. It is important to see if these trends are observed in other cohorts, and also to assess if subsequent VICS cohorts demonstrate a similar decline in motor functioning.

## 8. Behavior

There is little research quantitatively examining changes in behavioral outcomes over birth-eras for EP children. Mathewson and colleagues performed a meta-analysis of studies of behavior and mental health in ELBW survivors, all drawn from high-income countries (Europe, US, UK, Australia, and New Zealand) [44]. They found no major differences in mental health outcomes for children and adolescents who were born prior to 1990 compared with those born after 1990. The only exception to this was that self-ratings of attention deficit and hyperactivity disorder symptoms were slightly higher among ELBW adolescents in cohorts born prior to 1990 than controls, but slightly lower in ELBW samples born after 1990. However, parental ratings of attention deficit and hyperactivity disorder symptoms did not differ across the two periods. It therefore remains to be determined whether behavioral functioning and mental health outcomes are changing in those born EP since 1990 and how these outcomes may differ at different stages of development.

## 9. Research gaps

Tracking long-term neurodevelopment is critical to understand how advances in maternal and neonatal care have impacts outside the stringent conditions of randomized-controlled trials. An inherent problem with long-term follow up studies is the time needed to obtain outcome data, possibly limiting the relevance of the data to contemporary clinical care practices, and thus reducing the likelihood that findings will lead to changes in clinical care. However, whatever the long-term outcome data show, they are the most relevant to current practice until replaced by more contemporary data, and are the data that should be used in counselling and decision-making. There is currently no easy mechanism to monitor population effects on long-term outcomes following changes in clinical care, but that does not mean that no monitoring is acceptable. We must continue to monitor the long-term outcomes of neonatal intensive care.

Research networks, which have the capacity to collect ongoing data on acute care, and more recently longer-term outcomes, need to plan *a priori* to evaluate long-term outcomes at regular intervals and map these in conjunction with changes in care. Research studies need to plan follow-up recruitment of cohorts in order to assess changes in outcomes that are not readily available from routine administrative datasets, but are still clinically important. Finally, outcomes in late infancy and the pre-school period give a window into the future, but they are imperfect indicators of longer-term outcomes to school-age and beyond [45,46].

## 10. Conclusions

Advances in neonatal care have resulted in increased survival of preterm infants, especially those born EP. It was hoped that these advances would also be associated with improvements across multiple neurodevelopmental domains. However, published data are not convincing that this is the case; in fact, some neurodevelopmental outcomes may be worsening. It is imperative to understand contributory factors and to develop strategies to improve the most important outcomes of neonatal intensive care, the ones that occur well beyond discharge home and into later life.

### Practice points

- Survival of infants born preterm, especially those born extremely preterm, has improved over the last few decades.
- Despite advances in neonatal care, long-term neurosensory, cognitive, academic achievement and motor outcomes have not convincingly improved over a similar time period for children born extremely preterm.
- There are limited data on how behavior and mental health outcomes have changed over time.

### Research directions

- Neurodevelopmental outcomes should be reassessed repeatedly over time.
- Registry or administrative datasets can provide some information, but detailed neurodevelopmental assessments are required to fully understand important outcomes.
- Trials of perinatal interventions need to include follow up past infancy to fully understand the true neurodevelopmental impacts of the interventions being studied, which are best determined at school age or later.

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