HHS Public Access

Author manuscript

Semin Perinatol. Author manuscript; available in PMC 2017 January 26.

Published in final edited form as:

Semin Perinatol. 2016 October ; 40(6): 398–409. doi:10.1053/j.semperi.2016.05.011.

Changing Definitions of Long-Term Follow-up: Should "Long-Term" be Even Longer?

Susan R. Hintz, M.D., M.S. Epi,

Robert L. Hess Family Professor of Pediatrics, Associate Chief for Prenatal Services, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Medical Director, The Fetal and Pregnancy Health Program, 750 Welch Road, Suite 315, Palo Alto, CA 94304

Jamie E. Newman, Ph.D., MPH, and

NRN Follow-up Study Coordinator, Public Health Research Division, RTI International, 3040 East Cornwallis Road, Research Triangle Park, NC 27709

Betty R. Vohr, M.D.

Professor of Pediatrics, Alpert Medical School of Brown University, Medical Director, Neonatal Follow-up Program, Women & Infants Hospital of Rhode Island, Providence, RI 02905

Abstract

There have been amazing changes in outcomes of preterm (PT) infants in the past 200 years.[1] Whereas early studies reported only survival rates, Dr. Hess published the first outcome study of PT infants in Chicago in 1953.[1] Dr. Lubchenco then published the 10 year follow-up of premature infants born in 1947 to 1953 and identified a 68% handicap rate.[2] As a result of these early studies, the importance of evaluating NICU graduates both for surveillance and as an outcome of trials was recognized. During the 1970s there was a gradual expansion in the number of follow-up programs in the United States (US) with an increasing number of follow-up studies published. In the 1980s the importance of multicenter clinical research networks was recognized and the NICHD Neonatal Research Network (NRN) was initiated in 1986. Follow-up protocols, definitions, and outcomes have evolved over the last 30 years and will be reviewed with a focus on NICHD NRN studies.

Eunice Kennedy Shriver NICHD Neonatal Research Network Follow-Up Study Group

The NICHD NRN was initiated as a multicenter effort in the US with the main objective of providing a registry of uniformly collected baseline and morbidity and mortality data information to provide the basis for planning and implementing clinical trials. The NICHD NRN Follow-up Study Group was added in 1993 to provide neurodevelopmental follow-up for trials, and for those meeting NRN Follow-Up Study criteria, which now includes infants <27 weeks' gestation born at a NRN site, included in the NRN general data collection, and with appropriate site-specific institutional review board approval and consents. The NRN

From: Women & Infants Hospital of Rhode Island, 101 Dudley Street, Department of Pediatrics, Providence, Rhode Island 02905

Disclosure Statement

Financial Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

research objective is to utilize standardized protocols and definitions in order to provide outcomes for randomized control trials, longitudinal outcome studies, ongoing surveillance and observational studies. The NICHD NRN's primary focus is to improve the outcomes of premature infants and full term high risk infants.

Examiners and Certification Procedures in the NICHD NRN

An important component of the NRN follow-up protocols is the certification of NRN examiners in assessment procedures. Training of multiple examiners to code neurodevelopmental outcomes in young children is challenging because of heterogeneity of neurologic findings ranging from mild to severe which may not clearly fall into a specific category.[3] These challenges have been addressed with a rigorous training and certification protocol. Trained examiners are certified annually for the Bayley Scales of Infant Development III (BSID-III) and the neurologic exam. Each center designates a primary BSID-III examiner and a primary neurologic examiner, who are responsible for training and certifying additional examiners at their center. Each year, the primary BSID-III examiner from each center submits a video of him/her performing the exam with a 22–26 month old child to one of four NRN BSID-III Gold Standard examiners who provide feedback on administration and scoring. The annual certification process for the BSID has remained unchanged.

The annual certification process for the neurologic exam has evolved over time to improve quality and efficiency, identify problematic areas for training, and enhance inter-rater agreement as described in detail elsewhere.[3] In the early years of the NRN (1994–1999), patients with a variety of neurologic diagnoses were examined during centralized training. At present, the center primary neurologic examiner submits a video each year of him/her performing the exam with a child at 22–26 months corrected age (CA). The videos are reviewed by two NRN neurologic exam Gold Standards who choose 5–6 high quality exams with a spectrum of neurologic findings to place on the annual certification DVD. Prior to the annual training workshop, primary examiners view and score the exams on the certification DVD and their responses are keyed and transmitted to the RTI International data coordinating center for inter-rater agreement analysis. The annual training workshop provides targeted training on problematic items and concludes with examiners scoring a "test" video. Examiners receive feedback on the video they submit, their scoring of the certification DVD, the "test" video. This process has rendered improvements in inter-rater agreement as well as pre- and post-training within a single year.[3]

NICHD Follow-up Study Cohorts and Changes in NRN protocols; 1993 and 2016

Population

The NRN maintains a generic database (GDB) that includes all infants on whom neonatal data are collected. Infants in the GDB (401–1500 grams) whose follow-up window opened before January 1, 2008 were eligible for follow-up at 18–22 months CA if they had a birth weight of 401–1000 grams. Infants whose follow-up window opened January 1, 2008 or

later are eligible for follow-up if they fit either of the following criteria: GDB inborn infants born at ≤ 27 completed weeks gestational age (up to and including 26 6/7 weeks), or larger PT infants enrolled in a randomized trial or observational study with follow-up as a predefined primary or secondary outcome. This change was initiated in response to the improved survival of infants at the limits of viability.[4–6]

Age

For GDB infants born before July 1, 2012, the follow-up assessment was at 18–22 months CA. For infants born July 1, 2012 or later, the follow-up assessment is completed at 22–26 months CA which is consistent with other national and international networks.

Neurodevelopmental assessments and definitions

Neurodevelopmental outcomes have become increasingly important as survival of even the most extremely preterm (EPT) and highest risk term infants is increasingly in prospective studies of EPT infants have often taken place during the toddler period or in very early childhood (18 months of age corrected for prematurity to 3 years). At these ages, a battery of exams and tests can be performed including neurosensory and neurologic exams to assess for blindness, deafness and cerebral palsy (CP), and standardized cognitive and psychomotor assessments such as the Bayley Scales of Infant Development (BSID).[7] Interpretation and comparison of studies, however, may be difficult. Many studies report outcomes by categories, and frequently combine any adverse finding from various aspects of the overall visit to attain an “impaired” or “not impaired” status. The definitions of “adverse” outcomes may not be consistent across studies and cohorts; indeed, the definitions of the individual components of “impairment” such as CP, blindness, deafness, and developmental delay, may also differ across studies. The developmental tests themselves may change substantially over time and with new editions (i.e., BSID-II to BSID-III), from making comparison of outcomes to an earlier era complex.

Development and NDI

The NRN definition of neurodevelopmental impairment (NDI) has evolved over time and has included a composite of neurologic, developmental, vision, and hearing status. Changes were necessitated in response to the implementation of the BSID-III. Not all NRN studies use the composite outcome and in certain protocols it is more appropriate to identify specific language, cognitive, or neurosensory impairments as the primary outcome. Current component definitions include the following. Moderate to severe CP includes children with tone/reflexes abnormalities and a Gross Motor Function Classification Score ≥2.[8] Vision impairment is defined as bilateral acuity < 20–200 with amplification, and hearing impairment is defined as bilateral permanent hearing loss that does not permit the child to understand the examiner directions ± amplification.

Development

Most follow-up studies of extremely low birth weight (ELBW) infants prior to 2008 used the (BSID II).[9] The BSID -II scales were previously the most commonly reported assessment of development from 4 to 36 months of age and provides information for cognitive [the mental

developmental index (MDI)) and motor (the psychomotor developmental index (PDI)] domains. Bayley scores of 100 ± 15 represent the mean ± 1 standard deviation (SD) of a population of normal infants born at term. A score <70 (2 SDs below the mean) is interpreted as evidence of developmental delay. The BSID-III is currently used for assessments from 1 to 42 months of age.[7] The BSID-III was developed, in part, to separate cognitive from language domains to eliminate the bias imposed for children residing in a bilingual or non-English speaking household. In contrast to the BSID-II, the BSID-III consists of three domains: the Cognitive, Language and Motor Composite scores, in addition to subscores for receptive and expressive communication, fine and gross motor skills. A limitation of the BSID-III is that cognitive and motor scores have been shown by many investigators to be higher than BSID-II scores.[10] The reasons for this difference are not entirely clear. Although the BSID-II has not been a stellar predictor of school age outcomes, the predictive value of the BSID-III remains unknown. Higher mean values of the BSID-II have necessitated modifications of the cut-points of the BSID-III composite scores. Current NICHD NRN categories are moderate delay 70–84, severe delay < 70 and profound delay ≤ 54.

Behavior

The first standardized test for behavior implemented by the NRN was the Brief Infant Toddler Social Emotional Assessment (BITSEA) [11] which assesses emotional difficulties for infants 12 to 36 months and was appropriate for the NRN assessment age of 18–22 months. Parents rate 49 problem scale items and 11 competence scale items and two standardized scores are derived for the problem and competence scales. With the change in the 22 to 26 month assessment age in 2008, the NRN investigators changed to the Child Behavior Checklist (CBCL) [12] to better classify a spectrum of behavior disorders. The CBCL for ages 1.5–5 years is administered to parents and includes 99 items that describe specific kinds of behavioral, emotional, and social problems that characterize preschool children. In response to the concerns regarding increasing rates of autism spectrum disorder (ASD) in the US, the Pervasive Developmental Disorders Screening Test, Second edition (PDDST-II) Stage 2[13], a screening tool for children 12–48 months of age was added in November 2008. The Stage 2 parent report measure was used because it is specifically designed for use in developmental clinics. NRN investigators have examined behavior outcomes using these tools.[14–16] The current protocol does not include the PDDST-II.

CHALLENGES TO EARLY NEURODEVELOPMENTAL OUTCOME ASSESSMENT

Very early childhood developmental and neurologic outcomes evaluations should only be considered as a first step to comprehensive follow-up; assessments into school age, adolescence, and adulthood are critically important to understand the functional and societal outcomes of former PT infants.[17–23] Concerns regarding changes in cognitive and academic challenges over time, and an increasing recognition that physical and environmental effects as well as early intervention approaches may modify recovery, underscore the need for later assessments.[24–26] Some neurocognitive, executive function and behavioral challenges may only be detected at school age; even recognizing that such learning and attention problems

may occur in PT infants is a critical step to ensuring adequate support and services for families and teachers to help children achieve their best possible outcomes. Evaluation of neuromotor outcomes throughout childhood is critical, as later neuromotor and coordination problems such as developmental coordination disorder (DCD) are prevalent among school-age children born EPT compared with term, and can be associated with other functional challenges and academic difficulties.[27, 28]

Despite the many challenges, changes and provisos, a substantial body of literature exists on early neurologic, cognitive, neurodevelopmental and functional outcomes of PT infants published over the past decades ranging from small or single-center cohorts to multi-site observational analyses to follow-up after neonatal intervention. We do not attempt to present a comprehensive review of all published neurodevelopmental outcomes studies in the following sections of this chapter, but rather we will concentrate on results from the NICHD NRN, and also highlighting recent large cohorts and regional population-based studies (TABLE 1).

NEURODEVELOPMENTAL OUTCOMES OF EPT, ELBW INFANTS IN THE NICHD NRN

The NICHD NRN reported outcomes at 18–22 months of age corrected for prematurity for ELBW cohorts born 1993–94, 1995–96, and 1997–1998, stratified by EGA.[29] In regression analyses, rates of moderate-severe CP did not change over time during these eras, but not surprisingly, rates were significantly different between the gestational age groups. However, for developmental outcomes (assessed in these eras by BSID-II MDI and PDI) and the composite outcomes of NDI, a significant decrease in rates of MDI<70 and NDI was noted over the three eras, primarily explained by differences between rates in the earliest (1993–94) compared with the second (1995–96) eras. Although the rates of CP and NDI reported by the NICHD NRN and by other groups during these eras may be concerning, gross motor function in many of these children may in fact be relatively normal. In separate analyses of Gross Motor Function Classification System (GMFCS) findings in ELBW survivors born 1995–98, Vohr, et al. found many children with CP had normal or mildly delayed gross motor function.[30]

More recently, the NICHD NRN reported 18–22 months CA outcomes of infants inborn at an NRN site at <25 weeks' gestation during two epochs, 1999–2001 (epoch 1), and 2002–2004 (epoch 2).[31] Profound NDI in this study was defined as MDI<50, or GMFCS level 4 or 5, while "unimpaired or minimally impaired" was defined as having none of the following: moderate-severe CP, bilateral severe hearing loss or blindness, MDI or PDI <85. Only about 25% of both epoch follow up groups were composed of children born at or less than 23 weeks' gestation. Although results showed an apparent absolute increase in NDI of 50% to 59% from epoch 1 to 2, epoch was not found to be associated with NDI on multivariable analyses adjusting for baseline variable differences between the groups. Profound NDI was not increased between epoch 1 (17%) and epoch 2 (18%). Rates of adverse outcomes were higher for children <23 weeks' than 24 weeks' gestation for both epochs, although patient numbers were small for rarer outcomes. Despite more aggressive perinatal management with

increased cesarean section delivery (41% to 49%), and dramatic reduction in postnatal steroid use (64% to 33%) from epoch 1 to 2, no significant improvement in neurodevelopmental outcomes were observed. Nevertheless, approximately 22% of survivors in both epochs were unimpaired or minimally impaired at 18–22 months CA, which is slightly higher than the 16% unimpaired survival rate among ELBW children previously reported, although the definition of unimpaired was more stringent in that analysis.[32] This study differed from other international cohorts in that it narrowly focused on infants of less than 25+0/7 weeks, and they were evaluated at an earlier age. Of note, since this study, the NICHD NRN has changed the window for follow up to 22–26 months CA. Furthermore, these cohorts are not population-based, but rather representative of several US academic centers. As with previous studies and analyses from the NICHD NRN,[33] center differences in outcomes were also observed, suggesting that practice variability beyond what can be explained by perinatal risk factors and neonatal morbidities may play an important role.

Between-hospital variation in outcomes was further explored by Rysavy, et al. among infants inborn at an NRN site at <27 weeks' gestation between 2006–2011, assessing survival and NDI at 18–22 months.[5] During this period, the BSID-III was utilized. Impairment was defined similarly as above, with the exception that BSID-III cognitive scores of <70 were included in the severe NDI, and scores of 70–84 were included in the moderate NDI definitions. Outcomes were evaluated in relation to hospital rates of "active treatment" defined as potentially life-saving treatments initiated after delivery. For all infants, overall rates of survival without severe impairment were (mean) 3.4%, 17.9%, 44.7%, 61.1%, and 75.6% for 22, 23, 24, and 25 weeks' gestation. However, there significant differences among hospital rates of active treatment for those born at 22, 23, and 24 weeks, which accounted for a substantial proportion of variation in outcomes for children born at that gestational age range. The BSID-III was utilized during this study period, and there was no term control group. As noted previously, using BSID-III test cut points have been reported to underestimate impairment in EPT infants[10, 34] and results are difficult to compare to those of previous instruments.

FACTORS ASSOCIATED WITH NEURODEVELOPMENTAL OUTCOMES

Early childhood neurologic and developmental disability in PT infants may be associated with an enormous array of biologic, environmental, and iatrogenic factors. Furthermore, the risk factors themselves may be tightly associated with other variables, and one factor may modify or potentiate the effect of others; therefore, analyses can be complex and challenging to interpret. Some studies from the NICHD NRN have suggested that little of the variance in outcomes can be explained by identified major risk factors,[35] and that clinical factor models predict neurodevelopmental outcomes better than cranial ultrasound (CUS) factor. Nevertheless, several variables have been consistently recognized to be associated with adverse neuromotor outcomes and overall early childhood impairment among ELBW and very preterm (VPT) infants. Risk factors specifically for developmental or cognitive delay present greater challenges, in part due to differences among studies with respect to definition of delay, and to social-environmental interactions.

Antenatal, demographic, and social risk factors

Events and interventions prior to delivery may have significant influences on EPT neurodevelopmental outcomes. Antenatal steroid treatment has been shown to improve lung maturity and reduces neonatal morbidities including respiratory distress syndrome, necrotizing enterocolitis, severe ICH, and death.[36] Antenatal steroid exposure also appears to be associated with reduction in NDI at 18–22 months,[29] and death or NDI, among those born at 23 to 25 weeks.[37] Location of delivery may also be associated with death or NDI. As noted previously, NICHD NRN studies have demonstrated center differences with respect to neonatal intervention, death or NDI, and NDI among survivors.[5, 33] Serenius, et al. and the EXPRESS group,[38, 39] demonstrated significant regional variation in obstetric and neonatal intervention approaches in Sweden; in regions with more aggressive perinatal intervention, the risk of death or NDI among 22–24 weeks was reduced, without increase in NDI among survivors. A distinct male disadvantage for death, short-term morbidities, and neurodevelopmental outcomes including cognitive delay, cerebral palsy, and motor impairment has been frequently reported for extremely PT infants.[29, 40, 41] The reasons for this gender-specific vulnerability are obscure, but measurable risk factors and events do not appear to explain differential risk for adverse neurodevelopmental outcomes for boys.[41] Social disadvantage and lower level of maternal education is associated with increased rates of adverse early neurodevelopmental outcomes.[16, 31, 42–44] Maternal race and ethnicity also have an impact on early EPT language outcomes, even after adjustment for differences in neonatal morbidities and maternal education.[45] NICHD NRN investigators have also shown that EPT children whose primary language is Spanish have similar cognitive but lower language score than those whose primary language is English, thus suggesting that English language based testing tools may introduce bias.[14]

Infection, necrotizing enterocolitis, growth and nutrition

Extremely PT infants are at high risk for late-onset infection, although rates infection has decreased in the NICHD NRN between 2005–2012 for EPT infants across gestational age weeks.[6] Both neonatal sepsis and severe necrotizing enterocolitis (NEC) have been shown to be associated with adverse motor, cognitive, and growth outcomes at 18–22 months,[46–48] with high risk for death or NDI among those with *Candida* sepsis or meningitis.[49] White matter injury is a key component in the path from infection or NEC to poor neurodevelopmental outcome. The inherent vulnerability of the pre-oligodendroglial cell places the PT infant at high risk.[29, 30] Factors known to be injurious or directly toxic to developing white matter, such as systemic and cerebral hypoperfusion, ischemia-reperfusion, and cytokine elucidation during a systemic inflammatory response, can be expected during the clinical course of infection or NEC. Neonatal sepsis and NEC have been linked with progressive or higher rates of WMI on MRI; adverse 2-year outcomes associated with these morbidities may be mediated by WMI.[50, 51]

Numerous clinical investigations among EPT infants have demonstrated that better nutritional support is associated with reduced rates of extrauterine growth retardation (EUGR), and that improved growth and better nutritional support during the NICU hospitalization is associated with improved neurodevelopmental outcomes.[52] In a prospective observational study of ELBW infants in the NICHD NRN, those with higher in-

hospital growth velocity rates had decreased clinical morbidities and neurodevelopmental impairment, and were significantly less likely to fall below the 10th percentile for growth at 18–22 months CA.[53] In regression analyses adjusted for demographic and clinical confounders, NICU growth velocity remained significantly associated with growth and neurodevelopmental outcomes at 18–22 months CA. Additional analyses from the NICHD NRN Glutamine Trial[54] found that the influence of critical illness on the risk of adverse outcomes was mediated by total daily energy intake during the first week of life.[53] Vohr, et al. found a significant, independent association of breast milk provision during NICU hospitalization with 18–22 month CA outcomes, demonstrating that for every 10-ml/kg per day increase in breast milk ingestion, MDI increased by 0.53 points, and rate of re-hospitalization decreased by 6%,[55] and the positive effect of breast milk on outcome persisted to 30 months CA.[56] These studies and others have led to evidence-based standardized feeding guidelines, including early parenteral and enteral nutrition, strong support of breast milk provision, and focus on postnatal growth targets. Implementation of such guidelines have resulted in improvement of nutritional milestones, decreased rates of severe EUGR, decreased days of parenteral nutrition, and decreased rates of NEC.[57]

Bronchopulmonary dysplasia (BPD)

Extremely PT infants are at risk for BPD, which is often defined as requiring oxygen at 36 weeks' postconceptional age; it is diagnosed in 30–50% of EPT infants, with rates increasing between 2009–2012 among those 26 and 27 weeks' gestation.[6] Those with BPD been shown to be at higher risk for all components of early neurodevelopmental impairment, and later childhood global neurocognitive impairment.[58, 59] Perinatal infection and placental inflammation is associated with increased risk for BPD, and infants with BPD are also more likely to have other neonatal morbidities including late-onset sepsis and ICH. A cascade of events including recurrent hypoxic [60] and hypoperfusion episodes, purportedly leading to injury of the vulnerable developing brain. In addition, postnatal dexamethasone, used in an attempt to treat BPD, has been shown to be associated with adverse neurodevelopmental outcomes particularly when initiated early, possibly directly by inhibition of brain growth.[61, 62] Preterm infants with BPD also have respiratory challenges after NICU discharge, and impaired pulmonary function and exercise capacity through childhood. Therefore, concerted efforts to reduce BPD in the NICU could have lifelong positive effects for children born EPT. In a NICHD NRN cluster-randomized trial of benchmarking and quality improvement approaches, practices were changed at intervention sites, but BPD rates were not improved.[63] Nevertheless, a predictive model of BPD was developed from the detailed data collected in this trial, which is now available as a web-based tool to provide accurate estimates of BPD based on demographic variables and respiratory support by postnatal day. ([64], https://neonatal.rti.org). The NICHD NRN also performed a multicenter 2-by–2 factorial design trial, including random assignment to intubation and surfactant treatment or to CPAP in the delivery room among infants 24 to 27+6/7 weeks with a primary outcome of death or BPD.[65] Although no significant difference was found in the primary outcome between groups, secondary outcomes including postnatal steroid use and duration of ventilation were reduced in the CPAP group. At 18–22 months CA, there were also no differences between groups in death or neurodevelopmental impairment, or components of neurodevelopmental impairment,[66] but, those in the CPAP arm had less respiratory

morbidity as compared with intubation and surfactant as the initial delivery room approach.[67] Given the multidimensional nature and complex challenges to understanding BPD in the current era, the NHLBI developed the Prematurity and Respiratory Outcomes Program (PROP)[68] as a multidisciplinary, longitudinal approach, contributing additional high resolution data to results from previous studies to inform development of future interventions to improve outcomes.

Brain Injury

CUS abnormalities and early neurodevelopmental outcomes

Virtually every major study of early neurodevelopmental outcomes among PT and ELBW infants has confirmed a strong association between major CUS abnormalities and adverse neurologic and developmental outcomes. Definitions of CUS abnormalities as well as specific outcomes differ among studies, however most consider IPH, ventriculomegaly (VM), or cystic changes, regardless of laterality or extent of the findings, to be severe abnormalities. In some, persistence of periventricular echodensity or “flaring” is included.[69, 70] The diagnosis reported is frequently based on the results from a single CUS, either the “worst” or the “final” imaging study, but some prospective cohorts[70–73] include serial imaging.

The focus of many studies has been on exploring the association of major CUS findings with cerebral palsy. The Extremely Low Gestational Age Newborn (ELGAN) Study followed infants <28 weeks’ gestation from 14 institutions across 5 states in the US during 2002–2004.[71 73] Three study CUS were performed during hospitalization, scored by study radiologists. The investigators found strong independent associations of specific CUS findings with CP. About half the children with CUS echolucency or VM developed CP, and late occurrence of VM, bilateral echolucency, and IPH or PVL were strongly predictive of quadriparesis. Isolated intraventricular hemorrhage (IVH) was not strongly predictive of CP, and major CUS abnormalities have been shown not to be associated with developmental scores. Furthermore, O’Shea, et al. and the ELGAN study group showed that only when accompanied or followed by WM lesions was IVH associated with increased risk for motor or developmental impairment at 2 years, highlighting the limited predictive value of both early CUS findings and IVH alone.[74] However, almost half of the children in the ELGAN group with CP at 2 years had completely normal CUS, and NICHD NRN investigators[75] and others[40, 69] have demonstrated that 30–40% of those with normal CUS have neurodevelopmental challenges at 18–30 months. Nevertheless, much can be seen beyond ICH by CUS with careful, serial imaging. In a single center, deVries, et. al. found that the sensitivity and specificity of CUS abnormalities for CP at 2 years was an impressive 76% and 95% for patients <32 weeks EGA.[70] Of importance, among those with major CUS abnormalities who developed CP, approximately 30% were noted after 28 days. Using MRI at term equivalent age to refine specific CUS findings has resulted in positive predictive value (PPV) and negative predictive value (NPV) of 96% and 69%, respectively, for CP at 2 years.[72] Major CUS abnormalities were not strongly associated with cognitive delay at 2 years.

As with all imaging modalities, interpretation may be challenging. In an analysis of CUS central and local readings in the NICHD NRN PiNO trial, although interrater reliability and accuracy was shown to be very good to excellent for severe ICH, agreement was fair or poor for more subtle findings and periventricular leukomalacia alone.[76] Cerebellar hemorrhage is increasingly recognized to be associated with neurodevelopmental disabilities in children born PT[77, 78], a finding that may be missed without appropriate CUS views, and transient lesions may be missed, including echodense periventricular lesions or collapsing small cystic lesions.[70] Isolated intraparenchymal hemorrhages and of course large IVH can be seen by CUS; however, not all “severe” hemorrhages are equivalent with respect to early neurodevelopmental outcomes. Characteristics of the hemorrhage including laterality, midline shift, and extent of hemorrhage,[79, 80] as well as the presence or absence of other adverse clinical factors,[81] have been shown to impact prediction of neurodevelopmental outcomes.

Conventional MRI findings and early neurodevelopmental outcomes

Conventional MRI has been used more extensively in recent years among very PT infants, both for research and clinical indications. MRI allows for a more comprehensive and detailed picture of the brain, and better delineation of deep structure and cortical injury, as well as improved detection of white matter injury (WMI). This is common among PT infants at term, and critically important to understanding the structure-function relationship of the developing PT brain, influences on later neuromotor and cognitive outcomes, and developing future neuroprotective strategies.[82] Advanced MR imaging in PT infants at near-term have shown that subtle WM injury is associated with reduced total brain and gray matter volumes, reduced cerebellar volume, and reduced basal ganglia and thalamic volume,[83–87] which in turn, are associated with developmental impairment in childhood among PT infants.[88] These findings and others have provided evidence that WMI in the PT is associated with brain maturational disturbances, suggesting an overall link to impaired neural connectivity.[89] Thus, clinical investigations have focused on whether MRI may provide enhanced prognostic information.

Early studies attempting to compare term equivalent MRI with CUS predictive capabilities were primarily small, single center studies, and timing and approach to CUS differed.[90–92] Since that time, WMI scoring approaches have been developed, and larger cohort studies have been published, among the first of which was a multi-center effort in Australia and New Zealand comparing serial CUS with near-term MRI findings and their association with 2-year in 167 infants <30 weeks EGA.[93] This study demonstrated that moderate-severe WM abnormalities on near-term MRI were significantly associated with neuromotor delay and cerebral palsy, independent of CUS findings and other risk factors. Increasing WMI severity was also linearly related to worsening BSID-II MDI scores, but an independent association of moderate-severe WMI with severe cognitive delay was not reached. However, CUS was assessed only with regard to early findings including grade of ICH and periventricular cystic changes, and a substantial proportion of infants with moderate to severe WMI by MRI did not have adverse 2-year outcomes. The NICHD Neuroimaging and Neurodevelopmental Outcomes (NEURO) study was a prospective study of early and late CUS and near term MRI including approximately 500 infants <28 weeks’ gestation in NRN centers across the

US, with outcomes including BSID-III assessed at 18–22 months.[94] In multivariable models, both late CUS findings reflective of WM injury and MRI findings of significant cerebellar injury remained independently associated with adverse neurodevelopmental outcomes. In models that did not include late CUS, MRI findings of both moderate to severe WMI and significant cerebellar lesions were independently associated with adverse outcomes. Early CUS findings were not associated with adverse outcomes when any late neuroimaging was taken into account. These results demonstrate the need to understand the evolution of brain injury over time in outcomes prediction rather than to rely on early findings. The NICHD NEURO cohort is being followed to 6–7 years to examine absolute and relative value of neonatal CUS and MRI in predicting neurologic, coordination, cognitive and behaviors outcomes at school age.

Controversies and questions remain as to which neuroimaging studies to perform, when to perform them, and relative values in prognosis. These are not simple questions, as the "value" of additional information may be very different in varying clinical circumstances, and for individual parents and physicians.[95] Further investigation with longer-term follow up to school age, and with advanced MR techniques including DTI, fcMRI, surface morphometry, and volumetric methods hold enormous promise to help to explore these possibilities.[96]

Future studies Moderate and Late PT—Moderate PTs born at 32 to 33 weeks' gestation and late PTs born at 34 to 36 weeks' gestation make up the largest subgroup of PT infants contributing more than 80% of PT births in the US. There is a growing body of evidence that these infants are at increased risk of both neonatal and post-discharge morbidities. In the US in 2013, 447,875 (11.39%) of the 3,932,181 live births were PT (< 37 weeks) and 55, 443 (1%) were very low birth weight (VLBW) (< 1500 grams).[97] The second half of gestation is a critical period of brain maturation including neurogenesis, synaptogenesis, and dendritic arborization[98] and there is increasing evidence that both MPT and LPT infants are at increased risk of neurologic impairments, developmental disabilities, school failure, autism, and behavior and psychiatric problems that extend to adolescence and young adult age.[99–109]

Executive Function—Executive function encompasses high-level mental processes necessary to regulate behavior and cognition for goal-directed actions, and play an important role in school achievement.[110] They include working memory, inhibition, planning and organization, verbal fluency, and cognitive flexibility. These abilities depend on the integrity of the neural network that connects the prefrontal cortex to the brainstem, the cerebral lobes, and the limbic and subcortical regions.[111–114] Although the majority of studies of deficits in these domains have been reported in adolescents and young adults born PT,[115–119] executive dysfunctions can be assessed at 5–6 years of age.[119, 120] Neuroimaging studies have shown decreased white matter volumes and impaired white matter gains compared with FT controls, which indicates increased vulnerability of PTs. In the Indomethacin trial[115] adolescent PTs exhibited more problems than FT controls in executive functions, even after excluding those with neurosensory disabilities. Nosarti et al[117] reported similar findings in a cohort of VPT young adults. Because of the important contribution of executive functions to

educational achievement, further studies examining the trajectory of these functions and the role of intervention are recommended.

Mental health Outcomes—Extremely LBW survivors are at increased risk of behavior disorders including attention deficit, autism spectrum disorder, depression, and anxiety disorders.[108, 121, 122] In a prospective, longitudinal study, VPT children were three times more likely to meet criteria for a psychiatric disorder compared to their FT counterparts at seven years of age.[123] A meta analysis[124] of cohorts of former PTs 10–25 years of age identified increased rates of any psychiatric illness and anxiety and depressive disorders requiring ongoing management compared to term controls. A review[125] of 15 studies of adverse behavior/psychiatric disorders of former PTs concluded there is a lack of evidence to identify specific risk factors for these disorders among VPT/VLBW survivors and concluded that additional research of large well conducted studies is needed. In view of the current high rates of mental health disorders among children and adolescents and the increased rates among former PTs, an increased focus on causation and potential interventions for these disorders is recommended.[123, 125, 126]

Adult Medical Outcomes—Research networks in the US, currently do not have the finances to track cohorts to adult age. The expansion of electronic medical records in the US may provide the opportunity for population studies to explore adult-onset disease including obesity, pulmonary and cardiovascular morbidities, adult cognitive decline and dementia.[127–129] Epidemiologic studies from countries with population databases have identified links between prematurity and adult onset disease.[130] The study of Heinonen et al[131] identified a link between late PT birth and cognitive decline at a mean age of 68.1 years. This adds one more justification to the debate of length of follow-up.

How long should high risk infants be followed?—There is an increasing body of data indicating that disability rates change between early childhood and school age.[132–134] A large population based Canadian study[134] of PT infants followed for 10 years identified that although the majority of subjects remained in their 2 year disability category, there were shifts. Early PT had a decrease in the percent with severe disability, with a small shift from moderate and severe to no or mild disability. In contrast, there was a shift of moderate and late PTs with no or mild disability at age 2 to moderate or severe disability at age 10. Although 2 year outcomes cost less, there is general agreement that school age provides a more valid outcome.[102, 135–140]

A full-term (FT) control group—Although the NRN's primary focus is randomized clinical trials, a full term control group has not yet been incorporated as a comparison for the generic follow-up of PT infants, primarily because of cost. As noted previously, other multicenter studies and networks have included FT controls into their models of follow-up,[34, 115, 141–143] which has allowed for identification of impairment thresholds based on findings of a representative sample of FT children, and has demonstrated substantial limitations to relevance and validity of the findings, and may have important public policy and resource implications.[34, 144, 145] The NRN is currently evaluating a mechanism for time-limited inclusion of a full term, normal birth weight control group going forward.

Conclusion—Although, follow-up investigations and trials have come a long way since the early studies of Hess[1] and Lubchenco,[2] the population of high risk infants, the complexity, types, and depth of assessments, and the duration of follow-up studies have all changed significantly. There is ample evidence for the need for long term follow-up studies.

References

1. Hess J. Experience gained in a thirty year study of prematurely born infants. Pediatrics. 1953; 11:425–434. [PubMed: 13055354]
2. Lubchenco LO, Horner FA, Reed LH, et al. Sequelae of premature birth. Evaluation of premature infants of low birth weights at ten years of age. Am J Dis Child. 1963; 106:101–115. [PubMed: 13931360]
3. Newman JE, Bann CM, Vohr BR, Dusick AM, Higgins RD. Improving the Neonatal Research Network Annual Certification for Neurologic Examination of the 18–22 Month Child. J Pediatr. 2012
4. Hintz SR, Poole WK, Wright LL, et al. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. Arch Dis Child Fetal Neonatal Ed. 2005; 90:F128–F133. [PubMed: 15724036]
5. Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med. 2015; 372:1801–1811. [PubMed: 25946279]
6. Stoll BJ, Hansen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993–2012. JAMA. 2015; 314:1039–1051. [PubMed: 26348753]
7. Bayley, N. Bayley Scales of Infant and Toddler Development - Third edition. San Antonio, TX: Harcourt Assessment, Inc.; 2006.
8. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther. 2000; 80:974–985. [PubMed: 11002433]
9. Bayley, N. Bayley Scales of Infant Development-II. San Antonio, TX: Psychological Corporation; 1993.
10. Vohr BR, Stephens BE, Higgins RD, et al. Are Outcomes of Extremely Preterm Infants Improving? Impact of Bayley Assessment on Outcomes. J Pediatr. 2012 Aug; 161(2):222–228.e3. 222-228.e223. [PubMed: 22421261]
11. Briggs-Gowan, MaCA. BRIEF-Infant Toddler Social Emotional Assessment (BITSEA) verson 1.02001.
12. Achenbach, TM. Child Behavior Checklist 1.5-5. Burlington, VT: ASEBA; 2000.
13. Siegel, B. Pervasive Developmental Disorders Screening Test-II. San Antonio, TX: Psych Corp; 2004.
14. Lowe JR, Nolen TL, Vohr B, Adams-Chapman I, Duncan AF, Watterberg K. Effect of primary language on developmental testing in children born extremely preterm. Acta Paediatr. 2013; 102:896–900. [PubMed: 23735043]
15. Stephens BE, Bann CM, Watson VE, et al. Screening for Autism Spectrum Disorders in Extremely Preterm Infants. J Dev Behav Pediatr. 2012; 33:535–541. [PubMed: 22926660]
16. Hoffman L, Bann C, Higgins R, Vohr B, Eunice Kennedy Shriver National Institute of Child H, Human Development Neonatal Research N. Developmental outcomes of extremely preterm infants born to adolescent mothers. Pediatrics. 2015; 135:1082–1092. [PubMed: 25963007]
17. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med. 2002; 346:149–157. [PubMed: 11796848]
18. Saigal S, Rosenbaum P. What matters in the long term: reflections on the context of adult outcomes versus detailed measures in childhood. Semin Fetal Neonatal Med. 2007; 12:415–422. [PubMed: 17707702]
19. Saigal S, Tyson J. Measurement of quality of life of survivors of neonatal intensive care: critique and implications. Semin Perinatol. 2008; 32:59–66. [PubMed: 18249241]

20. Saigal, S. Premie Voices: Young men and women born very prematurely describe their lives, challenges and achievements. 1st. Victoria, BC: Friesen Press; 2014.
21. Hack M, Schluchter M, Forrest CB, et al. Self-reported adolescent health status of extremely low birth weight children born 1992–1995. Pediatrics. 2012; 130:46–53. [PubMed: 22665412]
22. Litt JS, Gerry Taylor H, Margevicius S, Schluchter M, Andreias L, Hack M. Academic achievement of adolescents born with extremely low birth weight. Acta Paediatr. 2012; 101:1240–1245. [PubMed: 22812699]
23. Hack M. Adult outcomes of preterm children. J Dev Behav Pediatr. 2009; 30:460–470. [PubMed: 19823140]
24. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics. 2005; 116:333–341. [PubMed: 16061586]
25. Ment LR, Vohr B, Allan W, et al. Change in cognitive function over time in very low-birth-weight infants. JAMA. 2003; 289:705–711. [PubMed: 12585948]
26. Spittle A, Orton J, Anderson P, Boyd R, Doyle LW. Early developmental intervention programmes post-hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database Syst Rev. 2012; 12:CD005495. [PubMed: 23235624]
27. Davis NM, Ford GW, Anderson PJ, Doyle LW, Victorian Infant Collaborative Study G. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. Dev Med Child Neurol. 2007; 49:325–330. [PubMed: 17489804]
28. Roberts G, Anderson PJ, Davis N, et al. Developmental coordination disorder in geographic cohorts of 8-year-old children born extremely preterm or extremely low birthweight in the 1990s. Dev Med Child Neurol. 2011; 53:55–60. [PubMed: 21039437]
29. Vohr BR, Wright LL, Poole WK, Mc Donald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics. 2005; 116:635–643. [PubMed: 16143580]
30. Vohr BR, Msall ME, Wilson D, Wright LL, Mc Donald S, Poole WK. Spectrum of gross motor function in extremely low birth weight children with cerebral palsy at 18 months of age. Pediatrics. 2005; 116:123–129. [PubMed: 15995042]
31. Hintz SR, Kendrick DE, Wilson-Costello DE, et al. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics. 2011; 127:62–70. [PubMed: 21187312]
32. Gargus RA, Vohr BR, Tyson JE, et al. Unimpaired outcomes for extremely low birth weight infants at 18 to 22 months. Pediatrics. 2009; 124:112–121. [PubMed: 19564290]
33. Vohr BR, Wright LL, Dusick AM, et al. Center differences and outcomes of extremely low birth weight infants. Pediatrics. 2004; 113:781–789. [PubMed: 15060228]
34. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med. 2010; 164:352–356. [PubMed: 20368488]
35. Ambalavanan N, Nelson KG, Alexander G, Johnson SE, Biasini F, Carlo WA. Prediction of neurologic morbidity in extremely low birth weight infants. J Perinatol. 2000; 20:496–503. [PubMed: 11190589]
36. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006
37. Carlo WA, McDonald SA, Fanaroff AA, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA. 2011; 306:2348–2358. [PubMed: 22147379]
38. Serenius F, Kallen K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. JAMA. 2013; 309:1810–1820. [PubMed: 23632725]
39. Serenius F, Blennow M, Marsal K, Sjors G, Kallen K, Group ES. Intensity of perinatal care for extremely preterm infants: outcomes at 2.5 years. Pediatrics. 2015; 135:e1163–e1172. [PubMed: 25896833]

40. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992–1995. Arch Pediatr Adolesc Med. 2000; 154:725–731. [PubMed: 10891026]
41. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD, For The NICHD Neonatal Research N. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. Acta Paediatr. 2006; 95:1239–1248. [PubMed: 16982497]
42. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics. 2005; 115:997–1003. [PubMed: 15805376]
43. Kumar P, Shankaran S, Ambalavanan N, et al. Characteristics of extremely low-birth-weight infant survivors with unimpaired outcomes at 30 months of age. J Perinatol. 2013; 33:800–805. [PubMed: 23807719]
44. Fily A, Pierrat V, Delporte V, Breart G, Truffert P. Group EN-P-d-CS. Factors associated with neurodevelopmental outcome at 2 years after very preterm birth: the population-based Nord-Pas-de-Calais EPIPAGE cohort. Pediatrics. 2006; 117:357–366. [PubMed: 16452354]
45. Duncan AF, Watterberg KL, Nolen TL, et al. Effect of ethnicity and race on cognitive and language testing at age 18–22 months in extremely preterm infants. J Pediatr. 2012; 160:966–971 e962. [PubMed: 22269248]
46. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004; 292:2357–2365. [PubMed: 15547163]
47. Hintz SR, Kendrick DE, Stoll BJ, et al. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics. 2005; 115:696–703. [PubMed: 15741374]
48. Blakely ML, Tyson JE, Lally KP, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis or isolated intestinal perforation in extremely low birth weight infants: outcomes through 18 months adjusted age. Pediatrics. 2006; 117:e680–687. [PubMed: 16549503]
49. Adams-Chapman I, Bann CM, Das A, et al. Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. J Pediatr. 2013; 163:961–967 e963. [PubMed: 23726546]
50. Glass HC, Bonifacio SL, Chau V, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. Pediatrics. 2008; 122:299–305. [PubMed: 18676547]
51. Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr. 2008; 153:170–175. 175 e171. [PubMed: 18534228]
52. Ehrenkranz RA. Nutrition, growth and clinical outcomes. World Rev Nutr Diet. 2014; 110:11–26. [PubMed: 24751619]
53. Ehrenkranz RA, Das A, Wrage LA, et al. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res. 2011; 69:522–529. [PubMed: 21378596]
54. Poindexter BB, Ehrenkranz RA, Stoll BJ, et al. Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. Pediatrics. 2004; 113:1209–1215. [PubMed: 15121931]
55. Vohr BR, Poindexter BB, Dusick AM, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. Pediatrics. 2006; 118:e115–e123. [PubMed: 16818526]
56. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics. 2007; 120:e953–e959. [PubMed: 17908750]
57. McCallie KR, Lee HC, Mayer O, Cohen RS, Hintz SR, Rhine WD. Improved outcomes with a standardized feeding protocol for very low birth weight infants. J Perinatol. 2011; 31(Suppl 1):S61–S67. [PubMed: 21448207]
58. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. Semin Perinatol. 2006; 30:227–232. [PubMed: 16860163]

59. Doyle LW, Anderson PJ. Long-term outcomes of bronchopulmonary dysplasia. Semin Fetal Neonatal Med. 2009; 14:391–395. [PubMed: 19766550]
60. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. J Pediatr. 2005; 146:798–804. [PubMed: 15973322]
61. Murphy BP, Inder TE, Huppi PS, et al. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. Pediatrics. 2001; 107:217–221. [PubMed: 11158449]
62. Cheong JL, Burnett AC, Lee KJ, et al. Association between postnatal dexamethasone for treatment of bronchopulmonary dysplasia and brain volumes at adolescence in infants born very preterm. J Pediatr. 2014; 164:737–743 e731. [PubMed: 24332820]
63. Walsh M, Laptook A, Kazzi SN, et al. A cluster-randomized trial of benchmarking and multimodal quality improvement to improve rates of survival free of bronchopulmonary dysplasia for infants with birth weights of less than 1250 grams. Pediatrics. 2007; 119:876–890. [PubMed: 17473087]
64. Laughon MM, Langer JC, Bose CL, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med. 2011; 183:1715–1722. [PubMed: 21471086]
65. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010; 362:1970–1979. [PubMed: 20472939]
66. Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. N Engl J Med. 2012; 367:2495–2504. [PubMed: 23268664]
67. Stevens TP, Finer NN, Carlo WA, et al. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). J Pediatr. 2014; 165:240–249 e244. [PubMed: 24725582]
68. Maitre NL, Ballard RA, Ellenberg JH, et al. Respiratory consequences of prematurity: evolution of a diagnosis and development of a comprehensive approach. J Perinatol. 2015; 35:313–321. [PubMed: 25811285]
69. Ancel PY, Livinec F, Larroque B, et al. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. Pediatrics. 2006; 117:828–835. [PubMed: 16510664]
70. De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004; 144:815–820. [PubMed: 15192633]
71. O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early Hum Dev. 2009; 85:719–725. [PubMed: 19765918]
72. de Vries LS, van Haastert IC, Benders MJ, Groenendaal F. Myth: cerebral palsy cannot be predicted by neonatal brain imaging. Semin Fetal Neonatal Med. 2011; 16:279–287. [PubMed: 21636334]
73. Kuban KC, Allred EN, O'Shea TM, et al. Cranial ultrasound lesions in the NICU predict cerebral palsy at age 2 years in children born at extremely low gestational age. J Child Neurol. 2009; 24:63–72. [PubMed: 19168819]
74. O'Shea TM, Allred EN, Kuban KC, et al. Intraventricular hemorrhage and developmental outcomes at 24 months of age in extremely preterm infants. J Child Neurol. 2012; 27:22–29. [PubMed: 22232137]
75. Laptook AR, O' Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. Pediatrics. 2005; 115:673–680. [PubMed: 15741371]
76. Hintz SR, Slovis T, Bulas D, et al. Interobserver reliability and accuracy of cranial ultrasound scanning interpretation in premature infants. J Pediatr. 2007; 150:592–596. 596 e591-595. [PubMed: 17517240]
77. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics. 2007; 120:584–593. [PubMed: 17766532]

78. Limperopoulos C, Chilingaryan G, Sullivan N, Guizard N, Robertson RL, du Plessis AJ. Injury to the premature cerebellum: outcome is related to remote cortical development. Cereb Cortex. 2014; 24:728–736. [PubMed: 23146968]

79. Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. Pediatrics. 2007; 120:785–792. [PubMed: 17908766]

80. Davis JM, Shepard NT, Stelmachowicz PG, Gorga MP. Characteristics of hearing-impaired children in the public schools: part II--psychoeducational data. J Speech Hear Disord. 1981; 46:130–137. [PubMed: 7253589]

81. Merhar SL, Tabangin ME, Meinzen-Derr J, Schibler KR. Grade and laterality of intraventricular haemorrhage to predict 18–22 month neurodevelopmental outcomes in extremely low birthweight infants. Acta Paediatr. 2012; 101:414–418. [PubMed: 22220735]

82. Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. Int J Dev Neurosci. 2011; 29:423–440. [PubMed: 21382469]

83. Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics. 2005; 115:286–294. [PubMed: 15687434]

84. Thompson DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. Brain. 2007; 130:667–677. [PubMed: 17008333]

85. Dyet LE. Natural History of brain lesions in extremely preterm infants studied with serial magnetc resonance imaging from birth and neurodevelopmental assessment. Pediatrics. 2005; 118:536–548.

86. Inder TE, Huppi PS, Warfield S, et al. Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. Ann Neurol. 1999; 46:755–760. [PubMed: 10553993]

87. Boardman JP, Counsell SJ, Rueckert D, et al. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. NeuroImage. 2006; 32:70–78. [PubMed: 16675269]

88. Peterson BS, Anderson AW, Ehrenkranz R, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics. 2003; 111:939–948. [PubMed: 12728069]

89. Dean JM, Bennet L, Back SA, McClendon E, Riddle A, Gunn AJ. What brakes the preterm brain? An arresting story. Pediatr Res. 2014; 75:227–233. [PubMed: 24336432]

90. Mirmiran M, Barnes PD, Keller K, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Pediatrics. 2004; 114:992–998. [PubMed: 15466096]

91. Roelants-van Rijn AM, Groenendaal F, Beek FJ, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. Neuropediatrics. 2001; 32:80–89. [PubMed: 11414648]

92. Sie LT, Hart AA, van Hof J, et al. Predictive value of neonatal MRI with respect to late MRI findings and clinical outcome. A study in infants with periventricular densities on neonatal ultrasound. Neuropediatrics. 2005; 36:78–89. [PubMed: 15822020]

93. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med. 2006; 355:685–694. [PubMed: 16914704]

94. Hintz SR, Barnes PD, Bulas D, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. Pediatrics. 2015; 135:e32–e42. [PubMed: 25554820]

95. Janvier A, Barrington K. Trying to predict the future of ex-preterm infants: who benefits from a brain MRI at term? Acta Paediatr. 2012; 101:1016–1017. [PubMed: 22804827]

96. Doyle LW, Clucas L, Roberts G, et al. The cost of long-term follow-up of high-risk infants for research studies. J Paediatr Child Health. 2015; 51:1012–1016. [PubMed: 25873356]

97. Guyer C, Huber R, Fontijn J, et al. Very preterm infants show earlier emergence of 24-hour sleep-wake rhythms compared to term infants. Early Hum Dev. 2015; 91:37–42. [PubMed: 25460255]

98. Huppi PS, Warfield S, Kikinis R, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol. 1998; 43:224–235. [PubMed: 9485064]

99. Baron IS, Litman FR, Ahronovich MD, Baker R. Late preterm birth: a review of medical and neuropsychological childhood outcomes. Neuropsychol Rev. 2012; 22:438–450. [PubMed: 22869055]
100. Vohr B. Long-term outcomes of moderately preterm, late preterm, and early term infants. Clin Perinatol. 2013; 40:739–751. [PubMed: 24182959]
101. Chyi LJ, Lee HC, Hintz SR, Gould JB, Sutcliffe TL. School outcomes of late preterm infants: special needs and challenges for infants born at 32 to 36 weeks gestation. J Pediatr. 2008; 153:25–31. [PubMed: 18571530]
102. Morse SB, Zheng H, Tang Y, Roth J. Early school-age outcomes of late preterm infants. Pediatrics. 2009; 123:e622–e629. [PubMed: 19336353]
103. Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr. 2009; 154:169–176. [PubMed: 19081113]
104. Baron IS, Erickson K, Ahronovich MD, Baker R, Litman FR. Cognitive deficit in preschoolers born late-preterm. Early Hum Dev. 2011; 87:115–119. [PubMed: 21131147]
105. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002; 288:728–737. [PubMed: 12169077]
106. Eide MG, Oyen N, Skjaerven R, Bjerkedal T. Associations of birth size, gestational, age, and adult size with intellectual performance: evidence from a cohort of Norwegian men. Pediatr Res. 2007; 62:636–642. [PubMed: 17805203]
107. Ekeus C, Lindstrom K, Lindblad F, Rasmussen F, Hjern A. Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19-year-old men. Pediatrics. 2010; 125:e67–e73. [PubMed: 19969613]
108. Lindstrom K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. Pediatrics. 2009; 123:e47–e53. [PubMed: 19117846]
109. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008; 359:262–273. [PubMed: 18635431]
110. St Clair-Thompson HL, Gathercole SE. Executive functions and achievements in school: Shifting, updating, inhibition, and working memory. Quarterly journal of experimental psychology. 2006; 59:745–759.
111. Kesler SR, Reiss AL, Vohr B, et al. Brain volume reductions within multiple cognitive systems in male preterm children at age twelve. J Pediatr. 2008; 152:513–520. 520 e511. [PubMed: 18346506]
112. Ment LR, Kesler S, Vohr B, et al. Longitudinal brain volume changes in preterm and term control subjects during late childhood and adolescence. Pediatrics. 2009; 123:503–511. [PubMed: 19171615]
113. Woodward LJ, Clark CA, Pritchard VE, Anderson PJ, Inder TE. Neonatal white matter abnormalities predict global executive function impairment in children born very preterm. Dev Neuropsychol. 2011; 36:22–41. [PubMed: 21253989]
114. Anderson PJ, Doyle LW. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. Pediatrics. 2004; 114:50–57. [PubMed: 15231907]
115. Luu TM, Ment L, Allan W, Schneider K, Vohr BR. Executive and memory function in adolescents born very preterm. Pediatrics. 2011; 127:e639–e646. [PubMed: 21300680]
116. Remine MD, Care E, Brown PM. Language ability and verbal and nonverbal executive functioning in deaf students communicating in spoken English. J Deaf Stud Deaf Educ. 2008; 13:531–545. [PubMed: 18400786]
117. Nosarti C, Giouroukou E, Micali N, Rifkin L, Morris RG, Murray RM. Impaired executive functioning in young adults born very preterm. J Int Neuropsychol Soc. 2007; 13:571–581. [PubMed: 17521479]
118. Mulder H, Pitchford NJ, Hagger MS, Marlow N. Development of executive function and attention in preterm children: a systematic review. Dev Neuropsychol. 2009; 34:393–421. [PubMed: 20183707]

119. Marlow N, Hennessy EM, Bracewell MA, Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. Pediatrics. 2007; 120:793–804. [PubMed: 17908767]
120. Aarnoudse-Moens CS, Smidts DP, Oosterlaan J, Duivenvoorden HJ, Weisglas-Kuperus N. Executive function in very preterm children at early school age. J Abnorm Child Psychol. 2009; 37:981–993. [PubMed: 19488851]
121. Hack M. Young adult outcomes of very-low-birth-weight children. Semin Fetal Neonatal Med. 2006; 11:127–137. [PubMed: 16364703]
122. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics. 2009; 123:1037–1044. [PubMed: 19255037]
123. Treyvaud K, Ure A, Doyle LW, et al. Psychiatric outcomes at age seven for very preterm children: rates and predictors. J Child Psychol Psychiatry. 2013; 54:772–779. [PubMed: 23347471]
124. Burnett AC, Anderson PJ, Cheong J, Doyle LW, Davey CG, Wood SJ. Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. Psychol Med. 2011; 41:2463–2474. [PubMed: 21733218]
125. Linsell L, Malouf R, Johnson S, Morris J, Kurinczuk JJ, Marlow N. Prognostic Factors for Behavioral Problems and Psychiatric Disorders in Children Born Very Preterm or Very Low Birth Weight: A Systematic Review. J Dev Behav Pediatr. 2016; 37:88–102. [PubMed: 26703327]
126. Breslau J, Miller E, Joanie Chung WJ, Schweitzer JB. Childhood and adolescent onset psychiatric disorders, substance use, and failure to graduate high school on time. J Psychiatr Res. 2011; 45:295–301. [PubMed: 20638079]
127. Vohr BR, Allan W, Katz KH, Schneider KC, Ment LR. Early predictors of hypertension in prematurely born adolescents. Acta Paediatr. 2010; 99:1812–1818. [PubMed: 20586997]
128. Hovi P, Andersson S, Raikkonen K, et al. Ambulatory blood pressure in young adults with very low birth weight. J Pediatr. 2010; 156:54–59 e51. [PubMed: 19796771]
129. Haley AP, Gunstad J, Cohen RA, Jerskey BA, Mulligan RC, Sweet LH. Neural correlates of visuopatial working memory in healthy young adults at risk for hypertension. Brain Imaging and Behavior. 2008; 2:192–199.
130. Vohr B. Expanding the definition of long-term follow-up to late adulthood. Pediatrics. 2015; 135:e1038–e1039. [PubMed: 25733756]
131. Heinonen K, Eriksson JG, Lahti J, et al. Late preterm birth and neurocognitive performance in late adulthood: a birth cohort study. Pediatrics. 2015; 135:e818–e825. [PubMed: 25733746]
132. Luu TM, Vohr BR, Allan W, Schneider KC, Ment LR. Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. Pediatrics. 2011; 128:313–322. [PubMed: 21768322]
133. Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. Pediatrics. 2007; 119:37–45. [PubMed: 17200269]
134. Johnston KM, Gooch K, Korol E, et al. The economic burden of prematurity in Canada. BMC Pediatr. 2014; 14:93. [PubMed: 24708755]
135. Vohr BR, Allan WC, Westerveld M, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2003; 111:e340–e346. [PubMed: 12671149]
136. Taylor HG, Klein N, Minich NM, Hack M. Middle-school-age outcomes in children with very low birthweight. Child Dev. 2000; 71:1495–1511. [PubMed: 11194251]
137. Saigal S, den Ouden L, Wolke D, et al. School-age outcomes in children who were extremely low birth weight from four international population-based cohorts. Pediatrics. 2003; 112:943–950. [PubMed: 14523190]
138. Lee ES, Yeatman JD, Luna B, Feldman HM. Specific language and reading skills in school-aged children and adolescents are associated with prematurity after controlling for IQ. Neuropsychologia. 2011; 49:906–913. [PubMed: 21195100]
139. Hack M, Taylor HG, Drotar D, et al. Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. JAMA. 2005; 294:318–325. [PubMed: 16030276]

140. Edwards J, Berube M, Erlandson K, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. J Dev Behav Pediatr. 2011; 32:678–687. [PubMed: 21900828]

141. Doyle LW, Anderson PJ. Improved neurosensory outcome at 8 years of age of extremely low birthweight children born in Victoria over three distinct eras. Arch Dis Child Fetal Neonatal Ed. 2005; 90:F484–F488. [PubMed: 15899930]

142. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. Pediatrics. 2003; 112:e30–e38. [PubMed: 12837903]

143. Boyle MH, Miskovic V, Van Lieshout R, et al. Psychopathology in young adults born at extremely low birth weight. Psychol Med. 2011; 41:1763–1774. [PubMed: 21134317]

144. Doyle LW, Roberts G, Anderson PJ. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. J Pediatr. 2010; 156:49–53 e41. [PubMed: 19783004]

145. Aylward GP, Aylward BS. The changing yardstick in measurement of cognitive abilities in infancy. J Dev Behav Pediatr. 2011; 32:465–468. [PubMed: 21555956]

TABLE 1

Early neurodevelopmental outcomes: Selected recent extremely preterm cohorts

	NICHD NRN[31]	**NICHD NRN [5]**	**VICS 2005[145]**	**Japan NRN[147]**	**EPICure 2 [148]**	**EXPRESS[38]**
Study group	<25 wk EGA	22–26 wk EGA	22–27+6/7 wk EGA	22–25 wk EGA	22–26+6/7 wk EGA	<27 wk EGA
Birth years	2002–2004	2006–2011	2005	2003–2005	2006	2004–2007
Age corrected for prematurity	18–22 months	18–22 months	2 years	36–42 months (chronological)	3 years	2.5 years
# (% follow-up of eligible survivors)	405 (93%)	2630 (92%)	163 (95%)	562 (72%)	576 (55%)†	415 (90%)
Blind	2.2%	0.4%	0	4.6%‡	1%	0.9%
Deaf/require aids	4.3%	1.4%	2.5%	Requires aids: 1.7%	Aids improve 0.2% do not Improve: 5%	Aids improve: 0.2% do not Improve: 0.7%
Developmental impairment	BSID-II MDI<70: 51% MDI<50: 19%	BSID-III Cognitive 70–84: 16.5% <70: 9.3%	*DQ None/1SD: 52% 1–2SD: 32% 2–3SD: 12% >3SD: 4%	*KSPD DQ <70: 35% <50: 11%	*Predicted MDI 70–84: 34% <70: 30%	*Cognitive/language None: 55% Mild: 25% Moderate: 11% Severe: 9%
CP or motor delay	Moderate: 8.7% Severe: 6.2%	Moderate: 3.4% Severe: 2.5%	Any CP: 9.8%	Any CP: 13.7% Profound CP: 8.2%	Any CP: 14% Moderate motor:3% Severe motor: 5%	Mild: 2.9% Moderate: 2.9% Severe: 1.3%
Overall disability or impairment	Any NDI: 58.5% Profound NDI:17.5% None/ minimal: 21.9%	Moderate NDI: 23.5% Severe NDI: 13.6%	None: 51% Mild: 29% Moderate: 16% Severe: 4%	§Any: 42.4% §Profound: 22.6%	None/mild: 75% Moderate: 12% Severe: 13%	None: 42% Mild: 31% Moderate: 16% Severe: 11%

*For VICS: DQ = developmental quotient compared with a contemporaneous NBW control group; for EPICure 2: Predicted MDI (Mental Developmental Index) BSID 2nd Edition from BSID-III; for EXPRESS: aggregated BSID-III cognitive and language score information, with mean and SD relative to a contemporaneous 37–41 week GA control group; for Japan NRN: formal evaluation by the Kyoto Scale of Psychological Development (KSPD) was available for only 318.

†Face to face study examiner evaluations occurred in 55.3%. Multiple imputation from complete perinatal, neonatal, and sociodemographic information estimated outcomes for the entire cohort.

‡Defined as no functional vision in one or both eyes

§Includes 173 with informal assessments of developmental delay by pediatricians, without formal developmental testing