

# Neurodevelopmental Outcomes of Extremely Preterm Infants

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## KEYWORDS

• Extremely preterm • Outcomes • Cognitive • Motor • Sensory

## KEY POINTS

- Continued improvements in perinatal and neonatal care continue to be associated with improved survival of extremely preterm infants less than 26 weeks gestation.
- Although there has been some evidence of improvement in neurodevelopmental impairment rates since the 1990s, rates are high and are inversely related to gestational age between 22 and 25 weeks.
- There are significant differences in rates of survival and neurodevelopmental impairment by geographic region and neonatal network related to multiple factors including population characteristics, perinatal/neonatal management, follow-up protocols, assessments, and definitions.

## CHALLENGES OF INTERPRETING NEURODEVELOPMENTAL OUTCOME STUDIES

When reviewing a survival or neurodevelopmental outcomes article, several factors that can impact the interpretation of the findings need to be considered. The first is the denominator for the percent of infants with a disability, which can vary from mothers presenting in labor with a live fetus, live births, infants admitted to the neonatal intensive care unit (NICU), infants discharged from the NICU, and infants seen in follow-up. For example, a hypothetical cohort of infants at 23 weeks is reported. In the first study 100 live births are reported and 10% survive, all are seen in follow-up at 24 months, and five have a major impairment. If one relates the follow-up data to live births the impairment rate is 5%, 5% have no major impairment, and 90% are deaths. The death or impairment rate is 95%. However, this may also be reported as major impairment seen in 5 (50%) of 10 of infants evaluated at 24 months. In addition, for greater generalizability, a population-based study (country, region, state) is preferable to multicenter, which is preferable to a single center study. A second variable of importance is the follow-up rate. Greater than 90% is ideal and validity of the

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outcome findings decreases as the lost-to-follow-up increases because of possible biases related to the lost cohort.<sup>1,2</sup> Third, is the time period because of the continually changing management of the NICU infant.<sup>3</sup> In addition, follow-up assessments administered may change by time period and country. Fourth, definitions, particularly of disability and impairment, and degree of severity may vary.

As an example, definitions, assessments, and protocols of neurodevelopmental outcomes for the National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Follow-up Study have been modified between 1993 and 2013. The initial follow-up subject criteria changed from a definition based on birth weight less than 1000 g of any gestational age to a definition based on gestational age less than or equal to 26 6/7 weeks. The change was made recognizing the advantage of a defined gestational age cohort and an effort to focus on the most vulnerable preterm (PT) infants at the limits of viability. Age of evaluation of 18 to 22 months corrected age (CA) was initially chosen because Bayley testing was believed to be reliable and that prolonging the time between discharge and follow-up beyond 18 to 22 months CA would increase the lost to follow-up. As evidence began to accumulate that older age of outcome improved the predictive validity of the neurologic assessment and developmental test scores, a decision was made to change the age of outcome to 22 to 26 months CA for infants born after July 1, 2012.

The NRN used the Bayley Scales of Infant Development (Bayley II)<sup>4</sup> from 1993 to October 2007. A limitation of the Bayley II was that it had two developmental scores: the Mental Developmental Index, a composite of cognitive and language tasks; and the Psychomotor Developmental Index, a composite of fine and gross motor skills. The new Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III),<sup>5</sup> consists of three separate developmental scores: a cognitive composite, a language composite (with receptive and expressive subscores), and a motor composite (with gross and fine motor subscores), in addition to social-emotional and adaptive behavior domains. Mean Bayley III cognitive scores, however, are approximately 12 points higher than mean Bayley II cognitive scores.<sup>3,6</sup> It is not yet entirely clear if the Bayley II underestimated scores or if the Bayley III overestimates scores. Caution is advised when comparing studies using different Bayley tests. In 2012, the NRN modified the threshold definitions for Bayley cognitive and motor impairment to moderate delay (70–84); severe delay (<70); and profound delay ( $\leq 54$ ).

Vision and hearing have been more difficult to categorize in terms of severity within the NICHD Network because of a single follow-up visit with limited-access diagnostic tests results. This has resulted in currently categorizing the vision as bilateral blind with corrected vision of less than 20/200 and hearing impairment as permanent hearing loss that does not permit the child to understand directions of the examiner and communicate with or without amplification.

The primary focus of most published outcome reports in infancy is the incidence of moderate to severe neurodevelopmental impairment (NDI), often defined in three categories of cognition, cerebral palsy (CP), and sensory (blindness or hearing impairment). This has been the outcome of interest because of the severity of the impact of severe and combined morbidities. In the NICHD NRN, rates of NDI at 18 to 22 months during the era of testing with the Bayley II were defined as the presence of any of the following: moderate to severe CP, cognitive or motor scores more than 2 standard deviations below the mean on standardized testing, bilateral hearing impairment requiring amplification, or bilateral blindness.<sup>7</sup> The most current definition for NDI includes separate categories of moderate (70–84), severe (55–69 for cognitive and 47–69 for motor), and profound (<55 for cognitive and <47 for motor) impairment for Bayley III scores for infants born after July 1, 2012.

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