Clinical Review
Preterm Birth and Neurodevelopment: A Review of Outcomes and Recommendations for Early Identification and Cost-effective Interventions

by Perri S. Sutton, and Gary L. Darmstadt
Family Health Division, Bill & Melinda Gates Foundation

Correspondence: Gary L. Darmstadt. E-mail <gary.darmstadt@gatesfoundation.org>.

Summary
This review summarizes research findings to date on neurological and health outcomes following preterm birth, tools to identify children at risk for neurodevelopmental impairment and interventions to prevent preterm birth and improve outcomes. We bring together findings from research in high- and low-income countries, with an aim to provide a global perspective on the issues. Around the world, preterm birth is rising in importance as a cause of under-five morbidity and mortality, and we project that this trend will continue over time, particularly given the lack of interventions to prevent the condition. With the development of improved screening instruments, further identification and scale up of cost-effective interventions to optimize early childhood development and accelerated research on the underlying biological mechanisms, we have an opportunity to reduce rates of neurodevelopmental impairment, particularly in countries with the highest burden.

Key words: childhood disability, impairment, neurodevelopment, preterm birth, low birthweight, low- and middle-income countries.

Overview of Disability among Children Born Preterm
Emerging data and analysis indicate that >1 of 10 babies born around the world in 2010 were premature, and this translates to an estimated 15 million preterm births [1]. Improved neonatal intensive care, technological advances and expanded access to life-saving commodities and equipment have resulted in increased survival rates for very premature and extremely premature infants since the 1960s (see Table 1 for preterm categories with corresponding birthweight and/or gestational age). However, the immature brain, lungs, gastrointestinal tract and skin of preterm infants are particularly susceptible to injury and abnormal development and function, often leading to long-term neurological and health problems [2, 3]. There is an inverse relationship between birthweight or gestational age and risk for developmental impairment, with increasing incidence as birthweight or gestational age decreases [4]. Serious impairment, defined as problems in body function or structure, which may be temporary or permanent, is generally a more stable condition and typically leads to a disability requiring rehabilitation; mild impairment is a more reversible condition amenable to early intervention. Studies that have followed extremely preterm and extremely low birthweight infants into school age and early adulthood have shown higher rates of motor, cognitive or behavioral impairments as compared with infants born at term [5].

Overall, it is difficult to define and quantify the tradeoff between death and disability associated...
with premature birth. Very few longitudinal studies have been conducted, and comparative analyses of existing reports on morbidity and mortality are challenging owing to variable definitions of live birth, and non-standardized tools for measurement of morbidities, as well as the fact that geographies vary considerably in terms of policies and resources related to the care provided for extremely premature infants [6]. It is also difficult to predict outcomes for today’s preterm infants based on data from cohorts born in earlier generations, given more recent advances in neonatal intensive care.

While it is well documented that survivors of extreme prematurity have higher rates of adverse health outcomes into adulthood, the majority of them lead productive and healthy lives and report either no differences or small reductions in quality of life compared with those who were born at term [7]. Viewing the tradeoff in economic terms, one study examined the relationship between gestational age at birth and outcomes in adulthood in a national cohort in Norway, and found that at 19–35 years of age, nearly one in nine persons who had been born at 23–27 weeks of gestation received a disability pension, as compared with 1 of 59 born at term [8]. This study also found significant associations between gestational age at birth and education level attained, income, receipt of Social Security benefits and the establishment of a family.

Preterm birth is one of a number of intrauterine and neonatal insults that increase risk of long-term medical disabilities. Importantly, a January 2012 systematic review of long-term neurodevelopmental outcomes after intrauterine and neonatal insults estimated that 8.1% of preterm neonates present with multiple insults including neonatal sepsis, meningitis, hypoxic ischemic encephalopathy, jaundice, tetanus and congenital infections including cytomegalovirus, herpes, rubella and toxoplasmosis [9]. Furthermore, this review reported that the incidence of impairment after preterm birth alone was 28% and that of infants with prematurity complicated by sepsis was 49%, suggesting that sepsis increases the likelihood of neurological impairment in preterm neonates. Another study that looked at neonatal mortality due to birth asphyxia in southern Nepal found that the strongest risk factors were the combined synergistic effects of maternal fever, as a sign of serious infection, and prematurity [10]. These data illustrate the increased vulnerability of preterm infants to additional insults.

Given that the likelihood and degree of impairment increases as preterm infants present with one or more additional insults, it is critical to prevent or minimize intrauterine and neonatal insults, particularly for at-risk mothers and infants. Policy makers should focus on strategies that make integrated maternal-neonatal care and highly cost-effective interventions available, including community-based recognition and treatment of maternal infections during pregnancy [11].

The most commonly reported medical disabilities for which risk increases with decreasing gestational age are cerebral palsy (CP), cognitive dysfunction, blindness and impaired vision, hearing loss and disorders of psychological development, behavior and emotion.

**Cerebral palsy**

CP describes a group of disorders of movement and posture that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain [12]. CP is one of the major neurological complications of extreme premature birth, with historical rates 70–80 times higher than in term infants [13]. There is emerging evidence, however, that CP rates in high-income settings are decreasing for all but the most immature (<28 weeks) and lowest birth-weight (<1000 g) babies, and this may be the result of brain-oriented intensive care [6].

**Cognitive function**

Children who were born preterm are at significant risk for reduced cognitive performance at school age. A meta-analysis of results from 15 case-control studies that followed preterm infants and evaluated them at age 5 years showed that lower birthweight and gestational age were significantly correlated with decreases in cognitive test scores (Fig. 1) [4].

Among extremely preterm infants, cognitive and neurologic impairment is common at school age. In an assessment of a cohort of children in the UK and Ireland born before 26 weeks of gestation, the Kaufman Assessment Battery for Children was used to measure cognitive impairment at 6 years of age. In this study, when classmates who were full term at birth were used as the reference group, 41% of extremely preterm children scored >2 standard deviation below the mean cognitive score [14].
In the same study, when test reference norms were used as the comparison, cognitive impairment was present in 21% of the children born extremely preterm. The significant difference in results within a single study depending on the use of normative data vs. contemporary comparison group data, points to the importance of establishing standardized tools for measuring and evaluating neurodevelopment.

A recent study that evaluated the effects of intrauterine growth restriction (IUGR) and very preterm birth on cognitive outcomes found that children born very preterm after IUGR have an increased risk of cognitive impairment compared with children delivered very preterm for other reasons. The same study found that differences in cognitive outcome were restricted to boys who may have been especially vulnerable to the influence of IUGR and very preterm birth [15]. It is unclear why gender may influence cognitive outcome in very preterm infants with IUGR. However, animal studies have revealed influences of biological gender and sex hormones on responses of the cardiovascular system to an adverse fetal environment [16, 17].

Late preterm birth compared with term birth has shown to more than double risk of borderline intellectual functioning, defined as full-scale intelligence quotient (IQ) and performance IQ scores <85 [18]. What remains unclear is whether the increased risk for cognitive impairment is owing to a reduction in gestational age, or more directly related to an underlying obstetric and/or neonatal complication.

Blindness and impaired vision
Retinopathy of prematurity (ROP) is a potentially blinding eye disorder that occurs when abnormal blood vessels grow and spread throughout the retina, and is known to be the leading cause of blindness in premature infants [19]. One study of ROP among very low birthweight infants in Singapore found an incidence of 29.2% and suggested that both immaturity and compromised pulmonary function are important etiological factors [20]. While there are few studies on the incidence of ROP in developing countries, one study in India reported an alarmingly high rate of 47% among high-risk preterm infants [21]. A study of preterm infants of gestational age <33 weeks admitted to the Special Care Nursery of Dhaka Shishu Hospital in Bangladesh found that 5 out the 114 (4.4%) children seen in follow-up were diagnosed with ROP [22].

Therapeutic interventions for extremely premature and low-birthweight infants include surfactant administration, mechanical ventilation, oxygen therapy and antenatal and postnatal corticosteroids, and it is disputed whether severe ROP is due to one or more of these interventions or due to the severity of illness. One study of premature infants with <1500 g birth-weight in a neonatal intensive care unit in Michigan found that prolonged use or higher cumulative dose of postnatal hydrocortisone was associated with an increased risk for ROP; however, this study did not determine whether postnatal steroid treatment was the risk factor or a marker of underlying illness severity [23]. Further studies need to focus on biologic markers to better understand the pathogenesis of ROP and the influence of therapies.

Hearing loss
Rates of hearing impairment in very low birthweight and extremely low birthweight infants are generally reported within a range of 1–7%, and variations are related mainly to differences in the definitions and age at reporting [24, 25]. Very low birthweight infants

FIG. 1. Correlations between mean cognitive scores, birth weight and gestational age.
Reprinted with permission [4].

[Image of graph showing correlations]
have been found to have central auditory processing disorders that make it difficult for them to discriminate simple speech sounds and limit auditory memory span, and these difficulties may have a detrimental effect on the acquisition of language skills and learning at school [26].

**Psychological development, behavior and emotion**

Negative behavioral sequelae of preterm birth have been extensively reported, and the most commonly studied outcomes include externalizing or internalizing behaviors and attention deficit hyperactivity disorder (ADHD). Externalizing behaviors constitute ‘acting out’ and can be described as aggressive, impulsive, coercive and non-compliant, and internalizing behaviors are typical of an inhibited style that can be described as withdrawn, lonely, depressed and anxious [27]. A 2002 meta-analysis of behavioral outcomes of school-aged children who were born preterm showed a 2.6-fold risk for developing ADHD and frequent manifestations of externalizing or internalizing behaviors [4].

Because multiple factors contribute to neurobehavioral outcomes, assessment of the contribution of any one factor is complex. In one study, birthweight was consistently the strongest predictor of parent ratings of behavioral outcome, and findings confirmed an inverse relationship between birthweight and behavior, indicating that the lower the birthweight the greater the behavioral problems [28].

A review of studies that followed preterm infants into adulthood found that despite higher rates of behavioral problems encountered during youth, most young adults demonstrate good recovery in adapting to roles of adult functioning and self-report a quality of life that is similar to their term-born peers [29].

**Identification of Children at Risk for Neurodevelopmental Impairment**

The absence of adequate data from low-income countries—where the vast majority of neonatal morbidity occurs—is a major constraint to understanding the incidence and burden of long-term neurodevelopmental impairments [11]. This lack of data is partly based on the lack of standardized tools for measurement.

Without standardized assessment of infants, behavioral problems that emerge later in childhood are often the first sign that development is not occurring along a normal trajectory [30]. Reducing this delay in the identification of impairment is important so that interventions may be started as early as possible to prevent or ameliorate progression [31].

Typically, a two-step approach is needed to identify young children at risk: a screening examination at population (or household or primary care clinic) level (administered by a frontline worker), followed by a definitive test at a health facility (administered by a health professional). A 2007 review of the literature on the prevalence of disabilities and impairments in <5-year-old children in low- and middle-income countries revealed that the most commonly used screening tool to assess disability is the Ten Questions questionnaire (TQ), an instrument that is good for assessing severe disabilities in children >2 years, but is not adequate for <2-year-old children or for identification of cognitive disabilities and moderate degrees of intellectual impairment [11]. To address the need for a home-based screening tool for <2-year-old children, a Developmental Screening Questionnaire (DSQ) was recently developed and validated in Bangladesh [32]. The DSQ has excellent sensitivity for impairments of vision, hearing and seizures, good sensitivity for speech and gross motor impairments and it was fair for identifying behavioral, cognitive and fine motor impairments; specificity ranged from 82% to 87%. Limitations in sensitivity underscore the importance of a system to also screen older children from high-risk populations to identify those who may have been missed by early screening.

Once a child has screened positive using a tool such as the TQ or DSQ, the presence of a disability or impairment must be verified through definitive testing, and the nature of the disability must be identified to direct intervention services most effectively. The Rapid Neurodevelopmental Assessment (RNDA) tool, recently validated for 0–5-year-olds, was developed to address the need for simplified tools for use by non-specialist health professionals to identify specific neurodevelopmental impairments and disabilities in infants, toddlers and preschoolers [33, 34]. Standardized tools used in western settings are too specialized and require levels of skills and resources rarely found in low- and middle-income settings. The RNDA is reliable and valid for identifying specific neurodevelopmental impairments including autism spectrum disorders, and when linked to appropriate interventions, the RNDA has great potential to reduce disability-adjusted life-years as a result of neurodevelopmental impairments. This tool can be administered by a range of health professionals; however, further evaluation of the RNDA is needed to determine validity when used by lower-skilled frontline health workers.

While there may be limited near-term applicability in low-income countries, magnetic resonance imaging (MRI) of the brain has been proposed as another method for identifying and predicting neurodevelopmental impairment. Preterm birth is known to be associated with long-term reductions in the volume of the basal ganglia, corpus callosum, amygdala and hippocampus, and these brain region volumes correlate with IQ measures in childhood [35]. One study found significant associations between white-matter and gray-matter abnormalities on MRI in very
Birth rates [38]. Key interventions during pregnancy are priority interventions to reduce preterm birth. Vaccinations and screen for sexually transmitted infections, provide folic acid supplementation, promote rubella vaccination and screen for sexually transmitted infections are priority interventions to reduce preterm birth rates [38]. Key interventions during pregnancy include provision of basic antenatal care; identification and treatment of malaria, tuberculosis and human immunodeficiency virus; nutritional supplementation including calcium; behavioral, social and financial support services; identification and treatment of hypertension disease; administration of progesterone to prolong pregnancy; and identification and treatment of structural abnormalities, e.g., cervical cerclage [39]. However, full deployment of existing antenatal interventions to prevent preterm birth would only avert about 10–15% of the burden. Therefore, interventions to mitigate the burden of disabilities and impairments are an imperative.

A 2009 Cochrane review examined the effectiveness of early developmental interventions after discharge from hospital for preterm infants on motor or cognitive development. They found that early interventions have a significant impact on cognitive development at infant and preschool age; however, there is little evidence of an effect on motor development [40]. As with neurodevelopmental screening tools, intervention programs vary significantly in regard to content, focus and intensity, and so we are limited in our ability to draw overarching conclusions from cross-study comparisons. However, a number of evidence-based and cost-effective interventions that are applicable in low- and middle-income countries have been identified (Table 2) [40–43].

A 2009 review focused on the effectiveness of community-based interventions to optimize early childhood development in low resource settings found that techniques such as play and reading are beneficial for cognitive development, and skin-to-skin-care promotes parent–child interaction (PCI) and has positive effects on motor development [44]. Play was considered to be any interaction between the mother/caregiver and the child involving toys/games. Reading was characterized as either shared reading of a book between the mother/caregiver and the child, or preschool education through teachers/parents.

### Interventions for Prevention and Improved Outcomes

The learning, behavioral and motor impairments in children born preterm are associated with medical risk factors such as birthweight and gestational age, and with non-medical factors such as social class, maternal education and the home environment [37]. These variable risk factors have important implications for the type, timing and focus of interventions that may improve short- and long-term outcomes of preterm infants.

Before describing interventions to treat preterm infants, it must be noted that interventions to prevent preterm birth are the preferred way to reduce mortality and morbidity associated with prematurity. This is particularly true in low resource settings where access to clinics, hospitals and life-saving technologies for infants born preterm may be limited. Preconception care services that prevent pregnancy in adolescence, prevent unintended pregnancies, promote birth spacing, optimize prepregnancy weight, provide folic acid supplementation, promote rubella vaccination and screen for sexually transmitted infections are priority interventions to reduce preterm birth rates [38]. Key interventions during pregnancy
High-quality PCI is an important component of early intervention programs, and there is evidence that it positively influences cognitive and social development in children [45]. The links between psychosocial factors in early childhood and brain development are becoming clearer, and a recent study found that maternal nurturance observed in early childhood was strongly predictive of hippocampal volume measured at school age [46]. In this study, maternal nurturance was objectively measured through structured observation during the preschool period of development.

An important component of interventions for at-risk children is education for parents and educators to help them detect early signs of impairment and to improve their understanding of the unique developmental needs of this vulnerable population. Also, interventions to reduce maternal stress such as counseling and peer-support groups are beneficial, particularly given that maternal stress is an important risk factor for preterm birth and subsequent neurodevelopmental morbidities in children [47]. Additionally, socioeconomic empowerment of families will facilitate primary and tertiary level care-seeking, improving access to more specialized services [48].

As with interventions developed to reduce perinatal and neonatal mortality, the real challenge is in generating political will and leadership, and resources, to apply these interventions at scale, particularly in countries with the highest burden of neurodevelopmental impairment among children [49].

Conclusions
For improved screening and identification of children at risk for neurodevelopmental impairment, research is needed to build on current efforts to develop standardized, culturally sensitive, valid screening instruments for use by frontline health workers and definitive tests for identifying specific disabilities and impairments by health professionals in low resource settings. Such tools must conform to standardized metrics to enable comparison of study results and improved understanding of global incidence and burden of disabilities and impairments among children born preterm. Furthermore, systems must be in place to reach infants and toddlers with these tools, and enable a two-step process whereby those who screen positive for impairment are seen by a health professional for definitive testing, diagnosis and rehabilitation.

To identify successful early development interventions for preterm infants, current research points to the need for randomized controlled trials combined with long-term follow-up studies focusing on both motor and cognitive outcomes [41]. Prospective long-term follow-up in low- and middle-income countries should address existing questions such as the following:

- Are preterm infants at elevated risk for future cardiovascular and metabolic disorders due to their small size at birth?
- Does skin-to-skin-care of preterm neonates promote healthy brain development at school age and beyond?
- Are cognitive skills of adolescents who had IUGR significantly different from their peers born at term, and does gender influence outcomes?
- What are the specific mechanisms in the pathogenesis of ROP and the role of biologic markers?
- What is the impact on neurodevelopmental outcome of life-saving therapies such as antenatal and postnatal corticosteroids, oxygen administration and duration of ventilation?

With advanced imaging techniques, we have an unprecedented opportunity to assess relationships between behavioral and cognitive outcomes of preterm infants and anatomic differences in brain structure. Recent findings of an association between early childhood maternal support and hippocampal brain volume must be replicated with further research, and further development of animal models is needed to build our understanding of the underlying biological mechanisms. Expanding our knowledge in this area is critical for the development of perinatal and childhood interventions, and will allow us to reduce the burden of brain injury and developmental impairment following preterm birth.

With further research and collaboration among scientists, health care providers, policy makers and donors, it is critical that we build on the global community’s understanding of neurodevelopmental outcomes associated with preterm birth, and identify cost-effective interventions that prevent and minimize impairment, and ultimately economic impact.

References


