Neurodevelopmental Outcomes of Preterm Children at School Age and Beyond

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KEYWORDS

• Preterm • Child development • Neuro development • Developmental disabilities • Follow-up • Outcomes • Cognitive • Motor

KEY POINTS

- Prematurity is associated with motor, cognitive, behavioral, psychiatric, and other disabilities in adolescents and adults and the frequency and severity is inversely associated with gestational age at birth.
- Most teens and adults with prematurity-associated disabilities were born moderately or late preterm, but this group is less well studied compared with those born extremely preterm.
- Preterm adolescents and young adults have similar well-being and greater risk avoidance than controls.
- Disability-free preterm survivors attain a lower level of education and income than term-born peers but health-related quality of life is unaffected.

IMPORTANCE OF THE PROBLEM

Globally, approximately 15 million infants every year (11.1% of all births) are born preterm, at less than 37 completed weeks' gestation, with national rates varying from 5% to 18%.[1] As a result of the large number of preterm births and the increasing preterm birth survival rates, the long-term sequelae of prematurity will impact annually approximately 14 million children, their families, and societies. Unfortunately, the advances in survival have not been accompanied by an equal reduction in adverse outcomes.[2]

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Most children born preterm are doing very well with a very good quality of life. The goal of this review was to highlight the challenges that some preterm survivors face so that they will receive the necessary supports and that we can strive to continuously improve the antenatal, perinatal, postnatal, and childhood care of these children.

Although many trials and cohort studies of preterm populations evaluate outcomes at 18 to 24 months of age, they are limited in their ability to describe the full neurodevelopmental impact of prematurity. A review of prematurity-associated school-age and adult outcomes is therefore important. The focus in this review is on neurodevelopment because of its clinical significance and frequency. Other health outcomes have been reviewed by Luu and colleagues.[3]

Most preterm births are late preterm, defined as occurring between 34 0/7 weeks and 36 6/7 weeks' gestational age or moderate preterm, 32 0/7 to 33 6/7 weeks' gestational age. In the United States in 2015, only 1.59% were born very preterm at less than 32 weeks' gestation and 0.68% extremely preterm at less than 28 weeks' gestation.[4] The frequency and severity of adverse outcomes vary inversely with gestational age. The research methods to describe outcomes in the larger late preterm cohorts often differ from those used in the smaller very preterm cohorts. Very preterm and moderate–late preterm outcomes are therefore described separately.

RESEARCH CHALLENGES

Research on school-age neurodevelopmental outcomes in the preterm population is derived mostly from observational cohort studies. The reader must therefore consider the potential biases and limitations of the research methods. Population-based samples are preferred over multicenter or single-center cohorts to minimize referral biases. Small sample size may be a problem in single-center cohorts, especially when studying the lowest gestational ages. With variability in preterm care between sites and over time, the region and year(s) of birth of the cohort need to be considered. Attention must be paid to the denominator. Especially for the most premature babies with the highest mortality, the incidence of adverse outcome(s) varies significantly for the denominators live births compared with all births (live and stillbirths). Less obvious but equally significant is when the denominator includes only children who could complete a test or when children with a sensory, behavioral, or very severe impairment are excluded. Much of the data related to neurodevelopmental outcomes for adults born preterm come from national birth registries and large birth cohorts with linkage to intelligence testing at time of conscription at 18 or 19 years of age.[5] Adults with disabilities may be excluded from conscription and therefore observed associations likely underestimate the effect of prematurity on adult outcome. In addition, typically only male adults were registered in conscription databases and results therefore may not be relevant to female adults born preterm. When subjects of different gestational ages are lumped together, comparisons between studies with different gestational age cutoffs are difficult. Attrition bias is a major concern, as children lost to follow-up differ from those assessed.[6] Whereas greater than 90% follow-up is ideal, in longitudinal cohort studies this gets increasingly difficult as children get older. Finally, many studies that examine adult outcome do not use a healthy, nonadmitted term control group as a comparison for late preterm infants, which limits the conclusions that can be drawn from any analysis.[7]

WHY LOOK AT SCHOOL-AGE AND LONGER-TERM OUTCOMES?

Parents, families, health care providers, and society are interested in knowing what the long-term future holds for the infant born preterm, either to support the child and the child's family, provide counseling, assist with decision making, providing postdischarge services, or planning for health care service needs.[8] Compared with the limited repertoire of the infant and preschooler, at older ages the human brain is capable of a multitude of complex tasks that can be evaluated reliably and provide a good estimate of adult functioning. When studying the adult outcomes of children born preterm, the benefits of longer-term studies must be balanced against the clinical irrelevance of neonatal intensive care unit (NICU) practices from a generation ago, the increasing attrition biases as NICU graduates leave their parents' homes, and the cost and logistics of performing longitudinal studies that span over 20 years. Despite these challenges, there are a few remarkable cohort studies that have successfully maintained contact and engaged a high proportion of their subjects into adulthood.

By school age, the researcher has a larger range of assessment tools to choose from. Children's abilities or traits can be measured on a continuous or categorical scale for a variety of domains, such as cognitive, executive function, language, behavior, motor, hearing, and vision. Continuous outcomes can be described using a measure of central tendency (eg, means or median) and measure of spread (eg, standard deviation and interquartile range) for each domain or categorically/dichotomously (eg, "normal" and "abnormal"), which requires choosing cutoff points. Composite outcomes require defining multiple cutoff points and there is a lack of consensus on how to define these composite outcomes.[9] The World Health Organization's international classification of functioning, disability, and health shifts the focus from disease to health, and considers outcomes from the perspective of body structures and functions, individual activities, and participation, with a version for children and youth (ICF-CY).[10] The ICF-CY detailed classification system is conceptually promising but challenging to use.[10] Further development of core sets, such as those developed for cerebral palsy will be helpful.[11]

Predicting the pattern, frequency, and severity of adult outcomes improves with age as neurocognitive abilities mature. In early childhood, the Bayley Scales of Infant and Toddler Development, third edition and earlier versions, measure development rather than cognitive potential, which has a poor predictive ability for school-age cognitive abilities.[12] It is well accepted that correction for prematurity by calculating age from the expected date of delivery should be used rather than chronologic age based on birth date for the first 2 years of life. However, differences between corrected and chronologic age are still apparent at 5 years of age.[13] Cognitive impairment is overestimated by early measures, and impairment rates fall with increasing age at assessment. As shown by Marlow and colleagues,[14] using the EPICure very preterm cohort assessed at 30 months and 6 years of age, degree of disability is also not static, as 40% of those with a severe disability at 30 months changed category and 25% initially considered as disability-free were classified as having a moderate to severe disability. In the Caffeine for Apnea of Prematurity trial, mean intelligence quotient (IQ) scores were 20 points higher than the 18 months corrected age mental developmental index on the Bayley Scales of Infant Development, second edition.[15] Multiple studies with similar findings have therefore supported the conclusion that outcomes at school age or beyond are more valid.[16] Please see **Box 1** for a summary of the pros and cons of using school-age outcomes.

THE VERY PRETERM CHILD: OUTCOMES AT SCHOOL AGE AND BEYOND

Neurodevelopmental outcomes in the older child can be described either using a broad-stroke picture or by zooming in on specific skills. In early childhood, a global

Box 1
Pros and cons of using school-age outcomes

- Pros
  - Predictive of adult outcomes
  - Able to measure a variety of specific abilities
  - Able to measure patient-reported health-related quality of life
- Cons
  - Reflects neonatal care from an earlier era
  - Typically higher attrition rates
  - More difficult and often more costly to collect

description of neurodevelopmental outcome using a composite outcome including one or more of cerebral palsy, cognitive, language, or motor developmental delay or a visual or hearing impairment is common. This is less common at school age where the evaluations performed in a study reflect more a sample of skills rather than a comprehensive measure. The Victorian Infant Collaborative Study Group evaluated 8-year-old extremely preterm children and compared major neurosensory disabilities, defined as IQ less than -2 SD, moderate or severe cerebral palsy, blindness or deafness, among 3 birth cohorts (1991–1992 vs 1997 vs 2005) and found rates unchanged at 18%, 15%, and 18% in these 3 time periods.[17] In a review of neurodevelopmental sequelae, recognizing that definitions varied, the 2 studies in which outcome was assessed at 5 years or beyond, 21% to 25% of subjects born extremely preterm at 26 weeks' gestation or less had sequelae.[18]

GLOBAL MEASURES OF OUTCOME

Other outcomes that have been used to give a global picture of neurodevelopment or health include the inability to work because of a medical disability, functional limitations, and quality of life. In a national registry of adults in Norway, Moster and colleagues,[19] described medical disability affecting working capacity as varying from 10.6% for adults born at 23 to 27 6/7 weeks' gestation to 2.4% for those born later preterm and 1.7% for term-born adults. A cohort of 241 very low birth weight (<1500 g birth weight) young adults from Cleveland, Ohio, reported similar health, wellness, and functioning compared with term-born controls but greater risk avoidance and less resilience.[20] Mental and emotional delays, restriction of activities of daily living, and self-care and chronic health disorders are more common in children born preterm than controls, which persists into adulthood.[20] Health-related quality of life when measured using parents as proxies, was lower in preschool and teenaged children born preterm.[21] Despite more functional limitations, extremely low birth weight teens and young adults rated their own quality of life as highly as controls.[21]

MOTOR OUTCOMES

Motor impairments are common in the preterm population. Cerebral palsy, the most severe form, is an umbrella term to describe a varied group of movement and posture disorders related to a static insult to the fetal or infant brain that may be accompanied by epilepsy and disorders of sensation, perception, cognition, communication, and behavior.[22] Prematurity is the most frequent cause of cerebral palsy, with an incidence of 9.1% in adults born at 23 to 27 weeks' gestation inclusive, 79 times higher than in term-born subjects.[23] However, developmental coordination disorder, a disorder of motor coordination not due to cerebral palsy, other medical conditions, or pervasive developmental disorder, that affects daily or academic functioning is also increased (odds ratio [OR] of 8.66 with a 95% confidence interval [CI] of 3.40–22.07) for very low birth weight infants compared with controls.[24] From a systematic review, in children born preterm, the incidence for mild-moderate motor impairment is 40.5% and for moderate impairment is 19.0%.[25] Compared with term-born children, motor skills are significantly lower in preterm children with a standardized mean difference (SMD) of −0.57 to −0.88 from infancy to 15 years of age.[24–26]

COGNITIVE OUTCOMES

Cognitive abilities, including intelligence, and academic performance are adversely affected by prematurity. In a Japanese cohort born at less than 28 weeks' gestation between 1992 and 2005, 31% had IQ scores <70 (< −2 SDs) at 6 years of age, although rates of 13% to 15% are more commonly reported in the extremely preterm population, with some reports of increasing impairment rates over time.[25,27–29] In a meta-analysis, prematurity had a significant impact on full-scale IQ (SMD −0.70) with a larger effect on performance (SMD –0.67) than verbal (SMD −0.53) IQ (**Table 1**).[30] Similar cognitive results were seen at all ages from preschool to adult.[30] The effect was greater for the more preterm population (see **Table 1**) and gestational age accounted for 39%, 38%, and 48% of the variance in full-scale IQ, verbal IQ, and performance IQ, respectively.[30] In children born preterm, cognitive scores are 11 to 12 points lower and in those free of disability, adjusting for sociodemographic variables, the mean IQ is 5 to 7 points lower (0.3–0.6 SD) than in controls.[30–33] Siblings of extremely low birth weight children have a higher IQ than their sibling in 84% of cases.[28] Cognitive function is complex, and aspects other than IQ need to be considered. Executive function encompasses the purposeful, goal-directed behaviors used to execute cognitive and other functions. Premature children with executive dysfunction have more difficulty with tasks such as initiating activities, organization, flexibility in generating ideas and problem solving, working memory, inhibition, and attention problems.[28,34] Weaknesses in working memory and visuo-motor integration have been documented as particular challenges in preterm survivors in multiple countries.[32] Working memory and processing speed are approximately 0.5 SD lower in preterm than term-born cohorts.[25] An advantaged home environment is associated with an improved cognitive trajectory from 20 months to 8 years of age.[31,33]

ACADEMIC OUTCOMES

Preterm children are 2.85 times more likely than their term-born peers to receive special education (see **Table 1**) and score significantly worse in arithmetic (SMD –0.6 to −0.78), reading (SMD −0.44 to −0.67), and spelling (SMD −0.52 to −0.76) (see **Table 1**).[30,35,36] Learning difficulties are reported in 50% to 70% of very low birth weight school-age children and inversely correlated with birth weight: 72% of children with a birth weight < 750 g, 53% with birth weight 750 to 1000 g and 13% of normal birth weight controls.[33,35] IQ is only one of several determinants of academic success. Academic achievement is often lower than anticipated by IQ in preterm children and may be explained by commonly identified weaknesses in attention, executive functioning, visual-motor skills, and verbal memory in preterm children.[33,34] Visual-motor integration (see **Table 1**), important for academic performance, which can be affected by the white matter pathways, is worse in the preterm population.[37]

Table 1
Domain-specific neurodevelopmental measures for extreme, very, and moderate to late preterm infants at school age and beyond

Domain	Extreme Preterm	Very Preterm	Moderate–Late Preterm	All Preterm
Global measures of outcome		[53]ASQ >2 SD below mean AOR 3.2 (1.9–5.4)[c]	[53]ASQ >2 SD below mean COR 2.1 (1.34–3.4)[c]	
Motor		[23]MABC < 5%ile OR 6.29 (4.37–9.05)[c] [23]MABC 5–15%ile OR 8.66 (3.40–22.07)[c] [26]MABC –0.65 (−0.70 to −0.60)[a] [26]BOTMP −0.57 (−0.68 to −0.46)[a]		[25]Motor −0.59 (−0.89 to −0.28)[a]
Cognitive	[25]Full-scale IQ −0.78 (−0.85 to −0.72)[c] [25]Performance IQ −0.89 (−1.05 to −0.72)[c] [25]Verbal IQ –0.67 (−0.83 to −0.51)[c]	[25]Full-scale IQ −0.73(−0.78 to −0.67) [c] [25]Performance IQ −0.65 (−0.73 to −0.57)[c] [25]Verbal IQ –0.55 (−0.63 to −0.48)[c]	[25]Full-scale IQ −0.24 (−0.35 to −0.12) [25]Performance IQ –0.28 (−0.53 to −0.02)[c] [25]Verbal IQ -0.14 (−0.35 to 0.07)	[25]Full-scale IQ −0.70 (−0.73 to −0.66)[c] [25]Performance IQ −0.67 (−0.73 to −0.60)[c] [25]Verbal IQ −0.53 (−0.60 to −0.47)[c] [30]Preterm IQ difference −11.94 (10.47–13.42)[c] lower in preterms
Academic		[34]Math −0.60 (−0.74 to −0.46)[a] [34]Reading −0.48 (−0.60 to −0.34)[a] [34]Spelling −0.76 (−1.13 to −0.40)[a]		[25]Reading −0.51 (−0.67 to −0.35)[a] [25]Math −0.42 (−0.90 to 0.006) [25]Spelling –0.51 (−0.92 to −0.09) [35]Math −0.71[a] [35]Reading −0.44[a] [35]Spelling −0.52[a] [35]Special education RR 2.85 (2.12 to 3.84)[a]

Language		[39]Expressive −0.71 (−0.86 to −0.55)[a] Expressive Semantics −0.40 (−0.50 to −0.31)[a] [39]Receptive −0.83 (−0.97 to −0.69)[a] [39]Receptive semantics −0.59 (−0.79 to −0.40)[a] [39]Receptive grammar −0.44 (−0.72 to −0.17)[a]		[42]Simple language −0.45 (−0.59 to −0.30)[b] [42]Complex language −0.62 (−0.82 to −0.43)
Behavior	[25]ADHD OR 3.3 (2.0,5.6)[c]	[25]ADHD 3.7 (1.8 to 7.7)[c] [34]CBCL internalizing −0.20 (−0.48 to 0.08) [34]TRF internalizing −0.28 (−.45 to −0.12)[a] [34]CBCL attention −0.59 (−0.74 to −0.44)[a] [34]TRF attention −0.43 (−0.61 to −0.25)[a] [34]Executive Function verbal fluency −0.57 (−0.82 to −0.32)[a] [34]Executive Function working memory −0.36 (−0.47 to −0.20)[a] [34]Executive Function cognitive flexibility −0.49 (−0.66 to −0.33)[a]	[25]ADHD 1.3 (1.1 to 1.5)[c]	[25]ADHD 1.6 (1.3 to 1.8)[c] [25]Behavior −0.72 (−0.97 to −0.47)[c]
Sensory visual-motor integration (VMI)		[37]Beery VMI −0.69 (−0.80 to −0.58)[a]		

Outcomes expressed as standard deviation units (95% confidence interval). Simple language measured using the Peabody Picture Vocabulary test, Complex language measured using the Clinical Evaluation of language Fundamentals. Only analyses including populations with school age or beyond and when stratified by age, older school age reported.

Abbreviations: ADHD, attention deficit hyperactivity disorder; AOR, adjusted odds ratio; ASQ, Ages and Stages Questionnaire; BOTMP, Bruininks-Oseretsky Test of Motor Proficiency; CBCL, child behavior checklist; COR, crude odds ratio; MABC, Movement Assessment Battery for Children; OR, odds ratio; RR, relative risk; TRF, teacher report form.

[a] $P<.01$.

[b] $P<.001$.

[c] P value not provided.

SPEECH AND LANGUAGE

Language is important for communication, social, and academic success. In early childhood, language development is more delayed than motor or cognitive abilities.[38] At older ages, expressive language, receptive language processing, and articulation difficulties with deficits in phonologic short-term memory are seen.[2,39,40] In very preterm adolescents, receptive language improved with age, especially with greater maternal education, better sociodemographic situation, and intact neurosensory function, but complex language problems become more prevalent.[41,42]

BEHAVIOR

Behavior problems, peer relationships, psychopathology, and antisocial behavior are best assessed at school age or later, although differences in temperament and self-regulation can be assessed earlier. Differences between premature and term-born infants have been identified using the Brazelton Neonatal Behavioral Assessment Scale: at term corrected age, preterm infants have a pattern of behaviors that is more variable, and overall less competent than term-born controls.[43] Preterm infants show evidence of maturational delays on brainstem auditory evoked potentials, video-somnography, and autonomic function with some correlation with longer-term outcomes.[44,45] Approximately 40% of preterm infants have an overall atypical pattern of behavior with respect to processing sensory stimuli using the parent-completed Sensory Profile questionnaire and almost 90% have a probable or definite abnormality in one or more sensory processing domains (eg, oral, auditory, tactile, visual).[46] On the Infant Toddler Social and Emotional Assessment at 2 years of age, preterm infants have higher mean internalizing and dysregulation scores, a pattern also seen at older ages with higher rates of depression and anxiety.[47] In the EPICure study, internalizing emotional disorders were present in 9% of extremely preterm children compared with 2% in the term-born controls.[48] A typical preterm behavioral phenotype, described by Johnson and Wolke,[49] includes inattention, introversion, anxiety, rigidity, and risk aversion. Overall, children born very preterm score worse on behavioral assessment tools, which increases with age: primary school age SMD −0.34; 95% CI −0.45 to −0.23 and secondary school SMD −0.72; 95% CI −0.47 to −0.97.[25] Attention deficit hyperactivity disorder is diagnosed 2.6 to 6.0 times more commonly in extremely preterm infants, 1.6 times greater among all preterm children (see **Table 1**), and may be preceded by poor attention in the toddler and preschool years.[2,25,28] Ten times more children born preterm screen positive for autism spectrum disorder (ASD) and 4 times as many are diagnosed with ASD with a prevalence of 7.1% in an extremely preterm cohort.[2] Psychiatric disorders occur in approximately 25% of adolescents born preterm.[49]

SENSORY IMPAIRMENTS

Prematurity is an important risk factor for hearing and visual impairments and early screening and treatment of sensory impairments are important to optimize function. The incidence is much lower than the neurodevelopmental outcomes described previously. In a Canadian national cohort born at less than 29 weeks' gestation, 1.9% had a significant unilateral or bilateral severe visual impairment, 1.6% a bilateral visual impairment, and 2.6% had a hearing aid or cochlear implant with a similar incidence in other studies ranging from 0% to 4.6% for severe visual impairment and 0.9% to 5.2% for severe to profound hearing impairment.[2,38] Sensory impairments may co-occur with and hinder the assessment of cognition and neurodevelopment.

THE MODERATE TO LATE PRETERM CHILD: OUTCOMES AT SCHOOL AGE AND BEYOND

Children born at moderate, 32 0/7 to 33 6/7 weeks, and late, 34 0/7 weeks and 36 6/7 weeks, preterm gestation represent most surviving preterm infants, and they are an important contributor to overall disability associated with prematurity.[50] Indeed, most total disability associated with preterm birth is for the moderate and late preterm group, given the higher rates of delivery and survival at these gestations. In a large Swedish national birth cohort study that linked birth history with adult health and psychiatric outcomes, 74% of the risk of disability and 85% of the risk of a psychiatric disorder associated with prematurity was in the moderate and late preterm groups.[51,52] Please see **Table 1** for a summary of domain-specific neurodevelopmental measures for extreme, very, and moderate to late preterm infants at school age and beyond.

GLOBAL MEASURES OF OUTCOME

Developmental delay at school entry can be captured using screening tools, but these global measures may not be predictive of later measures of IQ and domain-specific function. In the large prospective cohort Lollypop study, the Ages and Stages Questionnaire was used at school entry to assess for developmental delay.[53] Children born moderately preterm had twice the prevalence of developmental delay as compared with full-term infants (8.3% vs 4.2%), and more frequently had problems with fine motor, communication, and personal-social functioning.[53] In that same cohort, moderate prematurity and low socioeconomic status had a multiplicative effect on risk of developmental delay.[54] Rates of resolution of motor and communication problems were similar for children born moderate preterm and full-term.[55] Moster and colleagues[19] used linkage of birth registries and national health databases in Norway to examine medical issues and disabilities of more than 900,000 adults. Adults born at 31 to 33 6/7 weeks' gestation or late preterm, respectively, had increased odds of cerebral palsy (OR 14.1 and 2.7), mental retardation (OR 2.1 and 1.6), and conditions that interfere with an ability to work (OR 2.2 and 1.4). In a similar, large birth cohort study in Sweden, preterm birth was associated with lower chance of completing university education and a lower net salary.[51] In both studies, risk of adverse outcome as an adult increased with decreasing gestational age in a "dose-dependent" or linear fashion. Please see **Box 2** for a highlight of adult outcomes for individuals born preterm.

MOTOR OUTCOMES

At school age, approximately one-third of children born moderately preterm have difficulty in the school environment, particularly with fine motor skills.[7,53,56] In a large

Box 2
Highlights of outcomes for adults born preterm

- Prematurity continues to be associated with motor, cognitive, behavioral, and other disabilities in adults
- Disability-free preterm survivors attain a lower level of education and income than term-born peers
- Outcomes are inversely associated with gestational age
- Very low birth weight young adults have well-being and greater risk avoidance than controls
- Health-related quality of life is not affected by prematurity

cohort of 7-year-old children born moderately preterm, 31% struggled with fine motor skills and 12% were identified as struggling in physical education classes.[56] Male sex was a significant risk factor for poor motor skill outcome in this group.[56] Similar to Moster and colleagues,[19] a large cohort study that linked outpatient and hospitalization data from the Northern California Kaiser Permanente Medical Care Program of more than 140,000 children born at or more than 30 weeks, decreasing gestational age was related to increased rates of cerebral palsy for both moderate and late prematurity.[57] Children born late preterm were at least 3 times more likely than those born at term to be diagnosed with cerebral palsy (hazard ratio, 3.39; 95% CI 2.54–4.52).[57]

COGNITIVE OUTCOMES

Standardized cognitive assessments are often performed during the school years and in several countries at time of registration for conscription at 18 or 19 years of age. Several researchers have linked birth data to these educational and administrative registries to study the effect of prematurity on cognitive outcome. In a large case-control study, the IQ scores in first grade of children born late preterm were compared with a random sample of children born at term.[58] Late preterm birth was associated with increased risk of lower full-scale IQ, adjusted OR 2.35 (95% CI 1.20–4.61) and performance IQ, adjusted OR 2.04 (95% CI 1.09–3.82) but no difference was seen with verbal IQ.[58] In the Avon longitudinal study, moderate and late preterm birth was associated with lower verbal IQ, performance IQ, and full-scale IQ scores at 11 years of age in univariate but not multivariate analysis.[59] However, children born moderate and late preterm had a 56% increased risk of receiving special education services, and this could not be explained by differences in IQ.[59] In a large cohort study in Norway that linked birth registry data to Conscript Service Intelligence scores, late preterm birth was associated with lower adult intelligence scores when controlling for social confounders and adult body size.[5] Intelligence test scores increased in a linear fashion with gestational age at birth, birth weight, and birth length up until 41 weeks.[5] In a similar study from Sweden that used birth registry data and IQ testing at time of conscription, there was a small “dose-response” between lower gestational age at delivery and lower IQ.[60] As with many other studies, socioeconomic status was an important modifier of the relationship between prematurity and IQ.[60] Using a comprehensive assessment at 31 years of age, Dalziel and colleagues[61] compared 126 adults who had been born moderately preterm with 66 adults born at term and found that there were no differences in cognitive, academic, psychological, or functional measures.

ACADEMIC OUTCOMES

The Kindergarten Cohort of the Early Childhood Longitudinal Study used US national standardized testing data to compare 970 preterm infants and 13,761 control subjects in elementary school.[62] Children born moderate preterm had scores that were lower than those born at term for reading and for math in several grades up to grade 5. In multivariate analysis, there was twice the risk of individualized education plans and special education enrollment for the moderate but not the late preterm group. Challenges persisted at fifth grade and, as noted in other studies, there was a linear association between gestational age and test scores.[56,62] In the United Kingdom Millennium Cohort study, educational and health data of more than 6000 children were linked to examine the effect of late preterm birth on school performance at 7 years of age.[63] Preterm birth was a risk for poor performance in the areas of reading, writing and mathematics, with children born at moderate prematurity at greater risk than those born late preterm, relative risk (RR) 1.71 (95%CI 1.15–2.54) versus RR 1.36 (95% CI 1.09–1.68).[63] In a study of more than 200,000 children in New York City that linked birth data and standardized educational testing at third grade, children born moderate and late preterm were found to have increased adjusted odds of special education placement in comparison with term children, adjusted odds ratio (AOR) 1.53 (95% CI 1.30–1.69) and AOR 1.34 (95% CI 1.29–1.40), respectively.[64] Children born preterm also had lower English and math standardized scores and there was a "dose-response" for each week of prematurity.[64] Similarly, in a population-based retrospective study of almost 18,000 children linking birth and school census data, MacKay et al, found an adjusted OR of 1.53 (95% CI 1.43–1.63) for having a special education placement for children born moderately preterm.[65] Children born moderate and late preterm accounted for most preterm children in special educational classes and, as with many other studies, male sex was also an important risk factor for special education placement.[65] In a follow-up study of children born moderately preterm who were not admitted to the NICU compared with children born at term, there was a higher need for special education placement, 7.7% versus 2.8%. In addition, children born at moderate and late preterm gestations were more likely to not advance a grade when compared with children born at term, 19% versus 8%.[66] This risk of failure to advance grades is consistent with adult registry studies that found that there is an increasing risk of not completing basic school with decreasing gestational age.[67]

BEHAVIORAL OUTCOMES

In follow-up studies that capture behavioral outcomes, parent or teacher questionnaires are often used at school age, and functional or psychological outcomes used for adults. In several studies, children born late preterm had increased risk of borderline clinical internalizing, clinical attention problems in first or second grade, and had higher scores in domains of inattention, hyperactivity, and total problems as determined by standardized parent and teacher report.[56,58,68] In large cohort studies that link birth data with medical and psychiatric adult data, adults born moderate and late preterm were at increased risk of having been diagnosed with a psychiatric, autism spectrum, or addictive disorder.[19,52] In all of the examined adverse outcomes, there was an inverse relationship between decreasing gestational age and increasing risk.[19,52] Risk of unemployment and criminal activity were not associated with preterm birth.[19,52]

SPEECH AND LANGUAGE OUTCOMES AND SENSORY IMPAIRMENTS

There are limited data systematically examining moderate and late preterm birth and speech and language and sensory outcomes at school age and beyond.

FACTORS AFFECTING OUTCOMES

Prematurity per se is not inevitably associated with adverse neurodevelopmental outcome.[69] The actively maturing preterm brain is, however, vulnerable to a variety of injuries and additional factors affecting brain maturation. An understanding of these factors is essential to reducing the neurodevelopmental sequelae of prematurity. Optimizing outcomes starts with good obstetric care to promote fetal growth and well-being. Intrauterine growth restriction or small for gestational age are associated with poorer outcomes in preterm infants.[53,70] When preterm delivery is necessary or unavoidable, use of antenatal corticosteroids, magnesium sulfate for fetal neuroprotection, and antibiotics among other evidence-based practices is beneficial.[71–73] Delivery in a hospital with the appropriate level of expertise in neonatal resuscitation and neonatal intensive care is beneficial.[74] Quality improvement interventions have reduced preterm complications associated with adverse neurodevelopmental outcomes.[75] Golden hour care management has reduced intraventricular hemorrhage.[76] Avoiding complications of prematurity and attention to everyday management supports healthy brain maturation. Bronchopulmonary dysplasia, infection, necrotizing enterocolitis, and severe retinopathy of prematurity are predictors of neurodevelopmental disability.[77] Interventions, such as postnatal steroids, painful procedures, and general anesthetics, are associated with adverse outcomes.[2] Caffeine for apnea of prematurity has shown benefit at 18 months of age and improved motor outcomes at 5 years of age.[78,79] The child's family and sociodemographic characteristics become increasingly important in the older child, especially for cognitive and language outcomes. A strong home environment is associated with resilience, and postnatal events, primarily parent-child interactions, may moderate prenatal effects through epigenetic changes.[80,81]

FUTURE DIRECTIONS

Efforts to reduce the incidence of preterm deliveries have not been successful to date and, therefore, reducing the long-term neurodevelopmental impacts of prematurity is the next frontier. This will require a multipronged approach with identification and reduction of risk factors, promotion of healthy brain maturation, consideration of the risks and benefits of neonatal interventions, and support for parents, caregivers, and the home environment. Exciting new preventive strategies include erythropoiesis-stimulating agents and extreme preterm care units.[2] Developmental care, minimizing procedural pain and repetitive noxious stimuli, and postdischarge early intervention strategies to support parents and families show promise.[2]

REFERENCES

1. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10(Suppl 1):S2.
2. Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. Semin Perinatol 2016;40:497–509.
3. Luu TM, Rehman Mian MO, Nuyt AM. Long-term impact of preterm birth: neurodevelopmental and physical health outcomes. Clin Perinatol 2017;44:305–14.
4. Martin JA, Hamilton BE, Osterman MJK, et al. National vital statistics reports births: final data for 2015. Natl Vital Stat Rep 2017;66:1–70.
5. Eide MG, Øyen N, SkjÆrven R, et al. Associations of birth size, gestational age, and adult size with intellectual performance: evidence from a cohort of Norwegian men. Pediatr Res 2007;62:636–42.
6. Tin W, Fritz S, Wariyar U, et al. Outcome of very preterm birth: children reviewed with ease at 2 years differ from those followed up with difficulty. Arch Dis Child Fetal Neonatal Ed 1998;79:83–7.
7. McGowan JE, Alderdice FA, Holmes VA, et al. Early childhood development of late-preterm infants: a systematic review. Pediatrics 2011;127:1111–24.
8. Kilbride HW, Aylward GP, Doyle LW, et al. Prognostic neurodevelopmental testing of preterm infants: do we need to change the paradigm? J Perinatol 2017;37:1–5.
9. Haslam MD, Lisonkova S, Creighton D, et al. Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network. Severe neurodevelopmental impairment

in neonates born preterm: impact of varying definitions in a Canadian Cohort. J Pediatr 2018;197:75–81.
10. World Health Organization. International classification of functioning, disability and health: children and youth version. Geneva (Switzerland): WHO Press; 2007.
11. Schiariti V, Selb M, Cieza A, et al. International classification of functioning, disability and health core sets for children and youth with cerebral palsy: a consensus meeting. Dev Med Child Neurol 2015;57:149–58.
12. Hack M. Poor predictive validity of the Bayley scales of infant development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:333–41.
13. Van Veen S, Aarnoudse-Moens CSH, Van Kaam AH, et al. Consequences of correcting intelligence quotient for prematurity at age 5 years. J Pediatr 2016;173:90–5.
14. Marlow N, Wolke D, Bracewell M, et al. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9–19.
15. Schmidt B. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012;307:275.
16. Hintz SR, Newman JE, Vohr BR. Changing definitions of long-term follow-up: should “long term” be even longer? Semin Perinatol 2016;40:398–409.
17. Cheong JLY, Anderson PJ, Burnett AC, et al. Changing neurodevelopment at 8 years in children born extremely preterm since the 1990s. Pediatrics 2017;139: e20164086.
18. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261–9.
19. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med 2008;359:262–73.
20. Hack M, Cartar L, Schluchter M, et al. Self-perceived health, functioning, and well-being of very low birth weight infants at age 20 years. J Pediatr 2007;15: 635–41.e2.
21. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. Pediatrics 2008; 121:e366–76.
22. Rosenbaum P, Paneth N, Leviton A. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8–14.
23. 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;32:678–87.
24. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. Dev Med Child Neurol 2010;52:232–7.
25. Allotey J, Zamora J, Cheong-See F, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. BJOG 2018;125:16–25.
26. de Kieviet JF, Piek JP, Aarnoudse-Moens CS, et al. Motor development in very preterm and very low birth-weight children from birth to adolescence. JAMA 2009;302:2235.
27. Asami M, Kamei A, Nakakarumai M, et al. Intellectual outcomes of extremely preterm infants at school age. Pediatr Int 2017;59:570–7.
28. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. J Dev Behav Pediatr 2014;35:394–407.
29. Synnes AR, Anson S, Arkesteijn A, et al. School entry age outcomes for infants with birth weight ≤800 grams. J Pediatr 2010;157:989–94.e1.

30. Kerr-Wilson CO, MacKay DF, Smith GCS, et al. Meta-analysis of the association between preterm delivery and intelligence. J Public Health (Oxf) 2012;34:209–16.
31. Vohr B. Follow-up care of high-risk infants. Pediatrics 2004;114(Supplement 5): 1377–97.
32. 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;112:943–50.
33. Vohr BR. Neurodevelopmental outcomes of extremely preterm infants. Clin Perinatol 2014;41:241–55.
34. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, et al. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 2009;124:717–28.
35. Twilhaar ES, de Kieviet JF, Aarnoudse-Moens CS, et al. Academic performance of children born preterm: a meta-analysis and meta-regression. JAMA Pediatr 2018; 172:361–7.
36. Saigal S, Hoult LA, Streiner DL, et al. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. Pediatrics 2000;105:325–31.
37. Geldof CJA, van Wassenaer AG, de Kieviet JF, et al. Visual perception and visual-motor integration in very preterm and/or very low birth weight children: a meta-analysis. Res Dev Disabil 2012;33:726–36.
38. Synnes A, Luu TM, Moddemann D, et al. Determinants of developmental outcomes in a very preterm Canadian cohort. Arch Dis Child Fetal Neonatal Ed 2017;102. F235.
39. Barre N, Morgan A, Doyle LW, et al. Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. J Pediatr 2011;158: 766–74.e1.
40. Ortiz-Mantilla S, Choudhury N, Leevers H, et al. Understanding language and cognitive deficits in very low birth weight children. Dev Psychobiol 2008;50:107–26.
41. Luu TM, Vohr BR, Allan W, et al. Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. Pediatrics 2011;128:313–22.
42. van Noort-van der Spek IL, Franken M-CJP, Weisglas-Kuperus N. Language functions in preterm-born children: a systematic review and meta-analysis. Pediatrics 2012;129:745–54.
43. Ferrari F, Grosoli M, Fontana G. Neurobehavioural comparison of low-risk preterm and full term infants at term conceptional age. Dev Med Child Neurol 1983;25: 450–8.
44. Kaga K, Hashira S, Marsh RR. Auditory brainstem responses and behavioural responses in pre-term infants. Br J Audiol 1986;20:121–7.
45. Cohen SE, Parmelee AH, Beckwith L, et al. Cognitive development in preterm infants: birth to 8 years. J Dev Behav Pediatr 1986;7:102–10.
46. Wickremasinghe AC, Rogers EE, Johnson BC, et al. Children born prematurely have atypical Sensory Profiles. J Perinatol 2013;33:631–5.
47. Spittle AJ, Treyvaud K, Doyle LW, et al. Early emergence of behavior and social-emotional problems in very preterm infants. J Am Acad Child Adolesc Psychiatry 2009;48:909–18.
48. Johnson S, Hollis C, Kochhar P, et al. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. J Am Acad Child Adolesc Psychiatry 2010;49:453–63.e1.
49. Johnson S, Wolke D. Behavioural outcomes and psychopathology during adolescence. Early Hum Dev 2013;89:199–207.

50. Vohr B. Long-term outcomes of moderately preterm, late preterm, and early term infants. Clin Perinatol 2013;40(4):739–51.
51. Lindstrom K, Winbladh B, Haglund B, et al. Preterm infants as young adults: a Swedish national cohort study. Pediatrics 2007;120:70–7.
52. Lindstrom K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. Pediatrics 2009;123:e47–53.
53. Kerstjens JM, De Winter AF, Bocca-Tjeertes IF, et al. Developmental delay in moderately preterm-born children at school entry. J Pediatr 2011;159:92–8.
54. Potijk MR, Kerstjens JM, Bos AF, et al. Developmental delay in moderately preterm-born children with low socioeconomic status: risks multiply. J Pediatr 2013;163:1289–95.
55. Hornman J, de Winter AF, Kerstjens JM, et al. Stability of developmental problems after school entry of moderately-late preterm and early preterm-born children. J Pediatr 2017;187:73–9.
56. Huddy CLJ. Educational and behavioural problems in babies of 32-35 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;85:23–8.
57. Petrini JR, Dias T, McCormick MC, et al. Increased risk of adverse neurological development for late preterm infants. J Pediatr 2009;154:169–76.
58. Talge NM, Holzman C, Wang J, et al. Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. Pediatrics 2010;126:1124–31.
59. Odd DE, Emond A, Whitelaw A. Long-term cognitive outcomes of infants born moderately and late preterm. Dev Med Child Neurol 2012;54:704–9.
60. Ekeus C, Lindstrom K, Lindblad F, et al. Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19-year-old men. Pediatrics 2010;125:e67–73.
61. Dalziel SR, Lambert A, McCarthy D, et al. Psychological functioning and health-related quality of life in adulthood after preterm birth. Dev Med Child Neurol 2007;49:597–602.
62. Chyi LJ, Lee HC, Hintz SR, et al. 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.
63. Chan E, Quigley MA. School performance at age 7 years in late preterm and early term birth: a cohort study. Arch Dis Child Fetal Neonatal Ed 2014;99:F451–7.
64. Lipkind HS, Slopen ME, Pfeiffer MR, et al. School-age outcomes of late preterm infants in New York City. Am J Obstet Gynecol 2012;206:222.e1-6.
65. Mackay DF, Smith GCS, Dobbie R, et al. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. PLoS Med 2010;7:1–10.
66. van Baar AL, Vermaas J, Knots E, et al. Functioning at school age of moderately preterm children born at 32 to 36 weeks' gestational age. Pediatrics 2009;124:251–7.
67. Mathiasen R, Hansen BM, Andersen A-MNN, et al. Gestational age and basic school achievements: a national follow-up study in Denmark. Pediatrics 2010;126:e1553–61.
68. Talge NM, Holzman C, Van Egeren LA, et al. Late-preterm birth by delivery circumstance and its association with parent-reported attention problems in childhood. J Dev Behav Pediatr 2012;33:405–15.
69. Bonifacio S, Glass H, Chau V. Extreme premature birth is not associated with impaired development of brain microstructure. J Pediatr 2010;157:726–32.

70. Tanis JC, Van Braeckel KN, Kerstjens JM, et al. Functional outcomes at age 7 years of moderate preterm and full term children born small for gestational age. J Pediatr 2015;166:552–8.e1.
71. American Academy of Pediatrics. Antenatal corticosteroid therapy for fetal maturation. Pediatrics 2017;140:2016–8.
72. Magee L, Sawchuck D, Synnes A, et al. Magnesium sulphate for fetal neuroprotection. J Obstet Gynaecol Can 2011;33:516–29.
73. Puopolo KM, Beigi R, Silverman NS, et al. ACOG committee opinion: intrapartum management of intraamniotic infection. Obstet Gynecol 2017;130:95–101.
74. Chien LY, Whyte R, Aziz K, et al. Improved outcome of preterm infants when delivered in tertiary care centers. Obstet Gynecol 2001;98:247–52.
75. Lee SK, Shah PS, Singhal N, et al. Association of a quality improvement program with neonatal outcomes in extremely preterm infants: a prospective cohort study. CMAJ 2014;186:E485–94.
76. Reuter S, Messier S, Steven D. The neonatal golden hour - intervention to improve quality of care of the extremely low birth weight infant. S D Med 2014;67:397–403.
77. Patel R. Short- and long-term outcomes for extremely preterm infants. Am J Perinatol 2016;33(3):318–28.
78. Doyle LW, Schmidt B, Anderson PJ, et al. Reduction in developmental coordination disorder with neonatal caffeine therapy. J Pediatr 2014;165:356–9.e2.
79. Schmidt B, Roberts S, Davis P. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357:1893–902.
80. Monk C, Spicer J, Champagne F. Linking prenatal maternal adversity to developmental outcomes in infants: the role of epigenetic pathways. Dev Psychopathol 2012;24:1361–76.
81. Manley BJ, Roberts RS, Doyle LW, et al. Social variables predict gains in cognitive scores across the preschool years in children with birth weights 500 to 1250 grams. J Pediatr 2015;166:870–6.