Long-Term Healthcare Outcomes of Preterm Birth: An Executive Summary of a Conference Sponsored by the National Institutes of Health

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In 1998, Dr David Barker pioneered the novel idea that common chronic diseases result not only from bad genes and an unhealthy lifestyle, but also from alterations in the intrauterine and early postnatal environment.[1] The timing of these alterations, either during a "critical" period of growth and maturation or accumulating over longer intervals, can have a permanent effect on the organism. The impact of birth weight, maternal habitus, nutrition, and smoking, and the role of the placenta on developmental programming of metabolic syndrome, obesity, hypertension, and organ development have been well-studied. More recent studies have suggested that developmental programming on the background of preterm birth may be far more important than suboptimal intrauterine growth.

In the US, about 10%-12% of births occur before 37 completed weeks of postmenstrual age.[2] Worldwide rates vary. Today, more than 95% of these "preterm infants" survive to adulthood in most industrialized nations owing to remarkable advances in perinatal, neonatal, and pediatric care.[3-6] Survival may come at the expense of future adverse health and social risks characterized by failure to achieve optimal development or more rapid rates of decline in cardiovascular, pulmonary, and renal function or "accelerated aging."[7]

Individuals born preterm are at an increased risk for type 2 diabetes, cardiovascular and cerebrovascular diseases, hypertension, chronic kidney disease, asthma and pulmonary function abnormalities, and neurocognitive and psychosocial disorders and poorer social adaptation.[8-12] Even a modest increase (eg, 10%-20%) in risk for these chronic conditions can translate into a substantial population burden. Because of this, the US National Institutes of Health convened a conference of multidisciplinary experts to elucidate the evidence for the epidemiologic, public health, and societal burden of diseases among those born preterm, to review potential mechanisms and to consider future research priorities. An understanding of these areas is crucial for developing prevention and treatment strategies. This report summarizes the key concepts discussed at the conference, and poses many unanswered questions that may serve to guide future research endeavors in each domain (**Table**).

Epidemiology and Preterm Outcomes

Much of our knowledge about individuals born preterm has come from prospective birth cohort studies of large populations. Although longitudinal cohort studies have many advantages, there are significant challenges, such as the long duration of follow-up (and need for long-term funding) necessary to provide meaningful associations, lack of information on confounders, changes in classification of diseases and outcomes over time, and loss to follow-up.

With a few exceptions, our knowledge of the longer term outcomes of preterm birth comes from cohorts born outside of the US[13-15] who were followed through adulthood. A Swedish study of 679 981 singleton live births between 1973 and 1979, examined the association between preterm birth and all-cause and cause-specific mortality through 2008. The adjusted HRs for death (controlling for age, sex, birth order, maternal age, marital status, and education) were higher for preterm[16] and for "early term" births (37 and 38 weeks)[17] than for births at 39-42 weeks, illustrating that the lower the gestational age at birth, the higher the risk of death in the neonatal, postnatal, early childhood, and young adult age ranges.

Data from US cohorts permit comparisons of socioeconomic, ethnic, and cultural factors, important for generalizability to the broader US population. But US cohorts of individuals born preterm are few, owing in part to the difficulties of maintaining longitudinal cohorts into adulthood.[18,19] Additional research approaches should be considered to augment the paucity of data from US cohorts along with the comparison of international cohorts.

Other Research Approaches in Preterm Born Individuals

Randomized controlled trials are the "gold standard" to evaluate therapies, yet they may be more challenging to execute because of limitations, such as strict eligibility criteria, short observational periods, and poor study design. Case-control studies are particularly useful when evaluating rarer and long-term outcomes, especially when data and biological specimens are available from pregnancy and early postnatal life.

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*List of Adults Born Preterm Conference Speakers and Discussants is available at www.jpeds.com (**Appendix**).

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Table. Unanswered questions to guide future research in individuals born preterm

General
Which types of study designs and innovative tools are needed to accumulate evidence to guide the care of preterm born individuals into adulthood?
What contributes to more favorable outcomes or resiliency in some preterm born individuals?
How can existing preterm-born cohorts, trials, databases and samples be leveraged for the study of future health risks?
Pulmonary
Is the clinical syndrome labeled "asthma" the same for those born prematurely versus at term?
What characterizes the syndrome of obstructive lung disease in individuals born preterm?
What are the best strategies for maximizing lung health and disease prevention?
Have changes in NICU management altered/improved long-term respiratory outcomes?
Does lower lung function contribute to adult respiratory morbidity and if so, what type?
What are the mechanisms behind the reported lung function abnormalities?
What are the mechanisms of increased risk of OSAS?
What are the differences in responses to interventions for OSAS?
Do preterm infants start out with low lung function, followed by normal or accelerated growth later?
What is the relationship between preterm birth and age at peak lung function?
How does preterm lung pulmonary vascular growth change over time? Is there a relationship between preterm birth and exercise-induced pulmonary hypertension?
Cardiovascular, peripheral vascular and metabolic
Does the etiology of the preterm birth and degree of prematurity influence outcomes?
How do we balance immediate benefits versus long-term harm (eg, corticosteroids and optimal nutrition and growth)?
How can we decrease exogenous cortisol exposure during the postnatal period?
How can we assess the impact of postnatal complications versus lifestyle on cardiometabolic disease later in life?
What are the pathways that lead to reduced physical activity and fitness?
How can we address the many challenges faced in epigenetic studies such as differences in tissue and cell type differences, changes over time, external influences and the need for multiple comparisons?
What are the best study designs to address the limitations of long-term cohort follow-up studies and obtain outcomes in a reasonable period of time?
Which interventions should be tested to improve cardiometabolic health later in life?
How do we optimize the recognition, treatment, and prevention of thromboembolism in adults born at preterm gestations?
What are the best approaches to prevent obesity among those born preterm?
Renal
What are the best methods to assess kidney function in infants, children, and teens?
What biomarkers can accurately assess kidney health?
What are the long-term follow-up guidelines to assess kidney functions prospectively for high-risk infants after hospital discharge?
How can one assess kidney size relative to body mass in infants, children, and adults?
How can nutritional support be optimized to mitigate adverse renal health?
What are the independent effects of intrauterine growth restriction and prematurity on ultimate kidney health?
What are the effects of maternal hypertension, neonatal acute kidney injury, childhood hypertension, and chronic kidney disease among those born preterm?
How do we evaluate the impact of neonatal acute kidney injury on long-term renal function?
What are the effects of poor kidney function among preterm infants (eg, loss of growth factors or hormones in the urine) on general and organ-specific health during the life course of the individual?
Neurologic and neuropsychiatric
What are the clinical consequences of increased periodic limb movement syndrome?
What are the causes and consequences of preterm white matter injury?
Can early interventions mitigate adverse outcomes secondary to preterm brain injury from periventricular leukomalacia and intraventricular hemorrhage?
What specific interventions will improve learning of math and language skills?
What childhood and adolescent factors alter the trajectory of abnormal neurologic outcomes?
What are the biological bases for neuropsychiatric problems? Specifically:
How do various trajectories of structural and functional brain development affect or alter neuropsychiatric outcomes?
What is the role of neurotransmitters and neuromodulators implicated in psychiatric disorders?
What is the role of neuroimmune factors, such as maternal/fetal inflammatory responses, associated with neuropsychiatric outcomes?
What genetic risks are associated with an increased vulnerability to neuropsychiatric impairment, as well as modulating pathways for risk and resilience?
Which interventions can be developed to improve psychiatric outcomes and cognitive function?
What are the childhood and adolescent antecedent factors for psychiatric problems and their effects on long-term outcomes?
What is the value of early treatment? Specifically:
How do early developmental interventions change outcomes?
How do pain-related stressors and the effects of therapies for neonatal pain control alter the trajectories of personality development and long-term behavioral outcomes?
Mechanisms and basic science
What are the macro and molecular mechanistic pathways that might be affecting maturational processes after preterm birth?
Is it due to something missing (eg, micronutrients, oxygen), something altered (eg, infection, abnormal extrauterine environment, medications), the intrauterine environment or epigenetic effects?
Does the interrupted maturation and growth of various organs after preterm birth "recover"? What leads to recovery or compensation?
How do organs interact with each other after preterm birth?
Do individuals born prematurely develop diseases earlier because their threshold has changed and are they pathologically different from those born at term?
What are the mechanisms of resiliency? Why do so many preterm infants, even those born extremely preterm, do well?
How can we use the emerging fields of new imaging methods, molecular, and blood analyte studies to shed light on lifespan events that follow preterm birth?

OSAS, obstructive sleep apnea syndrome.

Using archived collections (maternal serum and newborn blood spots) to link later disorders in nested case-control studies could be a valuable approach to evaluating outcomes in individuals born preterm. However, observational studies have revealed useful insights into various early life risk factors on long-term adverse outcomes. Exposure to repeated doses of antenatal corticosteroids[20-22] and postnatal dexamethasone[23] are examples of adverse effects of medication exposure early in life.

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Famine during gestation in the Netherlands resulted in lower birth weights, and increased the risk for higher blood pressure 59 years later, highlighting the importance of early nutrition on offspring health.[24] Based on the latter observation, studies were conducted to improve infant outcomes by improving maternal nutrition during pregnancy,[25,26] encouraging regular aerobic exercise by pregnant women,[27] and avoidance of antigens to prevent infant atopic diseases[28]; however, these interventions had mixed results. In contrast, a prospective randomized trial of postnatal dietary interventions in 2 parallel cohorts of 926 premature infants had a positive influence on reducing mean arterial blood pressure at 13-16 years of age.[29]

More studies are needed to explore how specific treatments or prevention strategies will improve long-term adverse outcomes in survivors of preterm birth. Novel study designs, use of big data, trials embedded in registries, and transnational partnerships such as the Adults Born Preterm International Collaboration[30] should be explored to address the methodological challenges of studying preterm born individuals across the lifespan.

Pulmonary Outcomes in Individuals Born Preterm

Several publications have drawn attention to the pulmonary function abnormalities and chronic lung diseases in individuals born prematurely.[31-35] Human lungs develop in stages during gestation with airways forming during weeks 5-26 and alveoli during weeks 24-36 with continued development during childhood. A surge in pulmonary surfactant at 34-35 weeks of gestation is mediated by cortisol. Preterm birth disrupts these processes and leads to morphologically immature lungs compared with the lungs of term infants. If the preterm birth follows a pregnancy in which there is fetal programming in response to in utero gene-environment interactions (eg, maternal smoking, inadequate maternal diet), there may already be developmental problems in the lungs that are exacerbated by preterm birth. Adverse postnatal clinical events or exposures such as the use of oxygen, assisted ventilator support, gastroesophageal reflux, and postnatal environmental toxins (eg, secondhand smoke, air pollution) during key stages of maturation can contribute to additional injury. Typically, lung function peaks by early adulthood and then begins to decline, yet the trajectory of lung function in individuals born preterm is unclear and questions remain.

Arrested vascularization and augmented vasoreactivity[36-38] may lead to the development of pulmonary hypertension in the weeks and months after preterm birth, contributing to increased mortality in infants with bronchopulmonary dysplasia. Whether these individuals are more susceptible to developing baseline or exercise-induced pulmonary hypertension associated with right heart failure, compared with their term-born counterparts, is unknown.

Young adults with a history of bronchopulmonary dysplasia have worse lung function compared with healthy controls, and even those with no history of bronchopulmonary dysplasia manifested poorer lung function than those born at term.[35,39,40] These reductions in lung function are not trivial; they have been shown to be associated with reductions in aerobic exercise capacity,[41] with the potential to adversely affect long-term pulmonary and/or cardiovascular health. Individuals born preterm also have increased respiratory symptoms (cough, wheezing, exertional dyspnea) and nearly one-third are diagnosed with asthma during childhood. However, the "asthma" seen in these individuals may have phenotypes and treatment responses that are different from those seen in children and adults born at term, making testing and treatment more challenging. Infants born preterm who have experienced fetal programming that altered the development of the airways or lung parenchyma may have suboptimal lung function that tracks toward the bottom of the lung growth curves, setting them up for risk for chronic lung disease as adults.

Studies in pregnant primates infused with nicotine and in women who smoked during pregnancy found that the offspring of women with specific genotypes have reduced vitamin C levels and reduced lung function soon after birth, consistent with airway narrowing. Restoring vitamin C levels results in normal lung function in the offspring.[42] This demonstrates an important model of an in utero gene-environment interaction, the timing of which is as critical as the type of injurious exposure for its long-term effects on the structure and function of the developing lungs.

Sleep Issues

Sleep is important for health, learning, behavior, and executive functioning. Adults born preterm have a 3- to 5-fold higher risk of obstructive sleep apnea syndrome[43,44] and a 2-fold increased risk of snoring compared with those born at term.[45] Perinatal exposure to maternal chorioamnionitis increases the risk for obstructive sleep apnea,[46] whereas caffeine administration during the neonatal period is not a risk factor.[44] Children born preterm also have a higher prevalence of periodic limb movements, which may disrupt their sleep.[47] However, there is no clear understanding of the mechanistic roles of ventilatory-control abnormalities, upper airway muscle hypotonia, palatal deformation (owing to prolonged neonatal endotracheal intubation), adenotonsillar hypertrophy, and obesity in causing sleep-related disturbances. The causes and mechanisms for these conditions during childhood and adolescence remain to be addressed.[48]

Cardiovascular and Metabolic Outcomes

Interest in the cardiovascular consequences of preterm birth dates to the seminal observations of David Barker, who reported that birth weight was inversely related to adult blood pressure and later showed that lower birth weight was a risk factor for adult cardiovascular diseases, hypertension, and type 2 diabetes.[49] Even though initial research focused on low birth weight owing to intrauterine growth restriction and maternal nutrition, evolving data suggest that lower gestational age portends worse adult outcomes. However, the mechanism may

differ from Barker's initial hypothesis: it is quite likely that low birth weight and later cardiovascular disorders may reflect shared genetic and environmental risk factors in the families of affected infants.

One of the most consistent findings in individuals born preterm is higher blood pressure. In 2 meta-analyses of adults born preterm versus term, systolic and diastolic blood pressures were higher in the preterm groups.[9,50] Among those born to mothers with preeclampsia, a slightly greater increase was seen. Females had higher ambulatory blood pressures than males.[51,52] Whether preterm infants were small for gestational age or appropriate for gestational age made little difference.

Prematurity increases the risk of type 2 diabetes and insulin resistance during childhood into adulthood.[11,53-55] The evidence for risk of dyslipidemia among individuals born preterm is mixed. Few differences are seen between adults born preterm and at term for the majority of lipid outcomes, with the exception of increased concentrations of low-density lipoprotein cholesterol in those born preterm.[50,52,56] Another study reported higher fasting concentrations of triglycerides and very low-density lipoprotein cholesterol particles in individuals born preterm with birth weights of less than 1500 grams.[51]

Adults born preterm with birth weights of less than 1500 grams are shorter in stature than those born at term.[57,58] Although the average body mass index and waist-to-hip ratios[50] are not significantly different among individuals born preterm at any birth weight, some reports suggest that such individuals may have abnormal depositions of fat in organs that are relevant to cardiovascular disease risks.[52,59] A study of 23 adults born preterm and 25 at full term found differences in intrahepatic and visceral fat.[60] Other cardiovascular studies demonstrated increased right and left ventricular mass.[61,62]

The influence of birth weight and gestational age on coronary artery and cerebrovascular diseases during adulthood has been controversial.[12,63-66] Individuals do not seem to be at greater risk for coronary heart disease, which begs the question as to whether preterm birth confers some protection. Alternatively, the explanation could be "survivor bias." Before modern neonatal intensive care during the 1960s and 1970s, the chances of survival were poor for all preterm infants, especially for those born before 28 weeks of gestation.[4,6] Only the strongest and healthiest tended to survive, perhaps mitigating the risk for these more long-term outcomes.

Interestingly, women who deliver a preterm or a small for gestational age infant are themselves at higher risk for cardiovascular disease later in life.[67] Such associations also have been reported for paternal and grandparental cardiovascular disease risks.[68-70] These findings suggest an interaction among common genes that share environmental and genetic effects.

Potential Mechanisms for Cardiometabolic Outcomes

The precise causality for higher cardiometabolic risks among individuals born preterm has not been elucidated. One potential mechanism is the role of cortisol. Corticosteroids at doses several orders of magnitude higher than endogenous fetal cortisol levels are recommended for women in preterm labor (<34 weeks) to enhance fetal lung maturation. Glucocorticoids promote maturation and cell differentiation, but in large amounts, they may inhibit cell growth and division. In animals, exposure to excessive amounts of cortisol results in decreased brain, organ, and total body weights. A cardiovascular magnetic resonance imaging study in young adults born preterm found that individuals exposed to antenatal steroids had increased aortic stiffness normally seen in those about 10 years older.[71]

Altered prenatal and postnatal nutrition impacts cardiometabolic outcomes, but the timing of deprivation or abundance may result in different phenotypes. In animal and human pregnancies, reduced nutrient consumption is marked by more preterm births and smaller infants.[72-75] Nutrient restriction in pregnant and postpartum rats leads to a metabolic syndrome phenotype in the offspring, characterized by fewer satiety neurons in the hypothalamus.[76] Programmed epigenetic changes can produce this metabolic syndrome phenotype in subsequent generations by affecting appetite control and adiposity programming. Some researchers postulate that a "second-hit phenomenon," such as a high-fat, high-calorie diet during postnatal life in infants born preterm can tip the balance toward adult-onset metabolic syndrome.[77-79] There may be differences in participation in physical activity and sports, mediated by social withdrawal behavior as explained elsewhere in this article.

The cause of preterm birth may influence the cardiopulmonary disease trajectory. In experimental animals and human epidemiologic studies, infants born to women with preeclampsia have an increased risk of developing high blood pressure and double the risk of stroke in later life.[61,80-82] This risk may be secondary to abnormal placental development in preeclampsia, an effect independent of fetal growth restriction and preterm birth.[80,82]

Renal Outcomes

About 60% of human nephrons are formed during the second and third trimesters of gestation. Some research suggests that nephrogenesis may continue up to 40 days postnatal age or longer in preterm infants.[83,84] The mean number of nephrons in adults is reported to be about 1 million per kidney. Wide variations are seen (200 000-2 700 000), likely related to numerous prenatal factors (maternal smoking, vitamin deficiencies, medications, hyperglycemia) and postnatal factors (nutrition, hypertension, diabetes, nephrotoxic medications) that modulate nephrogenesis.[85-88] Preterm infants are born during the active phase of nephrogenesis, resulting in fewer nephrons. In a study of 40 school-age children with birth weights of less than 1000 grams, the glomerular filtration rate and the magnitude of tubular phosphate transports were significantly diminished, postulated to be due to impaired postnatal nephrogenesis.[89] It is also possible that there is an accelerated senescence in infants and children with low nephron endowment, potentially placing them at greater risk for chronic kidney disease in adulthood.[87,90,91]

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In addition to low nephron numbers as a risk factor for hypertension,[9,10] programming of the vascular structure and reactivity might contribute to hypertension later in life. It is not clear if the risk of hypertension and renal disease in individuals born preterm is exacerbated in those with birth weights that are low for gestational age. Preterm infants with an increased pace of catch-up growth and those who develop obesity are at higher risk for hypertension and renal dysfunction in adolescence and adulthood.[92] The prevalence of acute kidney injury after prematurity is estimated at 12%-39%.[86,93,94] It is postulated that infants who recover from acute kidney injury may develop abnormal "hyperfiltering" glomeruli persisting through early childhood, potentially increasing the risk for chronic kidney disease later in life.

In adults, there is an increased risk for chronic kidney disease after an initial acute kidney injury,[95] but the long-term relationship between neonatal acute kidney injury and later chronic kidney disease remains unclear.[96,97] In a study of 20 infants born extremely preterm with neonatal acute kidney injury, 45% developed progressive chronic kidney disease over 3-18 years.[98]

Neuropsychiatric, Cognitive, and Functional Outcomes

Preterm birth increases the risk for psychiatric disorders later in life,[99-103] with higher rates of subclinical psychiatric symptoms seen in all gestational age subgroups.[18] Several studies have shown that young adults born preterm have a lower tendency for risk-taking behaviors, such as smoking and drinking, than term controls.[104-107] They are more likely to exhibit social withdrawal, introversion, and neuroticism (the long-term tendency to be in a negative emotional state), but the results are inconsistent for other personality dimensions.[105,108-110] The neuroticism personality has been shown to be an independent risk factor in the general population for the first and recurrent episodes of depression.[111]

Extremely low birth weight infants (<1 kg) are at greater risk than term infants for developing the triad of psychiatric conditions, namely, anxiety, inattention, and autistic traits (relational difficulties/peer problems). The risk is also higher for psychosis, schizophrenia, mood disorders, and possibly for eating disorders.[99-103] The ORs of psychiatric disorders requiring hospitalization at adulthood in this population has ranged from 2.4 to 7.4, compared with 1.3 to 2.7 in moderate to late preterm infants.[102] Psychiatric disorders are often accompanied by other impairments in brain and motor function, speech, and learning.[112] Extremely low birth weight infants are also at higher risk for increased bullying and peer victimization,[113,114] social exclusion, and adverse psychiatric outcomes, replicated across cohorts.[114-117]

The key mechanisms underlying psychopathology risk in preterm infants are likely to be both genetic and epigenetic, including prenatal exposure to chemicals and stressors and adverse perinatal events, such as exposure to numerous painful procedures.[118,119] In 95 neonates born between 24 and 32 weeks of gestational age, diffusion tensor imaging was carried out at 32 and 40 weeks. Impaired postnatal growth in weight, length, and head circumference during the 8 weeks between studies was associated with delayed cortical gray matter microstructural development.[120] Many brain structural and functional changes are seen well into adulthood.[121-125] Similarly, preterm infants studied at term-equivalent ages demonstrated diminished connections between the thalamus and frontal cortices, supplementary motor area, occipital lobe, and temporal gyri.[126]

The findings discussed herein indicate that postnatal brain growth and maturational abnormalities in preterm infants might have a causative role for poor long-term socioemotional and cognitive outcomes.[127,128] For example, children exposed to dexamethasone after birth have lower IQ scores.[23] More than one-half of very low birth weight (<1500 g) young adults are reported to have an IQ score of more than 1 standard deviation below the mean, and IQ subtest profiles indicate problems especially on the arithmetic and visual-perceptual tasks.[129] Lower IQ scores (approximately 0.06-1.1 standard deviations below the mean), with poorer math and reading skills as seen in those born preterm, may contribute to poorer earning capacity in adulthood.[130-132] Young adults report significantly poorer health, higher unemployment, and a lower earning capacity.[130,133] They are more likely to remain single, have a lower rate of sexual intercourse, and lower self-esteem compared with their peers born at term.[133]

Although we have focused mainly on the outcome of very premature infants, we would like to emphasize that all prematurity, including birth at late preterm gestations (34-37 weeks) carries a certain amount of risk. There is a gradient of risk, and more mature infants present with subtle or milder problems. Continued surveillance of premature infants of all gestational ages should be considered for implementing timely interventions as needed.

Intraventricular Hemorrhage and White Matter Injury

State-of-the-art neuroimaging in preterm infants may emerge as a very useful biomarker of outcomes with the potential to define the brain's structural and functional signatures associated with different disorders, and the vulnerability to develop such disorders.[128] Recent evidence from neuroimaging suggests that brain maturation, from birth to term equivalent age, differs between toddlers with adverse versus typical neurodevelopmental outcomes.[134] Infants surviving into adult ages after neonatal intraventricular hemorrhage, or manifesting evidence of white matter injury continue to be at very high risk for poor neurologic outcomes.[135-137] A systematic review of motor outcomes among very preterm (<32 weeks) and very low birth weight (<1500 g) children at 5-18 years of age found a 6- to 8-fold higher likelihood of having a developmental coordination disorder.[138] Another report of 48 nondisabled extremely low birthweight children at 11-13 years of age found an increased risk for long-term motor impairment, especially among male children.[139] These complications, if they persist beyond childhood, can add to the burden of morbidity among adults born preterm. For the newly diagnosed annual

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cohort of US infants with intraventricular hemorrhage, the total lifetime cost of care has been estimated to be $4 billion.[140] In addition to the individual's and family's burden of suffering, societal healthcare costs can be substantial because 8%-10% of infants born at less than 1500 grams develop intraventricular hemorrhage and 25%-50% suffer white matter injury.[141]

Thromboembolic Events

The incidence of venous thromboembolic events has a bimodal distribution, occurring more commonly during the neonatal period and peaking again during adolescence.[142,143] Decreased physical activity, infections, dehydration, and prior use of central venous catheters can cause venous thromboembolic events during infancy. A case-control study of 38 infants with venous thromboembolism reported that preterm birth was associated with 5.5 times the risk of venous thromboembolism during infancy.[144] A population-based study examined 3.5 million live births (from 1973 to 2008) to assess the risk of venous thromboembolic events from birth through young adulthood.[143] Preterm birth, independent of family history, maternal smoking, fetal growth, and sociodemographic factors, increased the risk for such events among young adults by about 20%.[143] More longitudinal cohort studies are required to estimate the precise degrees of risk for adult thromboembolic disorders owing to prematurity alone, or in combination with neonatal thromboembolic complications.

Education

There is an urgent need to increase awareness among healthcare providers about outcomes for those born preterm at all gestations, because it may inform different phenotypes of disease and adequacy of response to interventions in this high-risk group. Communication between parents, teachers, and healthcare professionals is needed to increase appreciation for a preterm-born child's educational, behavioral, and psychological risks. This can help with surveillance of learning and intellectual progress, early recognition of deficits, and implementation of remedial programs as needed.

Rarely do healthcare providers seek birth histories from patients,[145,146] but this may be of particular importance when caring for adolescents born preterm. All adolescents face challenges of identity, independence, sexuality, and emotional maturation as they transition from childhood to adulthood. Adolescents born preterm face similar problems, but because of their increased risks for learning difficulties as well as behavioral and emotional problems, they may face additional challenges. Primary care physicians should be aware of these issues so that they can offer anticipatory evaluation and guidance to help teenagers to make a smooth and healthy transition into adulthood.

To inform strategies for healthcare delivery, more research is needed to determine the benefits of screening for preterm birth when collecting medical histories. Low gestational age at birth, birth weight, and the duration of initial hospitalization could suggest gathering of additional information, such as major perinatal complications and interventions that increase the risk for chronic health conditions in children, teens, and adults born preterm.

Summary and Conclusions

This report, summarizing the contributions of more than 60 experts, underscores that even a modest increase in the risk for future chronic illnesses and poor social outcomes among those born preterm represents a significant individual and societal healthcare burden. Obtaining a birth and neonatal health history should be considered when assessing patients seeking medical care, so that anticipatory and preventive measures can be undertaken, including early screening for adult-onset disorders. In addition to the organ-specific research outlined in the **Table**, we include additional questions that would help to elucidate the mechanistic underpinnings of poor long-term outcomes and the factors that mitigate them. Insights from current and future research should help to optimize care along the life continuum so that the burden of disease among those born preterm can be reduced or ameliorated. ■

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Appendix

Adults Born Preterm Conference Speakers and Discussants include (alphabetical):

Carolyn Abitbol, MD, University of Miami and Holtz Children's Hospital; Jennifer Charlton, MD, MSc, University of Virginia, Charleston, VA; Casey Crump, MD, PhD, Icahn School of Medicine at Mount Sinai, New York, NY; Mina Desai, PhD, MSc, David Geffen School of Medicine at the University of California–Los Angeles (UCLA), LABioMed, Harbor-UCLA Medical Center, Los Angeles, CA; Donna Dimichele, MD, National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD; Lex W Doyle, MD, MSc, The Royal Women's Hospital and the University of Melbourne, Melbourne, Australia; Neil Goldenberg, MD, PhD, Johns Hopkins All Children's Hospital, St. Petersburg, FL, and Johns Hopkins University School of Medicine, Baltimore, MD; Tina Hartert, MD, MPH, Vanderbilt University School of Medicine, Nashville, TN; Rosemary Higgins, MD, National Institute of Child Health and Human Development, Bethesda, MD; Petteri Hovi, MD, PhD, National Institute for Health and Welfare, Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; Marit S. Indredavik, MD, PhD, Norwegian University of Science and Technology, Trondheim, Norway; Julie R. Ingelfinger, MD, MassGeneral Hospital for Children at Massachusetts General Hospital, Boston, MA; Julia Jaekel, PhD, The University of Tennessee, Knoxville, TN; Eero Kajantie, MD, PhD, National Institute for Health and Welfare, Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; Norma Lerner, MD, MPH, NHLBI, Bethesda, MD; Andrew Lovering, PhD, University of Oregon, Eugene; OR; Valerie Luyckx, MBBCh, MSc, University of Zurich, Zurich, Switzerland; Carole L. Marcus, MBBCh, University of Pennsylvania, Philadelphia, PA; Ana Menezes, PhD, University of Pelotas, Pelotas, Brazil; Laura Ment, MD, Yale School of Medicine, New Haven, CT; Steven Paul Miller, MD, CM, FRCPC, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; Traci Mondoro, PhD, NHLBI, Bethesda, MD; Katherine Morrison, MD, FRCPC, McMaster University, Hamilton, Ontario, Canada; Chiara Nosarti, PhD, King's College, London, UK; Nigel Paneth, MD, MPH, Departments of Epidemiology & Biostatistics and Pediatrics & Human Development, Michigan State University, College of Human Medicine, East Lansing, MI; Katri Räikkönen, PhD, University of Helsinki, Helsinki, Finland; Michael Ross, MD, MPH, David Geffen School of Medicine at UCLA, Los Angeles, CA; Yoel Sadovsky, MD, Magee-Women's Research Institute, University of Pittsburgh, Pittsburgh, PA; Jon Tyson, MD, MPH, University of Texas Health Science Center, Houston, TX; Kristi Watterberg, MD, University of New Mexico School of Medicine, Albuquerque, NM; and Dieter Wolke, PhD, University of Warwick, Warwick, UK.