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.