Expanding the Definition of Long-term Follow-up to Late Adulthood

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In the United States, NICUs with training programs for fellows have follow-up programs for extremely preterm and very preterm infants who are considered at greatest risk of postdischarge neurodevelopmental morbidity. Late preterm (LPT) births (34–36 weeks) were for many years considered low risk, and their vulnerability was underestimated. Over the past few decades there has been a significant increase in the number of LPT births, related in part to induction of labor and cesarean delivery births and to a variety of risk factors.1,2 There has also been a proliferation in the number of studies reporting increased neonatal and postdischarge morbidities within the LPT population. The level of physiologic maturation has been shown to place these infants at increased risk of a spectrum of medical problems, including hypothermia, respiratory disorders, hypoglycemia, jaundice, immunologic problems, increased susceptibility to infection, and feeding problems.3 Vulnerability of the brain is now also recognized. The second half of gestation is a critical period of brain development; and at 34 weeks, the brain weight is 60% of term brain weight4 and there is a 5-fold increase in brain volume and brain maturation, including neurogenesis, synaptogenesis, and dendritic arborization between 35 and 41 weeks.5 The interruption of this process by delivery removes the infant and the developing brain from the natural protective environment of the uterus.6 A number of investigators have shown that this vulnerability of LPT infants is associated with an increased risk of neurologic impairments, developmental disabilities, school failure, behavior, autism spectrum disorder, and psychiatric problems that extend to adolescence and young adult age.7–16

The study in this issue by Heinonen et al17 addresses the subject of lifelong brain vulnerability in LPT infants and builds on their previous finding that LPT birth is associated with lower lifetime attained level of education at 56 to 66 years of age.18 The current study is a remarkable longitudinal investigation that raises the bar another notch for follow-up studies. First, the study investigates an important clinical risk factor, LPT birth, which currently represents 70% of all preterm births. Second, the data were retrieved from well-established national databases (the Helsinki birth cohort study with subjects born in 1934 to 1944 and the Statistics Finland database), which allowed the investigators to track, identify, link, and evaluate former LPT infants and term controls. Third, the duration of follow-up is extraordinary; the subjects were senior citizens with a mean age of 68.1 years. Fourth, the assessment used was the Consortium to Establish a Registry for Alzheimer’s Disease Neuropsychological Battery (CERAD), which provides subscores and a summary mild cognitive impairment (MCI) score. In models adjusted for multiple confounders, LPT infants scored significantly lower on word list recognition (a memory test of delayed recognition of 10 original words along with 10 new words) compared with controls. Consistent with previous

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work, the investigators reported that a lower level of educational attainment was associated with lower scores on the CERAD scales. Because a lower level of educational attainment is also a risk factor for MCI, analyses were done separately comparing groups with basic low primary or secondary education versus those with higher tertiary education. The basic low-education LPT group had lower adjusted scores for CERAD word list recognition, constructional praxis, clock drawing, Mini-Mental State Examination, memory total score, and CERAD total score compared with term controls, whereas there were no differences between former LPT infants with tertiary education compared with controls. This finding indicates that, although LPT infants have an almost threefold increased risk of MCI suggestive of early-onset Alzheimer disease, this outcome is mediated by a higher level of educational attainment. Although the increased risk of age-related MCI in this LPT population is disturbing, the data inform us of the potential for effective intervention. The findings are also an awakening to the fact that there is a need to examine not only neonatal, early childhood, school age, and young adult effects of risk factors such as LPT but also lifelong effects.

As the United States moves in the direction of electronic health records and health tracking systems of population health, analyses linking prenatal and perinatal factors to long-term outcomes will provide us with new epidemiologic data and opportunities to identify relationships and mechanisms contributing to both adverse and optimal outcomes and to potential new innovative educational interventions. Investigators in Finland and a number of other European countries appear to have a head start.

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