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The biological 'record' of extremely preterm birth differs in men and women

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Researchers at McMaster University have found distinct effects of adversity early in life in the genomes of men compared to women who were born extremely preterm.

The study, published online in the journal *Development and Psychopathology*, followed infants who weighed between 580 and 1000 grams at birth. The cohort was initiated by Saroj Saigal in the Department of Pediatrics in the late 1970's and has been prospectively followed over four decades.

Birth size is a rough indicator of the quality of the perinatal environment, explain researchers. The fetus adapts to cope with the adverse conditions leading to small birth size, which in turn may result in long-lasting changes in the epigenome. The epigenome is the dimension of genomic control that influences gene expression and, ultimately, physiology.

The scientists studied what are known as epigenetic adaptations to early environmental stress.

Being born small and extremely preterm exposes infants to early loss of the protective environment of the womb, postnatal separation from the mother, and life-saving but invasive medical procedures in the hospital. Infant boys are especially vulnerable to these stresses, and respond differently to them than infant girls.

"Premature birth is profoundly traumatic for infants," says Karen Mathewson, a research associate and lead author of the study, who conducted the work with Louis Schmidt, a professor in the Department of Psychology, Neuroscience & Behaviour at McMaster, and Patrick McGowan, an associate professor in the Department of Biological Sciences at the University of Toronto.

"They are simply not ready to lose the safety and protection of the womb or to be separated from the mother. Later in life, problems affecting cognition, emotion, and physical health may develop for some of them," Mathewson says.

For the study, researchers analyzed DNA samples from cheek swabs taken from 45 adults born at extremely low birth weight (ELBW) in the early days of neonatal intensive care, and a comparison group of adults born at normal birth weight, when both groups were in their early thirties.

Mathewson and her team examined DNA methylation (DNAm) levels at 850,000 sites across the genome of each adult in the study. They found multiple sex differences in DNAm in both groups (outside the sex chromosomes), but the number was hugely exaggerated in the ELBW group at nearly 78,000 sites, versus 3,400 sites in the normal birth weight adults. There were also more than 1,350 differences between ELBW men and control men, but women showed almost no differences.

Extreme perinatal adversity appeared to elicite wide-ranging epigenetic changes in men that remained detectable years later. Not only did males born extremely preterm differ greatly from females, they differed significantly from other males.

"The changes in the DNAm profile are a biological record of the past that stretches back to development in the womb. Yet they were still evident in men decades after their exposure to extreme adversity so early in life," says Mathewson.

The DNAm differences between ELBW men and control men were located on genes related to cellular and metabolic processes, neuron development, and interneuron communication, suggesting the possibility of altered long-term physical and mental health in males born extremely preterm.

Precisely how altered DNAm patterns may influence future health is an important follow-up question. The research team recently received additional funding to study how DNAm patterns change over time in

adults born at ELBW, and whether they are linked to long-term health or age-related decline.

More information: Karen J. Mathewson et al, DNA methylation profiles in adults born at extremely low birth weight, *Development and Psychopathology* (2020). DOI: 10.1017/S0954579420000899

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