Is There a Molecular Basis to Accelerated Aging?

Pam Factor-Litvak, PhD

In 1989, Barker et al\(^1\) proposed that poor maternal nutrition, as evidenced by reductions in birth weight, increased the risk of later-life adverse cardiovascular and metabolic outcomes in the offspring. This hypothesis was based on ecological and cohort data, which indicated that reduced birth weight, intrauterine growth retardation, and preterm birth were associated with increased risks of hypertension, coronary heart disease, and type II diabetes later in life.\(^2\) Now known as the Barker hypothesis, the thrifty phenotype hypothesis, the developmental origins of adult health, or the early determinant of health, this hypothesis has been expanded to include adverse events (eg, maternal stress, other maternal illnesses) or exposures (eg, heavy metals, endocrine disruptors, air pollution, psychosocial stress) during pregnancy and early life and numerous later-life outcomes and has spawned a new focus for epidemiology and a new name for what had been done for more than a century: life course epidemiology.\(^3\)

Since the explication of the Barker hypothesis, numerous investigations have been used to attempt to find its molecular basis. Explanations include reductions in telomere length\(^4\) and changes in the epigenetic profile,\(^5\) both hypothesized to result in increased rates of cellular aging.\(^6\) Specific patterns in DNA methylation thought to be age related define the construct of epigenetic clocks, which are used to estimate aging and age-related disease risk. Several epigenetic clocks have been proposed, each using a different set of methylated CpG sites on the DNA and/or different tissue sites to define the methylation patterns. In this issue of Pediatrics, Van Lieshout et al\(^7\) use a novel cohort of survivors with extremely low birth weight (ELBW) and matched participants with normal birth weight (NBW) to investigate whether there is evidence of accelerated biological aging, measured by using the Horvath epigenetic clock (the most commonly used epigenetic clock), among survivors with ELBW. Results suggest that among male infants, those with ELBW compared with those with NBW had a significantly elevated epigenetic age by \(\sim 4.6\) years. The authors posit that male infants born at \(<1000\) g experience accelerated changes in the epigenetic clock, perhaps because of increases in psychological and physiologic stress.

These findings are intriguing and open many questions for further study. First, from these data, it is unclear whether the epigenetic clock at birth in infants with ELBW differs from that in infants with NBW; differences would provide evidence that accelerated aging begins during the in utero period, perhaps because of maternal undernutrition, stress, or another exposure. Cumulative stress (which includes psychological, nutritional, and other forms of stress) is often operationalized by allostatic load, a construct that is operationalized by disruptions in the physiologic normal response to stress by the hypothalamic-pituitary-adrenal axis. Although there is growing interest in defining measures of allostatic load in children younger than \(\sim 9\) years of age, researchers are...
continuing to conceptualize cumulative stress in neonates and young children. As the authors point out, reductions in chronic stress levels, which may begin for neonates with ELBW in utero and in the first hours of life, may provide an opportunity for interventions. Interventions may involve the application of nurturescience, a relatively new area of inquiry in which emphasis is placed on early attachment between ELBW neonates, their mothers, and their immediate physical environment, with the ultimate goal of fostering resilience and wellness. Indeed, a recent cluster randomized trial found that for infants in the NICU, an integrated approach to care that emphasized parental participation in the care team and parental presence in the NICU reduced length of stay by 2.5 days.

A second interesting finding from this study is that the association was restricted to boys. The authors correctly point out that male neonates, especially those born preterm, are more susceptible to adverse outcomes. However, associations between allostatic load and biological aging differ by sex depending on which epigenetic clock metric is used; for example, in the Irish Longitudinal Study on Aging, metabolic dysregulation was associated with the Horvath and Levine epigenetic clocks in men but with only the Levine epigenetic clock in women, strongly suggesting that different epigenetic clocks have different implications for aging.

Finally, the authors also note that physiologic responses to stress may be mitigated by exposure to estrogen. The current study was restricted to follow-up at ages 30 to 35 years, and the women included likely did not yet undergo the menopausal transition. Thus, further follow-up is required to determine if the identified differences in epigenetic age will persist as the cohort ages.

In conclusion, the intriguing findings of this study warrant further investigation into the meaning and utility of epigenetic clocks, the individual trajectory of epigenetic clocks over the life span, and the mechanisms by which sex differences in health emerge. Further studies, including those in birth cohorts that follow neonates either exposed or not exposed to adverse circumstances during gestation are necessary to best elucidate these mechanisms. Finally, intervention need not wait for these results but can rely on previous work examining the benefits of providing nurture care to neonates at high risk.

### ABBREVIATIONS

ELBW: extremely low birth weight  
NBW: normal birth weight

### REFERENCES

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*Pediatrics* 2021;147;
DOI: 10.1542/peds.2020-038158 originally published online May 17, 2021;

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