Pediatric RESEARCH

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COMMENT

Understanding the impact of size at birth and prematurity on biological ageing: the utility and pitfalls of a life-course approach

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Since Leonard Hayflick's 1961 seminal observation of human cellular senescence,[1] the determinants of biological ageing have been a topic of particular interest to clinicians, scientists and health policy makers. If the present yearly increase in longevity is extrapolated, in some high-income countries most babies born since 2000 might be expected to celebrate their 100th birthdays.[2] This has wide-reaching implications both for society and for neonatal clinicians looking after very-low-birth-weight (VLBW) and preterm born infants. Recognising that life span, health span and disease span[3] are different, and have varying implications for society, is vital if we are to provide the best care and medical follow-up for graduates of neonatal care.

How might size at birth or prematurity impact upon biological ageing? As survival of smaller and more preterm babies into adulthood has increased, so has the concern that age-related diseases, particularly cardiovascular and metabolic, are more prevalent. Further, age-related disease may occur earlier, thereby decreasing health span and potentially decreasing life span.

The enclosed article by Professor Darlow and colleagues[4] explores whether or not babies born with a birthweight of <1500 g (VLBW infants), from the New Zealand 1986 VLBW Follow-Up study, assessed at between 26 and 30 years of age demonstrate different physiological functioning—potentially indicative of a different pace of ageing—in comparison to term born healthy infants. The study utilises, and combines into a summative measure, 10 different measurements, which between them cover metabolic, respiratory, cardiovascular, endothelial function and dental hygiene. This study finds poorer physiological functioning in the ex-VLBW group, amounting to a difference of 0.47 standard deviations in the summative measure, suggesting that former VLBW adults have a more advanced physiological age by the end of their third decade than term born controls.

The extent of follow-up (three decades) in this study is remarkable, and such studies are essential to better inform our understanding of the long-term health consequences of being a VLBW or preterm infant. The authors are to be congratulated, particularly on the 71% follow-up rate that they achieved at 26–30 years of age. This alone belies enormous foresight, commitment and ongoing engagement with this cohort. Their intent to follow this same cohort in a decade to further assess ageing is laudable, and will be another important contribution to neonatal, paediatric and adult research. This work raises important questions for those trying to assess life course physiology and biological ageing in VLBW and preterm populations.

Adopting a life-course approach is complicated by the absence of a gold-standard marker for aging, if indeed one exists. The choice of biomarker/s to measure biological ageing needs careful consideration. Key questions relate to the choice of a single biomarker versus the use of a summative combination, the choice of clinical or physiological markers and between those indicative of age-related disease processes or markers of cellular senescence. In this study, the authors examine a range of parameters covering a number of different systems that are all highly relevant to biological ageing. However, many of these individual measures have been previously shown to be different between VLBW/preterm born and term born populations, albeit at different time points. It is therefore unsurprising that a composite score of these measures shows the difference observed in the study. Where this study is a valuable addition to our knowledge regarding the life-course impact of VLBW is in the duration and completeness of follow-up and the range of physiological measures evaluated.

What about other markers reflective of cellular senescence? How might these contribute to our understanding of the long-term impact of VLBW and preterm birth, and relate to the physiological measurements used here? A well-studied biomarker of cellular senescence is telomere length,[5] but others including N-glycomic biomarkers[6] and cyclin-dependent kinase inhibitors[7] are also plausible markers of cellular senescence, although data in ex-VLBW and ex-preterm infants are scarce.[8] Unfortunately, it remains unclear the degree to which cellular markers such as these align with either life span or disease span, a fact perhaps best illustrated by the observation that no studied biomarker of biological ageing performs better than perceived age, at least in Danish dizygotic twins >70 years of age.[9]

By its very nature, this cohort reflects a historic era of care and the rapidly advancing nature of neonatal intensive care medicine must be considered when attempting to generalise these findings to current infants. Better obstetric and neonatal care, such as routine antenatal maternal corticosteroid administration, postnatal surfactant therapy and avoidance of hyperoxia, are all likely to mediate the outcomes measured in this study, hopefully in a beneficial manner. Similarly, the impact of a multitude of potential confounders during the long follow-up period is unknown. Such limitations are unavoidable in such long-term follow-up studies,

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and while they must be acknowledged, do not detract from the importance of this work.

Despite the very real challenges inherent in undertaking life-course research, such studies are essential to better understand the long-term health implications of being a VLBW or preterm infant, and inevitably lead to manifold further questions. What mechanisms drive the observations described here and by others in this field? How do population level data relate to an individual VLBW or preterm infant? Finally, and perhaps most critically, how do we identify those physiological parameters that are more influenced by environment (rather than genetic endowment) and therefore amenable to intervention? Ultimately, the valuable observations made by Darlow and colleagues[4] must be built upon with interventions to modify and improve health span, that part of a life span free from age-related disease, for current and future cohorts of VLBW and preterm babies.

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ADDITIONAL INFORMATION

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