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Commentary

Newborn telomere length and the early life origins of age-related disease

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In this *EBioMedicine* article, Dries Martens and colleagues report that newborn telomere length (TL) predicts TL in early childhood and young adulthood and that relative position within the TL distribution remains stable over time for the majority of study participants [1]. This work builds on previous studies that found evidence of so-called tracking and fixed ranking of TL in adults [2] and adolescents and their parents [3]. While the evidence for tracking and fixed ranking of TL appears to be somewhat weaker in childhood compared to adolescence and adulthood, taken together, the results of these studies draw attention to the importance of early life conditions in shaping trajectories of TL across the life course. This is particularly relevant in light of recent Mendelian randomization studies suggesting that TL plays a causal role in cardiovascular disease and cancer [4,5], the two leading causes of death in the US.

Although there is a growing body of literature examining predictors of newborn and child TL (see, for example [6,7]), the overwhelming majority of telomere studies have focused on adults. If TL trajectories are indeed established in the first decade of life, as suggested by prior research on tracking and fixed ranking of TL [1–3], then researchers and funding agencies should prioritize research on the determinants of newborn and child TL. In order to facilitate the development of interventions to promote optimal TL in infants and children, this research should focus on the identification of modifiable environmental exposures, such as material deprivation, discrimination, and air pollution, which may impact TL in early life.

In addition, more work is needed to determine whether apparent tracking and fixed ranking of TL can be explained by stability in environmental conditions that individuals experience as they age. For example, prior research suggests that educational attainment is highly correlated for parents and their children [8], and there is evidence that food preferences, which begin to develop *in utero*, persist throughout life [9]. Thus, the strong correlation between newborn TL and TL later in life may be partially attributable to the persistence of environmental conditions that promote shorter or longer TL, rather than programming of TL at birth. In order to tease apart the influence of early life conditions from those experienced later in life (and to disentangle genetic from environmental influences), it would be useful to look for evidence of tracking and fixed ranking of TL in a sample that includes a sufficient number of individuals who experienced substantial changes in environmental conditions over time. For example, studies could examine people who experienced significant upward or downward social mobility and compare the strength of the correlation between TL at birth and later in life for this group versus a group of individuals whose social status was the same in childhood and adulthood. Given evidence of declining intergenerational mobility in the US since the mid-19th century [10], however, this type of study may be challenging to conduct.

Another important issue that has not been adequately addressed in previous studies is the establishment of criteria for determining whether there is evidence for or against tracking and fixed ranking of TL. With respect to tracking, no specific cutpoint has been established for the observed correlation between baseline and follow-up measures of TL. In a study of four cohorts of adults, Benetos et al. [2] observed correlations ranging from 0.91 to 0.96; and in a later study, the same group reported a correlation of 0.91 in adolescents and a correlation of 0.86 in their parents [3]. While these correlations are close to one, Martens et al. [1] report lower correlations in two cohorts of newborns, ranging from 0.46 to 0.71. Differences in the strength of correlations observed across these studies could reflect differences in measurement technique, differences in the tissues examined, differences in the length of time between baseline and follow-up, and/or differences in the life stage examined. With respect to fixed ranking, Benetos et al. [2] argue that a change of two or more deciles in TL ranking is required to indicate a shift in rank, but this does not appear to be based on statistical or biological criteria. Similar to the findings for tracking, evidence for fixed ranking is weaker for newborns than for adults. Benetos et al. [2] report that just 5.9% of adults changed by two or more deciles in TL ranking, while Martens et al. [1] report that up to 27.4% of newborns shifted TL ranking by at least two quintiles.

While the clinical utility of TL has yet to be established, studies like the one by Martens and colleagues [1] are informative for population health. When considered alongside prior research on tracking and ranking of TL in adolescents and adults, this study helps establish the critical role that early life conditions play in shaping the longitudinal trajectory of TL. In order to determine potential points of

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intervention, more work is needed to identify predictors of newborn and child TL; and novel approaches are needed to test the hypothesis that TL is programmed at birth. Finally, future studies should evaluate the extent to which differences in measurement techniques and tissue types may have contributed to differences in findings reported by Martens et al. [1] and Benetos et al. [2,3] Knowing whether TL is, in fact, more malleable in childhood than in adolescence or adulthood has important implications for the timing of interventions to promote healthy aging across the life course.

Contributors

Belinda Needham drafted this commentary.

Declaration of Interests

Dr. Needham has nothing to disclose.

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