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The Importance of Early Life Studies of Telomere Attrition

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Olovnikov, a Russian theoretical biologist, was the first to recognise that the ends of chromosomes were not completely replicated during cell division, and to suggest that DNA sequences are lost during each cell division until the loss reaches a critical length, at which time the cell ceases to replicate.[1] In the mid-1980s, Elizabeth Blackburn and Carol Greider discovered the enzyme telomerase, the reverse transcriptase that lengthens telomeres, which protects the ends of the chromosomes.[2] It was not until the 1990s, however, that researchers began to study the health effects of telomere shortening.

Most epidemiologic studies of telomere length have focused on the associations between leucocyte telomere length (LTL) and disease in adults. These studies suggest that shorter LTL is associated with cardiovascular disease and decreased longevity. In contrast, longer LTL may be associated with some forms of cancer.[3–5] Further, in adults, LTL appears highly variable across individuals, and associations have been reported between LTL and older paternal age at conception (longer for older paternal age), sex (longer in females compared to males), and ethnicity (longer in African-Americans compared with those of European descent).[6–8] There is increasing evidence that LTL is determined well before adulthood, and possibly at birth. Recent longitudinal findings suggest that LTL tracks during adulthood so that persons with long/short LTL at baseline display long/short LTL as they age; in a longitudinal study (average 12 years of follow up) of four cohorts with mean ages 30, 31, 58, and 75 at baseline, individuals classified as having short, average, and long LTL at baseline generally retained their ranking over the follow-up period.[9]

In studies of adults, LTL is usually considered only as a biomarker for these health outcomes. Recent evidence suggests, however, that it may play a more causal role, and that LTL in adulthood may largely reflect LTL at birth and LTL shortening during childhood.[10] Understanding the determinants of LTL at birth and in childhood might, therefore, shed insights into possible mechanisms underlying associations between early life exposures and late life outcomes, i.e. the possible mediating effects of LTL, which reflects telomere length in other tissues.[11] In this regard, it is especially important to examine the impact of *in utero* and childhood exposures. Although evidence is still scant, some studies report that the rate of LTL shortening during childhood may be associated with exposure to stressful situations.

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Hence, identifying early life determinants of LTL has become increasingly important to life course epidemiology.

Among the open questions are, first, what are the determinants of LTL at birth and of LTL attrition over the first two decades of life; second, whether LTL tracks over the first two decades of life (as found in adults); third, is LTL at birth or during childhood associated with adult outcomes, especially cardiovascular disease and decreased longevity. Stathopoulou and colleagues,[12] in this issue of the Journal, describe an analysis looking at the genetic influences of LTL in children, an area which has been studied in adults but not in children. They did not find variants associated with LTL in adults to be associated with LTL in children, but in a gene discovery GWAS, they found several novel variants associated with LTL in children. Although the sample size is small, and the age range of the children spans from middle childhood (age 6 years) through puberty (age 17 years), this study raises the question of whether genetic determinants of LTL and its rate of shortening differ between adults and children.

What types of studies are needed to gain an understanding of LTL at birth and during childhood? Are the relationships observed in adults, described above, evident at birth or during childhood? We propose that these associations also be explored at birth and during the first two decades of life using longitudinally followed birth cohorts, both individually and in consortia. As part of these studies, we stress the need for careful measurement of LTL, as previous epidemiologic studies have usually employed either the gold-standard Southern blot method or the high-throughput quantitative polymerase chain reaction (qPCR) method. Although results from these two approaches are correlated, the qPCR method entails more measurement error and yields a result in the form of a ratio rather than an absolute value.[13] Thus, studies using qPCR need to be particularly attuned to having adequate sample sizes and proper accounting for measurement error, in light of the fact that those studies generally find small differences in LTL between groups (in the context of large inter-individual variation). Furthermore, because of the strong familial effects, LTL should ideally be measured in both parents as well as the newborns and in the children during follow-up, underscoring the need for more sophisticated epidemiologic study designs such as the case-parent trio design. Birth cohorts that begin during pregnancy and follow-up with the children also have the advantages that detailed data are collected during the prenatal periods, and that serial measures can be made in children of anthropometrics, stress/adversity, and other potentially relevant exposures. For example, there is a wide-open area of research regarding the influences of environmental contaminants, many of which may be associated with oxidative stress, on LTL; these are only beginning to be studied.

In conclusion, studies in adults suggest that LTL tracks during life, that there is familial patterning, and that there are variations based on race, sex, and possibly parental age at conception. Due to the paucity of data, these associations have not been confirmed in newborns and children. Early life LTL may well be an important risk indicator for later disease, but we need rigorous empirical data to support or refute this hypothesis. Longitudinal studies in birth cohorts, either singly or in consortia, are necessary to fully elucidate the determinants of LTL in early life and to evaluate associations with later life outcomes.

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