Early warning signs? Infant obesity and accelerated cellular ageing

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Worldwide, the number of people aged over 60 years is expected to reach 2 billion by 2050 (1), a rise that will be accompanied by an inevitable increase in the prevalence of age-related conditions (2). In particular, a concomitant rise in global obesity rates is resulting in a growing burden of cardiometabolic disease in many populations (3). The identification of potential determinants of aging trajectories and approaches to track these throughout life are therefore urgent priorities. An established indicator of cellular age that is also associated with human lifespan and cardiometabolic disease risk is leukocyte telomere length (LTL) (4-7).

Telomeres are protective structures that cap the ends of linear chromosomes. Vertebrate telomeres are composed of variable numbers of the repeat sequence (TTAGGG)n bound to the shelterin protein complex (8). In proliferative tissues such as leukocytes, telomeres shorten with each cell division due to the inherent properties of linear DNA replication. This process is accelerated by oxidative stress (9, 10). Mean LTL in adults is believed to reflect the initial telomere length at birth and the replicative history of the hematopoietic stem cell population (11). In addition, LTL is associated with known risk factors for cardiometabolic disease, including obesity and smoking (12), and with several common genetic variants (13).

Despite extensive research into factors associated with adult LTL, there is a relative paucity of studies into the determinants of telomere length in early life, although the rate of telomere shortening that occurs in infancy is far more rapid (11, 14). This is an important knowledge gap to address, especially given the wider evidence base that the foundations of healthy adulthood are laid in early life (15).

In this volume of The Journal, Baskind et al (16) report a negative association between obesity at six months of age and mean LTL in children of pre-school age (3-5yrs). They also found evidence for a positive association between pre-schooler LTL and breastfeeding at 6 months, a finding in line with their previous study of younger infants in another Latinx cohort (17). Although associations between obesity-related traits and LTL have been reported previously, for the most part these have been

carried out in populations of adults or older children (18, 19). The new study therefore adds another important piece to the puzzle, and highlights the importance of supportive public health measures to reduce risk of infant obesity.

These results are based on data from a relatively small sample, so await replication in larger cohorts recruited from different populations. Another intriguing finding that warrants further investigation is the lack of association between obesity at earlier ages (2-5yrs) and pre-schooler LTL in the same study. The authors speculate that this may indicate the first 6 months of life as being a critical period during which cells are particularly vulnerable to the adverse effects of obesity. The subsequent association with LTL could reflect increased levels of oxidative stress during this crucial window. Alternatively, it could be that any associations between pre-schooler LTL and obesity at younger ages are obscured by the wide inter-individual variation in growth trajectories during this time.

Given the relevance of LTL as a predictive biomarker for adult disease risk, additional research is needed to gain further insights into the factors associated with this biomarker throughout life. Longitudinal studies of LTL in other populations will be particularly valuable for shedding light on the mechanisms through which early-life factors may influence adult disease risk. Furthermore, such studies will help identify the most appropriate timepoints for effective early interventions to support healthy ageing trajectories.

1. World Population Prospects: The 2015 Revision, Key Findings and Advance Tables: United Nations, Department of Economic and Social Affairs, Population Division; 2015 [12th January 2021].
2. Chatterji S, Byles J, Cutler D, Seeman T, Verdes E. Health, functioning, and disability in older adults--present status and future implications. Lancet. 2015;385(9967):563-75.
3. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627-42.
4. Oeseburg H, de Boer RA, van Gilst WH, van der Harst P. Telomere biology in healthy aging and disease. Pflugers Archiv : European journal of physiology. 2010;459(2):259-68.

5. Mather KA, Jorm AF, Parslow RA, Christensen H. Is telomere length a biomarker of aging? A review. The journals of gerontology Series A, Biological sciences and medical sciences. 2011;66(2):202-13.
6. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 2014;349:g4227.
7. Zhao J, Zhu Y, Lin J, Matsuguchi T, Blackburn E, Zhang Y, et al. Short leukocyte telomere length predicts risk of diabetes in american indians: the strong heart family study. Diabetes. 2014;63(1):354-62.
8. de Lange T. Shelterin: the protein complex that shapes and safeguards human telomeres. Genes & development. 2005;19(18):2100-10.
9. Kurz DJ, Decary S, Hong Y, Trivier E, Akhmedov A, Erusalimsky JD. Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells. Journal of cell science. 2004;117(Pt 11):2417-26.
10. von Zglinicki T. Oxidative stress shortens telomeres. Trends in biochemical sciences. 2002;27(7):339-44.
11. Sidorov I, Kimura M, Yashin A, Aviv A. Leukocyte telomere dynamics and human hematopoietic stem cell kinetics during somatic growth. Experimental hematology. 2009;37(4):514-24.
12. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, et al. Obesity, cigarette smoking, and telomere length in women. Lancet. 2005;366(9486):662-4.
13. Li C, Stoma S, Lotta LA, Warner S, Albrecht E, Allione A, et al. Genome-wide Association Analysis in Humans Links Nucleotide Metabolism to Leukocyte Telomere Length. American journal of human genetics. 2020;106(3):389-404.
14. Frenck RW, Jr., Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. Proceedings of the National Academy of Sciences of the United States of America. 1998;95(10):5607-10.
15. Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, Gray K, et al. Developmental Origins of Health and Disease: Integrating Environmental Influences. Endocrinology. 2015;156(10):3416-21.
16. Baskind MJ, Hawkins J, Heyman MB, Wojcicki JM. Obesity at Age 6 Months Is Associated with Shorter Preschool Leukocyte Telomere Length Independent of Parental Telomere Length. The Journal of Pediatrics.
17. Wojcicki JM, Heyman MB, Elwan D, Lin J, Blackburn E, Epel E. Early exclusive breastfeeding is associated with longer telomeres in Latino preschool children. The American journal of clinical nutrition. 2016;104(2):397-405.
18. Mundstock E, Sarria EE, Zatti H, Mattos Louzada F, Kich Grun L, Herbert Jones M, et al. Effect of obesity on telomere length: Systematic review and meta-analysis. Obesity. 2015;23(11):2165-74.
19. Guyatt AL, Rodriguez S, Gaunt TR, Fraser A. Early life adiposity and telomere length across the life course: a systematic review and meta-analysis. 2017;2:118.