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Environmental Exposures, Telomere Length at Birth, and Disease Susceptibility in Later Life

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In this issue of *JAMA Pediatrics*, Martens et al[1] report an inverse association between exposure to air pollution during the second trimester of pregnancy and relative telomere length (RTL) in cord blood samples and placentae. Monitoring stations calibrated to estimate exposure to particles of diameter less than or equal to 2.5 μm ($PM_{2.5}$) measured exposure levels at the maternal residence. The RTL was measured using quantitative polymerase chain reaction (qPCR). If confirmed, this intriguing finding could help elucidate the association of environmental exposures with telomere length (TL) dynamics in utero, the period of most intense cell division during the entire human life course. In this editorial, we briefly discuss 4 topics relevant to interpretation of the key finding and related results: (1) biological meaning, (2) TL measurement, (3) timing of prenatal exposure, and (4) approaches to further testing of validity.

First, regarding the biological meaning of the main finding, we differentiate among the interpretations offered by the authors, separating those with the most solid foundation from others that require more caution. The authors have a sound basis for proposing that shorter RTL in cord blood, reflecting shorter leukocyte TL (LTL), might have ramifications for adult-onset cardiovascular disease risk and longevity. In adults, shorter LTL has been associated with cardiovascular disease and diminished longevity. Furthermore, LTL tracks over the adult life course, meaning that individuals who enter adulthood with comparatively short LTL are likely to have short LTL later in life.[2] This tracking has not yet been examined in children and adolescents but may well be present from birth onward. Thus, individuals born with a shorter LTL may be at a higher risk for cardiovascular disease and a shorter life span.

One should exercise caution, however, about interpreting this finding in terms of a broader hypothesis about TL and the aging process. The authors theorize that maternal exposure to

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$PM_{2.5}$ generates more reactive oxygen species in utero, which, in turn, increase the rate of TL shortening. They imply that this process sets a path toward accelerated biological aging and consider TL to be “a marker of biological aging.”Moreover, the authors interpret shorter birth TL after $PM_{2.5}$ exposure as evidence of “fetal programming at the molecular level” that has consequences for the pace of aging and for health over the life course.

We have some reservations about this interpretation. The premise for considering LTL as a biological marker of aging is that age-dependent LTL shortening reflects the “ticking” of an in vivo biological clock, which ticks faster owing to increased systemic burden of inflammation and oxidative stress. Shortening of LTL after birth ostensibly reflects TL dynamics in hematopoietic stem cells. It is reasonable to infer, therefore, that the pace of hematopoietic stem cell division may increase to sustain chronic and indolent inflammation that marks the aging process. It is also established that an increased level of reactive oxygen species augments TL shortening per each division of cultured somatic cells. Thus, LTL shortening from birth onward may capture to some extent the accruing burden of inflammation and oxidative stress.

However, the metaphor of a biological clock is only meaningful if at birth the zero time of the clock is identical in all individuals. This is not the case, as variation in LTL across newborns is wide and similar to variation observed in adults.[3] Short TL, then, may not be merely a reflection of biological pathways, such as inflammation and oxidative stress, associated with increased cardiovascular disease risk and shorter longevity. Rather, stemming from both genetic and environmental factors that affect TL dynamics in utero, short TL at birth may mediate outcomes later in life.[4] Furthermore, the ticking biological clock concept is inconsistent with recent research showing that a longer LTL is associated with increased risk for development of major cancers.[5, 6] The association of LTL, which reflects TL in somatic cells other than hematopoietic cells,[7] with both cancer and cardiovascular disease might best be understood as an evolutionary trade-off between cancer due to increased proliferative potential (longer telomeres) and cardiovascular disease due to diminished proliferative potential and poor repair capacity (short telomeres).[8] From this perspective, TL at birth and thereafter is hardly an aging biomarker, but it might represent susceptibility to different disease categories later in life.

Second, most epidemiological studies measure TL using the high-throughput qPCR-based method, instead of the costly, labor-intensive and time-consuming Southern blot method. While the qPCR method generates data in RTL units, which differ across laboratories, the Southern blot data are expressed in absolute unit length, ie, base pairs of TL. Because the relation between data generated by Southern blot and qPCR may not be linear,[9] it is difficult to assess the magnitude of the association of $PM_{2.5}$ exposure with cord blood and placenta TL in base pair units. Martens et al[1] reported mean maternal exposure during pregnancy of 13.4 $\mu g/m^3$ of $PM_{2.5}$. The mean RTL shortening due to second trimester maternal exposure was 9.4%in cord blood and was 7.1%in placenta. However, these data are expressed per 5$\mu g/m^3$ of $PM_{2.5}$, which means that maternal exposure to the average $PM_{2.5}$ compared with no $PM_{2.5}$ was associated with (9.4 × 13.4)/5 = 25.2%shorterRTL in cord blood and (7.1 × 13.4)/5 = 19.0% shorter RTL in the placenta. This degree of shortening, if applied to actual TL shortening in base pairs, would be highly unlikely.

Third, Martens et al's finding of opposite effects of exposure to $PM_{2.5}$ on TL during the second trimester (shortening) vs the third trimester (lengthening) is puzzling, as the relative concentrations of $PM_{2.5}$ track geographically. The authors' argument that these findings might reflect an adaptive process is less than convincing. According to homeostatic principles, one anticipates that adaptation might attenuate the effect of TL shortening due to $PM_{2.5}$ exposure rather than result in TL lengthening.

Finally, to strengthen the finding, the investigators could test associations between exposure after pregnancy and cord blood or placental TL; such exposure would not be expected to exhibit associations, a so-called negative control. If associations were found for exposure after pregnancy (controlling of course for pregnancy exposure), then the original finding could be questionable; if not, then more support could be given to this original finding.

In conclusion, if replicated by other studies, what is the import of the results reported by Martens et al? Because TL is highly heritable, parental TLs largely forecast the newborn TL. But that does not rule out the potential influence of environmental exposures on TL dynamics in utero and ultimately TL at birth. The outcome of these exposures on TL might be particularly pronounced because intrauterine growth is the most intense phase of cell division during the entire life course. Although telomerase, the reverse transcriptase that counters telomere shortening per each division, is active during early embryonic development, it is largely silent during subsequent fetal growth and extrauterine life.[10, 11] In theory, therefore, intrauterine growth might be the life phase most sensitive to environmental factors that exert their influence on TL dynamics by either or both of the following: (1) inhibiting telomerase activity and perhaps the alternate pathway to elongate telomeres during embryonic development,[11] and (2) increasing the amount of telomere shortening per cell division through mechanisms independent of telomerase and alternative pathway inhibition. Herein lies the relevance of this work, but clearly, further studies are essential to confirm its finding, quantitate the outcome of $PM_{2.5}$ exposure based on actual measurements that generate data in absolute values of TL, and elucidate the underlying mechanisms explaining the outcome.

References

1. Martens DS, Cox B, Janssen BG, et al. Prenatal air pollution and newborns' predisposition to accelerated biological aging [published online October 16, 2017]. JAMA Pediatr.
2. Benetos A, Kark JD, Susser E, et al. Tracking and fixed ranking of leukocyte telomere length across the adult life course. Aging Cell. 2013; 12(4):615–621. [PubMed: 23601089]
3. Factor-Litvak P, Susser E, Kezios K, et al. Leukocyte telomere length in newborns: implications for the role of telomeres in human disease. Pediatrics. 2016; 137(4):e20153927. [PubMed: 26969272]
4. Aviv A, Kark JD, Susser E. Telomeres, atherosclerosis, and human longevity: a causal hypothesis. Epidemiology. 2015; 26(3):295–299. [PubMed: 25774608]
5. Aviv A, Anderson JJ, Shay JW. Mutations, cancer and the telomere length paradox. Trends Cancer. 2017; 3(4):253–258. [PubMed: 28718437]
6. Haycock PC, Burgess S, Nounu A, et al. Telomeres Mendelian Randomization Collaboration. Association between telomere length and risk of cancer and non-neoplastic diseases: a mendelian randomization study. JAMA Oncol. 2017; 3(5):636–651. [PubMed: 28241208]
7. Daniali L, Benetos A, Susser E, et al. Telomeres shorten at equivalent rates in somatic tissues of adults. Nat Commun. 2013; 4:1597. [PubMed: 23511462]

8. Stone RC, Horvath K, Kark JD, Susser E, Tishkoff SA, Aviv A. Telomere length and the cancer-atherosclerosis trade-off. PLoS Genet. 2016; 12(7):e1006144. [PubMed: 27386863]

9. Verhulst S, Susser E, Factor-Litvak PR, et al. Response to: reliability and validity of telomere length measurements. Int J Epidemiol. 2016; 45(4):1298–1301. [PubMed: 27880696]

10. Yashima K, Maitra A, Rogers BB, et al. Expression of the RNA component of telomerase during human development and differentiation. Cell Growth Differ. 1998; 9(9):805–813. [PubMed: 9751124]

11. Ozturk S, Sozen B, Demir N. Telomere length and telomerase activity during oocyte maturation and early embryo development in mammalian species. Mol Hum Reprod. 2014; 20(1):15–30. [PubMed: 23928157]