Letters to the Editor

Non-Dynamic Association of Depressive and Anxiety Disorders With Leukocyte Telomere Length?

TO THE EDITOR: We applaud the attempt of Verhoeven and colleagues (1) to examine the relationship over time between depressive and anxiety disorders and leukocyte telomere length (LTL) shortening. We propose, however, that the absence of a relationship in their data may be due to measurement error. For the following reasons, measurement precision in their study was low relative to the effect that was assessed; that is, the variation related to depression or anxiety in the LTL shortening slope, which was on average 13.3 base pairs (bp) per year:

(i) The authors reported that over 6 years, 26% of participants showed LTL lengthening, which should not be expected for low measurement error. We showed that LTL lengthening is primarily an artifact of measurement error, especially for short-term follow-up periods such as 6 years (2).

(ii) Verhoeven et al. measured LTL using quantitative polymerase chain reaction, reporting interassay coefficients of variation of 4.6% at baseline and of 3.0% at follow-up of presumably the T/S ratio (the telomere product T divided by the single gene product S). Presuming an overall coefficient of variation of 3.8% (baseline=4.6%; follow-up=3.0%) and a mean LTL of about 5,400 bp (see Figure 1 in the original article), the standard deviation of replicate measurements would amount to about 205 bp. That is more than 2.5-fold higher than the average LTL shortening (13.3 bp per year×6 years=79.8 bp) reported in their study.

(iii) Verhoeven et al. reported r=0.48 for the association between baseline and follow-up LTL, which is considerably lower than correlations of 0.91–0.96 between baseline and follow-up LTL over approximately 12 years reported elsewhere (3).

(iv) The authors reported r=−0.72 between baseline LTL and LTL change. However, correlations between baseline LTL and LTL change largely reflect regression to the mean (4), a phenomenon exacerbated by measurement error.

Therefore, we suggest reexamination of the nexus between depressive and anxiety disorders and LTL in studies with more precise LTL measurements and longer follow-up periods (2, 5). Given the reported cross-sectional association between LTL and depressive and anxiety disorders, studying LTL in birth cohorts would be advantageous because a principal determinant of LTL throughout life is LTL at birth (6).

REFERENCES

1. Verhoeven JE, van Oppen P, Révész D, et al: Depressive and anxiety disorders showing robust, but non-dynamic, 6-year longitudinal association with short leukocyte telomere length. Am J Psychiatry 2016; 173:617–624
2. Steenstrup T, Hjelmborg JV, Kark JD, et al: The telomere lengthening conundrum: artifact or biology? Nucleic Acids Res 2013; 41:e131
3. Benetos A, Kark JD, Susser E, et al: Tracking and fixed ranking of leukocyte telomere length across the adult life course. Aging Cell 2013; 12:615–621
4. Verhulst S, Aviv A, Benetos A, et al: Do leukocyte telomere length dynamics depend on baseline telomere length? An analysis that corrects for 'regression to the mean'. Eur J Epidemiol 2013; 28: 859–866
5. Verhurlst S, Susser E, Factor-Litvak PR, et al: Reliability and validity of telomere length measurement. Int J Epidemiol (in press)
6. 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:e20153927

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Unresolved Issues in Longitudinal Telomere Length Research: Response to Susser et al.

TO THE EDITOR: We thank Dr. Susser and colleagues for their commentary on our article (1) regarding the longitudinal association of depressive and anxiety disorders with leukocyte telomere length (LTL) in which they argue that the lack of depression- and anxiety-related differences in LTL shortening, as well as the finding of apparent lengthening in LTL over time, might be due to measurement error. We agree that this is a very timely and important topic to discuss,