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Cumulative lifetime stress exposure and leukocyte telomere length attrition: The unique role of stressor duration and exposure timing

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ABSTRACT

Background: Stress exposure occurring across the lifespan increases risk for disease, potentially involving telomere length shortening. Stress exposure during childhood and adulthood has been cross-sectionally linked with shorter telomere length. However, few longitudinal studies have examined telomere length attrition over time, and none have investigated how stressor duration (acute life events vs. chronic difficulties), timing (childhood vs. adulthood), and perceived severity may be uniquely related to telomere length shortening.

Methods: To address these issues, we administered a standardized instrument for assessing cumulative lifetime stress exposure (Stress and Adversity Inventory; STRAIN) to 175 mothers of children with Autism Spectrum Disorder or neurotypical children and measured their leukocyte telomere length (LTL) at baseline and 2 years later.

Results: Greater count of lifetime stressors was associated with shorter LTL at baseline and greater LTL attrition over time. When separating lifetime stressors into acute life events and chronic difficulties, only greater count of chronic difficulties significantly predicted shorter baseline LTL and greater LTL attrition. Similarly, when examining timing of stressor exposure, only greater count of chronic childhood difficulties (age < 18) significantly predicted shorter baseline LTL and greater LTL attrition over the 2-year period in mid-life. Importantly, these results were robust while controlling for stressors occurring during the interim 2-year period. Post-hoc analyses suggested that chronic difficulties occurring during earlier childhood (0–12 years) were associated with greater LTL attrition. Cumulative stressor severity predicted LTL attrition in a parallel manner, but was less consistently associated with baseline LTL.

Conclusions: These data are the first to examine the effects of different aspects of cumulative lifetime stress exposure on LTL attrition over time, suggesting that accumulated chronic difficulties during childhood may play a unique role in shaping telomere shortening in midlife.

1. Introduction

Stress exposure occurring throughout the lifespan increases risk for psychiatric disorders and physical diseases of aging (Cohen et al., 2007), potentially mediated by telomere shortening. Telomeres are the protective caps at the ends of chromosomes. They shorten as cells divide (Blackburn et al., 2006), and shorter telomeres have been linked to depression and anxiety disorders (Darrow et al., 2016), as well as with cardiovascular and other chronic diseases (D'Mello et al., 2015; Zhao et al., 2013). Stress exposure occurring during childhood and adulthood have both been associated with shorter telomere length (TL) at a single point in time (Oliveira et al., 2016). To date, however, only a few studies have examined stress-related *changes* in TL across time and none have comprehensively assessed individuals' cumulative lifetime stress exposure while taking into account total stressor count, stressor duration (acute vs. chronic stressors), exposure timing (childhood vs. adulthood), and perceived severity.

Tyrka et al. (Tyrka et al., 2010) provided the first evidence for shortened TL in adults with a history of childhood maltreatment. Three meta-analyses have since demonstrated a dose-dependent relationship

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discrepancies with studies that have not found effects of life stressors on TL might be explained, at least in part, by the degree to which such studies assessed acute versus chronic life stressors (Oliveira et al., 2016). Overall, cumulative chronic stressors occurring over the lifespan played a key role in telomere shortening over time in the present sample, consistent with models of allostatic load/overload that highlight the role of cumulative chronic stressors in diseases of aging (Danese and McEwen, 2012; McEwen, 1998; Shields and Slavich, 2017).

The specific timing of chronic stressor exposure may also matter for LTL. In the present study, for example, only cumulative chronic stressors occurring during childhood were significantly related to shorter baseline LTL and LTL attrition over a 2-year period in mid-life. Moreover, these results were robust while controlling for stressors occurring during the interim 2-year period. These findings are consistent with results from a larger cohort study (Puterman et al., 2016), which found that cumulative childhood adversity predicted shortened TL at a single time point. Some other large-scale studies have not found effects of childhood adversity on TL (e.g., van Ockenburg et al., 2015; Verhoeven et al., 2015), which, again, may be due to differences in stress measurement (e.g., limited assessment of chronic childhood stressors). Nevertheless, the critical role of cumulative childhood adversity on LTL is consistent with mostly cross-sectional descriptive and meta-analytic findings (Coimbra et al., 2017; Hanssen et al., 2017; Li et al., 2017; Price et al., 2013; Ridout et al., 2017; Shalev et al., 2013a), as well as with prospective evidence (Shalev et al., 2013b). Our post-hoc results also suggest that the early developmental years may be particularly important for shaping LTL attrition in adulthood, though replication is needed in samples with greater stress exposure in early and middle childhood as well as adolescence. Cumulative lifetime stressor *severity* predicted LTL attrition in a manner similar to stressor *count*, but severity indices were less consistently associated with baseline LTL, perhaps because stressor exposure may matter more for LTL. In sum, our findings show that cumulative chronic adversity during childhood is related to shorter LTL and greater LTL attrition over time during mid-life.

In contrast to these effects, stress exposure occurring during adulthood was unrelated to LTL shortening, and chronic adulthood stressors did not predict LTL attrition above and beyond the effects of chronic childhood stressors. This finding is different than what has been observed in other studies of chronic adulthood stress (Oliveira et al., 2016). However, most prior studies have assessed only a limited number of adulthood stressors and have not assessed cumulative stressor exposure occurring throughout adulthood (e.g., van Ockenburg et al., 2015; Verhoeven et al., 2015). A nationally representative study that examined the effect of cumulative adulthood adversity on TL converges with the non-significant results presented here (Puterman et al., 2016). Therefore, cumulative stress exposure in adulthood may play a less important role than childhood adversity in relation to LTL, but additional research is needed.

One potential explanation for the relatively greater role of chronic childhood stressors in LTL shortening may be that chronic childhood stressors become more biologically embedded than later stressors (Berens et al., 2017). Childhood is a sensitive developmental period during which the brain and other biological systems mature. Exposure to cumulative chronic stressors during this time period can have lasting biopsychosocial effects (Danese and Lewis, 2017; Nelson, 2017; Shalev, 2012; Shonkoff and Garner, 2012), which may in turn transmit long-term risks that affect telomere dynamics and thereby impact adult TL and attrition over time. For example, childhood adversity sensitizes stress processes in later adult life, increasing psychobiological reactivity (Heim et al., 2000; Infurna et al., 2015; Weltz et al., 2016) and threat appraisals (Repetti et al., 2002), which have been linked with shorter TL (O'Donovan et al., 2012), altered repair mechanisms (e.g., telomerase activity; Choi et al., 2008; Epel et al., 2010), and other factors known to influence telomere shortening (e.g., inflammation; Sin et al., 2015; Slavich and Cole, 2013). Therefore, childhood adversity may still exert deleterious effects in adulthood insofar as it shapes individuals' responses to daily events, which may in turn create additional wear and tear and/or impact repair mechanisms that alter telomere dynamics. Understanding the pathways by which chronic childhood adversity accelerates TL shortening may allow us to identify malleable factors that can help minimize its detrimental health effects (Shalev, 2012).

Notably, approximately half of participants were caregivers of children with an autism disorder, but caregiver group status alone was not related to LTL at baseline or LTL attrition over time. This is consistent with findings from other caregiving samples (Epel et al., 2004; Litzelman et al., 2014; O'Donovan et al., 2009; Puterman et al., 2010), though exceptions exist in older and post-menopausal samples (Damjanovic et al., 2007). For example, in the first study linking psychosocial stress with shorter telomere length, Epel et al. (2004) showed that healthy pre-menopausal women caregiving for a chronically ill child did not differ from healthy control mothers in average telomere length. However, chronicity (years) of caregiving was related with shorter telomere length, and higher perceived stress was associated with shorter telomere length across the entire sample of both caregiver and control mothers (see also Puterman et al., 2010). Therefore, there may not be consistent caregiver group differences in telomere length, but the stress-telomere length relationship may exist across the continuum of indices of stress – with chronicity and subjective experience of the stressor being important aspects that shape telomere shortening (Oliveira et al., 2016), as is also shown in the present study.

Limitations of this study include a modest sample size, although longitudinal TL studies may need smaller samples to detect effects (Aviv et al., 2006). The study also only included women, requiring replication in males and mixed samples. Furthermore, lifetime stress exposure was only assessed retrospectively, potentially introducing reporting biases (e.g., underreporting; Hardt and Rutter, 2004). However, as a systematic assessment tool that clearly describes concrete stressors, the STRAIN might be less prone to recall bias than the types of short self-report checklist measures that are most frequently employed in stress research (Slavich and Auerbach, 2018). In addition, the STRAIN was only administered at baseline in this study, so questions about the impact of interim or concurrent stressor count, duration, and severity on LTL attrition over the 2-year period could not be examined with the STRAIN. Nevertheless, when we adjusted for life stressors occurring between baseline and follow-up using a brief stressor checklist (i.e., CSC), the main results remained unchanged. Also, current and past MDD were unrelated to TL in the present study, likely because rates of current MDD were low and an exclusion criterion for non-caregivers. Nevertheless, prior meta-analyses have demonstrated consistent links between depression and shortened telomere length (Lin et al., 2016b; Ridout et al., 2016; Schutte and Malouff, 2015). Therefore, depression will be an important factor to consider in future studies of chronic stress and cellular aging.

Lastly, measurement error in telomere assessment using quantitative PCR is a potential limitation of the present study. We extracted DNA from baseline and follow-up samples in the same batch and assayed baseline and follow-up samples in the same assay batch to minimize potential variations due to preanalytical and analytical factors, and the average coefficient of variation in this study was therefore low (2.1%). In addition, telomeres were measured in leukocytes, which consists of different cell types with different telomere lengths (Lin et al., 2016a). Our main stress-telomere attrition findings hold even while controlling for changes in cell type composition (percentages of lymphocytes, monocytes, neutrophils, eosinophils, and basophils), but it is possible that rates of shortening in specific cell types (T and B cell types; Lin et al., 2016a) impacted the results. Notably, each change in cell type alone was not significantly associated with LTL attrition, though trends existed. Among the largest relationships, relative lymphocyte increase was associated with telomere length increase ($r = .136$), whereas relative neutrophil increase was related to telomere shortening ($r =$

-.162). The reasons for these trends are unknown, and this remains an important issue to explore in future research. One possible interpretation is that if lymphocytes have longer TL than neutrophils, then a higher percentage of lymphocytes is correlated with longer whole blood LTL and a higher percentage of neutrophils is correlated with shorter whole blood LTL. We did not measure TL in the lymphocyte and neutrophil cell types for this study, but it has been previously shown that T cells, which constitute the majority of lymphocytes, have longer TL compared to neutrophils (Robertson et al., 2000). Also, B cells (the other lymphocyte cell type) have longer TL. Therefore, it is possible that cell composition changes may at least partially explain the LTL changes seen in whole blood. We subsequently controlled for changes in cell type composition, but the main results did not meaningfully change. In sum, cell type composition is rarely considered in the telomere literature (for a more in-depth discussion, see Epel, 2012; Lin et al., 2016a; Rehkopf et al., 2016), and future research is needed to examine whether changes in specific immune cell subsets (T and B lymphocytes cells, neutrophils and other leukocyte cell types) differentially impact LTL attrition and their relationship to cumulative stress exposure.

Notwithstanding these limitations, the present data are the first to elucidate the effects of different aspects of cumulative lifetime stressor exposure on baseline LTL and LTL attrition over time. These results were strongest for chronic stressors occurring in childhood. Future research is needed to replicate these results, to further dissect the effects of stress exposure during distinct developmental time periods (e.g., early childhood, middle childhood, and adolescence), and to examine their relevance for mental and physical health (Epel et al., 2018).

Conflict of interest

Jue Lin is a co-founder and scientific advisor to Telomere Diagnostic Inc. The company played no role in this study. Other authors declare no conflict of interest.

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Contributors

Dr. Stefanie E. Mayer led data analyses and interpretation. She wrote the first draft of the manuscript and was instrumental in editing the manuscript. Drs. Aric A. Prather, Eli Puterman, Jue Lin, Grant S. Shields, George M. Slavich, and Elissa S. Epel provided critical guidance and input for data analysis and interpretation, as well as manuscript editing. Dr. Elissa Epel designed the study and Dr. George Slavich oversaw all stress assessment procedures. Michael Coccia led data preparations and cleaning, and guided statistical data analyses, interpretation, and result descriptions. Justine Arenander had a leading role in data collection and contributed to manuscript editing. All authors contributed to and have approved the final manuscript.

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