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

between various types of childhood adversity and shorter telomeres (Hanssen et al., 2017; Li et al., 2017; Ridout et al., 2017). However, the vast majority of studies have assessed TL cross-sectionally (e.g., Puterman et al., 2016), limiting our understanding of how early adversity affects adult telomere shortening over time (i.e., "telomere attrition"). Although this methodological limitation is frequently highlighted in reviews (Coimbra et al., 2017; Price et al., 2013; Shalev et al., 2013a), only a few studies have examined TL attrition. Shalev and colleagues showed that children with greater exposure to traumatic violence during ages 5–10 years old had greater telomere attrition over the same 5-year period (Shalev et al., 2013b). Additionally, Révész et al. found that retrospectively assessed childhood trauma predicted adult TL attrition over a six-year period (Revesz et al., 2016). These studies provide important information regarding the impact of childhood traumatic events on TL attrition. However, a more comprehensive assessment of the many different adversities that individuals can potentially experience in childhood is needed to determine whether the cumulative effects of childhood stress exposure on telomere attrition in adulthood differ by stressor type and exposure timing.

Stress occurring during adulthood has also been linked to shorter telomeres in a dose-dependent manner (reviewed in Lin et al., 2012; Oliveira et al., 2016). Again, however, most studies have only assessed TL cross-sectionally, with a few exceptions. For example, Puterman and colleagues found that major life events occurring over the past year predicted greater telomere attrition during this period (Puterman et al., 2015). A population-based cohort study also found that greater number of life events over the past year predicted greater telomere attrition during the next six years (van Ockenburg et al., 2015). Associations between recent adult stressors and greater TL attrition provide valuable evidence of a concurrent relationship between these two factors, but studies examining the effects of cumulative stress exposure occurring throughout adulthood on TL attrition have been distinctly absent from this literature.

Cumulative stress exposure occurring over the entire lifespan, which includes both childhood and adulthood stressors, increases risk for physical and mental illness and early mortality (Albert et al., 2017; Lupien et al., 2009; McEwen, 1998), and may thus also play a role in telomere shortening. Cumulative lifetime stress exposure refers to the joint or combined effects of stressors occurring throughout life, including both acute negative life events (e.g., job loss) and persistent chronic difficulties (e.g., ongoing financial problems). Some large-scale studies have examined the impact of stressors across the life course on telomere length measured at a single time point (Jodczyk et al., 2014; Puterman et al., 2016; Surtees et al., 2011; Verhoeven et al., 2015). For example, Puterman et al. (2016) found that greater cumulative stress exposure occurring throughout childhood and adulthood predicted shorter salivary TL in the Health and Retirement Study. This study also compared the timing of stressor, revealing that accumulated childhood stressors were most strongly related to shorter TL. Although promising, this study only included a small number of lifetime stressors and did not examine the effects of cumulative lifetime stress exposure on TL changes over time.

Overall, studies examining the impact of stress on TL have been plagued by a lack of precision in how psychosocial stress has been conceptualized and measured (Oliveira et al., 2016). Stress is a multifaceted concept that includes both stressor exposure and individuals' perceptions of such exposures, such as perceived stressor severity (Slavich, 2016, 2019). However, previous studies examining stress-TL linkages have assessed a limited range of types of adversities over the lifespan and have lacked measures of stressor severity (e.g., Puterman et al., 2016; van Ockenburg et al., 2015; Verhoeven et al., 2015). Furthermore, no studies to date have distinguished between acute and chronic stressors, despite evidence that chronic stressors, in particular, may exert the type of biological "wear and tear" that most strongly increases risk for disease (McEwen, 1998).

In the present study, therefore, we adopted a lifespan approach and assessed the impact of cumulative lifetime stressor count, duration, exposure timing, and severity on both leukocyte telomere length (LTL) at baseline and LTL attrition over a 2-year period during mid-life. Based on the research summarized above, we hypothesized that greater cumulative lifetime stressor exposure would predict shorter LTL at baseline and greater LTL attrition over time. We also hypothesized that these associations would be strongest for chronic (vs. acute) stressors and childhood (vs. adulthood) stressors.

2. Methods and materials

2.1. Participants

Participants were mothers of a child diagnosed with an autism spectrum disorder (caregivers, *n* = 91) and mothers of a neurologically typical child (non-caregivers, *n* = 92). Recruitment and eligibility criteria are available elsewhere (Prather et al., 2015). Briefly, participants were 20–51 years old, premenopausal, non-smoking, with no major diseases (including no history of coronary heart disease, endocrine disorders, epilepsy, brain injury, autoimmune conditions, severe asthma or lung disease), and had at least one child between the ages of 2–16 years. Participants were excluded if they had a current psychiatric condition as determined by questions from the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders for Axis I Disorders (SCID), including bipolar disorder, posttraumatic stress disorder and eating disorders, and, for the non-caregivers, major depression. Depression and antidepressant use were permitted among caregivers because depression is a common response to chronic stress (9% of caregivers met DSM criteria for current major depressive disorder [MDD] at baseline). Participants were free of medication known to impact immune and endocrine systems, with the exception of antidepressant medication, thyroid supplementation, and oral contraceptives. Steroid use was permitted if it was infrequent and not used close to blood sampling periods. Eight participants had missing LTL samples at baseline, yielding a total sample size of 175 (91 caregiver) of which 121 (56 caregiver) had follow-up LTL data at 24-months.

2.2. Study design

Participants completed a laboratory visit at baseline, during which time they provided written informed consent, completed self-report and interview measures, and provided a fasting morning blood sample for LTL assessment. Participants returned 24 months later to provide another fasting morning blood sample. One third of the sample also participated in a 4-session mindfulness intervention during the last 6 months before the 24-months follow-up time point. Participants who underwent the intervention were included in analyses because intervention participation was unrelated to LTL attrition. Participants were paid $230 for completing the baseline and 24-month procedures. This study was approved by the local Institutional Review Board.

2.3. Baseline self-report measures

2.3.1. Sociodemographic and health-related information

We assessed chronological age, race, marital status, highest level of education, annual household income, and body mass index (BMI). Participants also reported medication use (e.g., antidepressant, antihistamine, thyroid supplement, Nonsteroidal Anti-Inflammatory Drugs-NSAIDs or analgesic, antihypertensive, occasional steroids) and depressive symptoms using the 30-item Inventory of Depressive Symptomatology (IDS; Rush et al., 1986). Questions from the SCID were used to assess if participants met criteria for current or past (life history) MDD.

2.3.2. Stress and Adversity Inventory

The Stress and Adversity Inventory for Adults (Adult STRAIN) is an

Table 1
Descriptive statistics ($M \pm SD$ or percentages) for demographic and health-related baseline variables.

Category	Variable	Entire Sample ($n = 175$)	Caregivers ($n = 91$)	Non-Caregivers ($n = 84$)
Demographic	Age (years)	42.52 (5.16)	42.79 (5.66)	42.23 (4.57)
	Race (% White)	75.4	75.8	75.0
	Marital status (% married)	86.8	90.0	83.3
	Education (% college degree or higher)	86.0	82.0	90.2
	Annual household income (% $\geq$ $100.000)	75.9[*]	67.8	84.5
Health-related	Body Mass Index (BMI)	25.57 (5.22)	25.87 (5.66)	25.24 (4.72)
	Medication use (% yes)	28.6[*]	35.2	21.4
	Depressive symptoms (IDS)	15.76 (8.15)*	19.30 (8.34)	11.97 (5.97)
	Current MDD (% yes)	4.8[*]	9.1	0.0
	Past (lifetime) MDD (% yes)	37.7[*]	46.0	28.7

Note. IDS = Inventory of Depressive Symptomatology; MDD = Major Depressive Disorder.
  * Indicates significant caregiver group differences ($p < .05$).

online system for assessing cumulative lifetime stress exposure (Slavich and Shields, 2018). The STRAIN enquires about 55 different major stressors, including 26 acute negative life events (present for a day or two, such as getting fired or the dissolution of an important relationship) and 29 chronic difficulties (present for at least one month, such as persistent caregiving, social isolation, or unemployment). Acute life events and chronic difficulties are probed with different questions, so that stressor types are not confounded. In the context of a job loss, for example, the actual event of learning that one is fired would be an acute life event, but the resulting long-term unemployment, if present, would be a chronic difficulty. The STRAIN also asks about several childhood adversities (i.e., before age 18), including emotional, physical, and sexual abuse (Felitti et al., 1998), other major interpersonal stressors (e.g., being separated from a parent, ongoing parental relationship problems, being bullied, harsh discipline), and socioeconomic adversity (e.g., stable place to live). For each stressor that is endorsed, participants reported the severity (perceived stressfulness/impact, rated from 1 to 5), frequency, exposure timing (if multiple exposures were endorsed, participants indicated their age for the most impactful incidence), and duration. Cumulative scores were then created by summing participants' stressor count and severity ratings over each time period (i.e., lifespan, childhood, adulthood), first together and then separately for acute life events and chronic difficulties. The STRAIN has demonstrated very good validity and excellent test-retest reliability (i.e., rs > .9 over 2–4 weeks) (Slavich and Shields, 2018; see http://www.strainsetup.com).

2.3.3. Current Stressors Checklist

The Current Stressors Checklist (CSC) measured the count (presence/absence of the stressor) and, if endorsed, severity (rated from 1 = *not at all stressful* to 5 = *extremely stressful*) of any new life stressors (i.e., financial problems, relationship issues, problems at work, problems with children, health issues or other) over the 2-year period. A sum across all time points (9, 18, 24 months) was calculated to measure count (CSC-count) and severity (CSC-severity) of new life stressors throughout the 2-year period.

2.4. Biological measures

Genomic DNA was purified from frozen whole blood with the QIAamp® DNA Mini kit (QIAGEN, Hilden, Germany; Cat#51104). Baseline and 24-month samples were purified as one batch. DNA quality criteria were OD260/OD280 between 1.7–2.0 and concentration > 10 ng/ul. All samples passed DNA quality check. DNA was stored at −80 °C for batch TL measurement. Baseline and 24-month samples from the same participant were always assayed in the same assay batch. The TL assay was adapted from the original published method by Cawthon (Cawthon, 2002; Lin et al., 2010). The T/S ratio for each sample was measured twice. When the duplicate T/S value and the initial value varied by more than 7%, the sample was run the third time

and the two closest values were reported. The average coefficient of variation (CV) from this study was 2.1% (± 1.5%). Lab personnel who performed the TL measurement were blind to all factors that could have influenced results, including participants' group status, demographic characteristics, and stress exposure. A complete blood count (CBC; Quest Diagnostics) was also obtained to quantify cell type composition (i.e., percentages of lymphocytes, monocytes, neutrophils, eosinophils, and basophils) at baseline and 24 months (change in percent cell type distribution was calculated as 24 months minus baseline).

2.5. Statistical analysis

LTL attrition was calculated as 24-months minus baseline, correcting for the regression to the mean effect (for formula, see Verhulst et al., 2013). One participant had a statistical outlier value for LTL attrition (mean + 4SD) and was excluded from analyses predicting LTL attrition. Primary analyses of interest used a series of multiple linear regression models (standardized betas are reported) to examine the impact of the STRAIN-derived variables on participants' LTL at baseline and their LTL attrition over time, controlling for covariates that were associated with LTL in this sample. We first examined the effects of all lifetime stressors on the LTL outcomes and then separately analyzed the effects for acute, chronic, childhood, and adulthood stressors.

3. Results

3.1. Participant characteristics

Demographic characteristics are presented in Table 1. Briefly, women were 42 years old, on average, and predominantly White, married, and college educated, with an annual household income of $100,000 or greater. Caregivers and non-caregivers did not differ in their demographic characteristics (ps > .10), except that caregivers were more frequently in the lower income category ($p < .05$). On average, participants were slightly overweight, with no group differences in BMI ($p > .20$). Caregivers were more frequently using medication, reported higher depressive symptoms, and were more likely to meet criteria for current and past MDD than non-caregivers (all ps < .05).

There was a loss of participants due to attrition between baseline and follow-up. Comparisons of completers versus non-completers showed that there were no statistically significant differences in basic demographic characteristics, but that there were significant differences in caregiver group status and mindfulness intervention participation. Not surprisingly, caregivers had more missing follow-up LTL samples as compared to non-caregivers ($p = .023$). Furthermore, participants who participated in the intervention were less likely to have a missing follow-up LTL sample as compared to those who chose not to participate ($p < .001$), perhaps suggesting that the intervention re-engaged participants – even higher-stressed caregivers.

Table 2

Descriptive statistics for the Stress and Adversity Inventory (STRAIN) and Leucocyte Telomere Length (LTL) variables.

Variable	Exposure Timespan	Stressor Index	Stressor Type	*M*	*SD*	Range
STRAIN	Entire Lifespan	Count	Total Stressors	19.09	10.46	1-48
			Acute Life Events	10.67	6.48	0-29
			Chronic Difficulties	8.41	5.00	0-24
		Severity	Total Stressors	49.94	27.03	3-131
			Acute Life Events	24.37	13.51	0-61
			Chronic Difficulties	25.57	15.90	0-77
	Childhood (age < 18)	Count	Total Stressors	3.20	2.35	0-10
			Acute Life Events	0.98	1.14	0-7
			Chronic Difficulties	2.60	2.15	0-9
			Chronic Difficulties: age 0-12	1.62	1.32	0-6
			Chronic Difficulties: age 0-6	0.75	0.88	0-5
			Chronic Difficulties: age 7-12	0.87	1.02	0-4
			Chronic Difficulties: age 13-18	0.60	0.93	0-5
		Severity	Total Stressors	10.16	8.77	0-38
			Acute Life Events	2.84	3.86	0-24
			Chronic Difficulties	7.43	7.02	0-33
			Chronic Difficulties: age 0-12	5.37	4.95	0-23
			Chronic Difficulties: age 0-6	2.47	3.36	0-20
			Chronic Difficulties: age 7-12	2.90	3.55	0-15
			Chronic Difficulties: age 13-18	2.14	3.70	0-23
	Adulthood (age ≥18)	Count	Total Stressors	6.06	4.24	0-21
			Acute Life Events	3.87	2.64	0-13
			Chronic Difficulties	5.81	3.68	0-18
		Severity	Total Stressors	39.31	22.25	3-104
			Acute Life Events	21.53	12.75	0-54
			Chronic Difficulties	18.14	12.30	0-53
LTL (T/S ratio)			Baseline	1.08	0.16	
			24-months	1.07	0.15	
			2-year Attrition[1]	−0.003	0.07	

STRAIN = Stress and Adversity Inventory; LTL = leukocyte telomere length.

[1] LTL attrition (24-months minus baseline) was adjusted for regression to the mean effects.

Descriptive statistics for the STRAIN-derived lifetime, childhood, and adulthood stress exposure variables are presented in Table 2. As expected, caregivers had significantly greater count and severity of chronic difficulties over the lifespan ($p = .002$; $p = .004$, respectively) and significantly greater count and severity of adulthood chronic difficulties ($p = .001$; $p = .004$, respectively). In contrast, caregivers and non-caregivers did not differ with respect to acute life events occurring over the lifespan or during adulthood (count or severity; all $ps > .10$).

3.2. Covariates associated with LTL

3.2.1. Covariates associated with baseline LTL

Older chronological age was associated with shorter baseline LTL, r(173) = -.245, $p = .001$. No other covariates were linked with baseline LTL over and above the age effect: race, $p = .234$, marital status, $p = .133$, education, $p = .898$, household income, $p = .607$, BMI, $p = .370$, medication use (most frequent types: antidepressant: $p = .264$, antihistamine: $p = .610$, thyroid supplement: $p = .960$, NSAID or analgesic: $p = .191$, antihypertensive: $p = .623$, occasional steroids: $p = .600$), depressive symptoms, $p = .704$, current MDD, $p = .264$, past MDD, $p = .405$, caregiver group status, $p = .413$, and cell type distribution (Lymphocytes, $p = .147$; Monocytes, $p = .150$; Neutrophils, $p = .140$; Eosinophils, $p = .118$; and Basophils, $p = .628$). Therefore, only older chronological age was significantly associated with shorter baseline LTL. Nevertheless, we also controlled for caregiver group status in all models given that caregivers had greater count and severity of chronic difficulties during adulthood and across the lifespan as compared to non-caregivers.

3.2.2. Covariates associated with LTL attrition

Baseline LTL did not predict LTL attrition, r(118) = -.006, $p = .949$, which was expected given that the regression to the mean adjusted change score already accounted for the correlation between LTL at baseline and 24-months ($r = .866$). Chronological age was not associated with LTL attrition, $p = .303$, and neither was race, $p = .989$, marital status, $p = .704$, education, $p = .875$, BMI, $p = .656$, depressive symptoms, $p = .436$, current MDD, $p = .178$, past MDD, $p = .176$, nor caregiver group status, $p = .476$. The slight increase in mean BMI from baseline to 24 months ($p = .056$; mean BMI increase: 0.3) did not significantly impact LTL attrition ($p > .20$). A similar number of caregivers and non-caregivers (i.e., approximately one-third of the sample) voluntarily enrolled in a mindfulness intervention during the last 6 months of the study, but the intervention was not related to LTL attrition ($p = .607$; nor LTL at baseline or 24 months, $ps > .20$). Greater household income, r(117) = -.160, $p = .082$, and occasional steroid use, t(118) = 2.048, $p = .084$ (but not: antidepressant: $p = .173$, antihistamine: $p = .840$, thyroid supplement: $p = .147$, NSAID or analgesic: $p = .910$, antihypertensive: $p = .483$), were both marginally associated with greater LTL attrition. Also, changes in percent cell type distribution predicted LTL attrition when entered simultaneously into a regression model (changes in Lymphocytes, $b = -2.485$, t(112) = -2.920, $p = .004$; Monocytes, $b = -0.536$, t(112) = -2.806, $p = .006$; Neutrophils, $b = -3.097$, t(112) = -3.100, $p = .002$; Eosinophils, $b = -0.726$, t(112) = -2.685, $p = .008$; Basophils, $b = -0.205$, t(112) = -2.089, $p = .039$). Given that co-linearity induces a challenge to examining all subtypes simultaneously, we also examined each cell type independently. Each cell type change alone was not significantly associated with LTL attrition, but some trends were evident (changes in Lymphocytes, r(117) = .136, $p = .142$; Monocytes, r(117) = .011, $p = .903$; Neutrophils, r(117) = -.162, $p = .079$; Eosinophils, r(117) = .091, $p = .326$; Basophils, r(117) = -.069, $p = .455$). We subsequently controlled for changes in cell type composition, but the main results were not meaningfully different.

Taken together, we controlled for household income, occasional steroid use, and changes in cell type distribution in models predicting LTL attrition over time. Despite non-significant associations with LTL attrition, we also subsequently controlled for caregiving group status and intervention participation in all of the main models because these

Table 3

STRAIN predicting Leucocyte Telomere Length (LTL) at baseline and LTL attrition over two years.

Exposure Timespan	Stressor Index	Stressor Type	LTL Baseline[1]			LTL Attrition[2]		
			b	*t*	*p*	*b*	*t*	*p*
Entire Lifespan	Count	Total Stressors	−0.161	−2.138	**0.034**	−0.194	−2.069	**0.041**
		Acute Life Events	−0.126	−1.682	0.094	−0.085	−0.892	0.375
		Chronic Difficulties	−0.173	−2.288	**0.023**	−0.285	−3.131	**0.002**
	Severity	Total Stressors	−0.156	−2.075	**0.039**	−0.164	−1.719	0.089
		Acute Life Events	−0.145	−1.947	0.053	−0.055	−0.572	0.569
		Chronic Difficulties	−0.141	−1.867	0.064	−0.227	−2.424	**0.017**
Childhood (age < 18)	Count	Total Stressors	−0.133	−1.811	0.072	−0.167	−1.852	0.067
		Acute Life Events	−0.061	−0.824	0.411	0.015	0.157	0.875
		Chronic Difficulties	−0.158	−2.141	**0.034**	−0.269	−3.090	**0.003**
		Chronic Difficulties: age 0-12	−0.110	−1.487	0.139	−0.230	−2.587	**0.011**
		Chronic Difficulties: age 0-6	−0.143	−1.931	0.055	−0.178	−1.968	0.052
		Chronic Difficulties: age 7-12	−0.020	−0.273	0.785	−0.160	−1.706	0.091
		Chronic Difficulties: age 13-18	−0.107	−1.449	0.149	−0.104	−1.132	0.260
	Severity	Total Stressors	−0.128	−1.728	0.086	−0.203	−2.290	**0.024**
		Acute Life Events	−0.060	−0.809	0.419	−0.033	−0.363	0.717
		Chronic Difficulties	−0.139	−1.880	0.062	−0.242	−2.755	**0.007**
		Chronic Difficulties: age 0-12	−0.114	−1.539	0.126	−0.252	−2.857	**0.005**
		Chronic Difficulties: age 0-6	−0.145	−1.972	0.050	−0.193	−2.183	**0.031**
		Chronic Difficulties: age 7-12	−0.021	−0.286	0.775	−0.182	−1.951	0.054
		Chronic Difficulties: age 13-18	−0.093	−1.260	0.209	−0.113	−1.235	0.219
Adulthood (age ≥ 18)	Count	Total Stressors	−0.102	−1.220	0.224	−0.110	−1.146	0.254
		Acute Life Events	−0.128	−1.555	0.122	−0.061	−0.650	0.517
		Chronic Difficulties	−0.139	−1.816	0.071	−0.233	−2.426	**0.017**
	Severity	Total Stressors	−0.123	−1.612	0.109	−0.106	−1.072	0.286
		Acute Life Events	−0.136	−1.813	0.072	−0.048	−0.494	0.622
		Chronic Difficulties	−0.100	−1.308	0.193	−0.139	−1.413	0.160

Notes. STRAIN = Stress and Adversity Inventory; LTL = leukocyte telomere length. All estimates (*b*) are standardized estimates.

[1] Regression models predicting baseline LTL control for chronological age and caregiver group status.

[2] Regression models predicting 2-year LTL attrition (24-months minus baseline; adjusted for regression to the mean) control for household income, occasional steroid use, percent changes in cell type distribution, caregiver group status, and intervention participation.

factors affected participant retention at follow-up.

3.3. STRAIN predicting LTL

Regression estimates and statistics for associations between the STRAIN and LTL are presented in Table 3, and the main findings are summarized below.

3.3.1. STRAIN predicting baseline LTL

Greater count of total lifetime stressors was significantly associated with shorter LTL at baseline (*p* = .034). When separating total lifetime stressor count into acute life events versus chronic difficulties, only greater count of chronic lifetime stressors predicted shorter baseline LTL (*p* = .023). Additionally, when examining exposure timing of lifetime stressors, only greater count of chronic childhood difficulties predicted shorter baseline LTL (*p* = .034). Post-hoc analyses did not reveal significant associations between baseline LTL and the specific timing of chronic childhood stressors (0–12 years old; 13–18 years old; all *p*s > .10), though a marginal trend emerged for chronic stressors occurring during the first 6 years of life predicting shorter LTL at baseline (0–6 years old: *p* = .055). In turn, with respect to severity, cumulative severity of total lifetime stressors predicted shorter baseline LTL (*p* = .039). However, these effects did not significantly differ based on the specific timing or chronicity of stressors experienced (i.e., acute life events vs. chronic difficulties).

3.3.2. STRAIN predicting LTL attrition

Greater count of total lifetime stressors was significantly associated with greater LTL attrition over time (*p* = .041). When separating total lifetime stressor count into acute life events versus chronic difficulties, only greater count of chronic stressors predicted greater LTL attrition over time (*p* = .002, see Fig. 1A). When separating lifetime stressors into those occurring during childhood versus adulthood, chronic

stressors occurring during childhood (*p* = .003; see Fig. 1B) and adulthood (*p* = .017) each predicted greater LTL attrition. However, when both predictors were simultaneously entered into the same model, only greater count of chronic stressors occurring during childhood predicted LTL attrition (*b* = -0.216, *t* = -2.159, *p* = .033). Post-hoc analyses revealed that greater LTL attrition was associated with greater count of chronic stressors occurring during early childhood (0–12 years old: *p* = .011), but not adolescence (13–18 years old: *p* =.260). When further dissecting early childhood stressors into those occurring during ages 0–6 and 7–12, marginally significant findings emerged for both age categories, with effects being slightly stronger for stressors occurring during the first 6 years of life (0–6 years old: *p* = .052) versus the second 6 years of life (7–12 years old: *p* = .091). We also re-ran significant childhood models while adjusting for count of new life stressors occurring over the 2-year period (CSC-count). CSC-count was marginally associated with LTL attrition over this time period (*b* = -.185, *p* = .069). However, adjusting for CSC-count did not alter the significant associations between count of chronic difficulties occurring from 0 to 18 years old or those occurring from 0 to 12 years old and accelerated LTL attrition over time in adulthood (*p* = .004 and *p* = .013, respectively). Similarly, re-running these models while adjusting for both cumulative adulthood STRAIN-count and CSC-count did not influence the primary finding that count of chronic difficulties occurring during childhood (age 0–18) predicted LTL attrition over time, though the timing effect for early adversity (age 0–12) was now only marginally significant (age 0-18: *p* = .026; age 0-12: *p* = .080).

This general pattern of results was similar when lifetime stressor severity (instead of count) was used. Namely, greater cumulative severity of chronic lifetime stressors was associated with greater LTL attrition over time (*p* = .017). When separating participants' severity of chronic lifetime stressors by exposure timing, only greater severity of chronic childhood stressors (0–18 years old) predicted greater LTL attrition (*p* = .007). Again, post-hoc analyses revealed that LTL attrition

a

b
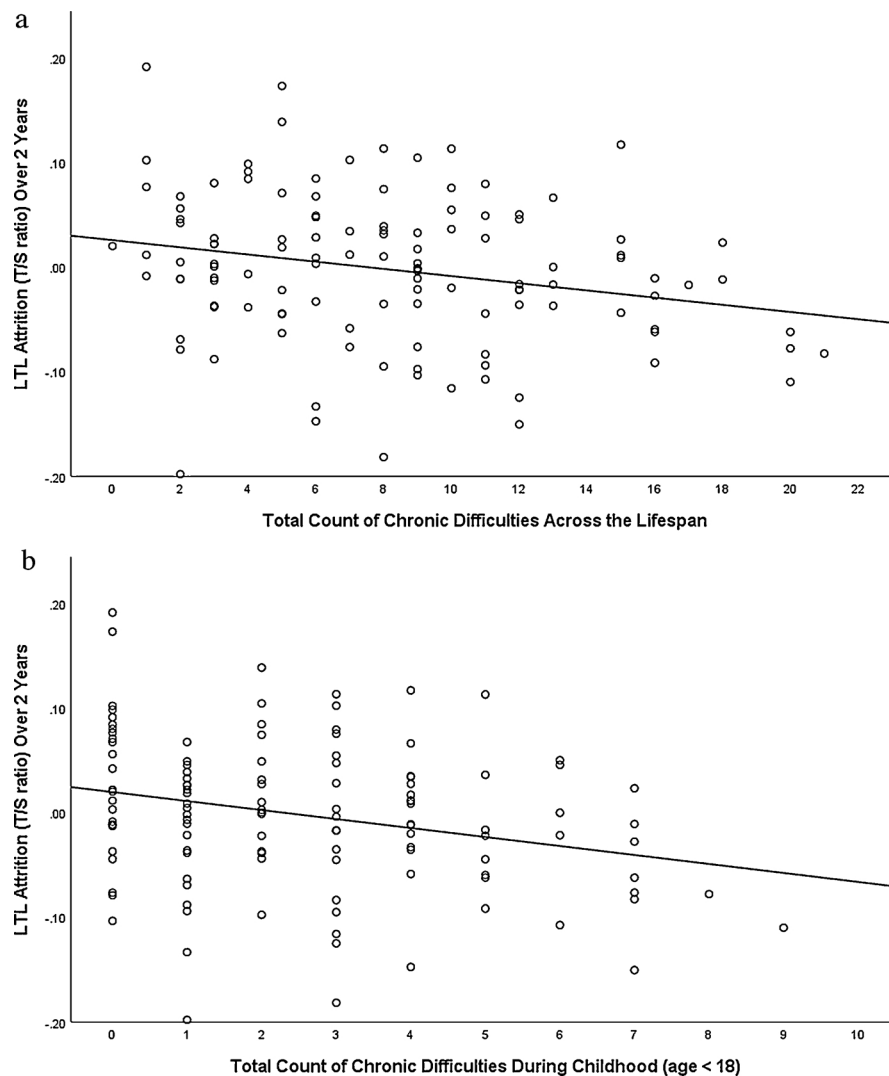
Fig. 1. Scatterplot showing the association between total count of chronic difficulties (A) across the entire lifespan and (B) during childhood (< age 18 years old) with Leucocyte Telomere Length (LTL) attrition (T/S ratio; 24 months minus baseline) over 2 years. Greater count of chronic difficulties, particularly during childhood, predicted greater LTL attrition over time, and these effects were robust while controlling for stressors occurring during the interim 2-year period.

was significantly associated with greater severity of chronic stressors occurring during early childhood (0–12 years old: $p = .005$), but not adolescence (13–18 years old: $p = .219$). When further dissecting early childhood into ages 0–6 and 7–12, significant findings emerged for the first 6 years of life (0–6 years old: $p = .031$) and marginally significant findings emerged for the second 6 years of life (7–12 years old: $p = .054$). Again, we re-ran the significant childhood models while adjusting for severity of life stressors occurring over the interim 2-year period (CSC-severity). However, CSC-severity was not significantly associated with LTL attrition over this time period ($b = -.158$, $p = .138$), and adjusting for CSC-severity did not alter the significant associations between severity of chronic difficulties occurring from 0–18, 0–12, or 0–6 years old and accelerated LTL attrition over time in adulthood ($p = .011$, $p = .008$, and $p = .046$, respectively). Similarly, re-running these models while adjusting for both cumulative adulthood STRAIN-severity and CSC-severity did not influence the primary finding that severity of chronic difficulties occurring during childhood (age 0–18) and early childhood (age 0–12) predicted LTL attrition over time (age 0-18: $p = .019$; age 0-12: $p = .013$; age 0–6: $p = .070$).

4. Discussion

This study examined how cumulative lifetime stressor exposure,

duration, timing, and severity are associated with baseline LTL in addition to changes in LTL over two years. As hypothesized, results revealed that greater count of total lifetime stressors predicted shorter LTL at baseline and greater LTL attrition over time. When we separately examined the effects of stressor duration (acute vs. chronic) and timing (childhood vs. adulthood) on LTL, only chronic lifetime stressors and chronic childhood stressors were significantly related to shorter baseline LTL and greater LTL attrition over time. Moreover, these latter results for LTL attrition were robust while controlling for stressors occurring between baseline and the two-year follow-up time-point. These findings thus reveal for the first time how stressor duration and timing of lifetime stressor exposure are associated with LTL shortening over time.

These results showing that greater lifetime stressor exposure predicts shorter baseline LTL and greater LTL attrition replicate findings from a nationally representative cross-sectional study, which revealed that cumulative lifetime adversity was associated with shorter telomere length (Puterman et al., 2016). However, the present results extend this work by providing novel evidence that cumulative lifetime stressors are associated with adult LTL attrition over time in a stressor-specific manner. Notably, when distinguishing between acute life events and chronic difficulties, only lifetime *chronic* stressors significantly predicted LTL at baseline and changes in LTL over time. Consequently,

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.

Role of the funding source

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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