Chapter 6

The association of early and recent psychosocial life stress with leukocyte telomere length

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ABSTRACT

Objectives: Chronic exposure to psychosocial stressors is related to worse somatic health. This applies to both stressors early in life, such as childhood adversities, and more recent life stress, such as stressful life events. This study examined whether accelerated telomere shortening, as an indicator of cellular aging, might be an explanatory mechanism.

Methods: We examined whether childhood adversities and recent stressful life events were associated with shorter telomeres in 2936 participants (18-65 years) of the Netherlands Study of Depression and Anxiety. Telomeres are specialized nucleic acid-protein complexes at the ends of linear DNA that shorten with age; telomere length (TL) was measured with qPCR.

Results: Childhood life events (β=.004; p=.805) and childhood trauma (β=-.023; p=.205) were not related to shorter TL. However, we found negative associations between recent stressful life events and TL. Persons had shorter telomeres if they reported more stressful life events in the past year (β=-.039; p=.028) and one to five years ago (β=-.042; p=.018, adjusted for sociodemographics). The relationship between stressful life events and TL became borderline significant when further adjusted for smoking status. No association was found when stressful life events occurred more than six years ago (p<.10).

Conclusions: Our results suggest that TL is adversely impacted by the occurrence of recent stressful life events, and not by psychosocial stressors that occur earlier in life. Whether these results are indicative of physiological resiliency, remains to be explored by future longitudinal research.

Key words: telomere length, cellular aging, childhood trauma, early life stress, psychosocial stress, stressful life events

INTRODUCTION

It has become a central assumption that chronic exposure to psychosocial stressors, whether early or recent in life, is related to worse health outcomes. Persons with adverse experiences during childhood show an increased onset risk of several mental disorders such as depression, anxiety disorders, schizophrenia and personality disorders (1-3); and childhood adversities have been associated with impaired somatic health in adulthood (4) and even premature mortality (5). Psychosocial stressors more recent in life, including stressful events such as divorce or losing a job, have similar relationships with decreased mental and somatic health (6,7). Research on the mechanisms that may explain these associations has focused on altered physiological systems such as dysregulation of the hypothalamic-pituitary-adrenal axis (HPA-axis) (8) and the immunological system (9). More recently, an accumulating body of research suggests that early and recent psychosocial stressors accelerate cellular aging (10,11), which might contribute to increased onset risks for a variety of somatic conditions (12).

A widely used indicator of cellular aging is the length of telomeres. Telomeres are specialized nucleic acid-protein complexes that cap the ends of linear DNA and protect DNA from damage. Chromosomes fail to replicate completely during each cell division, causing telomeres to become progressively shorter over time. Accelerated shortening, in part, results from increased exposure to oxidation and cytotoxins (13). When telomeres reach a critically short length, cells become susceptible to senescence or apoptosis, and may lose the ability to function healthy (14). Telomere shortening can be counteracted by the ribonucleoprotein cellular enzyme telomerase that adds telomeric DNA, thus preserving telomere length (TL) and healthy cell function. Shortened telomeres have frequently been associated with various somatic conditions such as cardiovascular disease (15), obesity (16), diabetes (17); mental disorders such as depression and anxiety disorders (18,19); and with earlier mortality (20); although the degree to which they are causally involved in these conditions remains unknown. Altogether, TL is thought to be a reflection of genetics, lifestyle factors and prior cumulative somatic and psychosocial stress exposure, and therefore serves as an indicator of biological age rather than chronological age.

In 2004, Epel and colleagues (21) first demonstrated a link between current psychosocial stress and shorter telomeres in a sample of stressed caregiving mothers with chronically ill children compared to age-matched controls. The years of providing care to a chronically ill child was related to shorter telomeres in the caregiving mothers, whereas the perception of stress was related to shorter telomeres across the complete sample. Others have found similar cross-sectional relationships between TL and current psychological stressors (22) or caregiver status (23), with one exception (24). Further, shorter telomeres have been evidenced in women with a history of partner violence (25)

and those with greater perceived stress after a recent major loss (26). In a large study with psychiatric cases and controls, however, no relationship between current stress and TL was found (27). Interestingly, one of the first prospective studies on this subject found that recent major stressors predicted the rate of telomere shortening over a one year period (28). In short, the cross-sectional association between current or recent stress and TL has been confirmed in various studies examining psychosocial stressors, with a few exceptions. It remains unknown, however, what specific stressors impact TL, how long these effects may last and importantly, whether telomere shortening is potentially reversible (29).

It is an interesting issue whether the effects of psychosocial stress on telomere shortening are limited to stressors in adulthood. Tyrka et al. (30) first showed that even stressors early in life may impact TL decades later. In a small-scale study with individuals with no lifetime Axis I mental disorder, 10 persons who reported histories of childhood maltreatment had shorter TL compared to 21 individuals without histories of maltreatment in childhood. Follow-up studies, however, showed mixed results (reviewed by Price et al. (10) and Shalev (31)): Kiecolt-Glaser et al. (32) found shorter TL for persons that experienced two or more childhood life events (such as death of a parent or severe parental marital problems), but no relationship with childhood abuse. Both Kananen et al. (27) and Surtees et al. (33) found that the number of adverse experiences during childhood (e.g., separation from parents and parental alcohol or drug abuse) was related to shorter TL, with the more adversities, the shorter the telomeres. Furthermore, O'Donovan and colleagues (34) also showed that multiple childhood traumas were associated with shorter TL, but only in PTSD patients; and similarly, a recent study found that only persons with both early-life stress and traumatic experiences across the lifespan had shorter telomeres (35). One of the largest studies on this subject (N=11,000), however, did not detect a difference in TL between individuals who experience childhood trauma and those who did not (36). Literature thus remains inconclusive and it is not entirely clear to what extent early life adversities are associated with TL in adulthood.

This paper examines the association between leukocyte TL and early life stressors (adverse life events during childhood and childhood trauma) as well as recent life stressors (recent stressful life events) in the Netherlands Study of Depression and Anxiety. This large sample (N=2936) allowed us to thoroughly examine the relationship of several stressors with cellular aging in persons with and without psychiatric disorders. As short TL is found to be associated with depression and anxiety disorders (18,19) and also with perceived stress (26,37), possible psychosocial stress-TL relationships may be distinct for subgroups with a lifetime depression or anxiety disorder and those without.

METHODS

Study sample

Data are from the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study examining the course and consequences of depressive and anxiety disorders. The NESDA sample consists of 2981 persons between 18 and 65 years including persons with a current or remitted diagnosis of a depressive and/or anxiety disorder (74%) and healthy controls (26%). Persons with insufficient command of the Dutch language or a primary clinical diagnosis of other severe mental disorders, such as bipolar disorder, obsessive-compulsive disorder, PTSD, severe substance use disorder or a psychotic disorder, self-reported or reported by their mental health practitioner, were excluded. Participants were recruited between September 2004 and February 2007 and assessed during a 4-hour clinic visit. For the current study, a total of 45 participants were excluded from analyses because of missing TL data, leaving 2936 individuals including 644 controls, 620 persons with a remitted depressive or anxiety disorder diagnosis and 1672 persons with a current diagnosis, see Table 1. The study was approved by the Ethical Review Boards of participating centers, and all participants signed informed consent. The population and methods of the NESDA study have been described in more detail elsewhere (38).

Measurements

Telomere length. Fasting blood was drawn from participants in the morning between 8:30 and 9:30 am and blood samples were stored in a -20°C freezer afterwards. Leukocyte TL was determined at the laboratory of Telomere Diagnostics, Inc. (Menlo Park, CA, USA), using quantitative polymerase chain reaction (qPCR), adapted from the published original method by Cawthon et al. (39). Telomere sequence copy number in each patient's sample (T) was compared to a single-copy gene copy number (S), relative to a reference sample. The resulting T/S ratio is proportional to mean leukocyte TL (39,40). The detailed method is described elsewhere (18).

To compare T/S ratios to telomere restriction fragments (TRF) reported by studies using Southern blot analysis, we used the following steps to derive a conversion formula. Lin et al. (41) used a formula of base pairs (bp)=3274+2413 *T/S based on comparison of T/S ratios and TRF analysis of a series of genomic DNA samples from the human fibroblast cell line IMR90. Comparison of the T/S ratios of eight quality control DNA samples from the Telome Health Inc. lab that were included on each PCR run, generated the following formula: $T/S_{(Lin\ et\ al.)}=(T/S_{(TelomereDiagnostics)}-0.0545)/1.16$. Therefore the final formula we used to convert T/S ratios to bp is: bp=3274+2413x((T/S-0.0545)/1.16). The reliability of the assay was adequate: eight included quality control DNA samples on each PCR run

illustrated a small intra-assay coefficient of variation (CV=5.1%), and the inter-assay CV was also sufficiently low (CV=4.6%).

Childhood life events and trauma. Childhood life events were assessed retrospectively and included three categories of life events: 1) divorce of parents, 2) parental loss and 3) separation from home (placed in a juvenile prison, raised in a foster family and placed in a child home) before age 16. Each event was scored as 0 (did not happen) or 1 (did happen) and all scores were summed to create a variable with the number of childhood life events.

Childhood trauma was assessed with the Childhood Trauma Interview (CTI) (42). In this interview, participants were asked whether they were emotionally neglected, psychologically abused, physically abused or sexually abused before the age of 16. The CTI reports the sum of the categories that were scored from 0 to 2 (0: never happened; 1: sometimes; 2: happened regularly), resulting in an index score between 0 and 8. Evidence for the clinical relevance of the CTI has been collected in numerous studies showing that the CTI scale is related to prevalence, incidence and course of depression and anxiety disorders (43-45). As a validity check, a second measure of childhood trauma was obtained from the four year NESDA follow-up assessment with a response of 80.6% (N=2402): the Childhood Trauma Questionnaire (CTQ) (46). This measure was used to determine the consistency of the reported information on childhood trauma, since such retrospective measures might be limited by several factors. The CTQ is a 28-item self-report instrument that assesses five types of maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (46). Each scale is represented with five items that are scored on a 5-point Likert-type scale ranging from 'never true' to 'very often true'. The sum scores of CTI and CTQ were highly correlated in this study (r=.77), as were the subscales (range r=.57-.61) (47), which further confirmed the validity of these instruments. Further, the CTI was moderately correlated to the number of childhood life events (r=.25; p<.001). In an earlier study in the same NESDA sample, however, only childhood trauma was related to the incidence of depression and anxiety disorders, while life events were not (43).

Assessment of stressful life events. The incidence of twelve stressful life events (e.g., the death of close friend or relative, unemployment, major financial loss, serious illness and injury, and loss of important relationships) was assessed with a standardized interview based on Brugha's List of Threatening Events Questionnaire (LTE-Q) (48). When any event was endorsed, participants were asked to indicate whether it occurred in the past year (12 months) or longer than one year ago and in what year specifically. Life events were categorized into three time periods: 1) the past year, 2) between 1 and 5 years or 3) 6 or

more years ago. The absence or presence of an event was scored as 0 versus 1. Subsequently, all scores were summed to create three variables: the number of stressful life events in 1) the past year, 2) between 1 and 5 years and 3) 6 or more years ago.

Covariates. Sex, age and years of education and all other covariates were assessed during the baseline interview. Body mass index (BMI) was calculated as measured weight divided by height-squared. Alcohol consumption was categorized as non-drinker, moderate drinker (female<14 and male<21 drinks/week) or heavy drinker (female≥14 and male≥21 drinks/week). Smoking status was categorized into current, former or never smoker. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) (49) and expressed as overall energy expenditure in Metabolic Equivalent Total (MET) minutes per week (MET level * minutes of activity * events per week). The number of self-reported current somatic diseases for which participants received medical treatment (i.e. heart disease, epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung-disease, thyroid disease, liver disease, intestinal disorders and ulcers) was counted. Depression and anxiety disorders were assessed by the *DSM-IV Composite International Diagnostic Interview (CIDI)* version 2.1 and included major depressive disorder, dysthymia, panic disorder, social phobia, agoraphobia and generalized anxiety disorder. In the NESDA study, disorder status has been associated with TL (18,19). To check whether disorder status influenced the possible relationships, we categorized persons as having had a diagnosis during their lifetime (N=2292) or no lifetime depressive and/or anxiety disorder (N=644).

Statistical analyses

Means and standard deviations or percentages of baseline characteristics were calculated. We tested which sociodemographic and lifestyle variables were associated with TL. Sociodemographic factors were seen as potentially confounding variables; lifestyle factors and somatic health, in turn, were considered as possible explanatory factors. Linear regression analyses were performed for all early (childhood life events and childhood trauma) and recent (stressful life events) psychosocial stressor variables in separate models. Analyses were adjusted for sociodemographics and additionally for all lifestyle and somatic health variables. Effect modification for age, sex and physical activity was tested by adding life stress * sex / life stress * standardized age / life stress * physical activity interaction terms to the model. Further, as two previous studies in the NESDA sample showed that depression and anxiety disorder diagnosis status was related to shorter TL (18,19), interaction terms were tested to see whether relationships differed for persons with and without a lifetime depression or anxiety disorder, by testing a life stress * lifetime diagnosis interaction. To examine the impact of each specific life stressor,

regression coefficients and confidence intervals were calculated for separate life events in three time periods: past years, between 1 to 5 years ago, more than 6 years ago. As a post-hoc analysis, we tested whether possible associations between life stress and TL were mediated by lifestyle variables (BMI, smoking, alcohol and physical activity), using the indirect method by Preacher and Hayes (5000 bootstraps) for the analyses, which estimates the direct and indirect unstandardized effect of the independent variable on the dependent variable through the mediator variable, controlling for age and sex (50). All analyses were conducted using SPSS version 20 (IBM Corp., Armonk, NY, USA).

RESULTS

Table 1 shows baseline characteristics of the study sample (N=2936). Participants were on average 42 years old (range 18 to 65) and two-thirds were women. Most participants were modest alcohol drinkers and current smokers, approximately one-third had one or more somatic diseases and just over half of the sample had a BMI classified as normal. A large majority (78.1%) had a lifetime depression or anxiety disorder diagnosis. Almost a quarter of all participants had experienced at least one childhood life event, more specifically: 13.1% had experienced the divorce of their parents, 5.9% experienced the death of a parent and 6.2% was separated from home before the age of 16. Emotional neglect was reported as the most frequent form of childhood trauma, followed by psychological abuse and physical abuse. Sexual abuse was most often reported as a form of abuse that happened sometimes. As expected, childhood trauma was more prevalent in those with lifetime depression or anxiety disorder diagnosis compared to those without (see also Hovens et al. (43)). Enquiries of life events showed that participants experienced on average 0.8 (SD=1.1) stressful life events in the past year and 1.9 (SD=1.6) life events between 1 and 5 years ago and 3.0 (SD=2.1) life events more than 6 years ago.

The average TL of the total sample was 5468 bp (SD=617). TL was normally distributed and exhibited, as expected, a significant negative correlation with age (r=-.307, p<.001) that corresponded to a mean shortening rate of 15 bp/year. Female subjects had longer TL than male subjects (F=12.66; p<.001, corrected for age). TL was significantly negatively associated with alcohol use (non-drinker: B=-28.9; p=.347; heavy drinker: -122.3; p<.001), smoking status (former smoker: B=-130.4; p<.001; current smoker: B=--120.1; p<.001), BMI (B=-13.4; p<.001) and number of chronic diseases (B=-73.6; p<.001), but not with education (B=4.0; p=249) or physical activity (B=-0.0; p=.481).

Table 1. Characteristics of the total sample (N=2936)

Demographics	
Age (mean ± s.d.)	41.8 ± 13.1
Sex (N, % female)	1950 (66.4%)
Years of education (mean ± s.d.)	12.2 ± 3.3
Lifestyle & health	
Body Mass Index (mean ± s.d.)	25.6 ± 5.0
Smoking status (N, %)	
Never	826 (28.1%)
Former	974 (33.2%)
Current	1136 (38.7%)
Alcohol Status (N, %)	
Non-drinker	500 (17.0%)
Modest drinker	2063 (70.3%)
Heavy drinker	373 (12.7%)
Physical Activity (in 1000 MET-minutes/week; mean ± s.d.)	3.7 ± 3.0
Number of somatic diseases (mean ± s.d.)	0.6 ± 0.9
Depressive or anxiety disorder diagnosis status (N, %)	
Controls (no lifetime diagnosis)	644 (21.9%)
Remitted diagnosis	620 (21.1%)
Current diagnosis	1672 (56.9%)
Early life stress	
Number of childhood life events (mean ± s.d.)	0.3 ± 0.5
Emotional neglect (N, %)	
Sometimes	153 (5.2%)
Regularly	986 (33.7%)
Psychological abuse (N, %)	
Sometimes	124 (4.2%)
Regularly	602 (20.5%)
Physical abuse (N, %)	
Sometimes	193 (6.6%)
Regularly	209 (7.1%)
Sexual abuse (N, %)	
Sometimes	414 (14.1%)
Regularly	126 (4.3%)

Recent life stress	
Number of stressful life events in the past year (mean ± s.d.)	0.8 ± 1.1
Number of stressful life events, 1 to 5 years ago (mean ± s.d.)	1.9 ± 1.5
Number of stressful life events, 6 or more years ago (mean ± s.d.)	3.0 ± 2.1
Telomere length	
Base pairs (mean ± s.d.)	5468 ± 617

Abbreviation. MET-minutes = metabolic equivalent of number of calories spent per minute

Table 2 shows results of regression analyses of early and recent psychosocial stressors on TL, adjusted for sociodemographic variables and additionally adjusted for lifestyle (smoking and alcohol). Neither childhood life events nor childhood trauma were related to TL. We analyzed the childhood life events and childhood trauma categories separately (data not shown), but none of the subcategories were associated with TL ($p>.10$). Also, no associations were found between TL and the CTQ at year 4 (sociodemographic-adjusted $\beta=-.015$; $p=.470$), and neither with any of the childhood trauma category subscales ($p>.40$). For the psychosocial stressors recent in life, we a found sociodemographic-adjusted association between TL and the number of experienced life events in the past year ($\beta=-.039$; $p=.028$). This association remained in the same direction but became borderline significant when additionally adjusted for lifestyle ($\beta=-.032$; $p=.070$). The number of stressful life events experienced 1 to 5 years ago was also significantly associated with TL, adjusted for sociodemographics ($\beta=-.042$; $p=.018$); and the association again became borderline significant with further adjustment ($\beta=-.032$; $p=.074$). These results suggest that the found relationships may party be explained by smoking status and alcohol use; those with more negative life events were namely more often a current smoker or a heavy alcohol drinker. The number of stressful life events experienced more than 6 years ago was not associated with TL, in both sociodemographic and lifestyle adjusted analyses, however, the coefficients were of smaller magnitude, but remained in the same direction. When the three variables were entered in the sociodemographic adjusted model simultaneously, stressful life events in the past year ($\beta=-.041$; $p=.023$) and life events 1 to 5 years ago ($\beta=-.039$; $p=.028$) remained significantly associated with TL, while life events more than 6 years ago remained unrelated ($\beta=-.030$; $p=.130$). Because the effect of stressful life events in the past year and 1 to 5 years ago on TL was no longer significant after adjusting for lifestyle variables, we performed mediation analyses to test if BMI, smoking, alcohol or physical activity could be considered as mediators in the relationship. Results are presented in Table 3 and show that both for life events in the past year and 1 to 5 years ago, smoking

Table 2. Associations between telomere length and psychosocial stressors in total sample (N=2936) based on multivariate linear regression analyses

Early life stressors	B	SE	β	p-value
Childhood life events				
Sociodemographic adjustment	5.3	21.4	.004	.805
Full adjustment	11.4	21.4	.009	.596
Childhood trauma (CTI)				
Sociodemographic adjustment	-12.3	9.7	-.023	.205
Full adjustment	-7.9	9.8	-.015	.420
Recent life stressors				
Stressful life events in the past year				
Sociodemographic adjustment	-22.7	10.3	-.039	.028
Full adjustment	-18.8	10.4	-.032	.070
Stressful life events 1 to 5 years ago				
Sociodemographic adjustment	-17.1	7.2	-.042	.018
Full adjustment	-13.1	7.3	-.032	.074
Stressful life events 6 or more years ago				
Sociodemographic adjustment	-9.4	5.7	-.032	.100
Full adjustment	-6.8	5.7	-.023	.238

Sociodemographic adjustment = adjusted for age, sex & education; Full adjustment = additionally adjusted for BMI, smoking & alcohol status, physical activity and number of somatic diseases
Abbreviations. CTI = Childhood Trauma Interview

status was a significant mediator. Table 3 also shows that experienced life stress had no effect on BMI, alcohol or physical activity, and these variables in turn had no direct effect on TL.

Effect modification was tested for age (continuous and standardized) and sex (male vs. female). There were no significant age or sex moderation effects on any of the early or recent life stressor variables and TL, except for an interaction between age and childhood life events (B=3.4; SE=1.7; p=.040). Further, we checked whether childhood life events, childhood trauma and more recent stressful life events were differently associated with TL in persons with psychopathology versus those without. No interaction effects were found for lifetime or remitted or current depression and/or anxiety diagnosis for the relation between TL and childhood life events, childhood trauma or recent stressful life events. Consequently, both in persons with and without psychopathology no association between childhood adversity and TL was found. To test whether physical activity could

act as a buffer for effect of life stress, we tested whether physical activity was an effect moderator. Interaction analyses (data not shown, all p-values>.20) showed that the relation between psychosocial life stress and TL was not dependent on level of physical activity. Of all 20 interaction terms, only one was significant (between age and childhood life events, see above), however this might be interpreted as a statistical chance finding. Possible interaction effects between childhood adversities and age on TL could be addressed in future research. Last, we did not find interaction effects between childhood life events or trauma and the experience of recent stressful life events on TL.

Subsequently, in order to test whether specific life events were driving the association with TL or whether associations were consistent across stressful life events, we calculated whether each separate life event had occurred (yes/no) in the past year, 1 to 5 years ago and 6 or more years ago and examined whether the occurrence (for each event at each time frame) was associated with TL. Figure 1 shows the adjusted regression coefficients and Confidence Intervals (C.I.) from sociodemographic-adjusted regression analyses for each life event separately, and for the sum of life events. Persons that reported contact with police or justice by misdemeanor showed a relatively strong negative relationship with TL. The overall associations, however, did not appear to be driven by only one or two life events; in contrast, the figure shows that overall, there was a rather consistent negative association for most stressful life events and TL.

DISCUSSION

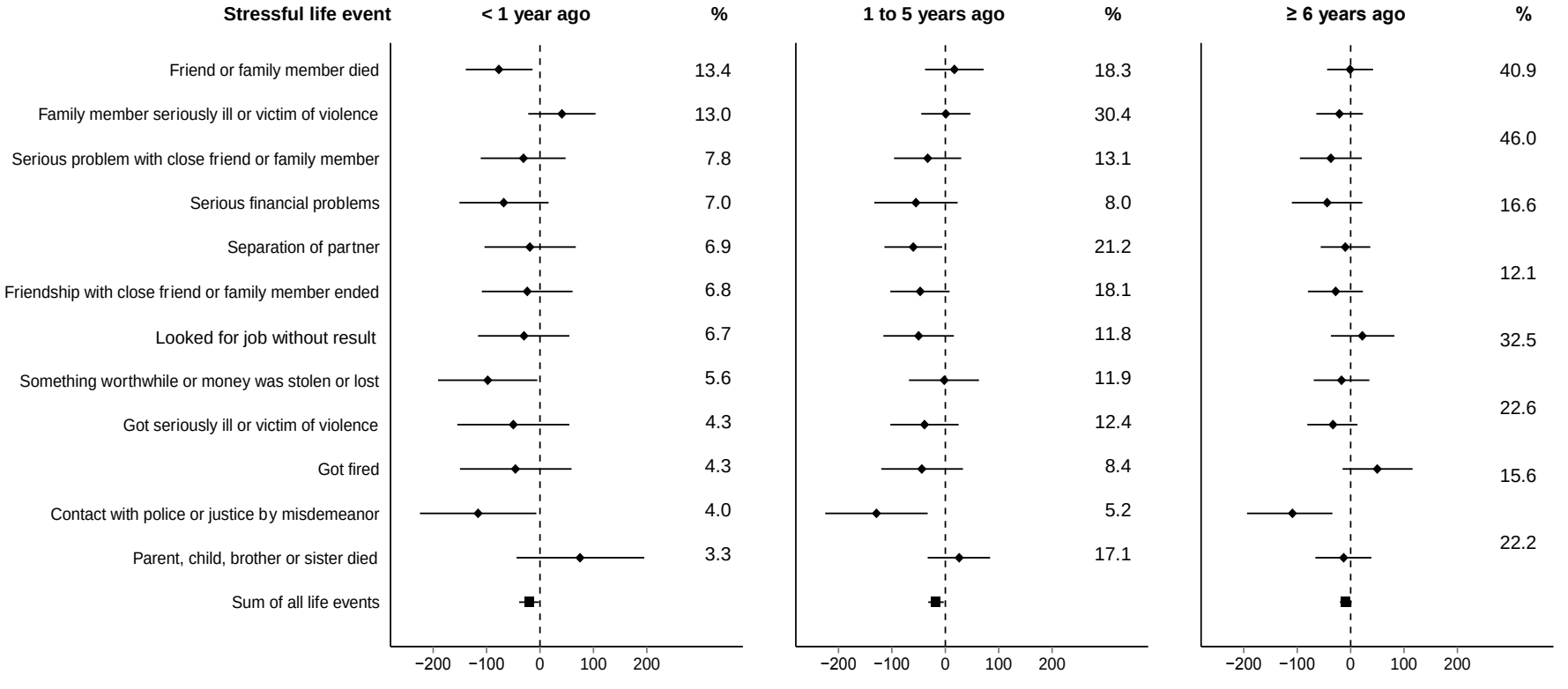
This study sought to examine whether psychosocial stressors that occur across the lifespan are associated with accelerated telomere shortening. Our findings show that the more proximal the stressor occurred to telomere length (TL) measurement, the more likely they were associated. The associations between stressors and TL became weaker or disappeared as the duration since the adversities was longer. In more detail, we found that persons who experienced stressful life events in the past 12 months had on average shorter telomeres compared to those without recent life stressors, adjusted for age, sex and education. A similar relationship was found for the number of stressful life events experienced between one and five years ago. Both associations reduced to borderline significance when lifestyle variables were added to the model, and mediation analyses showed that smoking status may partly explain these relationships. The number of stressful life events that occurred more than six years ago was unrelated to TL. It could be that as time passes, life events are truly less strongly associated to TL. Alternatively, it is also possible that life events that occurred further in the past are less reliably assessed or that the high reporting rate of at least two stressful life events that occurred more than 6

Table 3. Summary of Preacher and Hayes mediator model analyses between life stress (IV) and telomere length (DV)

Life stress (IV)	Lifestyle (M)	Effect of IV on M (a)		Effect of M on DV (b)		Direct effect (c') of IV on DV		Indirect (SE) effect of IV on DV (a x b)	95% CI (a x b)
		effect (SE)	p	effect (SE)	p	effect (SE)	p		
Stressful life events in the past year	BMI	.13 (.08)	.119	-3.1 (2.2)	.173	-22.4 (10.3)	.029	-.40 (.44)	(-1.72 to 0.13)
	Smoking status	.07 (.01)	<.001	-44.7 (13.4)	<.001	-19.6 (10.3)	.056	-3.18 (1.23)	(-6.00 to -0.25)**
	Alcohol status	-.00 (.00)	.954	-22.3 (19.9)	.263	-22.8 (10.3)	.026	.01 (.32)	(-0.58 to 0.76)
	Physical activity	32.3 (52.9)	.541	-.003 (.00)	.381	-22.7 (10.3)	.027	-.10 (.28)	(-1.32 to 0.21)
Stressful life events 1 to 5 years ago	BMI	.12 (.06)	.054	-3.1 (2.2)	.163	-16.8 (7.2)	.020	-.36 (.35)	(-1.47 to 0.09)
	Smoking status	.08 (.01)	<.001	-44.2 (13.5)	.001	-13.5 (7.3)	.064	-3.59 (1.22)	(-6.50 to -1.52)**
	Alcohol status	.00 (.01)	.609	-22.5 (19.9)	.259	-17.0 (7.2)	.018	-.08 (.21)	(-0.96 to 0.16)
	Physical activity	23.4 (37.2)	.529	-.003 (.00)	.397	-17.0 (7.2)	.018	-.07 (.19)	(-0.81 to 0.12)

Abbreviations. DV = dependent variable; IV = independent variable; M = mediator; SE = standard error
Note. Analyses are controlled for age and sex
** significant based on 95% confidence interval (CI)

Figure 1. Associations (adjusted B and Confidence Interval) between telomere length and stressful life events for different time frames



% = prevalence of life event among total sample in specific time period. All analyses are adjusted for age, sex and education.

years ago (73%) may lead to less discriminatory power in analyses with TL. These relationships were not different for persons with a lifetime depression or anxiety disorder diagnosis compared to those without a lifetime diagnosis, nor did they differ across age and sex groups. Adversities that happened earlier in life, specifically childhood life events or trauma, were unrelated to TL in adulthood in the current study. These results suggest that psychosocial stressors recent in life are more likely to be associated with accelerated telomere shortening than stressors that occurred earlier in life.

Our finding of a relationship between recent psychosocial life stress and TL is consistent with most studies on this topic (10,13). Earlier research, in line with our findings, showed shorter TL for persons with psychosocial stress such as caring for a chronically ill child (21), spouse or parent (23), a history of partner violence (25), and perceived stress after a recent major loss (e.g., death of a family member, and loss of marital partnership) (26). In some of these studies, TL was inversely correlated with the severity and chronicity of the psychological stress, suggesting a "dose-response" relationship (21). Our measure of total number of stressful life events was significantly associated with TL, also suggesting a dose-response, as TL was shorter when a person was exposed to more life events. Furthermore, the breadth of the types of stressors we measured (i.e., the death of a close family member, separation of a partner, getting fired, serious financial problems) speaks to the possible wide shadow that stress casts on our physiology. The impact of life stressors that may have occurred at different periods in adulthood has, to our knowledge, never been examined in detail. Interestingly, we found that the more recent the stressful life events occurred, the greater the impact. This novel finding possibly suggests that people are able to physiologically recover from the impact of stressful life events as events fade into the past.

We did not find any associations between adverse events that occurred in childhood and adulthood TL. Major life events during childhood such as the death of a parent or early parental separation were not related to TL at adult age. Further, we did not find emotional neglect, psychological abuse, physical abuse or sexual abuse before the age of 16, to be associated with TL. This was confirmed by examining the widely used CTQ, which was administered at the four-year follow-up assessment. Our findings were rather surprising as they contrast two recent reviews on early-life stress and adult TL by Shalev (31) and Price et al. (10). They conclude that most well-controlled studies support the suggestion of such a relationship, and that the effect is presumably dose-dependent. Two of the previous studies, however, found effects of childhood adversities on TL, but only in specific samples, for example in PTSD patients (34) or persons that also experienced traumatic events across the life span (35), suggesting that it might have been the combination of trauma in childhood and recent in life that caused the impact on TL. At the baseline measurement of the NESDA study, persons with a clinically overt PTSD

diagnosis were in principle excluded, potentially explaining our lack of findings (although we know that in NESDA, some persons did report PTSD symptoms as identified on a dimensional scale assessed at the 4-year follow-up (51)). Further, it might be possible that childhood trauma in the NESDA sample is not severe enough to affect health outcomes, although we have confirmed that childhood trauma in our sample has an impact on psychiatric status (43), brain structure (52) and metabolic health (53); or effects may be country-specific, since every country has a different child welfare system, with one system probably being better equipped to meet the needs of maltreated children than the other. Another explanation is that the large prevalence of depression and anxiety disorders in this specific cohort overruled effects of childhood adversities in TL. Having a depression or anxiety disorder was found to be associated with shorter TL (18,19); therefore, effects of adverse experiences in childhood might not be detectable. However, in our sample without lifetime psychiatric diagnoses (N=644), no associations were found either. Overall, out of the five other large (n>500) studies up until now, which vary in participant characteristics and study design, two detected TL associations with childhood adversities (27,33) whereas three did not (35,36), including the present study. In light of these seemingly conflicting reports, clarification of the effects of childhood adversities on TL is warranted, preferably by longitudinal nationally representative samples with large sample sizes.

The relationship between psychosocial stress and TL might be partially mediated by dysregulated bodily stress responses. Several in vivo and in vitro studies show that telomere shortening has been associated with a hyperactive HPA-axis (54,55), increased vagal autonomic tone (56), but also with increased inflammation (57,58) and oxidative stress (59). Moreover, simultaneous dysregulations of these factors have a cumulative impact on TL (60), supporting the notion of a dose-response effect. Further, an unhealthier lifestyle might also partly explain the relationship between psychosocial stress and TL. We found that smoking status significantly mediated the relationship between stressful life events and TL. Persons that experience stressful events may be more susceptible for unhealthy smoking habits (61), and this may further impact their physiology. An important future direction is to examine whether specific behaviors or lifestyle changes can buffer the effects of psychosocial stress on peripheral systems. Although no proof was found in the present study, two earlier studies provide evidence for such an effect: physical exercise (22) and high levels of healthy behaviors (28) were found to moderate the association between stress and shorter telomeres. This raises hope for lifestyle interventions to prevent detrimental effects of stress (see Verhoeven et al. for an overview (29)). Also, future research should preferably follow children longitudinally into adulthood, to determine what the influence of stress on telomeres is at different time points and developmental periods.

One of the major strengths of the present study is the large study sample and the purposeful inclusion of persons with a lifetime diagnosis of depression or anxiety disorder and persons with no lifetime history of any psychiatric disorder. These are important strengths since both childhood adversities and recent major life events are known to be associated with psychiatric disorders. Therefore, we were able to examine whether the relation between TL and those stressors was different for these subsamples. Another strength is the wide age range, and the assessment of important covariates such as health and lifestyle variables. Some limitations of the present study should also be noted. As in most studies, early-life stressors were measured retrospectively, and may therefore be limited by factors such as errors in recall due to the passage of time, the possible inaccessibility of memories for traumatic events and the lack of independent records to determine the validity of the measures. The two childhood trauma assessments used in this study, however, correlated highly with each other, which supports the reliability of the data. Similarly, reported stressful life events in adulthood may also be erroneously recalled. The reliability of events reporting may decrease when events occurred more distal to the assessment. These may have in part contributed to our findings that the strongest associations with TL were found for the more recent events. Also, in our study, recent stressful life events were not divided into equivalent time periods; instead, we used a one year, four year and a variable timespan. Another limitation is the cross-sectional nature of this study that limits the ability to draw causal conclusions. Future longitudinal observational studies or experimental studies in non-humans could shed more light on the causality of the association between life stress and for example telomere shortening rate or reversibility, and should confirm whether the association is indeed mediated by smoking status. Furthermore, it should be noted that we measured the occurrence of adverse life events, both in childhood and recent in life, rather than the extent to which life events resulted in perceived stress levels. A recent meta-analysis demonstrated that perceived stress is significantly related to shorter telomeres (62). Understanding the differential or combined impacts of actual events and the perception of stress on telomere length is of particular interest for future studies. Next, as in nearly all studies we used leukocytes for TL measurement, which is a validated and an often used indicator for cellular aging. Leukocyte TL has been found to have high consistency and similar shortening rates with other somatic tissues (i.e. skeletal muscle, skin, and subcutaneous fat) (63), suggesting that the results of studies conducted in leukocytes are generalizable to other cell types. A limitation of using average leukocyte TL is that it consists of different cell types. Recent studies found different TL change rates for T-cells, B-cells and monocytes, which makes it difficult to distinguish whether TL differences are due to actual shortening or rather to a redistribution of cell types (64,65). Last, telomerase activity has not been measured in the current study, but information

regarding telomere repair and maintenance would be interesting in future research since telomerase activity was found to be decreased in a chronically stressed sample (66).

This study showed that recently experienced stressful life events are associated with shorter telomere length, suggestive of accelerated cellular aging. We found recent stressful life events up to five years earlier than telomere measurement to be related to shorter telomeres, whereas stressful life events more than six years ago, or adversities experienced in childhood, such as early separation or maltreatment, were not related to adult TL. Whether these results are indicative of biological resiliency that enables people to physiologically recover from psychosocial stressors, as opposed to leaving an irreversible physiological "scar", remains to be further explored.

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