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CHILDHOOD TRAUMA ASSOCIATED WITH SHORT LEUKOCYTE TELOMERE LENGTH IN POST-TRAUMATIC STRESS DISORDER

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Abstract

Background—Post-traumatic stress disorder (PTSD) is associated with increased risk for age-related diseases and early mortality. An accelerated rate of biological aging could contribute to this increased risk. To investigate, we assessed leukocyte telomere length (LTL), an emerging marker of biological age, in men and women with and without PTSD. We also examined childhood trauma, a risk factor for both PTSD and short LTL, as a potential contributor to short LTL in PTSD.

Methods—Participants included 43 adults with chronic PTSD (n=18 with multiple categories of childhood trauma) and 47 controls (none with multiple categories of childhood trauma) (*M* age = 30.55, *SD* = 7.44). Exclusion criteria included physical illness, medication use, obesity, alcohol or substance abuse, and pregnancy. Structured clinical interviews were conducted to assess PTSD and other psychiatric disorders and childhood trauma exposure. LTL was measured with quantitative polymerase chain reaction.

Results—As predicted, participants with PTSD had shorter age-adjusted LTL than controls. Exposure to childhood trauma was also associated with short LTL. In fact, childhood trauma appeared to account for the PTSD group difference in LTL; only participants with PTSD and exposure to multiple categories of childhood trauma had significantly shorter LTL than controls.

Conclusions—Childhood trauma is associated with short LTL in individuals with PTSD. Chronic exposure to the psychobiological sequelae of childhood trauma could increase risk for PTSD and short LTL. Thus, the lasting psychological impact of exposure to trauma in childhood may be accompanied by equally enduring changes at the molecular level.

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Keywords

anxiety; biological aging; childhood trauma; post-traumatic stress disorder; telomere length

Post-traumatic stress disorder (PTSD) is an anxiety disorder that develops in a minority of individuals following exposure to traumatic stress (1). Accumulating evidence indicates that PTSD substantially increases risk for age-related diseases, such as cardiovascular, autoimmune, and neurodegenerative diseases, and early mortality (2–6). However, the biological mechanisms mediating these associations remain unclear. Accelerated biological aging is a potential mechanism of such increased risk, and PTSD is associated with dysregulation of bodily systems that have been linked with biological aging (7,8). However, to our knowledge, there are no studies examining indices of biological aging in PTSD.

Leukocyte telomere length (LTL) is an emerging marker of biological age that predicts incidence of age-related diseases and mortality (9–12). Factors associated with shorter LTL include higher body mass index (BMI), cigarette smoking, and male gender (13–15). Exposure to chronic psychological stress and affective disorders has been also associated with short LTL (16–18). Repeated and prolonged activation of the biological stress response is a potential contributor to an accelerated rate of leukocyte telomere shortening in chronically stressed individuals. As evidence, shorter LTL has been observed in individuals who have higher nocturnal levels of the stress hormones cortisol and catecholamines (19,20). Furthermore, anxiety and depression related elevations in inflammatory activity may promote telomere shortening by increasing cell turnover and promoting the release of reactive oxygen species that damage telomeric DNA via oxidative stress (7,21,22). Individuals with PTSD, who demonstrate dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased sympathetic nervous system (SNS) activation, and elevated inflammatory activity (8,23–25), may also be susceptible to accelerated shortening of LTL.

Childhood trauma is a significant risk factor for the development of PTSD later in life (26,27), and is also associated with short LTL in some, but not all, studies of all adult samples (28–30). These consequences of childhood trauma may be due to early life experiences shaping later life biological stress responses (31,32). Individuals who experience childhood trauma have increased neuroendocrine and immune system responses to stress, glucocorticoid resistance, and reduced hippocampal volume compared to those who do not experience childhood trauma (33,34). Many of these biological factors confer increased risk for developing PTSD after exposure to trauma (35). Insofar as childhood trauma leads to exaggerated and prolonged biological stress responses, childhood trauma may also increase risk for short LTL in adulthood. Thus, it is possible that childhood trauma may play a role in any observed association between PTSD and LTL.

In the present study, we examined LTL in individuals with PTSD with and without exposure to multiple categories of childhood trauma and in control participants, hypothesizing that: 1) the PTSD group overall would have shorter LTL than controls; 2) across the sample, childhood trauma would be related to shorter LTL; and 3) participants with PTSD would have greater childhood trauma exposure, which could account for any observations of short LTL in PTSD.

Methods

Design and Sample

The present study has a cross-sectional, 2×2 design (PTSD/ Control \times Male/Female) with medically healthy medication-free subjects. Participants were recruited through ads and

flyers distributed in the community, as well as through relevant local clinics for the PTSD sample. The final sample included 43 individuals with current chronic PTSD (47% female; M age = 30.60, SD = 6.63) and 47 controls without PTSD (56% female; M age = 30.68, SD = 8.19), ranging in age from 21 to 49 years. Chronic PTSD was defined by fulfillment of DSM-IV criteria or Clinician Administered PTSD Scale (CAPS, 36) score > 40 for at least three months. Controls were negative for lifetime PTSD and had current CAPS scores < 20. Women took part in the study during the follicular phase of the menstrual cycle. Exclusion criteria included the presence of neurologic disorders or systemic illness, use of psychiatric, anticonvulsant, antihypertensive, sympathomimetic, estrogen replacement therapy, steroidal, statin or other prescription medications, obesity (BMI > 30), alcohol abuse or dependence in the previous two years, substance abuse or dependence in the previous year, any psychiatric disorder with psychotic features, bipolar disorder, or obsessive-compulsive disorder, and pregnancy. Controls were excluded if they had a lifetime history of PTSD, major depressive disorder (MDD) or panic disorder. All participants provided written informed consent and the study protocol was approved by the Committee on Human Research at the University of California, San Francisco and at the San Francisco Veteran's Affairs Medical Center.

Psychiatric Diagnoses

Lifetime and current PTSD were assessed with the Clinician-Administered PTSD Scale (CAPS), a structured interview measure that corresponds to DSM-IV criteria for PTSD (36). The CAPS is a 30-item scale that assesses the frequency and intensity of re-experiencing, avoidance and hyperarousal symptoms of PTSD. Diagnosis of PTSD was based on symptoms experienced in the previous month associated with the subject's self-identified worst traumatic event. Other psychiatric disorders were assessed by administration of the Structured Clinical Interview for DSM-IV (37). All diagnoses were made by trained clinical interviewers who calibrated their assessments at weekly case consensus meetings, supervised by an experienced PhD-level clinical psychologist.

Childhood Trauma

Five items from the interview version of the Life Stressor Checklist (LSC) were modified to assess exposure to childhood trauma at or before age 14 (38). Participants were asked if they had been exposed to any of the following experiences to the extent that they felt that they could die or be physically harmed, physical neglect, family violence, physical abuse, forced sexual touch, or forced sexual intercourse at or before age 14. These items were administered during a structured interview conducted by trained clinical interviewers who calibrated their assessments at weekly case consensus meetings, supervised by an experienced PhD-level clinical psychologist. Childhood trauma data was missing for one participant with PTSD.

Leukocyte Telomere Length (LTL)

Samples were collected in 10-ml heparin tubes (Becton–Dickinson, Franklin Lakes, NJ). Leukocytes were isolated and frozen at -80°C . DNA was extracted from leukocytes by the University of California San Francisco DNA bank. Genomic DNA isolation was performed using a standardized and quality-controlled PureGene DNA isolation system (Gentra Systems, Minneapolis). The quantity and quality of the genomic DNA isolate was determined by 260/280 UV spectrophotometry. At regular intervals, the integrity of isolated DNA was evaluated by agarose gel electrophoresis performed on randomly selected isolates. DNA was analyzed for LTL using quantitative polymerase chain reaction (qPCR) as previously described (39) with modifications as described in (40). The quantities of telomeric product (T) and single copy gene (S) were determined relative to the reference DNA by the standard curve method (see Supplementary Materials). All PCRs were carried out on a Roche Lightcycler 480 real-time PCR machine with 384-tube capacity (Roche

Diagnostics Corporation, Indianapolis, IN). To convert T/S values to basepairs, the T/S ratios for a set of genomic DNA samples from the human fibroblast primary cell line IMR90 at different population doubling (PD) as well as with the telomerase protein subunit gene hTERT in a lentiviral construct were determined. This set of DNA samples represents different T/S ratios from the same parental cell line. The mean telomeric restriction fragment (TRF) length from these DNA samples is determined using Southern blot analysis and the slope of the plot of mean TRF length versus T/S for these samples serves as the conversion factor for calculation of approximate telomere length, in base-pairs (bp), for each T/S ratio in this study. The conversion formula was determined to be: base pairs = $3274 + 2413 * (T/S)$.

Statistical Analysis

Data screening procedures showed that both PTSD and control groups included one statistical outlier on LTL, defined as LTL greater than twice the interquartile range. Data from these two participants were excluded for the purpose of analysis. When excluding these outliers, LTL was normally distributed (Shapiro-Wilks = .98, $df = 88$, $p = .34$) with acceptable skewness (skewness = .24, $SE = .26$) and kurtosis (kurtosis = -.31, $SE = .51$). Our primary hypothesis was tested using an analysis of covariance (ANCOVA) model, comparing differences in LTL in participants with and without PTSD. Partial correlation was used to explore the association between PTSD severity (assessed by CAPS score) and LTL. To examine if MDD contributed to our findings, we examined if participants with PTSD and a history of MDD had significantly shorter LTL than participants with PTSD who were without a history of MDD. For our childhood trauma analyses, we used a partial correlation to examine the association between number of categories of childhood trauma exposure and LTL. For categorical analyses, given that children exposed to more than one category of childhood trauma have been found to be more at risk for PTSD and other adverse outcomes compared with those exposed to one category or none (26,27,41), we categorized participants into two groups: those having none or one category of exposure and two or more categories of exposure and examined differences in LTL between these two groups using ANCOVA. Age was included as a covariate in all primary LTL analyses. Given the directionality of our hypotheses regarding LTL, one-tailed p values were used to assess statistical significance in analyses with LTL as outcome. For the purpose of graphically representing our findings, age-adjusted LTL for each participant was calculated as the observed LTL plus the difference between the mean and actual age multiplied by the unstandardized beta obtained by regressing LTL on age. We also reran our correlational analyses using this age-adjusted LTL variable, and found that Spearman's correlations on this age-adjusted LTL variable yielded the same pattern of results as observed using Pearson's partial correlations. Data analysis was conducted with PASW Statistics 18 (SPSS Inc., 2009).

Results

Descriptive data for the sample are presented in Table 1. There were no significant age differences between PTSD (age range: 21–49) and control participants (age range: 20–50), and there were no gender distribution or education differences between groups ($p = ns$). However, participants with PTSD did have significantly higher BMI than controls ($t = 2.62$, $p = .01$). There were no differences between male and female participants in LTL ($p = ns$). Shortening LTL was associated with increasing age ($r = -.29$, $p = .007$), but BMI, smoking and years of education were not associated with LTL and there were no gender differences in LTL ($p = ns$). Participants with PTSD had high mean CAPS scores, indicating moderately severe symptoms of PTSD ($M = 54.7$, $SD = 15.8$). Eighteen participants with PTSD and no controls reported a history of exposure to multiple categories of childhood trauma.

PTSD and LTL

Participants with PTSD had significantly shorter age-adjusted LTL than control participants, $F(1,85) = 3.29, p = .03, \text{partial } \eta^2 = .04$, (Figure 1). On average, participants with PTSD had age-adjusted LTL 204 base pairs shorter ($M = 6594.10, SE = 81.50$) than control participants ($M = 6798.61, SE = 77.88$). Next, we examined if PTSD symptom severity as assessed by CAPS was associated with LTL within participants with PTSD, but found no significant associations between CAPS scores and LTL ($r_{\text{partial}} = -.12, p = \text{ns}$). Finally, we examined if the 31 participants in our sample with PTSD and a history of MDD had significantly shorter LTL than those participants with PTSD who did not have a history of MDD. First, we confirmed that there was no significant difference in the gender composition of groups with and without a history of MDD, $\chi^2 = 2.47, p = \text{ns}$. Then, using ANCOVA, we found no difference in LTL between the 31 participants with PTSD and a history of MDD and the participants with PTSD who did not have a history of MDD, $F(1,39) = 2.15, p = \text{ns}$.

Childhood Trauma

Exposure to more categories of childhood trauma, or cumulative childhood trauma exposure, was linearly associated with shortening LTL in the combined sample of participants with PTSD and controls ($r_{\text{partial}} = -.27, p = .005$; Figure 2). However, childhood trauma was significantly more prevalent in participants with PTSD and no controls had experienced more than one category of childhood trauma (Table 1). Because there was insufficient variance in childhood trauma to examine relations between childhood trauma and LTL within the control group, and because PTSD and childhood trauma were confounded, we focused subsequent analyses on the effect of childhood trauma on LTL within participants with PTSD.

Cumulative childhood trauma exposure was even more strongly associated with shortening LTL in the subsample including only participants with PTSD ($r = -.42, p = .003$). Participants with PTSD who endorsed experiences of multiple childhood traumas ($n = 18$) versus one or no categories of childhood trauma ($n = 23$) were not significantly different in gender, BMI, years of education, or PTSD severity. However, results indicated that participants with PTSD who had experienced multiple childhood traumas ($M \text{ TL} = 6480.45, SD = 107.80$) had significantly shorter LTL than those who had experienced one category of childhood trauma or none ($M \text{ TL} = 6727.88, SD = 94.94$), exhibiting LTL on average 247 base pairs shorter, $F(1,38) = 2.86, p = .04, \text{partial } \eta^2 = .07$.

We then examined the relative contribution of participants with PTSD and childhood trauma to the observed association between PTSD and LTL. Results indicated that only participants with PTSD and more than one type of childhood trauma had significantly shorter LTL than controls. Specifically, participants with PTSD and more than one category of childhood trauma had LTL 316 base pairs shorter than controls, $F(1,61) = 4.07, p = .02, \text{partial } \eta^2 = .06$, whereas participants with PTSD and one or no categories of childhood trauma were not significantly different from controls on LTL, $F(1,66) = .41, p = \text{ns}$. Furthermore, the group difference in LTL between participants with PTSD and controls was no longer significant when controlling for childhood trauma. Overall, these results indicated that only participants with the combination of PTSD and childhood trauma were significantly different than control participants in LTL, and that these participants accounted for the observed group difference in LTL between participants with PTSD and controls.

Discussion

The present data demonstrate that young to middle-aged adults with PTSD have shorter LTL than do non-psychiatric control persons, even in the absence of chronic physical illness. This

finding extends a small but growing body of literature showing short LTL in individuals experiencing chronic psychological stress (17,18) or psychiatric illness (16,42). However, our data additionally indicated that only participants with PTSD who had been exposed to multiple types of childhood trauma had significantly shorter LTL than controls, indicating that childhood trauma may have accounted for the observed finding of short LTL in PTSD. Moreover, our data indicated that exposure to multiple categories of childhood trauma may have a cumulative effect on LTL, as number of categories of trauma exposure was linearly associated with shortening LTL across the entire sample and within the group of participants with PTSD. These findings of short LTL in association with childhood trauma add to a growing literature specifically showing short LTL in individuals exposed to traumatic events in childhood (29,30). Our results are particularly compelling in light of the relatively young age and good physical health of our sample.

Our primary finding was that individuals with PTSD and multiple categories of childhood trauma had significantly shorter LTL than both controls and participants with PTSD who had none or one category of childhood trauma. Childhood trauma and PTSD could exert separate and combined effects on the rate of telomere shortening through biological and behavioral pathways. First, both childhood trauma and PTSD are associated with exaggerated reactivity to negative stimuli and events, which may lead to repeated and prolonged activation of the biological stress response (43–45). Products of the biological stress response, in turn, have been causally linked with leukocyte telomere shortening. High levels of stress hormones including cortisol and catecholamines indexing activation of the HPA axis and SNS respectively have been associated with short LTL (8,19,20,23–25). Stress-related elevations in inflammatory activity may also promote leukocyte telomere shortening in individuals with PTSD and childhood trauma (8,21,46,47). Second, individuals with PTSD or childhood trauma exposure may be less likely to engage in the kinds of behaviors, such as maintaining a healthy weight, exercising regularly and not smoking, that could protect against the negative effects of psychological stress on TL (48–52). While smoking and obesity, two major risk factors for short LTL, did not appear to contribute to our findings, other behavioral factors such as exercise and diet remain plausible as mediators of the relationship between PTSD and childhood trauma and LTL.

A particularly striking finding from our study is that childhood trauma was linearly associated with shorter LTL across the full sample and in the subsample with PTSD, indicating an additive effect of childhood trauma on LTL. Previous research has shown that cumulative childhood trauma is associated with increased risk for PTSD and other adverse outcomes (26,27,41). In our sample, groups with and without cumulative childhood trauma were not significantly different on severity of overall or domain-specific symptoms of PTSD. However, exposure to multiple traumatic events in childhood has been associated with greater complexity of trauma-related symptoms in adulthood (53,54). Thus, participants in our study with more categories of childhood trauma may have greater complexity of trauma-related symptoms, which could extend to greater physiological dysregulation and more accelerated telomere shortening. Further research will be necessary to test this hypothesis.

Our finding of short LTL in participants with PTSD and multiple categories of childhood trauma contributes to a recent debate concerning observed associations between childhood trauma and short LTL. In particular, one published study indicated that self-reported childhood maltreatment, including neglect, was associated with short LTL in a sample of 31 women and men without current Axis I disorders (29). In a subsequent study, 20 participants who reported experiences of physical abuse in childhood did not have significantly different LTL than 520 controls, and 34 participants who reported experiences of sexual abuse in childhood did not have significantly different LTL than 516 controls (28). The authors of the

first paper argue that difficulties with accurate measurement of childhood trauma with only 2 questionnaire items in the latter study, as well as disparate controls for concomitant psychiatric and medical illnesses and medications may have contributed to the inconsistent findings between the two studies (55). Our study has the potential to contribute to this debate. First, our study was focused on PTSD and trauma exposure and as such, childhood trauma was carefully assessed and quantified by expert clinical interviewers using methods validated by our group in previous research (45,56). Second, we had strict inclusion criteria for both participants with PTSD and controls, selecting participants who were physically healthy and free of potential confounding medications. Finally, we tested for the contribution of age, sex, smoking, BMI and education to our findings. Thus, we believe that our finding reinforces the conclusion that childhood trauma impacts LTL.

Primary limitations of the present study include the cross-sectional design, the relatively small sample size and the absence of a control sample who experienced multiple categories of childhood trauma. Combined, these limitations reduce the extent to which any statements can be made about causality in relationships among PTSD, childhood trauma and short LTL. In particular, it is not clear whether more chronic experiences of PTSD or childhood trauma *per se* contributed to the observed difference in LTL between groups. However, given that cumulative childhood trauma is such a strong risk factor for the development of later PTSD, individuals with PTSD and childhood trauma form a large proportion of the PTSD population (27). Thus, the present findings may be applicable to a large number of the approximately 8% of people who experience PTSD in their lifetime (57).

A further limitation is the use of a mixed sample of leukocytes including both granulocytes and agranulocytes in our measurement of telomere length. Future research focused on elucidating the relationship between psychosocial factors and LTL might productively measure telomere length in specific leukocyte subpopulations. A history of serious illness may lead to T-cell clonal expansion and thus contribute to short leukocyte telomere length in later life. We excluded participants with current chronic illness, but did not systematically assess experiences of chronic illness throughout the life course. We did collect data on lifetime history of hospitalization and found that participants who had experienced either childhood or lifetime hospitalization for illness ($n = 10$ and $n = 20$ respectively) or any cause ($n = 12$ and $n = 33$ respectively) were not significantly different from other participants in leukocyte telomere length (all p 's $> .44$). Our data indicates that the relationship of PTSD and childhood trauma with short LTL is independent of several major potential confounds and mediators including age, BMI, gender and years of education. However, behavioral factors including supplement use and physical activity and indicators of socioeconomic status beyond years of education were not assessed in our study and cannot be ruled out as potential confounds or mediators of the observed relationships.

Conclusions

This study represents the first demonstration of short LTL in PTSD, and additionally indicates that only patients with PTSD and a substantial history of childhood trauma have short LTL. Our findings that even physically healthy young to middle-aged adults with PTSD and childhood trauma bear markers of cellular aging suggest the need for further research to understand the biologic affects of trauma and to prevent future adverse health outcomes in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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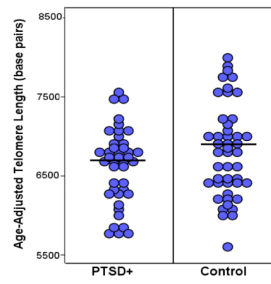


Figure 1.

Dot plot illustrating age-adjusted LTL in participants with PTSD and controls. Participants with PTSD had significantly shorter age-adjusted LTL than control participants, $F(1,85) = 3.29$, $\eta^2 = .04$, $p = .03$.

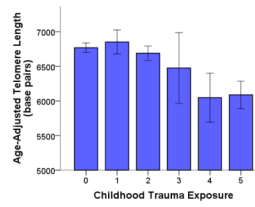


Figure 2.

Cumulative exposure to traumatic events in childhood is associated with short leukocyte telomere length (LTL). Age-adjusted LTL tended to decrease across participants exposed to more categories of childhood trauma, controlling for gender ($r_{\text{partial}} = -.27, p = .005$). Notably, however, all of the participants exposed to two or more categories of childhood trauma had a diagnosis of PTSD.

Table 1

Characteristics of the sample

	Female		Male		Group	Gender
	PTSD+ (n=20)	Control (n=25)	PTSD+ (n=22)	Control (n=21)		
Age	29.4 (6.1)	30.6 (8.1)	30.9 (6.4)	30.7 (8.7)	.75	.61
Education	15.2 (2.1)	15.4 (2.0)	14.4 (2.3)	15.5 (2.1)	.16	.45
Body mass index	23.9 (4.3)	25.2 (4.2)	29.5 (4.3)	23.6 (3.1)	.005*	.01*
Current Smoker n (%)	6 (30)	5 (20)	4 (18)	3 (14)	.46	.34
Marital Status n (%)						
Single	16 (80)	20 (80)	16 (73)	19 (90)		
Married	1 (5)	4 (16)	1 (4)	2 (10)		
Divorced/Separated	3 (15)	1 (4)	5 (23)	0 (0)	.04*	.85
Ethnicity n (%)						
African American	2 (10)	0 (0)	3 (14)	1 (5)		
Asian American	2 (10)	3 (12)	1 (4)	3 (14)		
White	12 (60)	18 (72)	10 (45)	17 (81)		
Hispanic	0 (0)	1 (4)	0 (0)	0 (0)		
Hawaiian	0 (0)	0 (0)	2 (9)	0 (0)		
Pacific Islander	1 (5)	0 (0)	3 (14)	0 (0)		
Multi-ethnic	3 (15)	3 (12)	3 (14)	0 (0)	.07	.40
Alcohol Use n (%)						
Past Abuse	4 (20)	0 (0)	4 (18)	1 (5)		
Past Dependence	4 (20)	0 (0)	3 (14)	0 (0)	.002*	.85
Substance Use n (%)						
Past Abuse	1 (5)	1 (4)	0 (0)	0 (0)		
Past Dependence	2 (10)	0 (0)	4 (18)	0 (0)	.03*	.26

	Female		Male		Group	Gender
	PTSD+ (n=20)	Control (n=25)	PTSD+ (n=22)	Control (n=21)		
MDD History n (%)						
Current	3 (15)	0 (0)	5 (23)	0 (0)	.002*	.42
Past	14 (70)	0 (0)	9 (41)	0 (0)	<.001*	.61
Lifetime						
Childhood Trauma n (%)						
Neglect	11 (55)	2 (8)	9 (43)	2 (10)		
Family Violence	3 (15)	0 (0)	3 (14)	0 (0)		
Physical Abuse	9 (45)	2 (8)	7 (33)	1 (5)		
Forced Touch	2 (10)	0 (0)	7 (33)	0 (0)		
Forced Sex	4 (20)	0 (0)	6 (28)	2 (10)		
	5 (25)	0 (0)	4 (19)	1 (5)	<.001*	.53

Notes. Numbers refer to mean and standard deviation for age, education and body mass index, and to number of participants and percentage of cell for all other variables. Childhood trauma information was missing for one male participant with PTSD; thus, percentages are based on n = 21 for that cell. Some participants experienced multiple categories of childhood trauma. P values are based on Student's t-tests for continuous data and on Mann Whitney U tests for categorical data.

* denotes statistical significance at $p < .05$.