Review

Telomere Length and Telomerase in Post-Traumatic Stress Disorder: An Update and a Reappraisal of the Evidence

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Telomere Length and Telomerase in Post-Traumatic Stress Disorder: An Update and a Reappraisal of the Evidence

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Abstract: Post-traumatic stress disorder (PTSD), a mental disorder caused by exposure to traumatic stress, affects 5-10% of the world's population. PTSD is associated with several medical and neurological comorbidities. It has been suggested that these are due to accelerated aging, and that changes in telomere length (TL) and telomerase enzyme activity may serve as biomarkers of this process. Early research in this field suggested that TL was significantly reduced in PTSD. The current review was conducted to provide a critical analysis of recent clinical and translational research on telomere length and telomerase in PTSD. The results of 26 clinical studies suggest that TL in PTSD is highly variable, and may be influenced by methodological, demographic, trauma-related and psychosocial factors. There is no evidence for altered telomerase activity in PTSD, though this was hypothesized by earlier workers in the field. Translational research suggests that exposure to traumatic stress does lead to TL shortening. Overall, it is likely that TL in PTSD depends on several variables that are specific to individuals and groups. Other markers of cellular aging, such as epigenetic changes, may be more specific indices of accelerated aging in patients with PTSD.

Keywords: post-traumatic stress disorder; trauma; stress; telomere length; telomerase; aging

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental disorder affecting approximately 5-10% of the world's population. PTSD develops following exposure to severe or life-threatening traumatic events, such as physical or sexual assault, combat experiences, accidents, or disasters. The symptoms of PTSD include repeated and intrusive recollections of the traumatic incident, increased vigilance and arousal, emotional "numbing" or withdrawal, and avoidance of situations that could trigger memories of the incident [1]. Historically, PTSD was understood as a psychological response to severe trauma, particularly in the context of armed combat. For this reason, it was formerly known as "shell-shock", "combat fatigue" or "war neurosis" [2]. The contemporary understanding of PTSD is that it is a psychophysiological disorder which can affect both military personnel and civilians. PTSD does not inevitably follow any exposure to trauma. The likelihood of developing this disorder is influenced by three sets of factors: (a) innate vulnerabilities, which may be either genetic or related to early life adversity, (b) the duration and severity of trauma exposure, and (c) factors associated with or following the trauma, such as physical injury, poor social support, stigmatization, or a lack of access to mental health care [3].

To date, 95 genetic variants that confer vulnerability to PTSD have been identified [4], and persons with symptoms of PTSD show altered patterns of expression of these genes that reflect stress-induced epigenetic changes [5]. The genes implicated in the development of PTSD are not confined to those affecting neurotransmitters, neuronal ion channels or synaptic plasticity, but also include components of neuroendocrine and immune signaling mechanisms [4,6]. For this reason, PTSD is not just a "psychological" disorder, but a "systemic" disorder associated with high levels of physical comorbidity. This includes elevated risks of autoimmune, endocrine-metabolic, and cardiovascular

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disorders [7,8]. The pathogenesis of these physical complications in PTSD is complex, and probably involves increased oxidative stress and dysregulation of neuroendocrine and immune-inflammatory pathways [9,10].

2. PTSD, Accelerated Aging, and Neurodegeneration

Over the past two decades, evidence has accumulated that PTSD may be associated with accelerated aging at a cellular level. In 2011, Miller and Sadeh hypothesized that the "re-experiencing" phenomena seen in persons with this disorder, which include nightmares or "flashbacks" of the traumatic incident, lead to recurrent activation of brain circuitry related to fear responses, increased peripheral activity of the sympathetic nervous system, and dysregulation of the hypothalamic-pituitary-adrenal axis. This is hypothesized to lead to increased oxidative stress, which in turn inhibits the activity of the telomerase enzyme, leading to telomere shortening [11].

Telomeres are tandem repeating sequences of DNA, with the nucleotide sequence TTAGGG, that coexist with a protein complex at the ends of chromosomes. Shortened telomere length is a reliable marker of cellular aging and senescence. Telomerase is a ribonucleoprotein complex composed of the telomerase reverse transcriptase (TERT) protein, a telomerase RNA component (TERC), and a number of associated proteins. The function of telomerase is to catalyze telomere synthesis and lengthening, leading to increased cellular longevity and protection from aging and apoptosis [12–14]. Inhibition of telomerase, and accelerated telomere shortening, may occur in PTSD not only because of the primary disease itself, but because of its psychosocial consequences. These include comorbid anxiety and depression, insomnia, substance use as a form of "self-medication", and further stress resulting from disability, unemployment, or disturbed interpersonal relationships – all of which can lead to increased oxidative stress [3,11,15]. The relationship between PTSD and accelerated cellular aging is thought to be associated with premature mortality and with an elevated risk for several age-related medical disorders. These include systemic hypertension, ischemic heart disease, peptic ulcer disease, and type 2 diabetes mellitus [16].

Over the past decade, attention has been drawn to a significant association between PTSD and neurodegenerative disorders, particularly dementia. Patients with PTSD have cognitive impairments across multiple domains, particularly affecting attention and memory. These deficits are associated with alterations in frontal, temporal and parietal cortical volumes, impaired cerebral white matter integrity and functional connectivity, and reduced levels of brain-derived neurotrophic factor (BDNF) [17,18]. In a proportion of cases, it has been observed that these deficits progress to dementia. A recent meta-analysis of the existing literature found that PTSD was associated with a 1.5-1.6-fold increase in the risk of all-cause dementia. This association was almost twice as strong in civilians as in military veterans, suggesting that it was independent of combat-related traumatic brain injuries [19]. A number of cellular mechanisms have been proposed to account for the increased risk of dementia in PTSD, including specific genetic vulnerabilities, neuroinflammation, and oxidative stress. It has been suggested that the final common pathway through which these mechanisms act is accelerated cellular aging [16].

3. Telomerase and Telomere Length in PTSD

The available evidence on telomere length in relation to mental disorders, including PTSD, was evaluated in two earlier meta-analyses. In the first, a significant reduction in leukocyte telomere length (LTL) was observed in a wide range of mental disorders, including mood disorders, schizophrenia, anxiety disorders, and PTSD. The overall magnitude of this effect was moderate (Hedges' g = -0.5). In subgroup analyses, it was found that shortened LTL was more prominent in patients with PTSD (g = -1.3) than in those with other disorders (g = -0.2 to -0.6) [20]. In the second, which considered only patients with a diagnosis of PTSD, five studies involving 3851 subjects were evaluated. It was found that PTSD was associated with a standardized mean decrease of -0.19 in telomere length. There was no significant gender difference in telomere shortening. Among trauma types, sexual assault and childhood abuse were more specifically linked to reduced telomere length. The authors' interpretation of this result was similar to that given by Miller and Sadeh: they

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suggested that oxidative stress, chronic inflammation and medical or psychiatric comorbidities could all contribute to the telomere shortening seen in this disorder [21].

The results of both these meta-analyses support the hypothesis that PTSD is associated with shortened telomere length, but caution is needed in appraising them due to certain methodological concerns common to both analyses. These include a relatively small number of studies focused on PTSD, a high degree of heterogeneity across studies, concerns about the method used to assess telomere length, and the need to adjust for confounding factors in the analyses [12,21]. Likewise, it was not clear from the available literature whether telomere shortening was specifically associated with PTSD, or was linked to stress and / or mental illness in general [20]. Both meta-analyses relied on the same five studies of PTSD. Several relevant studies published in the review period were not included, for reasons that are unclear.

Over the past seven years, several researchers have independently examined the relationship between PTSD and telomere-related markers of cellular aging. The purpose of the current review is to examine this research from a conceptual perspective, with a specific focus on correlates, underlying mechanisms, and possible links to neurodegenerative disorders. As the focus is on these specific themes rather than on the magnitude of any individual effect, a narrative review method was adopted. Standard guidelines for this type of review were followed [22,23]. Relevant literature was retrieved from the PubMed, Scopus and ScienceDirect databases, with the Google Scholar search engine used as a secondary source for possible grey literature. The search terms "post-traumatic stress disorder", "posttraumatic stress disorder" or "PTSD" were used in conjunction with "telomere", "telomeres", "telomere length", "telomerase" or "telomere shortening". Both translational and clinical studies were included.

3.1. Re-Evaluating the Studies Included in the Original Meta-Analyses

Both the earlier meta-analyses included five studies of patients with PTSD, all published in the period 2011-2014 [24–28]. The characteristics of these studies are summarized in Table 1.

Table 1. Studies of telomere shortening in post-traumatic stress disorder included in earlier (2017) systematic reviews.

Study	Sample size and characteristics	Main results	Sub-group and other analyses
Malan et al., 2011 [24]	Women who are rape survivors (n = 64; 31 with MDD, 9 with PTSD). Diagnoses made using DSM-IV criteria.	Marginal association (p = .05) between PTSD and reduced relative LTL, after adjusting for age	No association between relative LTL and MDD or self-reported resilience
O'Donovan et al., 2011 [25]	Adults with PTSD related to childhood trauma (n = 43) and healthy controls (n = 47). Diagnoses made using DSM-IV criteria.	Significantly reduced LTL in PTSD vs. controls after age adjustment (F = 3.29, p = .03); significant negative correlation between childhood trauma and LTL (partial r = -.27, p = .005)	PTSD associated with reduced LTL only in those with multiple types of childhood trauma.
Ladwig et al., 2013 [26]	Adults from the general population (n = 3000; 51 with PTSD, 262 with	Both "partial" and full PTSD associated with reduced TL after	Unadjusted average TL not significantly different across

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	"partial PTSD"). Diagnoses made using PDS and IES.	adjusting for age, sex and BMI, with a small effect size (β = -.05 to -.11, p = .007 to .014)	groups; significant correlation between age and PTSD diagnosis.
Jergovic et al., 2014 [27]	Military veterans with combat-related PTSD (n = 30); age-matched healthy controls (n = 17); elderly volunteers without PTSD (n = 15). Diagnoses made using ICD-10 criteria	Both PTSD and elderly volunteers had shorter average TL than health controls; no difference in telomerase activity between PTSD and healthy controls	Lower telomerase in elderly volunteers than healthy controls.
Zhang et al., 2014 [28]	Military veterans (n = 650; 84 with PTSD). Diagnoses made using DSM-IV criteria and PCL score ≥ 50.	PTSD associated with reduced relative LTL even after adjusting for age (p < .01).	Stressful life events associated with increased LTL in non-PTSD subjects. Age negatively correlated with LTL in non-PTSD but not in PTSD subjects. No association between childhood trauma and LTL.

Abbreviations: BMI, body mass index; DSM, Diagnostic and Statistical Manual for Mental Disorders; IES, Impact of Event Scale; LTL, leukocyte telomere length; MDD, major depressive disorder; PCL, Posttraumatic Stress Disorder Checklist; PDS, Posttraumatic Diagnostic Scale; PTSD, post-traumatic stress disorder; TL, telomere length.

Three of these studies were conducted in civilians, and two in military veterans with combat-related PTSD. In three studies, comparisons were made with apparently healthy controls without PTSD, while in the others, the comparator group had also undergone trauma but did not qualify for a diagnosis of PTSD. As the average telomere length declines naturally with age, all these studies adjusted or controlled for age in their analyses.

In four of the studies, PTSD was associated with a significant reduction in telomere length (TL) when compared with the control group. In the fifth, this association was of marginal significance, but this may reflect the fact that the "controls" were women with a history of sexual assault who did not fulfill the criteria for PTSD [24]. Interestingly, in one study, TL was comparable in veterans with PTSD and in healthy elderly volunteers.

Only one of these studies examined telomerase in patients with PTSD. In this study, there was no difference in telomerase activity between the PTSD and the age-matched control groups. The third group in this study, consisting of elderly volunteers, had significantly lower telomerase activity than both the PTSD and control groups [27]. Though this result suggests that telomere shortening in PTSD is not directly related to altered telomerase activity, such a conclusion cannot be sustained on the basis of a single study.

Taken together, these findings provide some support for "accelerated aging" in PTSD, characterized by reduced TL which is comparable to that seen in the elderly. However, the overall magnitude of the difference in TL was modest [26]. In one the studies involving civilians, a subgroup analysis revealed that only those PTSD patients with a history of multiple types of childhood trauma

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had a significant reduction in TL [25]. TL differed only marginally between rape victims with or without PTSD [24]. Therefore, an alternative interpretation of these results is that exposure to trauma, rather than PTSD, may result in TL, particularly in civilian samples.

3.2. Recent Research on TL and Telomerase in PTSD

Since the publication of Li et al.'s meta-analysis, several independent researchers have investigated the links between PTSD and TL, telomerase activity, or both [29–49]. A summary of this research is presented in Table 2.

Table 2. Recent studies of telomere length and telomerase in post-traumatic stress disorder.

Study	Sample size and characteristics	Main results	Sub-group and other analyses
Shalev et al., 2014 [29]	Adults from the general population (n = 758, 113 with MDD, 51 with GAD, 32 with PTSD). Diagnoses made using DSM-III-R or DSM-IV criteria	Non-significant association between PTSD in men at age 26-38 and LTL erosion at age 38 (β = -.07, p = .12)	Significant LTL erosion in men, but not women, with MDD or GAD.
Boks et al., 2015 [30]	Soldiers exposed to combat trauma (n = 96; 32 with significant PTSD symptoms). PTSD symptoms measured using SRIP.	PTSD associated with increased TL compared to pre-deployment value (p = .018) even after adjustment for possible confounders.	Severity of trauma exposure associated with reduced TL compared to pre-deployment value.
Bersani et al., 2016 [31]	Military veterans exposed to combat (n = 76; 18 with PTSD, 17 with both PTSD and MDD). Diagnoses made using DSM-IV criteria. PTSD symptoms measured using CAPS.	No significant association between either PTSD diagnosis or PTSD symptom severity and TL.	TL significantly and negatively associated with childhood trauma, general psychological symptoms, and perceived stress. No association between MDD and TL.
Kuffer et al., 2016 [32]	Elderly former indentured laborers (n = 62, 21 with "partial or full" PTSD) and elderly healthy controls (n = 58). PTSD symptoms measured using SSS.	Significantly longer buccal TL in persons with PTSD than in controls (p = .04). No difference in buccal TL between laborers with and without PTSD.	Childhood trauma marginally associated with longer buccal TL (p = .05)
Watkins et al., 2016 [33]	Military veterans (n = 468; 83 with lifetime	No association between PTSD and shortened TL	TL shortening significantly

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	PTSD or MDD). Diagnoses made using DSM-IV criteria. PTSD symptoms measured using PCL.	in univariate or multivariate analyses.	associated with nicotine dependence and self-reported hostility and anger. No association between MDD and TL.
Kim et al., 2017 [34]	Military veterans with (*n* = 122) and without (*n* = 120) PTSD. Diagnoses made using DSM-IV-TR criteria. PTSD symptoms measured using CAPS.	No difference in TL between PTSD and non-PTSD groups.	In a sub-group of 45 veterans exposed to "severe combat", PTSD modestly associated with reduced TL (p = .029). Age negatively correlated, and education and antidepressant use positively correlated with TL in this group.
Roberts et al., 2017 [35]	Civilian nurses (*n* = 116; 25 with PTSD, 66 with "subclinical" PTSD). Diagnoses made using DSM-IV criteria.	Significant but modest association between PTSD and shortened TL (β = -.11, p < .05) even after adjusting for confounders. Non-significant association between subclinical PTSD and shortened TL.	Type of trauma not associated with TL, and did not mediate the association between PTSD and TL.
Solomon et al., 2017 [36]	Former prisoners of war (*n* = 90) evaluated up to 42 years after repatriation and healthy controls (*n* = 79). Diagnoses made using DSM-IV-TR criteria.	No significant effect of PTSD on TL	Shorter TL in prisoners compared to controls. Chronic depression associated with reduced TL in prisoner group.
Connolly et al., 2018 [37]	Trauma-exposed adults (*n* = 453; 314 veterans, 139 civilians; 177 with PTSD). Diagnoses made using DSM-IV criteria. PTSD symptoms measured using CAPS.	No significant association between PTSD and TL when controlling for age.	PTSD negatively associated with TL in subjects older than 55. Temperamental traits of positive emotionality and drive to achieve

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			positively associated with TL.
Stein et al., 2018 [38]	Former prisoners of war (*n* = 99) evaluated 42 years after repatriation. Diagnoses made using DSM-IV criteria. PTSD symptoms measured using PTSD-I.	No significant association between either PTSD diagnosis or PTSD symptom score and TL.	TL significantly and negatively associated with aspects of captivity (solitary confinement) and post-captivity life (loss of family after release, being accused after repatriation, loneliness)
Tsur et al., 2018 [39]	Former prisoners of war (*n* = 88) evaluated up to 42 years after repatriation. Diagnoses made using DSM-5 criteria. PTSD symptoms measured using PTSD-I.	No significant association between PTSD and TL in univariate or multivariate analyses.	Self-rated health positively correlated with TL. PTSD negatively associated with self-rated health.
Verhoeven et al., 2018 [40]	Military veterans with combat exposure (*n* = 160; 79 with PTSD). Diagnoses made using DSM-IV criteria. PTSD symptoms measured using CAPS.	No significant association between PTSD and TL or telomerase activity after adjusting for age.	Telomerase activity negatively associated with epigenetic age in PTSD group only.
Avetyan et al., 2019 [41]	Military veterans with PTSD (*n* = 41) and matched healthy controls (*n* = 49). Diagnoses made using DSM-IV-TR criteria. PTSD symptoms measured using CAPS.	Average LTL reduced approximately 1.5-fold in PTSD patients compared with controls (p = .03). No correlation between CAPS score and LTL.	*TERT* rs2736100 T allele 1.6 times more common in PTSD than in control group. No association between *TERT* genotype and CAPS score or LTL. No association between *TERC* genotype and PTSD.
Zhang et al., 2019 [42]	Military veterans with combat exposure (*n* = 474). PTSD symptoms measured using PCL.	PTSD not significantly correlated with LTL overall.	PTSD associated with higher hostility scores. Hostility associated with shorter LTL in veterans with PTSD.

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			Hostility, especially hostile impulses, negatively associated with LTL.
Wolf et al., 2019 [43]	Military veterans with combat exposure (*n* = 309; 198 with PTSD). Diagnoses made using DSM-IV criteria. PTSD symptoms measured using CAPS.	No significant association between PTSD symptom severity and TL.	Age significantly associated with reduced TL. No associations between functional polymorphisms of *KL* gene and TL.
Ein-Dor et al., 2020 [44]	Former prisoners of war (*n* = 88) assessed up to 42 years after repatriation. PTSD symptoms measured using PTSD-I.	No significant association between PTSD and TL.	TL negatively associated with subjects' attachment avoidance and their spouses' attachment anxiety. Spousal attachment avoidance associated with longer TL.
Kang et al., 2020 [45]	Male military veterans with (*n* = 102) or without (*n* = 111) PTSD. Diagnoses made using DSM-IV criteria. PTSD symptoms measured using CAPS.	No significant association between PTSD and TL.	PTSD associated with shorter TL in veterans with high, but not low trauma exposure. Urinary norepinephrine negatively correlated with TL.
Burgin et al., 2022 [46]	Young adults leaving residential care (*n* = 130; 29 with lifetime PTSD).	Lifetime PTSD associated with longer TL ($p < .001$).	Exposure to traumatic stress associated with longer TL.
Carvalho et al., 2022 [47]	Women with PTSD following sexual assault followed up for 1 year (*n* = 64); healthy controls (*n* = 60). Diagnoses made using DSM-III / DSM-IV criteria. PTSD symptoms measured using CAPS.	Baseline PTSD re-experiencing symptoms associated with reduced relative LTL ($\beta = -.02$, $p = .02$). No association between other PTSD symptom dimensions and LTL	No longitudinal association between PTSD and relative LTL. Trend towards shorter LTL in those whose PTSD had remitted at follow-up.
Womersley et al., 2022 [48]	Men residing in areas with high rates of	PTSD symptom severity positively correlated	Among PTSD symptoms, flashbacks

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	community violence (n = 290; 138 with high PTSD symptoms). PTSD symptoms measured using PSS-I.	with relative TL (p = .016).	and emotional numbing positively associated with relative TL. Measures of aggression and of exposure to community violence positively correlated with relative TL.
Ratanatharathorn et al., 2023 [49]	Nurses (n = 1868; 834 with lifetime trauma but no diagnosis; 238 with PTSD alone; 327 with MDD; 175 with both PTSD and MDD). Diagnoses made using DSM-5 criteria. PTSD symptoms measured using SSS.	No significant association between PTSD and LTL.	Neither trauma nor MDD associated with LTL. Comorbid PTSD and MDD associated with significantly shorter LTL, particularly in those with higher PTSD symptom scores.

Abbreviations: CAPS, Clinician-Administered PTSD Scale; DSM, Diagnostic and Statistical Manual for Mental Disorders; GAD, generalized anxiety disorder; *KL,* Klotho gene; LTL, leukocyte telomere length; MDD, major depressive disorder; PCL, PTSD Checklist; PSS-I, PTSD Symptom Scale – Interview; PTSD, post-traumatic stress disorder; PTSD-I, PTSD Inventory; SRIP, Self-Rating Inventory for PTSD; SSS, Short Screening Scale for PTSD; *TERT*, telomerase reverse transcriptase gene; *TERC,* telomerase RNA component gene; TL, telomere length.

A total of twenty published reports, not included in the earlier meta-analyses, have examined the relationship between PTSD and these measures of cellular aging. Four of the reports [36,38,39,44] were analyses of data from a single cohort, with PTSD as the primary exposure of interest in only one of them. Results related to PTSD across these four papers were identical and can be combined for the purpose of discussion. Therefore, strictly speaking, there were seventeen publications of relevance to this review.

3.2.1. Telomere Length

a. Telomere shortening. Of the seventeen reports, only two found an unequivocal association between a diagnosis of PTSD and telomere shortening. In the first, clinical – but not subclinical – PTSD was associated with a modest reduction in TL in a sample of 116 nurses [35]. In the second, there was a 1.5-fold reduction in leukocyte TL (LTL) in military veterans with PTSD when compared with matched healthy controls, but there was no direct correlation between PTSD symptom severity and LTL [41]. A third study found a trend-level association (p = .12) between PTSD and reduced TL in men, but not in women: this result may have been due to a small sample size, as only 32 of this study's 758 participants had PTSD [29].

Five studies found an association between PTSD and telomere shortening only in relation to specific subgroups. Two independent studies of military veterans both found a link between PTSD and shorter TL only in those with a history of more severe combat-related trauma exposure [34,45]. A study involving a mixed sample of civilians and veterans found that PTSD was linked with telomere shortening only in older adults (age ≥ 55 years) [37]. In a study that examined different

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dimensions of PTSD in relation to TL, only the re-experiencing dimension (i.e., flashbacks and other intrusive recollections of the traumatic event) was correlated with reduced TL [47]. A large study of nurses found that LTL was reduced only in those with comorbid PTSD and major depression (MDD) following trauma; on a closer analysis of data, it was found that only those with higher PTSD symptom scores and MDD had significant telomere shortening [49].

b. Telomere lengthening. In four studies, PTSD was associated with an apparently paradoxical increase in TL, contrary to the Miller-Sadeh hypothesis discussed in Section 2. Three of these studies involved civilians exposed to particularly prolonged stress and trauma – indentured laborers [32], adults in residential or juvenile justice homes with high rates of childhood abuse [46], and Black South African young men living in communities with high levels of crime and violence [48]. The fourth involved military veterans with a history of combat trauma [30]. In all these studies, PTSD was associated with a significant increase in TL, even after adjustment for potential confounders. In the three civilian studies, a history of exposure to trauma was also independently associated with telomere lengthening, regardless of the presence of PTSD [32,46,48].

c. Null results. Analyses in six independent samples found no evidence of an association between PTSD and TL in either direction. Five of these samples involved military veterans with combat exposure [31,33,40,42,43]. In three of these studies, other factors – but not PTSD – were significantly linked to telomere shortening. These included childhood trauma [31], general psychological symptoms not qualifying for a diagnosis of PTSD or MDD [31], perceived stress [31], nicotine dependence [33], and hostility [33,42]. Depression was not specifically associated with TL in any of these samples. The fifth sample involved prisoners of war captured during the 1973 Yom Kippur War, who were followed up until 42 years after release and repatriation. These individuals had significant TL shortening when compared with healthy controls, but this was not associated with PTSD [36]. Other variables, such as solitary confinement [38], experiences of rejection or isolation after repatriation [38], self-rated health [39], attachment insecurity in participants or their spouses [44] and chronic depression [36] were associated with reduced TL in this sample.

d. Differences between military and civilian samples. Among the studies included in this review, there were twelve datasets involving military personnel and twelve involving civilians. Among the military studies, eight obtained a null result, three found evidence of TL shortening, and one found evidence of increased TL. Among the civilian studies, five obtained a null result, four found evidence of telomere shortening, and three found an increase in TL. This difference was not statistically significant ($p = .56$, Fisher's exact test). Thus, the military or civilian status of a PTSD study population did not appear to affect the likelihood of a specific finding related to TL.

3.2.2. Telomerase

In contrast with the numerous studies examining TL in patients with PTSD, only one study examined the potential association between PTSD and telomerase activity. In a sample of 160 military veterans, 79 of whom had PTSD, there was no association between PTSD and measured telomerase activity, even after adjusting for age [40]. This result is similar to that seen in an earlier study of veterans [27].

A second study examined genetic variants in the telomerase reverse transcriptase (*TERT*) and telomerase RNA component (*TERC*) genes, which encode the major components of the telomerase enzyme complex. In this study, which compared veterans with PTSD and controls, the minor (T) allele of a single nucleotide polymorphism (*rs2736100*) of *TERT*, which encodes the active component of telomerase, was positively associated with a diagnosis of PTSD. No association was found a functional polymorphism of *TERC* and PTSD.

3.2.3. Relationship between Medical Comorbidities and TL in Patients with PTSD

A limited number of the included studies examined the relationship between TL and medical comorbidities in patients with PTSD. These results are summarized in Table 3. The presence of medical comorbidities was not independently associated with TL in any of these reports. When controlling for the effects of medical comorbidities, three of four reports found that PTSD was still

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significantly associated with TL shortening [26,35,49]. It should also be noted that there was marked heterogeneity in the assessment of chronic medical conditions: some researchers screened for these conditions using a single general question [46], while others focused on a limited number of specific conditions [35,49].

Table 3. Associations between medical comorbidities and telomere length in post-traumatic stress disorder.

Study	Significant result(s)
Ladwig et al., 2013 [26]	Chronic medical illnesses present in 20-23% of those with PTSD. Association between PTSD and TL shortening significant even after adjusting for medical comorbidities.
Bersani et al., 2015 [31]	Negative correlation between PTSD symptom severity and TL no longer significant after adjusting for medical comorbidity.
Watkins et al., 2016 [33]	Neither number of chronic medical illnesses nor PTSD significantly associated with TL.
Roberts et al., 2017 [35]	Hypercholesterolemia present in 12% and systemic hypertension in 8% of participants with PTSD. Association between PTSD and TL shortening significant even after adjusting for these comorbidities.
Tsur et al., 2018 [39]	No significant correlation between the presence of medical comorbidities (cardiovascular, pulmonary, neurological, renal, or metabolic) and TL.
Burgin et al., 2022 [46]	Presence of "any acute or chronic illness" associated with longer TL in only one of the four multivariate models.
Ratanatharathorn et al., 2022 [49]	Systemic hypertension, type II diabetes mellitus or hypercholesterolemia present in 10-11% of participants with PTSD and 21-27% of participants with comorbid PTSD / MDD. Association between comorbid PTSD / MDD and TL shortening significant even after adjusting for these comorbidities.

Abbreviations: MDD, major depressive disorder; PTSD, post-traumatic stress disorder; TL, telomere length.

3.3. Translational Research

Research in birds and mammals has provided additional insights into the relationship between exposure to stress and telomere length. These studies are summarized in Table 4.

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Table 4. Animal studies of telomere length and telomerase in relation to severe stress.

Study	Species and description	Stress exposure	Results
Dong et al., 2016 [50]	Male Wistar rats	Single Prolonged Stress (SPS) – forced restraint for 2 hours followed by forced swimming for 20 minutes.	SPS associated with accelerated telomere shortening. PTSD-like behaviours due to SPS associated with increased expression of TRF1 and TRF2, which are negative regulators of TL.
Cram et al., 2017 [51]	Wild meerkat pups	Competition from other pups in the group for limited nutritional resources.	High competition for nutrition associated with reduced TL. This effect was reversed when maternal nutrition was improved. Pup TL positively associated with survival to adulthood.
Karkkainen et al., 2019 [52]	Pied flycatchers	Predator threat from pygmy owls.	Shortened TL in parent birds at owl-exposed sites. Increased TL in chicks reared at owl-exposed sites.
Lee et al., 2021 [53]	Male Sprague-Dawley rats	Chronic Variable Stress – physical restraint, cold exposure and cage shaking twice a day at irregular times, along with social crowding, restricted food, wet bedding, and light exposure during the night for 3 weeks	Significant reduction in TL in lymphocytes and hippocampal neurons of stressed rats.
Marasco et al., 2021 [54]	Female zebra finches	Exposure to "challenging" environment – unavailability of food	Stress-exposed birds had reduced telomere loss in middle adulthood. Reduced

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	for one-third of the day – at random for four days a week, starting from the age of 5 months.	mortality in middle age, but not old age, in stress-exposed birds.

Abbreviations: TL, telomere length; TRF, telomeric repeat binding factor.

In four of these five studies, exposure to either a single stressor of high intensity, or to chronic stress over several weeks or months, was associated with reduced TL in mammals [50,51,53] and birds [52]. In two of the mammalian studies, the stressor was of a clearly traumatic nature, involving physical restraint and threats to the animal's safety, though only one study explicitly examined PTSD-like behaviors in the stress-exposed group. In this study, exposure to trauma was associated not only with telomere shortening, but with increased expression of the telomeric repeat binding factor proteins TRF1 and TRF2, which have a negative regulatory effect on TL [50]. A study of rats exposed to chronic stress found evidence of reduced TL not only in leukocytes, but in neurons of the dentate gyrus of the hippocampus [53]. In meerkat pups exposed to competition for limited food, reduced TL was associated with reduced survival to adulthood [51].

Certain results in the opposite direction were also observed in avian studies. In pied flycatchers exposed to predator threat, adult birds exhibited TL shortening, but nestlings reared at these sites had longer TL [52]. In zebra finches exposed to chronic stress over several months and years, characterized by periods where food was unavailable, there was an increase in TL in middle adulthood, but not in old age. This was associated with reduced mortality at this stage of the life cycle [54].

A further study of interest in this context, though not involving exposure to stress or trauma, was conducted in mice in which the telomerase gene was knocked out. In old age, these mice showed evidence of reduced TL, reduced hippocampal neurogenesis, neuroinflammation, and impaired memory. However, when these were mated with a mouse strain vulnerable to amyloid plaque accumulation, shortened TL was paradoxically associated with preserved neurogenesis, reduced plaque formation, reduced inflammation, and better learning on experimental tasks [55].

4. Synthesis

4.1. Telomere Length

Recent research suggests that the relationship between PTSD and telomere length is not linear. Though initial meta-analyses suggested that PTSD was significantly associated with telomere shortening or erosion, results from the past decade have yielded more mixed results that do not lend themselves to simple explanations. These results can be summarized as follows:

- Depending on the population studied and the methods used, PTSD may be associated with either an increase, a decrease, or no significant change in TL.
- There does not appear to be any significant correlation between PTSD symptom severity, as measured using standardized instruments, and TL.
- Other psychological variables may have a significant effect on TL in persons with PTSD.
- There is no clear evidence that TL in PTSD predicts physical health outcomes, such as chronic medical illnesses or neurodegenerative disorders.

Several factors may account for this marked variability in results across studies.

4.1.1. Methodological Issues

There are various methods of measuring TL, but not all of them correlate well with physiological outcomes. For example, the shortest TL, rather than the average TL, is a reliable biomarker of the onset of cellular aging and cessation of cell division [12,56,57]. Moreover, variations in the cell type used to estimate TL, the equipment used for estimation, or time of sample processing may also lead

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to variations in this parameter. This was illustrated in a study of PTSD in veterans, in which TL varied significantly across the two batches of samples processed [43]. Studies with small sample sizes, with few participants having PTSD, may lack the statistical power to identify meaningful differences in TL between cases and controls. On the other hand, studies that do not control for possible confounders may over-estimate the association between PTSD and changes in TL. Other sources of bias, including a low participation rate, or a lack of precision in defining criteria for cases and controls, are also important in biomarker research in general, and may have affected study outcomes either positively or negatively in some cases [58].

4.1.2. Other Variables Associated with TL in Persons with PTSD

When evaluating the results of the research cited above, it is sometimes assumed that there is – or could be – a specific association between PTSD and TL. As has been noted in the first meta-analysis by Darrow et al., reduced TL has been observed in a number of mental disorders, including anxiety disorders, mood disorders, and schizophrenia. Sub-group analyses revealed a relatively weaker effect for severe mental disorders – schizophrenia and bipolar disorder – and a larger effect for "common" or stress-related disorders such as depression, anxiety disorders and PTSD [20]. Some mental disorders, such as eating disorders, do not seem to be associated with TL shortening [59]. For this reason, some experts have suggested that TL is a common biomarker for both depression and PTSD [60], or for stress in general [61]. The associations between stress or stress-related illnesses and TL are modest in magnitude, and are influenced by specific variables such as gender, socioeconomic status, the severity of the stressor, and its consequences [62,63].

Table 5. Psychological factors associated with telomere length in patients with PTSD.

Variable	Effect on telomere length	References
Demographic		
Gender (male)	↓	[29]
Education	↑	[34]
Stress and trauma-related		
Severity of trauma	↓ (military)	[30,45]
	↑ (civilian)	[46]
Exposure to community violence	↑	[48]
Self-reported stress	⇔	[28,31]
Childhood adversity	↓ (in four of six studies)	[25,28,31,32,64,65]
Mental health-related		
Specific PTSD symptoms of flashbacks and numbing	↑	[48]
Depression	⇔	[36,49]
Nicotine dependence	↓	[33]
General psychological symptoms	↓	[31]
Antidepressant treatment	↑	[34]
Psychological and behavioural		
Resilience	⇔	[24,66]
Hostility	↓↓	[33,42]
Aggression	↑	[48]
Attachment avoidance	↓	[44]

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Positive emotionality	↑	[37]
Drive to achieve	↑	[39]
Others		
Self-rated health	↑	[39]
Spouse's attachment anxiety	↓	[44]
Spouse's attachment avoidance	↑	[44]

Abbreviations: TL, telomere length; ↓, TL reduced in a single study or in most studies; ↓↓, TL consistently reduced across multiple studies; ↑, TL increased in a single study; ⇔, inconclusive or insufficient evidence across studies. See the text for more details.

Psychosocial factors that have been associated with TL in patients with PTSD are summarized in **Table 5** above. The most replicated findings suggest that childhood adversity, trauma severity in soldiers exposed to combat, and hostility are significantly associated with reduced TL.

Childhood adversity was associated with telomere shortening or erosion in four out of six studies; the other two did not find a statistically significant association for this outcome. There also appears to be a "dose-response" relationship for this association: a single type of childhood abuse or neglect was not associated with significant TL shortening, while those with two, three or more such types of adversity showed an ordinal decrease in TL [65]. Similarly, only multiple types of childhood trauma, but not single types, were associated with reduced TL in patients with PTSD [25].

Combat trauma is one of the main causes of PTSD in military personnel, particularly those deployed in zones of armed conflict [67]. Exposure to combat trauma has been found to reduce TL even in a sample where PTSD was linked to longer TL [30], and, like childhood adversity, the severity of combat trauma appears to influence the likelihood of telomere shortening in veterans with combat-related PTSD [45]. Combat trauma is a complex form of traumatic stress that involves actual and threatened physical injury or death, either of oneself or one's comrades, as well as moral injury (e.g., guilt over causing injury or death to opposing combatants) [68,69]. This could explain its observed, specific relationship with telomere shortening.

Hostility can be understood as a "cognitive component of anger", characterized by cynicism and a tendency to interpret others' actions as harmful or hurtful to oneself. This leads to emotions of anger and disgust towards others [70]. Over 30% of those suffering from PTSD, whether civilian, or military, have high levels of hostility. These patients tend to have higher functional impairment, more comorbid depression, poorer social support, and an increased risk of suicidal behavior [70,71]. No studies have evaluated the effect of hostility on TL in persons without PTSD. Therefore, it is not clear if hostility is specifically associated with TL shortening, or if it simply a marker for a more severe form of PTSD with more psychiatric comorbidities and social adversity.

Synergy between these factors in influencing TL is also possible. In a longitudinal study of over 1200 veterans, it was found that childhood adversity influenced the risk of developing PTSD after combat trauma through a hypothesized process of "stress sensitization" [72]. Such a process could lead to exaggerated stress responses that accelerate telomere loss or erosion.

Several other factors have been associated with significant changes in TL in patients with PTSD, but these findings require replication. Their chief significance is that they need to be considered as confounders or interacting variables when analyzing data on PTSD and TL. One finding of interest is that antidepressant treatment may be associated with a preserved or longer TL [34]. This suggests that timely treatment for PTSD, whether pharmacological or psychological, could protect patients from accelerated cellular aging.

4.1.3. Insights from Animal Research

In contrast to the mixed results obtained in human studies, most animal studies examining the effects of chronic stress or trauma have found evidence of telomere shortening. This effect is so marked that telomere attrition has been put forward as a candidate biomarker of animal welfare, especially in the context of husbandry or laboratory research [73]. This consistency may result from

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the greater ease of standardizing exposures and minimizing confounders in the context of a controlled experiment involving animals.

In the one study in which stress was associated with increased rather than decreased TL, the experimental stressor was of a more chronic and naturalistic nature, involving periodic food reduction without a threat to the animal's life or physical safety [54]. Three of the human studies that found evidence of increased TL involved individuals exposed to chronic stress, both traumatic and non-traumatic, over prolonged periods. In these studies, TL was positively correlated with measures of stress exposure. It is possible, as the authors of one of these papers has speculated, that chronic stress may lead to "the induction of protective homoeostatic mechanisms" both in animals and in humans, but that this occurs only under specific circumstances. Such a mechanism of cellular resilience or "antifragility" may protect against age-related diseases and improve survival, as was observed in the animal model, but this possibility is yet to be verified in humans [74].

4.2. Telomerase

There are relatively few findings linking telomerase to PTSD, particularly when compared to the volume of research on TL in PTSD. Two studies, both involving military veterans exposed to combat, found no difference in telomerase activity between patients and controls. There is some evidence linking chronic stress to reduced telomerase activity, but this relationship is complex. For example, emotional abuse in childhood has been associated with an increase in telomerase activity, and similar findings have been observed in patients with depression [75,76]. It has also been observed that the leukocytes of individuals experiencing stress in the absence of social support or other protective factors show a paradoxical combination of short telomeres and increased telomerase activity [77]. This may reflect the involvement of other cellular mechanisms causing telomere shortening even in the presence of normal or increased telomerase activity. For example, in an animal model of PTSD, shortened TL was associated with increased expression of TRF1 and TRF2 [50]. These proteins are components of the six-protein shelterin complex that maintains telomere integrity. Increased expression of TRF1 has been found to reduce telomere length, and it has been suggested that this occurs through binding to the ends of telomeres, preventing the telomerase enzyme complex from accessing them [78].

Though PTSD is associated with an increased risk of subsequent neurodegenerative disorders, it is not clear whether telomerase activity is related to this outcome. Translational research suggests that telomerase enzyme activity has variable effects on the risk of neurodegeneration or dementia. In "normal" mice, reduced telomerase appears to promote neuronal loss and inflammation, but in those with a genetic risk of Alzheimer's disease, reduced telomerase appears to be protective, perhaps by promoting the senescence and death of cells involved in amyloid deposition [55].

From the limited evidence available, it can be tentatively concluded that telomerase activity is not significantly altered in PTSD, and does not appear to link this disorder to subsequent health outcomes.

4.3. Relationship between TL and Health Outcomes in PTSD

There is evidence from clinical research that PTSD is associated with multiple medical conditions related to ageing, as well as with dementia [16,79,80]. In this context, it would be relevant to know whether the occurrence of these disorders in patients with PTSD is associated with telomere erosion or altered telomerase activity. As per the evidence reviewed in Table 3, there does not appear to be a specific association between the presence of any medical illness and TL in these patients. Moreover, the association between PTSD and TL is not consistently influenced by these comorbidities. To date, there is no research in this field examining a specific link between TL and neurodegeneration or cognition in PTSD. On a related note, PTSD does not appear to be associated with a significantly elevated risk of cancers. However, there is evidence of a link between PTSD and ovarian carcinoma, which is characterized by increased rather than decreased telomerase activity [81,82].

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4.4. Clinical and Research Implications

Based on the existing research, it is not possible to arrive at a definitive conclusion on the relationship between PTSD and TL. There is some evidence for telomere shortening or erosion in PTSD, but there is also evidence that in certain specific circumstances, where traumatic stress occurs against a longer background of chronic social stress, there are mechanisms that may lead to the preservation or even the lengthening of telomeres. There is no evidence to support alterations in telomerase activity in PTSD, and if telomere shortening occurs in this disorder, it may result from molecular processes that block the access of telomerase to the ends of chromosomes. In addition, there is no data to suggest that reduced TL is associated with the presence of specific medical or neurological comorbidities in patients with PTSD. Overall, there are no consistent results to suggest that TL is a biomarker of PTSD, or a biomarker of premature aging in PTSD. It is unlikely that pharmacological manipulation of telomerase is a viable therapeutic strategy in this condition or its medical comorbidities, despite its promise as a treatment for aging-related or neurodegenerative diseases in general [83].

On the other hand, the available research highlights the need for more methodologically rigorous research on the biological mechanisms of premature aging and medical morbidity in PTSD. Such research would ideally involve both cross-sectional and longitudinal methods, control for the confounding variables enumerated in Table 5, and use the most accurate methods of TL estimation (for example, the shortest TL rather than the average TL). Telomere research in PTSD also underlines the need for a deeper testing of the accelerated aging hypothesis, through the examination of other markers of cellular aging. While a complete review of these markers is beyond the scope of this review, there is evidence that PTSD may be associated with altered DNA methylation patterns that serve as epigenetic markers of cellular aging [84,85], age-related inflammatory markers such as interleukin-6 [16,86], and accelerated brain aging associated with cognitive decline [86,87]. Measuring these parameters in conjunction with measures of TL and telomerase may provide a more accurate picture of changes in the aging process associated with PTSD, and may elucidate the molecular mechanisms that link traumatic stress, PTSD, and medical or neurological comorbidities.

5. Conclusions

Though initial reports suggested that post-traumatic stress disorder was associated with telomere shortening, a marker of cellular aging, subsequent research has failed to confirm this possibility. Telomere length in PTSD is highly variable and influenced by a number of demographic, trauma-specific and psychological and social variables. Furthermore, is no evidence to support earlier speculations on reduced telomerase activity in PTSD leading to telomere shortening. Some of this variability is also due to methodological factors, and these can be addressed through larger sample sizes and better study designs. It is possible that, in the near future, other markers of cellular aging can be used for more sensitive and specific testing of the "accelerated aging" hypothesis in PTSD.

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