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Review

Association of Telomere Length, a Cellular Aging Marker, with Depression, PTSD and Hostility

Lei Zhang [1,*], Xian-Zhang Hu [1], Xiaoxia Li [1], Jacob Dohl [2], Tianzheng Yu [2], Robert J. Ursano [1]

1. Center for the Study of Traumatic Stress, Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA; E-Mails: lei.zhang@usuhs.edu; xianzhang.hu.ctr@usuhs.edu; xiaoxia.li@usuhs.edu; robert.ursano@usuhs.edu
2. Consortium for Health and Military Performance, Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA; E-Mails: jacob.dohl.ctr@usuhs.edu; tianzheng.yu.ctr@usuhs.edu

* **Correspondence:** Lei Zhang; E-Mail: lei.zhang@usuhs.edu

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Abstract

Depression, PTSD, and hostility are common mental conditions that are associated with aging. A growing body of research has highlighted the possible effects of depression, PTSD, and hostility on aging and telomere length (TL), a cellular aging marker. Individuals who exhibit excessive responses to stressors show notable circulating inflammatory responses with high cortisol reactivity, which increases cell turnover and oxidative stress and may subsequently contribute to shortened TL. This review focuses on the most recent discoveries in the relationship between TL and depression, PTSD and/or hostility, particularly in a unique military population (US active service members during the Afghanistan and Iraq wars). Current findings indicate that there is a solid association between leucocyte TL (LTL) and psychological conditions, such as depression, PTSD, and hostility. Future work should include controlled studies to test these associations.

Keywords
Telomere length; cellular aging marker; depression; PTSD; hostility

1. Introduction

Mental disorders may be associated with aging. Accumulated evidence show that aging is a biological process in which there is a progressive telomere functional decline within the tissue [1, 2]. However, there are limited information available on aging biomarkers in mental disorders. Recently, several studies demonstrate a solid association between telomere length (TL) and mental conditions including depression, post-traumatic stress disorder, and hostility. In human, telomeres are tandem TTAGGG repeats at the ends of chromosomes, which are incompletely replicated during cellular division, eventually resulting in decreased telomere function. The decline in telomere function can result in an inability for cells to sustain replication and division and has consequences for aging [1, 2]. The relationships between TL and senescence have been demonstrated in cultured human cells. Hermann Muller was the first to name the "telomere" in the 1930s, describing it as a region of nonsense nucleotide sequences found at the end of each chromosome [3]. Without these special end structures, chromosomes would fuse and often break upon mitosis, resulting in chromosome instability which is detrimental to cells [3]. Muller and McClintock demonstrated that the basic roles of "telomeres" is providing chromosome stability, and ensuring faithful segregation of genetic material into daughter cells upon cell division [3]. Telomeres protect chromosomes from degradation, fusion, and recombination [4].The average TL is set and maintained in cells of the germline. In somatic cells, TL declines with age, contributing not only to overall cell loss, but incrementally progressive cellular dysfunction. With each cell division, TL declines, which can ultimately impact cell survival unless counteracted or reversed by the telomere-lengthening enzyme, telomerase [4-6]. Telomerase works by combining the function of an active enzyme, telomerase reverse transcriptase (TERT or hTERT in humans), with an essential RNA sequence, telomerase RNA component (hTERC), which provides the template for hTERT to generate additional tandem DNA repeats, in addition to several other stabilization and localization proteins including dyskerin, NHP2, NOP10 and GAR1. While certain cells including germ, stem, and cancer cells, demonstrate telomerase activity through the use of telomere maintenance mechanisms, somatic cells generally show little to no telomerase activity and are thus susceptible to TL shortening. Shortening of TL increases cellular susceptibility to apoptosis and cell death [7]. It is generally accepted that when telomeres are too short, DNA replication machinery cannot copy chromosome ends completely. As telomeres become critically short, both protein turnover and DNA repair proteins also begin to be down-regulated, resulting in an increase in DNA damage and denatured proteins (as well as the secondary results, such as mitochondrial inefficiency, lipid membrane defects, etc.) [8]. Subsequently, an "end replication problem" occurs and further cell division is impaired. Thus, telomeres have been repeatedly shown to determine cell senescence, i.e., the Hayflick limit, as resetting telomere length resets cell senescence [9-15].

TL is not only a robust indicator of human biological age (as distinguished from chronological age), but also a potential marker of disease risk showing in the earliest clinically oriented works [16-20]. TL may represent a cumulative log of factors such as the number of cell divisions and of

exposure to cytotoxic processes such as excessive oxidation and inflammation [21-27]. In brief, the shortening of telomeres is associated with a number of diseases, from atherosclerosis to dementia [16, 17].

Recently, knowledge of the role telomeres play in diseases has advanced. In addition to the role of telomeres in cell fate and aging by adjusting the cellular response to biological stress, telomeres also play a role in response to psychological stress, which has been tested using leukocytes [28, 29]. In fact, TL shows both tissue and cell specificity. For example, shorter telomeres in leukocytes have been linked to psychosocial stress, depression, and PTSD [28]. Leukocytes TL (LTL) is significantly negatively correlated with lifetime depression. Chronically stressed individuals (e.g., maternal caregivers of chronically ill children and family caregivers of demented individuals) showed significantly shorter LTL compared to age matched controls [28, 29]. LTL is negatively correlated with the duration of caregiving. Women with a greater cumulative duration of caregiving stress had shorter telomeres [30]. Accelerated LTL shortening in individuals with Major Depressive Disorder (MDD) and PTSD could help explain the increased of medical morbidity seen in depression [7, 16, 21, 25, 31, 32] and accelerated aging in PTSD [33]. In addition, decreased in LTL is associated with an increase in hostility [1, 2].

The majority of studies on TL in mental disorders including MDD and Alzheimer's disease (AD) are based on leukocyte DNA. Subjects with AD had significantly shortening of LTL [34]. For example, shortened LTL is associated with risks for dementia and mortality [35] [36], and shorter LTL is a risk for earlier onset of dementia in females. Shorter LTL is also causally associated with a higher risk for AD [37]. There is a good correlation between TL in glial cell (particularly microglial cell) and CNS disease, such as AD [38]. There are potential implications of glial cell shortening for other CNS syndromes. Moreover, it is possible TL shortening is related to dementia [39]. Human subjects with high brain amyloid loads show a significantly higher degree of microglial dystrophy than amyloid-free controls [40]. In addition, the expression of serum telomere repeat binding factor 1 (TRF1) is significantly higher in patients with AD than that of the controls [41]. The duration of AD is significantly negatively correlated with telomere length [40].

In a rat model, significant telomere shortening and reduction of telomerase activity are also observed in microglia during normal aging. Telomere shortening correlates with microglial cell senescence. Mood stabilizer lithium effects the maintenance of TL in mouse model. Chronic lithium treatment was associated with longer telomeres in the samples from hippocampus and in the parietal cortex of triple-transgenic mouse model (3xTg-AD) compared to wild type mouse [42]. Here, we focus on the discussion of findings of the relationships between LTL and depression, PTSD, and hostility.

2. Telomeres and Depression

Major Depressive Disorder (MDD) is the most common psychiatric disorder and one of the leading causes of disability around the world. The worldwide number of subjects living with depression is estimated to be 322 million, 4.4% of the world's population [43]. The burden of depression reaches far beyond both mental condition and quality of life, extending to somatic health. It has been noted to not only increase the risk of cardiovascular diseases, stroke, diabetes and obesity morbidity, but also aging-related medical problems [43]. The association of depression and aging may partly be explained by processes of accelerated cellular aging, such as deterioration

of telomere maintenance mechanisms [44]. TL is significantly negatively correlated with the duration of long-term depression and was inversely correlated with both inflammation and oxidative stress in depressed subjects [16, 32]. Average TL in depressed subjects who were above the median for long-term depression was 281 base pairs shorter than that in controls, corresponding to approximately seven years of accelerated cell aging [30]. Compared to healthy controls, subjects suffering from MDD had significantly shortened TL [16]. Shortening TL in MDD represents approximately 6-8 years of ‘‘accelerated aging’’ [45]. In addition, individuals with MDD at baseline have greater LTL shortening over two years than individuals without MDD, even after controlling for differences in age, sex, and body mass index [46]. Those with remitted MDD also had shorter TL than controls [47]. Moreover, MDD is associated with smaller right hippocampal volume. When corrected for age, sex, diagnostic group and total brain volume, TL was no longer associated with left or right hippocampal volume. These data indicate that cellular and neural processes may be mechanistically distinct during adolescence [48]. It is possible that TL shortening and hippocampal volume reduction are already present in early-onset MDD subjects [48]. Another study shows that MDD patients with diabetes who took Actos, an anti-diabetic drug specializing in lowering blood sugar levels, responded better to anti-depressant treatment and has longer telomeres, possibly indicating that lower blood sugar levels can result in less damage to both telomeres and the brain [49]. The shortened TL in depression may relate to the elevation of oxidative stress [50-53] and associates with a pro-inflammatory milieu [54-57], which is observed in PTSD and in preclinical models [55, 58-61]. TL shortening is more likely to result in secondary epigenetic shifts, which can occur in the duration of depression or throughout a subject’s lifetime [30, 62-67].

Those studies demonstrate novel insights into the relationship between depression and LTL. Shortened LTL is related to not only the MDD episode, but also the remitted stage. The mechanism for LTL shortening in MDD may involve the elevation of oxidative stress and pro-inflammatory milieu. In addition, Actos-induced LTL increase provides a possibility to identify drugs, which have new indication for alleviating aging induced LTL shortening. Further study is needed to elucidate whether increased TL shortening is the consequence of TL repair mechanisms failing to recover after a depressive episode, the result of long-term effects on cellular aging, or whether an underlying putative third factor, such as inflammation, altered metabolism, or shared genetic effects, impacts depression vulnerability, and accelerates TL shortening [68].

3. Telomeres and PTSD

TL is also associated with PTSD, which has been linked with biological aging as well [69, 70]. PTSD is an anxiety disorder that develops in individuals after exposure to traumatic stress and commonly accompanies age-related diseases, such as cardiovascular, autoimmune, neurodegenerative diseases, and early mortality [56, 71-74]. Repeated and prolonged stress responses potentially result in an accelerated rate of TL shortening. Higher levels of the stress hormone cortisol and catecholamines are associated with shorter TL [75, 76]. Short LTL is also observed in both PTSD patients and subjects who experienced multiple categories of childhood trauma. A possible mechanism for TL shortening in PTSD is an inflammatory response with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system activation [77-80]. It is possible that inflammation may promote telomere shortening by increasing

cell turnover and promoting the release of reactive oxygen species, which can damage telomeric DNA *via* oxidative stress [69, 81]. The dysfunction of the HPA axis and inflammatory response may increase the risk of PTSD and the susceptibility to accelerated shortening of LTL. It seems early life traumatic experiences shape later life biological stress responses [82, 83]. It has been an accepted recommendation that cellular senescence may play roles in epigenetic and inflammation as well as induction of ROS. For example, the senescence possibly promotes inflammation [84] and increases both ROS and the ROS/ATP ratio as mitochondria lose efficiency due to decreased turnover of required aerobic enzymes and increasingly leaky mitochondrial lipid membranes [85, 86].

A recent study shows that, among the soldiers that served during the Iraq and/or Afghanistan war, participants with PTSD have shorter LTL than non-PTSD controls (Figure 1a) [33]. This data indicates that TL might be a potential blood based biomarker for PTSD. The younger non-PTSD controls who experienced more stressful life events tend to have longer LTL (Figure 1b and c). A negative association between LTL and age is observed in the non-PTSD controls, but not in PTSD subjects (Figure 1d). These data suggest that the mechanism of LTL was not the same in the PTSD and non- PTSD groups. It is possible that the age effects are not detectable in the PTSD group because they already have shorter telomeres, making it difficult to detect an additional age effect. However, LTL's are inherently unreliable as a measure of immune stress unless followed over long time intervals (e.g., months to years). The interpretation of these data should be further explored and/or determined.

There are several possible explanations for the relationships between LTL and PTSD. First, PTSD subjects with shorter LTL may be those with poor resilience for both PTSD and stress-related cellular aging. These data suggest that stress-related changes in telomere integrity may be one possible mechanism linking psychosocial stress and age-related disease [16, 25, 28, 67, 81, 87]. Second, those non-PTSD subjects who experienced more stressful life events and did not have a significant reduction of LTL may be a population resilient against both stress-related cellular aging and PTSD. That there are no significant differences in TL between subjects with and without childhood trauma events suggests that childhood trauma is not uniquely associated with changes in TL in that population. However, these findings contrast with a report [67] that childhood trauma was associated with changes in TL. These contradictory findings may be attributable to sampling differences (soldiers versus civilians), types of trauma exposure, or other factors including measuring current versus lifetime PTSD [67].

Taking all together, although substantial evidence indicates that TL alteration is associated with both traumatic stress and PTSD occurrence, further comprehensive research design is needed to test those contradictory findings.

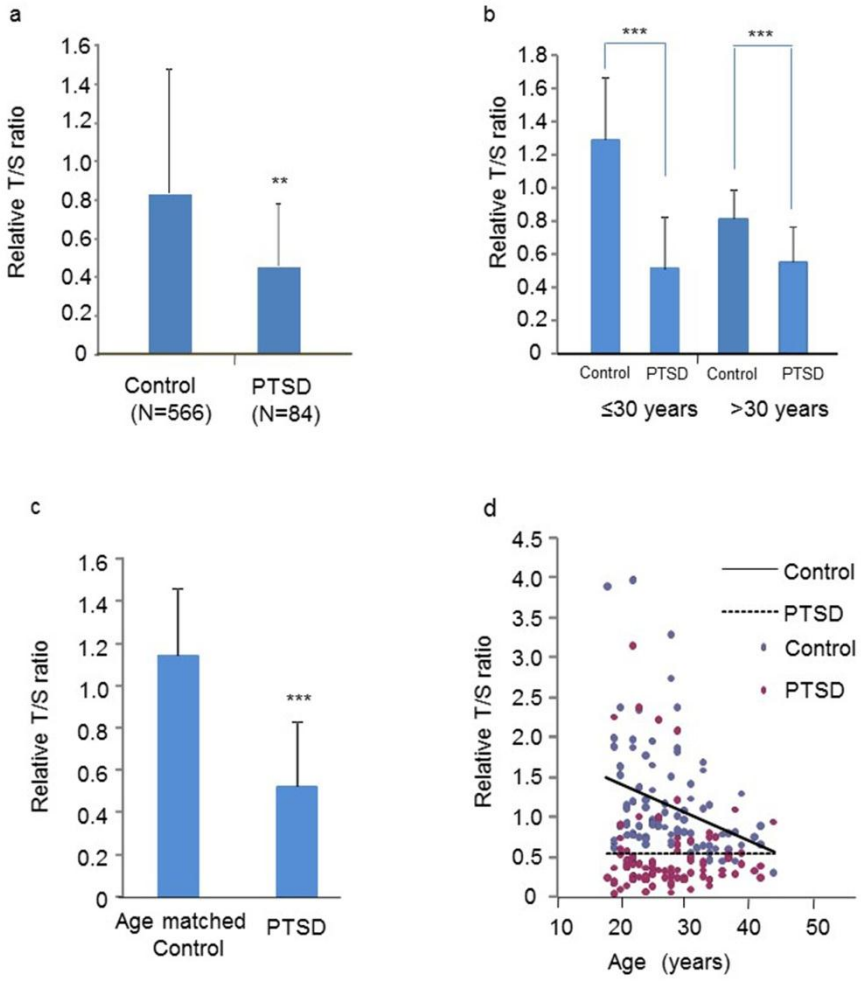

Figure 1 The telomere repeat copy number to single gene copy number (T/S) in subjects with and without PTSD. a. The relative T/S ratio in all subjects with or without PTSD. Subjects with PTSD (n=84) had significantly lower relative T/S ratio than non-PTSD controls (n=566). b. The Relative T/S ratio in the PTSD and non-PTSD control aged ⩽ 30 or >30 years. c. Relative T/S ratio was significantly lower for the PTSD subjects (n=84) compared with age-matched non-PTSD controls (n=84). d. The relationships between age and relative T/S ratio in PTSD subjects and age-matched non-PTSD controls. The association of relative T/S ratio with age was observed in non-PTSD controls (n=84; r=-0.32, $p<0.05$). Such relationship was not obtained in the PTSD subjects (n=84; r=-0.03, $p>0.05$). The curves in different colors represent expected T/S ratio for the proportion of non-PTSD subjects. Relative T/S ratio of subjects with PTSD was presented as open circles. **$p<0.01$; *** $p<0.001$.

4. Telomeres and Hostility

In addition to the association of TL with depression and PTSD, it is known that shortened telomeres are significantly associated with greater levels of hostility. Hostility is an enduring personality trait that reflects a predisposition to exhibit interpersonal animosity and mistrust. Hostility is associated with negative health outcomes, including age-related disorders [88, 89].

Individuals reporting higher-levels of hostility have shorter LTL than those reporting lower levels of hostility [1, 2].

A growing body of research has highlighted the possible effects of hostility and anger on cortisol and inflammatory marker levels [90, 91]. Individuals who exhibit strong psychological reactions, including hostility, to environmental stressors show notable inflammatory responses and high cortisol reactivity, which increases cell turnover and oxidative stress and may subsequently contribute to shortened TL [64, 92-98]. Research further suggests that hostile individuals are more prone to undertake risky health behaviors (e.g., alcohol and tobacco), which also lessen TL [99-102]. There are varying levels of prevalence across sub-populations and demographics, and therefore warrant focused attention. For example, the prevalence rates of negative emotions (i.e., hostility and anger) and mental health outcomes (i.e., PTSD) increase in military populations following an operational deployment [103, 104]. Such outcomes may serve as an underlying factor driving the acceleration of age-related health outcomes amongst military veterans [1, 96].

Recently, we have investigated the relationship between hostility, post-traumatic stress and LTL in a sample of United States Army Special Operations personnel (n= 474) who were deployed to Iraq and/or Afghanistan as part of combat operations. Hostility was measured with five items from the Brief Symptom Inventory (BSI). LTL was assessed using quantitative polymerase chain reaction methods, and linear regression analyses were conducted to determine the association of hostility and telomere length. We found that PTSD subjects reported higher hostility scores compared with those without PTSD. In addition, those reported high hostility score had shorter TL.

Univariate regression showed that the total score of hostility was negatively associated with LTL (95% CI: -0.06 to -0.002, Beta= -0.095, $p < 0.039$) and the presence of a significant correlation between LTL, hostility impulse (95% CI: -0.108 to -0.009, Beta= -0.106, $p < 0.021$), and hostility control (95% CI: -0.071 to -0.002, Beta= -0.095, $p < 0.004$). Multiple linear regression analyses revealed that hostility control does not enter the equation, while hostility impulse was still negatively correlated with the LTL ($p = 0.021$). Our data indicate that LTL is associated with hostility impulse.

In summary, the data particularly from a unique military sample demonstrate that TL shortening is associated with hostility, especially with impulsive hostility. Although the molecular mechanism for the interaction of TL with hostility is still unknown, prevention and treatment efforts designed to reduce hostility may help mitigate risk for LTL shortening, a process of cellular aging, and thus slow accelerated aged-related health outcomes.

5. Conclusions

This review presents direct evidence that short TL is associated with depression, PTSD, and hostility, particularly within PTSD subjects who have a substantial history of childhood trauma. One study demonstrates that even physically healthy young to middle-aged adults with PTSD and childhood trauma bear markers of cellular aging. However, another study within a military population did not find significant differences in TL between subjects with and without childhood trauma events. Those diverse results may be due to several factors, such as different stressors, methods, sample populations (soldiers vs. civilians), and the stages of the disorder in the studies. The intricate involvement of telomeres in both aging and mental disorders, such as depression,

PTSD, and hostility, ensures that pathways involving telomeres and telomerase will remain the subject of intensive studies for many years to come.

Author Contributions

Lei Zhang, Xian-Zhang Hu, Xiaoxia Li, Jacob Dohl, Tianzheng Yu, and Robert J. Ursano wrote the manuscript. Lei Zhang and Xian-Zhang Hu contributed to the figures.

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Competing Interests

The authors have declared that no competing interests exist.

References

1. Watkins LE, Harpaz-Rotem I, Sippel LM, Krystal JH, Southwick SM, Pietrzak RH. Hostility and telomere shortening among u.S. Military veterans: Results from the national health and resilience in veterans study. Psychoneuroendocrinology. 2016; 74: 251-257.
2. Brydon L, Lin J, Butcher L, Hamer M, Erusalimsky JD, Blackburn EH, et al. Hostility and cellular aging in men from the whitehall ii cohort. Biol Psychiat. 2012; 71: 767-773.
3. Aubert G, Lansdorp PM. Telomeres and aging. Physiological reviews. 2008; 88: 557-579.
4. Blackburn EH. Structure and function of telomeres. Nature. 1991; 350: 569-573.
5. Blackburn EH. Telomere states and cell fates. Nature. 2000; 408: 53-56.
6. Beyne-Rauzy O, Prade-Houdellier N, Demur C, Recher C, Ayel J, Laurent G, et al. Tumor necrosis factor-alpha inhibits htert gene expression in human myeloid normal and leukemic cells. Blood. 2005; 106: 3200-3205.
7. Zhang P, Dilley C, Mattson MP. DNA damage responses in neural cells: Focus on the telomere. Neuroscience. 2007; 145: 1439-1448.
8. M. F. Cells, aging, and human disease. New York: Oxford University Press; 2004.
9. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. Nature. 1990; 345: 458-460.
10. Allsopp RC, Chang E, Kashefi-Aazam M, Rogaev EI, Piatyszek MA, Shay JW, et al. Telomere shortening is associated with cell division in vitro and in vivo. Exp Cell Res. 1995; 220: 194-200.
11. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, et al. Telomere length predicts replicative capacity of human fibroblasts. P Natl Acad Sci USA. 1992; 89: 10114-10118.
12. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961; 25: 585-621.
13. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, et al. Extension of life-span by introduction of telomerase into normal human cells. Science. 1998; 279: 349-352.
14. Funk WD, Wang CK, Shelton DN, Harley CB, Pagon GD, Hoeffler WK. Telomerase expression restores dermal integrity to in vitro-aged fibroblasts in a reconstituted skin model. Exp Cell Res. 2000; 258: 270-278.

15. Yang J, Nagavarapu U, Relloma K, Sjaastad MD, Moss WC, Passaniti A, et al. Telomerized human microvasculature is functional in vivo. Nat Biotechnol. 2001; 19: 219-224.
16. Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, et al. Telomere shortening and mood disorders: Preliminary support for a chronic stress model of accelerated aging. Biol Psychiat. 2006; 60: 432-435.
17. Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, et al. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. Am J Epidemiol. 2007; 165: 14-21.
18. Fossel M. Telomerase and the aging cell: Implications for human health. JAMA: J Am Med Assoc. 1998; 279: 1732-1735.
19. Fossel M. Cell senescence in human aging: A review of the theory. In Vivo. 2000; 14: 29-34.
20. Banks DA, Fossel M. Telomeres, cancer, and aging. Altering the human life span. JAMA: J Am Med Assoc. 1997; 278: 1345-1348.
21. Blackburn EH, Greider CW, Szostak JW. Telomeres and telomerase: The path from maize, tetrahymena and yeast to human cancer and aging. Nat Med. 2006; 12: 1133-1138.
22. De Meyer T, Rietzschel ER, De Buyzere ML, Van Criekinge W, Bekaert S. Studying telomeres in a longitudinal population based study. Front Biosci. 2008; 13: 2960-2970.
23. Aviv A. Telomeres and human aging: Facts and fibs. Science of aging knowledge environment: SAGE KE. 2004; 2004: pe43.
24. Hezel AF, Bardeesy N, Maser RS. Telomere induced senescence: End game signaling. Curr Mol Med. 2005; 5: 145-152.
25. Epel ES. Psychological and metabolic stress: A recipe for accelerated cellular aging? Hormones (Athens). 2009; 8: 7-22.
26. Aviv A. Telomeres and human somatic fitness. J Gerontol A-Biol Sci Med Sci. 2006; 61: 871-873.
27. Brouilette S, Singh RK, Thompson JR, Goodall AH, Samani NJ. White cell telomere length and risk of premature myocardial infarction. Arterioscl Throm Vasc Biol. 2003; 23: 842-846.
28. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. P Natl Acad Sci USA. 2004; 101: 17312-17315.
29. Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B, et al. Accelerated telomere erosion is associated with a declining immune function of caregivers of alzheimer's disease patients. J Immunol. 2007; 179: 4249-4254.
30. Wolkowitz OM, Mellon SH, Epel ES, Lin J, Dhabhar FS, Su Y, et al. Leukocyte telomere length in major depression: Correlations with chronicity, inflammation and oxidative stress--preliminary findings. PloS one. 2011; 6: e17837.
31. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, et al. Mood disorders in the medically ill: Scientific review and recommendations. Biol Psychiat. 2005; 58: 175-189.
32. Lung FW, Chen NC, Shu BC. Genetic pathway of major depressive disorder in shortening telomeric length. Psychiat Genet. 2007; 17: 195-199.
33. Zhang L, Hu XZ, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, et al. The interaction between stressful life events and leukocyte telomere length is associated with ptsd. Mol Psychiat. 2014; 19: 856-857.
34. Boccardi V, Arosio B, Cari L, Bastiani P, Scamosci M, Casati M, et al. Beta-carotene, telomerase activity and alzheimer's disease in old age subjects. Eur J Nutr. 2019.

35. Herrmann M, Pusceddu I, Marz W, Herrmann W. Telomere biology and age-related diseases. Clin Chem Lab Med. 2018; 56: 1210-1222.
36. Scarabino D, Broggio E, Gambina G, Corbo RM. Leukocyte telomere length in mild cognitive impairment and alzheimer's disease patients. Exp Gerontol. 2017; 98: 143-147.
37. Zhan Y, Song C, Karlsson R, Tillander A, Reynolds CA, Pedersen NL, et al. Telomere length shortening and alzheimer disease--a mendelian randomization study. JAMA Neurol. 2015; 72: 1202-1203.
38. Flanary BE, Sammons NW, Nguyen C, Walker D, Streit WJ. Evidence that aging and amyloid promote microglial cell senescence. Rejuvenation Res. 2007; 10: 61-74.
39. Zhan Y, Hagg S. Telomere length shortening in alzheimer's disease: Procedures for a causal investigation using single nucleotide polymorphisms in a mendelian randomization study. Meth Mol Biol. 2018; 1750: 293-306.
40. Liu M, Huo YR, Wang J, Wang C, Liu S, Liu S, et al. Telomere shortening in alzheimer's disease patients. Ann Clin Lab Sci. 2016; 46: 260-265.
41. Wu Q, Han D, Zhang J, Li X. Expression of telomere repeat binding factor 1 and trf2 in alzheimer's disease and correlation with clinical parameters. Neurol Res. 2019: 1-6.
42. Cardillo GM, De-Paula VJR, Ikenaga EH, Costa LR, Catanozi S, Schaeffer EL, et al. Chronic lithium treatment increases telomere length in parietal cortex and hippocampus of triple-transgenic alzheimer's disease mice. J Alzheimers Dis. 2018; 63: 93-101.
43. Friedrich MJ. Depression is the leading cause of disability around the world. JAMA: J Am Med Assoc. 2017; 317: 1517.
44. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. BMC Med. 2013; 11: 129.
45. Hartmann N, Boehner M, Groenen F, Kalb R. Telomere length of patients with major depression is shortened but independent from therapy and severity of the disease. Depress Anxiety. 2010; 27: 1111-1116.
46. Vance MC, Bui E, Hoeppner SS, Kovachy B, Prescott J, Mischoulon D, et al. Prospective association between major depressive disorder and leukocyte telomere length over two years. Psychoneuroendocrinology. 2018; 90: 157-164.
47. Verhoeven JE, Revesz D, Epel ES, Lin J, Wolkowitz OM, Penninx BW. Major depressive disorder and accelerated cellular aging: Results from a large psychiatric cohort study. Mol Psychiat. 2014; 19: 895-901.
48. Henje Blom E, Han LK, Connolly CG, Ho TC, Lin J, LeWinn KZ, et al. Peripheral telomere length and hippocampal volume in adolescents with major depressive disorder. Transl Psychiat. 2015; 5: e676.
49. Rasgon N, Lin KW, Lin J, Epel E, Blackburn E. Telomere length as a predictor of response to pioglitazone in patients with unremitted depression: A preliminary study. Transl Psychiat. 2016; 6: e709.
50. Wolkowitz OM, Epel ES, Reus VI, Mellon SH. Depression gets old fast: Do stress and depression accelerate cell aging? Depress Anxiety. 2010; 27: 327-338.
51. Irie M, Miyata M, Kasai H. Depression and possible cancer risk due to oxidative DNA damage. J Psychiat Res. 2005; 39: 553-560.

52. Forlenza MJ, Miller GE. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. Psychosom Med. 2006; 68: 1-7.
53. Tsuboi H, Shimoi K, Kinae N, Oguni I, Hori R, Kobayashi F. Depressive symptoms are independently correlated with lipid peroxidation in a female population: Comparison with vitamins and carotenoids. J Psychosom Res. 2004; 56: 53-58.
54. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain Behav Immun. 2007; 21: 374-383.
55. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27: 24-31.
56. Cohen BE, Marmar CR, Neylan TC, Schiller NB, Ali S, Whooley MA. Posttraumatic stress disorder and health-related quality of life in patients with coronary heart disease: Findings from the heart and soul study. Arch Gen Psychiat. 2009; 66: 1214-1220.
57. Maes M, Yirmyia R, Noraberg J, Brene S, Hibbeln J, Perini G, et al. The inflammatory & neurodegenerative (i&nd) hypothesis of depression: Leads for future research and new drug developments in depression. Metab Brain Dis. 2009; 24: 27-53.
58. Leonard B. Stress, depression and the activation of the immune system. World J Biol Psychiat. 2000; 1: 17-25.
59. Aviv A. Telomeres, sex, reactive oxygen species, and human cardiovascular aging. J Mol Med (Berl). 2002; 80: 689-695.
60. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, et al. Obesity, cigarette smoking, and telomere length in women. Lancet. 2005; 366: 662-664.
61. Ilmonen P, Kotrschal A, Penn DJ. Telomere attrition due to infection. PloS one. 2008; 3: e2143.
62. Prather AA, Puterman E, Lin J, O'Donovan A, Krauss J, Tomiyama AJ, et al. Shorter leukocyte telomere length in midlife women with poor sleep quality. J Aging Res. 2011; 2011: 721390.
63. Aviv A, Hunt SC, Lin J, Cao X, Kimura M, Blackburn E. Impartial comparative analysis of measurement of leukocyte telomere length/DNA content by southern blots and qpcr. Nucleic Acids Res. 2011; 39: e134.
64. O'Donovan A, Pantell MS, Puterman E, Dhabhar FS, Blackburn EH, Yaffe K, et al. Cumulative inflammatory load is associated with short leukocyte telomere length in the health, aging and body composition study. PloS one. 2011; 6: e19687.
65. Hoen PW, de Jonge P, Na BY, Farzaneh-Far R, Epel E, Lin J, et al. Depression and leukocyte telomere length in patients with coronary heart disease: Data from the heart and soul study. Psychosom Med. 2011; 73: 541-547.
66. Steptoe A, Hamer M, Butcher L, Lin J, Brydon L, Kivimaki M, et al. Educational attainment but not measures of current socioeconomic circumstances are associated with leukocyte telomere length in healthy older men and women. Brain Behave Immun. 2011; 25: 1292-1298.
67. O'Donovan A, Epel E, Lin J, Wolkowitz O, Cohen B, Maguen S, et al. Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. Biol Psychiat. 2011; 70: 465-471.
68. Verhoeven JE, Revesz D, Picard M, Epel EE, Wolkowitz OM, Matthews KA, et al. Depression, telomeres and mitochondrial DNA: Between- and within-person associations from a 10-year longitudinal study. Mol Psychiat. 2018; 23: 850-857.

69. O'Donovan A, Hughes BM, Slavich GM, Lynch L, Cronin MT, O'Farrelly C, et al. Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion-biology relationships. Brain Behav Immun. 2010; 24: 1074-1077.
70. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: Insights from hpa axis studies in humans. Psychoneuroendocrinology. 2008; 33: 693-710.
71. Durel LA, Carver CS, Spitzer SB, Llabre MM, Weintraub JK, Saab PG, et al. Associations of blood pressure with self-report measures of anger and hostility among black and white men and women. Health Psychol. 1989; 8: 557-575.
72. Boscarino JA, Forsberg CW, Goldberg J. A twin study of the association between ptsd symptoms and rheumatoid arthritis. Psychosom Med. 2010; 72: 481-486.
73. Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, et al. Posttraumatic stress disorder and risk of dementia among us veterans. Arch Gen Psychiat. 2010; 67: 608-613.
74. Qureshi SU, Pyne JM, Magruder KM, Schulz PE, Kunik ME. The link between post-traumatic stress disorder and physical comorbidities: A systematic review. Psychiat Q. 2009; 80: 87-97.
75. Parks CG, Miller DB, McCanlies EC, Cawthon RM, Andrew ME, DeRoo LA, et al. Telomere length, current perceived stress, and urinary stress hormones in women. Cancer Epidem Biomark Prev. 2009; 18: 551-560.
76. Epel ES, Lin J, Wilhelm FH, Wolkowitz OM, Cawthon R, Adler NE, et al. Cell aging in relation to stress arousal and cardiovascular disease risk factors. Psychoneuroendocrinology. 2006; 31: 277-287.
77. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depress Anxiety. 2009; 26: 447-455.
78. Young EA, Breslau N. Cortisol and catecholamines in posttraumatic stress disorder: An epidemiologic community study. Arch Gen Psychiat. 2004; 61: 394-401.
79. Yehuda R, Golier JA, Yang RK, Tischler L. Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. Biol Psychiat. 2004; 55: 1110-1116.
80. Neylan TC, Brunet A, Pole N, Best SR, Metzler TJ, Yehuda R, et al. Ptsd symptoms predict waking salivary cortisol levels in police officers. Psychoneuroendocrinology. 2005; 30: 373-381.
81. Miller GE, Rohleder N, Stetler C, Kirschbaum C. Clinical depression and regulation of the inflammatory response during acute stress. Psychosom Med. 2005; 67: 679-687.
82. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. JAMA: J Am Med Assoc. 2009; 301: 2252-2259.
83. Hertzman C. The biological embedding of early experience and its effects on health in adulthood. Ann NY Acad Sci. 1999; 896: 85-95.
84. Lasry A, Ben-Neriah Y. Senescence-associated inflammatory responses: Aging and cancer perspectives. Trends Immunol. 2015; 36: 217-228.
85. Abdul-Ghani MA, Jani R, Chavez A, Molina-Carrion M, Tripathy D, DeFronzo RA. Mitochondrial reactive oxygen species generation in obese non-diabetic and type 2 diabetic participants. Diabetologia. 2009; 52: 574-582.

86. Roussel D, Boel M, Mortz M, Romestaing C, Duchamp C, Voituron Y. Threshold effect in the h2o2 production of skeletal muscle mitochondria during fasting and refeeding. J Exp Biol. 2019; 222.
87. Liu Y, Bohr VA, Lansdorp P. Telomere, telomerase and aging. Mech Ageing Dev. 2008; 129: 1-2.
88. Elbogen EB, Wagner HR, Fuller SR, Calhoun PS, Kinneer PM, Mid-Atlantic Mental Illness Research E, et al. Correlates of anger and hostility in iraq and afghanistan war veterans. Am J Psychiat. 2010; 167: 1051-1058.
89. Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallet AJ. A meta-analytic review of research on hostility and physical health. Psychol Bull. 1996; 119: 322-348.
90. Coccaro EF, Lee R, Coussons-Read M. Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans. JAMA Psychiat. 2014; 71: 158-165.
91. Marsland AL, Prather AA, Petersen KL, Cohen S, Manuck SB. Antagonistic characteristics are positively associated with inflammatory markers independently of trait negative emotionality. Brain Behav Immun. 2008; 22: 753-761.
92. Graham JE, Robles TF, Kiecolt-Glaser JK, Malarkey WB, Bissell MG, Glaser R. Hostility and pain are related to inflammation in older adults. Brain Behav Immun. 2006; 20: 389-400.
93. Ranjit N, Diez-Roux AV, Sanchez B, Seeman T, Shea S, Shrager S, et al. Association of salivary cortisol circadian pattern with cynical hostility: Multi-ethnic study of atherosclerosis. Psychosom Med. 2009; 71: 748-755.
94. Smith TW, Glazer K, Ruiz JM, Gallo LC. Hostility, anger, aggressiveness, and coronary heart disease: An interpersonal perspective on personality, emotion, and health. J Personality. 2004; 72: 1217-1270.
95. Smith TW, Ruiz JM, Uchino BN. Mental activation of supportive ties, hostility, and cardiovascular reactivity to laboratory stress in young men and women. Health Psychol. 2004; 23: 476-485.
96. Brydon L, Strike PC, Bhattacharyya MR, Whitehead DL, McEwan J, Zachary I, et al. Hostility and physiological responses to laboratory stress in acute coronary syndrome patients. J Pychosom Res. 2010; 68: 109-116.
97. Chida Y, Hamer M. Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: A quantitative review of 30 years of investigations. Psychol Bull. 2008; 134: 829-885.
98. Suarez EC, Kuhn CM, Schanberg SM, Williams RB, Jr., Zimmermann EA. Neuroendocrine, cardiovascular, and emotional responses of hostile men: The role of interpersonal challenge. Psychosom Med. 1998; 60: 78-88.
99. Suzuki N, Nakanishi K, Yoneda M, Hirofuji T, Hanioka T. Relationship between salivary stress biomarker levels and cigarette smoking in healthy young adults: An exploratory analysis. Tob Induc Dis. 2016; 14: 20.
100. Appleton KM, Woodside JV, Arveiler D, Haas B, Amouyel P, Montaye M, et al. A role for behavior in the relationships between depression and hostility and cardiovascular disease incidence, mortality, and all-cause mortality: The prime study. Ann Behav Med. 2016; 50: 582-591.

101. Kim D, Kubzansky LD, Baccarelli A, Sparrow D, Spiro A, 3rd, Tarantini L, et al. Psychological factors and DNA methylation of genes related to immune/inflammatory system markers: The va normative aging study. BMJ Open. 2016; 6: e009790.
102. Potijk MR, Janszky I, Reijneveld SA, Falkstedt D. Risk of coronary heart disease in men with poor emotional control: A prospective study. Psychosom Med. 2016; 78: 60-67.
103. McHugh T, Forbes D, Bates G, Hopwood M, Creamer M. Anger in ptsd: Is there a need for a concept of ptsd-related posttraumatic anger? Clin Psychol Rev. 2012; 32: 93-104.
104. Heesink L, Rademaker A, Vermetten E, Geuze E, Kleber R. Longitudinal measures of hostility in deployed military personnel. Psychiat Res. 2015; 229: 479-484.