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Telomeres, Early-Life Stress and Mental Illness

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Abstract

Telomeres are structures of tandem TTAGGG repeats at the ends of chromosomes which preserve the encoding DNA by serving as a disposable brake to terminate DNA duplication during chromosome replication. In this process, the telomere itself shortens with each cell division, and can consequently be thought of as a cellular “clock” reflecting the age of a cell and the time until senescence. Telomere shortening, and changes in levels of telomerase, the enzyme that maintains telomeres, occur in the context of certain somatic diseases and in response to selected physical stressors. Emerging evidence indicates that telomeres shorten with exposure to psychosocial stress (including early-life stress [ELS]), and perhaps in association with some psychiatric disorders. These discoveries suggest that telomere shortening might be a useful biomarker for the overall stress response of an organism to various pathogenic conditions. In this regard, telomeres and their response to both somatic and psychiatric illness could serve as a unifying biomarker of stress response that crosses the brain/body distinction often made in medicine. Prospective studies will help to clarify whether this biomarker has broad utility in psychiatry and medicine in the evaluation of responses to psychosocial stressors. The possibility that telomere shortening can be slowed or reversed by psychiatric and psychosocial interventions could represent an opportunity for developing novel preventative and therapeutic approaches.

Introduction

The idea that early life experiences have enduring sequelae has been at the core of psychiatric theory since the early 20th century. Initial formulations of this idea emphasized clinical implications, particularly in classical psychoanalytic theory, and there is now ample empirical evidence that childhood adversity increases risk for major depression (MDD), bipolar disorder, anxiety disorders, substance disorders, schizophrenia, eating disorders, personality disorders, and suicidality [1]. Risk appears to be dose-dependent, and these

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disorders may be more treatment-resistant in individuals with a history of childhood maltreatment [1].

In recent years, an etiological role for early-life stress (ELS) has also been linked to several prevalent somatic conditions, including irritable bowel syndrome [2], fibromyalgia [3], chronic fatigue syndrome [4], obesity [5], migraine [6], and chronic pain [7]. These disorders have in common an unclear, probably multifactorial, etiology and pathophysiology. However, emerging findings suggest that early environmental factors can even impact the risk for conditions generally thought to have a relatively clear pathogenesis, such as cardiovascular disease and type 2 diabetes [8]. Consistent with such findings, individuals with a history of ELS show increased risk for premature death, with one recent study reporting that adults with six or more adverse childhood experiences died nearly 20 years earlier than those without [9].

The hypothalamic-pituitary-adrenal (HPA) axis is a primary system for maintaining homeostasis in physiologic stress, and research on how ELS impacts physiological function has focused on this system [1]. Other work has demonstrated roles for neuroimmunological, autonomic, oxidative, and non-HPA neuroendocrine responses to stress in linking ELS and disease [10, 11]. Most recently, clinical findings have suggested that telomere biology might offer new insights into the adverse health effects of childhood maltreatment. This chapter, updating our earlier review [12], examines the current understanding of the relationship between telomeres, illness, and stress, including key methodological issues.

Basic Concepts of Telomere Biology

Human DNA is sequentially organized into chromosomes, and that sequencing must be preserved through cell replication to ensure stability and fidelity of the genome. DNA replication occurs utilizing a mechanism of discontinuous synthesis on the lagging strand, which would lead to progressive shortening of chromosome ends with each cell replication. To prevent this shortening, chromosome ends contain a specific sequence of nucleotides consisting of tandem TTAGGG repeats ranging from a few to 15 kilobases in length, called telomeres (Figure 1). These, along with the enzyme telomerase, help elongate and protect the ends of chromosomes so that vital genomic DNA is not lost with each cellular replication [13]. Telomeres are associated with a number of proteins that combine to form a complex that helps preserve the ends of chromosomes from degradation or recognition by DNA repair enzymes, which can trigger repair mechanisms, apoptosis or cellular senescence cascades [14–16].

Telomeres shorten with each cell division [17], and maintenance of telomere function depends on both a minimal length of TTAGGG repeats and telomere-binding proteins [18]. Telomere length is maintained by telomerase, a ribonucleoprotein reverse transcriptase mainly expressed in stem cells, germ cells, and regenerating tissues. There is insufficient telomerase in somatic cells to indefinitely maintain telomere length, and most tissues have very low telomerase levels. Consequently, telomeres shorten with age in most somatic tissues, and telomere length can therefore serve as a marker of biological age [19]. Telomere shortening is also influenced by recombination, epigenetic regulation, and genetic factors, as

well as by oxidative stress; the ability of telomerase to counteract these influences is limited. Recently, genome-wide association studies (GWAS) have identified loci that might affect variation in telomere length [20, 21]. In a study of subjects with a history of familial longevity, Lee *et al.* [20] found that three loci, 4q25, 17q23.2, and 10q11.21, were associated with telomere length. Mangino *et al.* [21] have also identified a locus on chromosome 18q12.2 associated with telomere length.

Measurement of Telomere Length

The Southern blot has been the gold standard for measuring telomere length, but limitations to this method are its time-consuming and labor-intensive nature, the large amounts of genomic DNA required, the difficulty of deducing telomere length from the resulting smear, and reproducibility. Cawthon [22] developed a method for telomere length measurement utilizing quantitative polymerase chain reaction (qPCR), based on mechanisms involved in DNA replication. Cawthon's method entails separate PCRs to measure telomeres (T), which are normalized to a single copy gene (S), yielding a T/S ratio as a measure of telomere length. qPCR correlates highly with results from Southern blot analyses and is now widely used; most psychiatric studies examining telomere length have used one of these two methods. However, qPCR has greater measurement error than Southern blot and can show substantial variability across laboratories [23]. Since individual laboratories internally calibrate their measurements of telomere length, it can be difficult to compare measurements across research groups.

There are also methods employing cytometry hybridization techniques [24, 25], designed to measure the shortest telomeres and telomeres from specific chromosomes. Once the shortest telomeres are depleted, cells either die or become senescent, so the length of the shortest telomeres is a better indicator of cellular aging than average telomere length. A more detailed discussion of telomere measurement is available in Aubert *et al.* [26].

Cross-sectional vs. Longitudinal Approaches in Studies of Telomere Length

A major drawback to using telomere length as a clinical measure is its high variability between individuals, which is determined at birth [27, 28]. Moreover, although telomere length is equal between the sexes at birth, shortening with age occurs more rapidly in males than females, and rates may also differ between ethnic groups [29]. These factors limit the power of cross-sectional studies, which utilize measurements at a single time-point. In addition to careful controls for age and sex, such studies require large sample sizes because of the resulting marked variability of telomere length. Aviv *et al.* [28] have estimated that longitudinal studies, measuring actual telomere erosion rates within individuals over time, would require five times fewer subjects than cross-sectional studies. Accordingly, longitudinal studies are more powerful than cross-sectional designs for demonstrating causal effects.

Despite these considerations, very few longitudinal telomere studies have been conducted, particularly in psychiatric or stress-related conditions. An alternative approach would be to

standardize telomere length in an easily accessible proliferative tissue, representing the effects of exposure to the putative causal variable, against telomere length in a postmitotic source, since telomere lengths in such tissues change little from birth. However, obtaining samples from postmitotic tissues (i.e., nerves, skeletal muscle, bone) presents practical obstacles. Indeed, even peripheral blood can be difficult to obtain in a longitudinal context.

Source Tissue and Telomere Length

Telomeric DNA shortens with each cell division in somatic cells. Studies comparing telomere length from different source tissues show that intra-individual telomere length in disparate tissue types is significantly correlated in healthy subjects [30]. Due to convenience, most human studies have utilized telomeres derived from peripheral blood leukocytes. A possible drawback to this approach is that telomere length may differ among different leukocyte subsets, so that factors favoring predominance of one subset over another can introduce bias [28]. In studies of populations with disease states that exert such effects, such as human immunodeficiency virus (HIV) infection, telomere length might be more appropriately ascertained in a specific subset of leukocytes. The major determinants of aging, including cell replication, inflammation, and oxidative stress, are all demonstrable in leukocyte telomeres [19, 31, 32]. As a result, controlling for factors that alter leukocyte turnover or subsets (e.g., inflammatory conditions) can help minimize bias. An alternative approach is to use buccal mucosa cells obtained by oral swab, which is less invasive than venipuncture and therefore useful for studies with children [33–35]; however, there is less experience with this tissue source.

Telomere Length and Dynamics in Somatic Diseases

A number of disease states have been associated with changes in telomere length, including diabetes mellitus, obesity, and heart disease. There is, as yet, no clear unitary mechanism to account for telomere shortening across these various conditions. One common factor, however, is that they all entail physiologic stress, or a state of disequilibrium. GWAS have identified sites associated with telomere shortening during physiologic stress in various patient populations and in several disease states. This is a first step towards developing a mechanistic understanding of how telomere shortening can be observed as a common outcome of physiologic disequilibrium due to multiple etiologies. Recent findings in several diseases that are of major public health concern are discussed below.

Diabetes Mellitus

Diabetes mellitus has been consistently correlated with shortened leukocyte telomere length [36]. Moreover, pancreatic beta cell telomere length is inversely correlated with levels of hemoglobin A1c (HbA1c), a measure of diabetes control [37]. Even gestational diabetes, reflecting intra-uterine exposure to stress, has been associated with shorter fetal telomere length [38]. Gene variants in subpopulations may link telomere length with diabetes [39]. Saxena *et al.* [39] reported that variants in the casein kinase II gene were associated with telomere length in diabetics of Punjabi Sikh heritage. Liu *et al.* [40], in a study comparing 71 patients with newly diagnosed type II diabetes and 52 controls, found that depressive

symptoms were associated with diabetes and that telomere length correlated negatively with depressive symptoms, age, HbA1c, and measures of insulin resistance.

Obesity

Obesity is associated with significantly shortened leukocyte telomere length even when controlling for covariates such as age, smoking, C-reactive protein (CRP), diabetes, and hypertension [41]. Severely obese patients demonstrated shorter relative telomere length at baseline and one year after bariatric surgery, irrespective of whether they also had metabolic syndrome [42]. Indeed, in the setting of the accelerated catabolic state immediately after bariatric surgery, telomere length attrition was accelerated [42]. It is unclear whether beneficial effects on telomere length and telomerase activity might become evident further out from the point of bariatric surgery, especially in patients who maintain weight loss for several years.

Heart Disease

Rate of telomere length attrition has been correlated with cardiovascular damage in middle-aged adults, even after adjustment for traditional cardiovascular risk factors [43]. In cross-sectional studies, leukocyte telomere length was inversely associated with carotid intima medial thickness, a marker of cardiovascular disease risk and atherosclerotic damage, in obese men [44]. In a longitudinal study, telomere length correlated negatively with cardiovascular disease risk, incident carotid artery plaque, and plaque progression [45].

A study examining cardiovascular health and telomere length in young men with a history of intra-uterine growth restriction (IUGR) reported higher cardiovascular risk factors in the IUGR group as compared to control men, as expected; however, the IUGR group unexpectedly had longer leukocyte telomere length [46]. The authors acknowledged that this finding contradicts the large body of existing data on telomere length, disease risk, and progression. Noting that age and telomere length were inversely correlated in the IUGR group, they suggested that accelerated telomere shortening might occur in the IUGR men as they aged further, which would be consistent with their apparent increased risk for cardiovascular disease. These findings underscore the perils of cross-sectional assessment of telomere length as a predictor of disease risk in specific patient populations, and the importance of study designs that can capture dynamic changes in telomere length over time.

Asthma and Pulmonary Disease

Lifelong asthma was associated with reduced leukocyte telomere length in a study cohort of individuals aged 26–38 years ($n = 1,037$) [47]. This reduction was correlated with blood eosinophil counts, suggesting a contributing role of inflammation, findings which persisted even after adjusting for obesity and smoking status. There was no association between telomere length and asthma only in childhood or in adolescent/adult-onset asthma. In a large study of 934 chronic obstructive pulmonary disease (COPD) cases, 2,834 asthma cases and 15,846 control subjects, Albrecht *et al.* [48] found that telomeres were shorter in asthmatics and patients with COPD after adjusting for age, sex and smoking status. Additionally, they found that tests of lung function (forced expiratory volume in 1 second, forced vital capacity, and their ratio) were positively associated with telomere length, indicating that

better lung function within the diseased population was associated with longer telomeres; the same association was evident in healthy controls, although weaker. The authors suggested that cellular senescence might contribute to the pathogenesis of lung disease, with decrements in lung function observed in the general population due to intrinsic processes associated with aging.

Telomeres in Somatic Diseases: Summary

While telomere length in these conditions could be merely a disease marker (i.e., an indicator of ongoing disease), other evidence implicates telomere length as a risk marker (i.e., a predictor of the likelihood of disease despite current clinical health). For example, in a study of healthy older adults, Cawthon *et al.* [49] found telomere length highly predictive of eventual mortality, even though cause of death was variable. Other studies implicate telomere length as a risk marker for cancer [50, 51] and hypertension [52]. Reports of reduced telomere length in association with smoking [53], obesity [54], and alcohol abuse [55] are consistent with these conditions as risk factors for increased mortality.

Telomere dysfunction can play a causal role in disease. Telomerase deficiency has been causally linked with the genetic disorder dyskeratosis congenita, familial idiopathic pulmonary fibrosis, and familial bone marrow failure syndromes [19]. Progeroid syndromes, characterized by clinical manifestations of accelerated aging and molecular evidence of defective DNA repair, may also reflect causal involvement of telomeres [19]. One report suggests an increased rate of neuropsychiatric disorders in dyskeratosis congenita [56]. At this point, it would be premature to exclude an etiologic contribution of telomere dysfunction in other conditions.

Telomere Length and Dynamics in Psychiatric Conditions

Independent of stress, most of the findings implicating telomeres in psychiatry have involved mood disorders. In an initial epidemiological study ($n = 433$), Lung *et al.* [57] reported an association of reduced leukocyte telomere length with the high-activity allele of the monoamine oxidase A (MAOA) promoter polymorphism, which has been linked to aggression and impulsivity; this association was later found to be mediated by MDD [58]. Simon *et al.* [59] demonstrated shorter telomeres in patients with MDD ($n = 15$) or bipolar disorder (type I or II not stated) ($n = 29$) compared with healthy controls ($n = 44$) [59]. This was replicated by Hartmann *et al.* [60], who found no effect of illness duration or severity, or nature or intensity of treatment, in a study comparing MDD patients ($n = 54$) with controls ($n = 20$). Similarly, Karabatsiakakis *et al.* [61] reported that a history of depression ($n = 44$), regardless of current symptomatology or disease severity, was associated with shortened telomeres in the main effector populations of the adaptive immune system compared to controls ($n = 50$). In a cohort study by Verhoeven *et al.* [62] involving 1,095 MDD patients, 802 remitted patients, and 510 control subjects, patients with MDD had shorter telomeres; higher symptom severity and longer symptom duration in the last 4 years were associated with shorter telomeres, suggesting a dose-response relationship. The telomere shortening in MDD was not entirely state-dependent, as the effect was evident even in remitted patients. In the prospective Dunedin Study ($n = 1,037$) [63], one of the few studies to evaluate telomere length at two time points, persistent internalizing disorders

predicted greater telomere shortening at the 38-year time point in a dose-response manner. This was particularly true in men, and independent of other covariates often associated with telomere shortening (e.g., childhood maltreatment, tobacco use, low socioeconomic status).

Elvsåshagen *et al.* [64], describing reduced telomere length in bipolar II patients ($n = 28$) compared with controls ($n = 28$), detected an association with lifetime number of depressive episodes, but not illness duration. Wikgren *et al.* [65], reporting shorter telomeres in MDD patients ($n = 91$) vs. controls ($n = 451$), also noted an association with hypocortisolism in both groups. Wolkowitz *et al.* [66] found no difference in telomere length between drug-free MDD ($n = 18$) and control ($n = 17$) subjects, but inverse correlations with lifetime depression exposure and measures of oxidative stress and inflammation. These authors also reported increased telomerase activity in drug-free MDD patients vs. controls, with superior antidepressant responses in patients showing the greatest further increases [67]. In an epidemiological study of 952 patients with coronary heart disease, Hoen *et al.* [68] found MDD associated with shorter telomeres. In the only study reviewed in this section that did not utilize leukocytes, no differences from controls were found in telomere length in occipital cortex of patients with MDD ($n = 24$) [69] or in cerebellar gray matter of patients with MDD ($n = 15$), bipolar disorder ($n = 46$), or schizophrenia ($n = 46$) [70]. Zhang *et al.* [71] found reduced telomere length in soldiers with PTSD ($n = 84$) compared to age-matched non-PTSD controls ($n = 566$). Similarly, Jergovi *et al.* [72] reported shorter telomere length in 30 middle-aged war veterans with current PTSD compared to 17 age-matched healthy controls, but no difference in telomerase activity. Martinsson *et al.* [73] found that long-term lithium treatment in bipolar disorder ($n = 256$) was associated with longer telomeres and that an increasing number of depressive episodes in bipolar disorder was associated with shorter telomeres compared to healthy controls ($n = 139$).

Shorter leukocyte telomeres have been reported in schizophrenia [74] (with one study failing to replicate this finding [75]), schizophrenia with lower global assessment of functioning [76], obstructive sleep apnea [77], migraine [78], mild cognitive impairment [79], and Alzheimer disease [80] (with one study failing to replicate the latter two findings [81]). Reduced telomere length correlated with decreased mental health in chronic heart failure [82] (but not in community-dwelling elderly men [83]), poorer cognition in community-dwelling elders [84] and healthy women [85], unspecified poor sleep quality in healthy women [86], and pessimism in postmenopausal women [87]. It is still unclear whether the shorter telomeres observed in these conditions reflect a specific or nonspecific pre-existing marker of illness vulnerability, a specific or nonspecific marker of ongoing disease, or an entirely nonspecific sequela of the psychosocial stress or lifestyle factors (e.g., smoking, obesity) with which these conditions are associated.

Telomere Length and Dynamics with Psychosocial Stressors

Telomere dynamics are known to be impacted by biophysical stress and stressors (e.g., radiation, toxins) [88, 89]. The first evidence that psychosocial stress might also have such effects was a study by Epel *et al.* [90] comparing highly stressed mothers caring for a chronically ill child ($n = 39$) and low stress mothers with a healthy child ($n = 19$). Mothers in the highest quartile of perceived stress had shorter telomeres and lower telomerase

activity than mothers in the lowest quartile. In a follow-up study of 62 women, these investigators found that reduced telomere length correlated with increased nocturnal urinary cortisol and catecholamines, while low telomerase activity correlated with increased nocturnal urinary epinephrine and greater decreases in heart rate variability during the Trier Social Stress Test (TSST) [91]. Subsequent studies have examined telomere length and telomerase activity in various stress-related contexts. Damjanovic *et al.* [92] reported shorter telomeres and increased telomerase activity in caregivers of Alzheimer's disease patients ($n = 41$) compared with controls ($n = 41$). Kiefer *et al.* [93], in a study of 56 women, observed reduced telomere length with greater dietary restraint, defined as chronic preoccupation with weight and attempts at restricting food intake leading to chronic psychological stress. In an epidemiological study of 647 sisters of women with breast cancer, Parks *et al.* [94] found that reduced telomere length correlated with perceived stress, especially in women who were >55 years old, had a recent major loss, or had higher morning urinary epinephrine levels. Humphreys *et al.* [95] detected shorter telomeres in women exposed to intimate partner violence ($n = 61$) compared with controls ($n = 41$). In a study of female caregivers of dementia partners ($n = 14$) and controls ($n = 9$), Tomiyama *et al.* [96] found that shorter telomeres were associated with greater salivary cortisol responses to the TSST and higher overnight urinary free cortisol. In an expanded sample from this study ($n = 22$ caregivers, $n = 22$ controls), telomerase activity was lower at baseline in caregivers but rose in both groups during the TSST [97]; in another expanded sample ($n = 27$ caregivers, $n = 23$ controls), reduced telomere length correlated with higher anticipatory threat appraisal, which correlated in turn with caregiver status, even though telomere length did not differ between the two groups [98].

Kroenke *et al.* [33] found that buccal telomere length was inversely correlated with heart rate and cortisol reactivity in 78 children during mildly stressful laboratory challenge tasks. Malan *et al.* [99] observed shorter telomeres in women who developed posttraumatic stress disorder (PTSD) following rape ($n = 9$) compared with those who did not ($n = 53$). In a study of patients with ($n = 18$) and without ($n = 18$) chronic osteoarthritis pain, Sibille *et al.* [100] found reduced telomere length in those with chronic pain and high stress versus those with no pain and low stress. Reasoning that hostility correlates with heightened stress reactivity, Brydon *et al.* [101] found hostility inversely correlated with telomere length and positively correlated with telomerase activity, in men but not women, in an epidemiological sample of 434 adults. Supporting these observational findings in humans, Kotrschal *et al.* [102] showed that a 6-month exposure to reproductive stress in female mice and crowding stress in male mice induced telomere shortening compared with unstressed control mice. In a study of 333 healthy men and women ages 54–76 years, Zalli *et al.* [103] demonstrated that shorter telomere length and increased telomerase activity were associated with reduced social support, lower optimism, higher hostility, and greater early life adversity in men but not women. Finally, reduced telomere length has been correlated with sociodemographic variables thought to be proxies for sustained psychosocial stress, including lower socioeconomic status [34, 104], African-American ethnicity [29], lower educational attainment [105, 106], and current and long-term work schedule [107].

Telomeres and Early-Life Stress

The first evidence linking ELS with reduced telomere length came from Tyrka *et al.* [108], in a study of healthy adults with ($n = 10$) or without ($n = 21$) a reported history of childhood maltreatment. Other studies have since appeared examining this issue including the Twins United Kingdom study, in which no difference in telomere length was detected between individuals who endorsed childhood sexual ($n = 34$) or physical abuse ($n = 20$) and those who did not ($n = 516$ and $n = 520$, respectively; Glass *et al.* [109]). Similarly, Jodczyk *et al.* [110] reported that leukocyte telomere length in participants aged 28–30 ($n = 677$) did not correlate with 26 measures of life course adversity or stress which occurred prior to 25 years of age, or with the summary risk scores for each developmental domain. However, Kananen *et al.* [111] confirmed an association of shorter telomere length with increasing number of reported childhood adverse life events in 974 adults in the Finnish Health 2000 project, even absent a relationship with current psychological distress or DSM-IV anxiety disorder diagnosis. Similarly, in a study of 215 older adults recalling ELS, Savolainen *et al.* [112] found that although temporary separation from parents or a self-reported history of trauma were not associated with telomere length, participants reporting both experiences had shorter telomeres, suggesting an additive effect of stress and traumatic events on telomere length. Kiecolt-Glaser *et al.* [113] reported that shorter telomeres were associated with multiple childhood adversities in a study comprising dementia family caregivers ($n = 58$) and control subjects ($n = 74$). Surtees *et al.* [114], studying 4,441 women in the United Kingdom European Prospective Investigation into Cancer-Norfolk database, found that shorter telomeres correlated with increased reported childhood adversity experiences, although not with current social adversity or emotional health. Consistent with Malan *et al.* [99], O'Donovan *et al.* [115] observed reduced telomere length in adults with chronic PTSD ($n = 43$) vs. healthy control subjects ($n = 47$); this was accounted for by those PTSD subjects reporting multiple categories of childhood trauma ($n = 18$).

In the first study to show effects of early adversity on telomere length in children, Drury *et al.* [116] found that greater time spent in institutional care correlated with reduced buccal cell telomere length in 100 children aged 6 to 10 years in the prospective Bucharest Early Intervention Project. In a population of children aged 5–15 ($n = 80$), Drury *et al.* [117] reported that buccal cell telomere length was significantly shorter in children with higher exposure to family violence and disruption, and that witnessing family violence had an especially potent impact on telomere length in girls but not boys. Entringer *et al.* [118] demonstrated that maternal experience of severe psychosocial stress during pregnancy was associated with shorter telomeres in young adult offspring ($n = 45$) vs. control subjects ($n = 49$), suggesting that telomere vulnerability to ELS could extend even to the antenatal period. In the first prospective longitudinal study to determine telomere length at two time points, involving 236 children tested at age 5 and again at age 10 years, Shalev *et al.* [35] found greater buccal cell telomere shortening in children exposed to >2 forms of violence ($n = 39$) compared with those unexposed ($n = 128$) or less exposed ($n = 69$). The social environment to which a child is exposed has also been shown to have an effect on telomere length. Theall *et al.* [119], in a study of neighborhood stress, found that salivary telomere length in 99 children aged 4–14 was significantly shorter in children exposed to highly disordered

neighborhood environments. Similarly, Mitchell *et al.* [120] found reduced telomere length in 40 9-year-old African American boys associated with low income, low maternal education, unstable family structure, and harsh parenting. This effect was moderated by genetic variants in serotonergic and dopaminergic pathways, suggesting interplay between telomere length and genetic sensitivity with environmental exposure. Emerging data suggests early intervention with at-risk children might have a beneficial impact on telomere length. Asok *et al.* [121], in a study of 89 children, found that parental responsiveness to their child's cues moderated the association between ELS and telomere length, resulting in longer telomeres even with exposure to ELS, suggesting that there could be measures that might provide protective effects if implemented early. Taken together, these studies support a relationship between ELS and reduced telomere length, and suggest that this effect is dose-dependent and might be susceptible to amelioration or reversal with appropriate intervention.

Potential Mechanisms Mediating Telomere Length in ELS

Wolkowitz *et al.* [122] observed that many of the biochemical derangements in depression, and in chronic stress, result in cellular effects indistinguishable from aging. Indeed, one interpretation of the high comorbidity of depression with diseases of aging, such as cardiovascular disease, cerebrovascular disease, and metabolic syndrome, might be that stress-engendered depression is itself such a disease. In this conceptualization, telomere shortening would be an expected concomitant, and/or consequence, of the HPA axis dysregulation, enhanced glutamatergic excitotoxicity, increased oxidative stress, impaired neurotrophin function, and immune dysregulation reported in chronic stress and depression. Supporting this is evidence that cortisol can reduce telomerase activity [96, 123]. Further supporting the interaction between stress response and telomere length, Zalli *et al.* [103] reported that shorter telomeres and increased telomerase activity were associated with such impaired physiologic stress responses as blunted post-stress systolic blood pressure recovery, heart rate variability, and cortisol. Revesz *et al.* [124] showed that inflammation, as measured by CRP and IL-6 levels, high awakening cortisol response, and increased heart rate were associated with shorter telomere length. Szebeni *et al.* [125] demonstrated that oligodendrocytes in post-mortem brains of patients with MDD had shorter telomeres compared to normal controls; telomerase reverse transcriptase (TERT) was lower in MDD patients as well. Enzymes involved in oxidative stress, such as oligodendrocyte superoxide dismutase, catalase, and glutathione peroxidase gene expression, were also lower in oligodendrocytes from the MDD patients. Szebeni *et al.* hypothesized that blunted responses to oxidative stress, as well as reduced telomerase activity, might contribute to telomere shortening in depression. Animal models support the idea that oxidative stress can shorten telomeres, as evidenced by direct effects of oxidizing substances and antioxidants on telomere length [126].

Review of the biochemistry of aging and telomere dynamics [19, 31, 32, 88, 89] is beyond the present scope, but it is notable that there has yet to be direct demonstration of these mechanisms in affected human subjects. And as attention has turned to the role of epigenetics as a major transductive mechanism for adult sequelae of ELS [127, 128], there are still no direct studies of telomere dynamics in this regard. Lifestyle factors such as

smoking, obesity, and alcohol abuse are frequent sequelae of ELS, and these factors also affect telomere length. While most studies have controlled for such influences, it is possible that these or other factors could account for the association between reduced telomere length and ELS in cohort studies.

Telomeres and Early-Life Stress: Methodological Issues

Nearly all of the human studies examining health implications of telomere length have been cross-sectional in design *with respect to telomere assessment*, limiting the ability to draw causal inferences about telomere shortening; the same is true for all but one [35] of the 15 studies addressing the effects of ELS. Analogously, *assessment of ELS* can be either prospective or retrospective; all but three [35, 116, 121] studies in this area have been retrospective.

The limitations of cross-sectional vs. longitudinal measurement of telomere length have been discussed. Determination of ELS retrospectively is highly variable across studies, but more systematic and comprehensive approaches are more likely to compensate for the bias toward false negatives [129]. Several studies have correlated the number of discrete childhood adversities to telomere length, suggesting that early stressors may have additive effects. Ideally, assessment tools should have good psychometric properties; short of that, ascertainment methods requiring the least amount of judgment or interpretation may be more reliable. Such considerations may explain why Glass *et al.* [109] and Jodczyk *et al.* [110] failed to replicate an association between ELS and reduced telomere length. Timing and type of ELS, and the impact of mitigating psychosocial or genetic factors (“resilience”) [130], could also affect findings.

Effects of Therapeutic Stress Reduction on Telomeres

Therapeutic interventions designed to mitigate the adverse effects of psychosocial stress (e.g., threat appraisal, rumination, negative affect, stress arousal) might promote telomere maintenance [131]. Supporting this, Epel *et al.* [132] showed that vigorous exercise attenuated the correlation between perceived stress and reduced telomere length in a sample of 63 healthy women. In a prospective study, Jacobs *et al.* [133] found that a three-month intensive meditation retreat increased telomerase activity in participants ($n = 30$) compared with controls ($n = 30$); this effect was mediated by increased perceived control and decreased neuroticism. Daubenmier *et al.* [134] found that decreased chronic stress, anxiety, dietary restraint, dietary fat intake, cortisol, and glucose were correlated with increased telomerase activity both in overweight women receiving a four-month mindfulness-based intervention for stress eating ($n = 47$) and in wait-list controls ($n = 47$). Lin *et al.* [135] have summarized studies examining effects of lifestyle interventions on telomere length and general health status.

Preliminary data suggest that lifestyle intervention increases in telomere length may be durable, as demonstrated in a 5-year follow-up study by Ornish *et al.* [136]. In a small group of men with low-risk prostate cancer undergoing active surveillance, one group ($n = 10$) received diet, activity, stress management and social support intervention, while controls ($n = 25$) received only standard active surveillance. Telomere length after 5 years was

associated with adherence to the lifestyle intervention, and there was a statistically significant increase in telomere length and preservation of telomerase activity in the intervention group. Positive results in a small sample study such as this are intriguing, as they support the idea that telomere length could serve as an objective measure to be tracked over time to evaluate intervention efficacy, in addition to its potential role as a marker of health and disease. Lengacher *et al.* [137] provided preliminary evidence that mindfulness-based stress reduction over 12 weeks increased telomerase activity in peripheral blood mononuclear cells from 142 breast cancer survivors.

Summary and Implications

The number of papers published on telomeres has more than tripled in recent years, from roughly 5,000 articles in 2008 [19] to nearly 16,000 to date. Most studies on the relationship between telomere length, psychosocial stress, and psychiatric illness have been published during this brief period. At present, support is strongest for an association of reduced telomere length with psychosocial stress and depression. Given the relationship between stress and depression, this is not surprising, but the mechanisms underlying this effect are still unknown.

The emerging association of reduced telomere length with ELS presents new opportunities for understanding the relationship between stress and psychiatric illness. As proposed by Wolkowitz *et al.* [122], the downstream consequences of early adversity could be conceptualized as accelerated aging, as it is associated with adverse health outcomes in adults. ELS could also be thought of as predisposing to dysregulated homeostasis/allostatic load [138]. Alternatively, it is possible that ELS does not cause reduced telomere length, but is rather a pre-existing (risk) or acquired (disease) marker for those individuals who subsequently *characterize* their early-life experiences as stressful. At this point, it is still unclear what components of ELS are responsible for its observed association with reduced telomere length.

Research also points to the role of telomerase in understanding telomere dynamics in ELS. Telomerase maintains telomere length, and might be expected to strongly correlate with telomere shortening, suggesting that the effects of chronic stress on this enzyme rather than on the telomere itself are important. However, work to date does not support a simple relationship between telomere length and telomerase activity, with some findings suggesting that telomerase activity might compensatorily increase in response to stress and/or telomere shortening. These uncertainties, in conjunction with the technical difficulty associated with the telomerase assay, may limit the utility of telomerase activity for informing our understanding in this area.

As in most rapidly emerging areas, publication bias in favor of positive findings could be a factor in overstating the robustness of the association of ELS with reduced telomere length. Additionally, many publications to date are based on secondary analyses from studies originally designed for other purposes, using banked blood specimens to determine telomere length. It is clear that telomere length is affected by many factors, including genetic susceptibility, cellular replication, and oxidative stress. Cross-sectional measurements of

telomere length reflect the interplay of these factors, making it difficult to establish the causal effects of specific experiential exposures. Indeed, such cross-sectional measurements must be recognized as a second-order proxy for the true variable of interest, *change* in telomere length, which can only be directly assessed by measuring telomere length before and after an exposure. This consideration, in conjunction with the great variability in telomere length between individuals, will make it very difficult to develop telomere length as a clinical biomarker of ELS.

Despite these limitations, the findings reviewed here suggest that telomere length has real potential as a biomarker for use in studies aimed at clarifying the sequelae of ELS, and perhaps in studies designed to identify future vulnerability and evaluate intervention efficacy. Well-designed prospective studies will determine whether telomere length and dynamics will serve merely as an additional biomarker of general health or as a primary target to evaluate severity of disease and treatment efficacy.

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Figure 1.