ANNUAL REVIEWS

Annual Review of Public Health

Psychosocial Stressors and Telomere Length: A Current Review of the Science

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Annu. Rev. Public Health 2020. 41:223–45

First published as a Review in Advance on January 3, 2020

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

https://doi.org/10.1146/annurev-publhealth-040119-094239

Keywords

psychosocial stress, early life adversity, perceived stress, stressful life events, telomere length, cellular aging

Abstract

A growing literature suggests that exposure to adverse social conditions may accelerate biological aging, offering one mechanism through which adversity may increase risk for age-related disease. As one of the most extensively studied biological markers of aging, telomere length (TL) provides a valuable tool to understand potential influences of social adversity on the aging process. Indeed, a sizeable literature now links a wide range of stressors to TL across the life span. The aim of this article is to review and evaluate this extant literature with a focus on studies that investigate psychosocial stress exposures and experiences in early life and adulthood. We conclude by outlining potential biological and behavioral mechanisms through which psychosocial stress may influence TL, and we discuss directions for future research in this area.

1. INTRODUCTION

Chronic psychosocial stress experienced in childhood and adulthood is thought to impact long-term health and disease risk. Psychosocial stressors have been proposed to accelerate biological aging, offering one mechanism through which social adversity may impact age-related disease risk, including diabetes, atherosclerosis, neurodegeneration, and cancer. Specifically, chronic stress is thought to directly impact cellular processes relevant to disease, through prolonged or repeated activation of the sympathoadrenal system and the release of neuroendocrine mediators, which is thought to have a cumulative impact on key biological aging pathways, namely inflammation and cell stress, and can drive telomere length (TL) shortening in peripheral blood leukocytes (36, 51, 104, 109). Telomeres are repeat sequences of noncoding DNA that cap the ends of chromosomes and naturally shorten over time with cell replication but are vulnerable to accelerated shortening under conditions of high cell stress and inflammation (7, 8, 125). Short telomeres are predictive of greater disease burden and mortality (3, 39, 40, 106) and are one biomarker of the aging process that allows researchers to investigate potential contributors to biological aging decades prior to disease morbidity and mortality. Although limitations of the TL measure have been noted (see Section 6.2 for a discussion), a considerable body of research has utilized TL as an estimate of biological age, and it remains the most extensively studied hallmark of accumulated cellular aging in humans. Research also suggests that telomeres may contribute to the aging process, as telomeres that reach a critically short length can initiate a replicative senescence response (8, 70). Thus, TL may serve as a useful biomarker of both system senescence and biological aging.

Population studies have used a number of DNA sources to estimate overall TL, including collection of peripheral blood leukocytes, buccal cells, and saliva (which is composed predominantly of leukocytes). TL estimates from blood cells have been inversely correlated with the percentage of senescent T cells in the peripheral circulation, which appears to reflect both the decline in naïve T cells and the accumulation of senescent T cells observed with aging (64). Although salivary and buccal TL have not been directly tied to the aging process or disease risk, length estimates from these sources are highly correlated with estimates derived from blood (117). In the current review, we note the sample source of TL by indicating buccal (bTL), salivary (sTL), and leukocyte (LTL) sources.

The first study of psychological stress and TL was published by Elissa Epel and colleagues in 2004 (37). Over the last 15 years, research on this topic has flourished, with more than 60 publications linking a wide range of stressors to TL across the life span. Psychosocial stress can be defined in several ways, which Epel and colleagues (38) recently outlined in a transdisciplinary model of stress. In this review, we have adopted a broad working definition of stress to better understand how the exposure and experience of psychosocial stress impact cellular processes linked to disease. Thus, we have conceptually defined psychosocial stress as a prolonged or repeated (*a*) exposure to adverse social conditions [e.g., early life adversity (ELA), long-term caregiving for a sick loved one], in which a psychological response is assumed but not always directly measured, or (*b*) psychological response to an exposure that is characterized by feelings of overwhelm and anxiety and/or the perception that one lacks personal or social resources to cope with environmental demands (e.g., perceived stress, lack of social support) (25, 60), all of which results in activation of the stress response system. Of note, although we recognize that poor socioeconomic environments in adulthood are conceivably also stress exposures, this literature is beyond the scope of the present review. The aim of this review is to evaluate the extant literature with a focus on studies that investigate psychosocial stress in early life and adulthood and to summarize key advances and shortcomings in the current science to inform future research in this area (see **Supplemental Table 1** for study details).

Supplemental Material >

2. CHILDHOOD STRESS EXPOSURE

The examination of adversity in childhood, broadly defined, has received significant attention in the TL literature. Childhood exposure to severe forms of stress is thought to heighten sensitivity and responsivity to future stressor exposures, and this responsiveness can persist into adulthood, leading to alterations in sympathoadrenal system responses to stress throughout the life course (109). We have reviewed three distinct forms of stress exposure in childhood, namely childhood abuse, childhood socioeconomic status, and ELA. These experiences are thought to have immediate and long-term impacts on telomere biology. This literature comes from more than 30 studies that focused specifically on childhood exposures. Of these studies, 50% had sample sizes of less than 200, 28% between 200 and 1,000, and 22% over 1,000 participants. In addition, 50% of the samples measured LTL, 25% measured sTL, and the remaining involved a mix of tissue types. Despite these differences, there was no discernible pattern in the effects by sample source or sample size.

2.1. Childhood Abuse

Some of the first research to link psychosocial stressors and TL investigated exposure to childhood abuse, including physical maltreatment, sexual abuse, psychological abuse, and/or emotional neglect. Of the 9 studies identified, 1 was excluded owing to poor reliability of TL measurement (i.e., coefficients of variation >15%; 56). We note that two of the studies were based on the same sample of participants.

In one of the most substantial longitudinal studies to date, Shalev et al. (110) reported that two or more exposures to violence or abuse in childhood (i.e., maternal domestic violence, frequent bullying exposure, physical maltreatment by an adult) was associated with greater bTL shortening from age 5 to 10, compared with children who had one type of violence exposure or who were not exposed to violence; however, when each exposure was examined separately, only exposure to physical maltreatment was significantly associated with bTL shortening. In addition, Révész et al. (100) reported that greater childhood abuse (i.e., emotional neglect; psychological, physical, and sexual abuse before age 16) was associated with more rapid attrition of LTL over a six-year period in adulthood.

Cross-sectional studies examining retrospective recall of childhood abuse are less convincing; the majority of findings to date report no significant associations of abuse with TL. A study by Kiecolt-Glaser et al. (57), which found links to other ELA, found that neither childhood abuse nor neglect were associated with whole blood TL. This result was also true for Schaakxs et al. (108) and Mitchell et al. (77), who found associations with various other stressors but not with child abuse and LTL. In addition, Verhoeven et al. (124) reported that childhood abuse (i.e., emotional neglect; psychological, physical, and sexual abuse before age 16) was not associated with LTL. In one of the few studies to use a non–quantitative polymerase chain reaction (qPCR) measurement of TL, Jodczyk et al. (54) used Southern Blot to assay adult LTL (ages 28–30) and found no association with childhood abuse or family violence (measured prospectively between ages 0 and 16). Of note, these null findings are from predominantly cross-sectional studies that were conducted in adulthood and relied on recall of childhood abuse. In contrast, Cai et al. (12) reported that exposure to childhood sexual abuse was associated with less saliva telomeric material in adulthood, assessed using whole genome sequencing. This study is notable owing to its unique measurement of TL and highly selective sample of adults who experienced sexual abuse (measured with an in-depth questionnaire) and major depressive disorder, compared with a control group with no history of abuse. The authors propose that depression mediates the effect of abuse on TL, and they also attempt to show this result in animal models. The selectivity of the sample diminishes

the depression mediation conclusion but clearly calls for more focused research on this particular mechanism.

2.2. Childhood Socioeconomic Status

A second type of childhood exposure that has received special attention is that of socioeconomic status (SES). Childhood SES is often used as a proxy indicator of exposure to other forms of chronic stress, such as financial hardship, food insecurity, residential instability, poor health care, exposure to violence, and crowding (78). Of the six studies identified, most define childhood SES by assessing parental education or income, whereas another study captured childhood SES using data on the neighborhood environment such as average income or education level. We note that four of the studies were based on the same sample of participants.

Needham et al. (80) reported that higher parental educational attainment (for both parents or the father only) was associated with longer child LTL in a sample of children aged 7 to 13 years. In the Fragile Families and Child Wellbeing Study, associations of childhood family income, parental education, and childhood neighborhood SES with sTL have been reported in both childhood and early adulthood (75, 78, 79). Of note, Mitchell et al. (77) reported that lower perceived childhood social class, in addition to maternal and paternal educational attainment, was associated with shorter adult LTL, suggesting that child experience of social class plays an important role. In contrast, Carroll et al. (15) reported no association of parental education with older adult LTL in white and black participants, while an inverse association of parental education with LTL was present in the Hispanic subset of participants, a sample that included non-native-born Americans. Taken as a whole, lower childhood SES environments have been linked to shorter TL, and the effect might be most pronounced when social hardship experiences and TL are measured more proximally to childhood because the strongest findings were noted in children and young adults. These studies are consistent with the use of the qPCR method of assessing TL, while sample sources include both blood and saliva. We note that although many other child TL studies account for SES in the analyses, investigators often do not report it. Future work is needed that examines the effects of childhood SES on longitudinal change in TL and better characterizes the environment that contributes to the SES effects.

2.3. Early Life Adversity

Early life adversity (ELA), including exposure to conflict and violence, parental loss, family instability, traumatic life events, and peer victimization, has been well documented to impact health (111), and a substantial literature has connected ELA to shortened TL. Of the 28 studies that have focused on ELA, more than half examined the association between a count measure of adversity (i.e., a checklist approach in which the total number of adverse exposures was summed) and TL. In many cases, secondary post hoc analyses followed the main analysis and did not account for multiple comparisons, but they were instead treated as exploratory or sensitivity analyses to understand if one type of adversity was more detrimental than another. The other half of this literature focused on a specific measure or class of measures of adversity. The count model of ELA consistently detected an effect, albeit often a small effect. In contrast, the specific type of ELA model was less likely to show an effect. Of these studies, two were excluded owing to poor reliability of TL measurement (78, 86), and five were based on the same sample of participants (two from one sample and three from another).

In examining the effects of the number of ELA exposures, one should note that the count approach is rarely summing the same events in each study. Although this might suggest that the

measure is more robust, it does make interpretation of the literature challenging. That said, the studies on ELA using count measures are consistent, with more ELA related to shorter TL, including LTL (22, 57), sTL (78), and bTL (32). Of note, Ridout et al. (101) showed that a more stressful early family environment was associated with shorter sTL at baseline of a longitudinal study (but was unrelated to change in sTL). Across a number of studies, childhood adversities tend to have a stronger association with TL than do adulthood stressors. For instance, Puterman et al. (94) and Osler et al. (84) reported ELA to be related to shorter LTL, whereas adult stressful life events did not relate to LTL. In addition, Bersani et al. (6) found a large association between early life trauma (i.e., childhood abuse, loss, natural disaster) and granulocyte TL in a sample of combat-exposed veterans. Of note, Schaakxs et al. (108) found that the experience of any adverse childhood events (not including abuse) was associated with shorter LTL, although the authors state that it would not pass multiple testing correction.

Studies focused on specific ELA events have also been examined in association with LTL and sTL, including early maternal and parental loss (79, 128), exposure to household dysfunction (22), and nonsupportive parenting (11). In addition, TL has been inversely related to a child's adverse environment, including contact with the child welfare system (2), exposure to institutionalized care (33), family violence and instability (32, 78), negative mood reactivity to parental conflict, neighborhood disorder (75, 119), and peer social victimization during adolescence (45). Of note, Theall et al. (119) reported a very large association [odds ratio (OR) = 3.4] between high neighborhood disorder (the presence of 4 or more instances of garbage, graffiti, abandoned buildings and vehicles, and broken steps, glass, or toys outside the child's home—more than 36% of the sample) and having an sTL 1 standard deviation or more below the mean. However, not all studies found an association between childhood adversity and TL. Jodczyk et al. (54), Van Ockenburg et al. (123), Kuffer et al. (59), and Verhoeven et al. (124) found that various types of ELA were unrelated to LTL in early, middle, and late adulthood. Despite the often small samples and small main effects of the exposures, several studies have tested and found significant interactions with gender, age, birth weight, parental responsiveness, maternal education, and parental age at conception (2, 32, 33). In addition, alcohol consumption and smoking during young adulthood (5) and genetic sensitivity (78) were found to mediate associations between ELA and TL.

Of particular importance is work by Brody et al. (11), demonstrating a critical need to intervene early in a child's life course to improve outcomes, including cellular aging. In this research with families recruited for participation in a six-week family-based group intervention for rural African American preadolescents ($n = 114$) and controls ($n = 102$), nonsupportive parenting (parent–child conflict without parent emotional support) was associated with shorter whole blood TL five years later among young adults in the control condition but not among those in the intervention condition (see also Reference 5). These findings highlight an important role of family-based interventions in preventing the early effects of harsh environments on childhood TL. Likewise, and of particular note as a place to intervene, stress exposure occurring before birth might also be particularly important. Greater maternal pregnancy-related stress (34) and maternal psychosocial stress during pregnancy (74) were associated with shorter newborn cord blood TL but not with LTL at age 11 in a birth cohort (113). This research highlights the relative importance of providing support to expectant mothers to reduce stress and anxiety during this important developmental period.

2.4. Summary of Childhood Stress Exposure

Taken as a whole, there appears to be a lasting imprint of childhood stress exposure on TL estimates of biological aging. The findings are most striking for ELA in the family environment.

ELA during this critical window of time could impact telomere biology directly by altering telomerase enzymatic activity during clonal expansion that occurs during rapid growth, resulting in shortened TL as compared with that of peers who are not exposed to stressors during this window of development. A second pathway commonly presented is that altered responsivity to stress is programmed in early life, and this response pattern is carried into adulthood. Because childhood is a highly sensitive developmental period during which time the physiological system may be more vulnerable, interventions designed to help children and families recover from trauma, increase resources, and reduce toxic stress are important intervention targets (13, 46, 55).

3. ADULT STRESS EXPOSURE

Adulthood offers numerous opportunities for exposure to stressful life experiences, and a sizeable literature links adult stress exposure to TL. We review four distinct forms of adulthood stress exposure, namely stressful life events (major adverse events within a specific time frame, such as serious illness, job loss, divorce, and the death of a child or other close relative), informal caregiving (providing unpaid care to a family member or friend with an illness or disability), work-related stressors (work schedules, strain, and exhaustion), and financial strain (distress related to insufficient resources). Although stressful events are typically episodic in nature, their influence on psychological and physiological stress responses can become a source of chronic stress. Likewise, ongoing caregiving responsibilities, work-related stressors, and financial strain are thought to place emotional, psychological, and physical demands on individuals that can impact telomere biology through gradual wear and tear (i.e., unrepaired damage) at the cellular and systemic levels. This literature is composed of 20 studies that focus specifically on adult stress exposures, including stressful life events, caregiving for an ill or disabled family member, work-related stressors, and financial hardship. Of these studies, 30% involved sample sizes of less than 200, 40% between 200 and 1,000, and 30% over 1,000 participants. In addition, 80% of the samples measured LTL, 10% measured sTL, and the remaining involved other tissue types.

3.1. Stressful Life Events

Stressful life events (SLEs) are major adverse events that are often episodic in nature and occur in adulthood, including diagnosis with a serious illness, job loss, divorce, and the death of a child or other close relative. A review of the literature testing associations between SLEs and TL yielded 13 studies, in which a majority used a checklist approach to assess the occurrence of SLEs within a specific time frame, such as the past year, during adulthood, or over the life course. Of these, two were excluded owing to poor reliability of TL measurement (107, 118), and two were based on the same sample of participants.

Of particular value are studies that examine change in TL as it relates to SLEs, which can provide information about biological aging rates. Although associations are typically small, the most convincing evidence comes from studies that assessed exposure to SLEs during the same time period as the measurement of TL change. For instance, Puterman et al. (96) and Van Ockenburg et al. (123) found that SLE exposure predicted greater LTL shortening over a 1- to 6-year period, suggesting that the experience of SLEs may contribute to biological aging rates. In contrast, two additional studies that did not yield significant TL attrition either reported a low average number of SLEs over a one-year period, which may have constrained the ability to detect a significant association with sTL (101), or used an assessment of SLEs at baseline to predict change in LTL over a six-year period (100).

In two larger population-based studies, SLEs in adulthood were concurrently related to shorter TL; however, in both cases the magnitude of the association was reduced when adjusting for covariates. For example, Puterman et al. (94) reported that adults with greater life course SLEs had shorter sTL, but the association was reduced to nonsignificance when accounting for exposure to ELA. In addition, Verhoeven et al. (124) reported that among adults with a lifetime diagnosis of depression and anxiety and healthy controls, SLE exposure within the previous year and previous 1–5 years was associated with shorter LTL, whereas exposure to SLEs 6 or more years ago was not; however, these associations were reduced when accounting for health behaviors and current medical conditions.

Smaller cohort studies also report variable findings. In a sample of adults with severe SLE exposure and controls, Lopizzo et al. (71) found that those who had experienced a severe SLE in the previous six months had shorter LTL compared with those who had not. Likewise, Jodczyk et al. (54) found that exposure to SLEs from age 16 to age 25 was associated with shorter LTL at ages 28–30. However, null findings have also been reported in studies with high-quality measures of stress and TL, including a sample of middle-aged parents (99), adult males (84), and older adults with a depressive disorder and healthy controls (108). We note that the average number of SLEs in these studies tended to be low, which may have constrained the associations.

Together, these findings highlight the importance of future studies to assess SLEs over a time period that is (*a*) sufficient to capture variability in SLE exposure and (*b*) during the same time period as the measurement of TL. The majority of studies that focused on adult SLEs used a qPCR approach to measure LTL, with two studies measuring sTL. The larger, population-based studies in this review suggest that an association between adult SLEs and TL is observable but small. Likewise, some of the effect may be attributable to early life experiences that program stress response patterns later in life and alter health trajectories. Additional research will be important to tease apart the contributions of early life and adulthood exposures more thoroughly, including whether ELA may promote age acceleration in adulthood and if modifiable health behaviors may provide protection.

3.2. Caregiving

Existing research on informal caregiving, or providing unpaid care to a family member or friend with an illness or disability, suggests that caregivers can experience a significant degree of stress. Caregiving has been most commonly characterized in the literature using objective measures of caregiving status (i.e., a comparison of caregivers and noncaregiver controls) or caregiving duration (i.e., length of time spent as a caregiver); fewer studies have examined subjective perceptions of caregiver burden. Of the seven studies identified, one was excluded owing to poor reliability of TL measurement (21), and two were based on the same sample of participants.

Of the six studies that have examined differences in TL based on caregiving status, two reported that caregivers had shorter TL than did noncaregivers (although they were based on the same sample; 11, 24) and three reported no difference (37, 66, 81). Of note, the age of the sample may influence the presence of an association, as the study with significant findings was composed predominantly of older adult participants. In the first study of any psychosocial stress and TL, Epel and colleagues (37) found that among maternal caregivers of a chronically ill child, longer caregiving duration (in years) was moderately associated with shorter peripheral blood mononuclear cell (PBMC) TL. Similarly, Litzelman et al. (66) found that among caregivers of a family member or friend with a long-term illness or disability, reports of a higher number of caregiving hours per week and greater caregiver burden were associated with shorter sTL and LTL (mixed source). In contrast, one study with a sample of adults in the Philippines reported no association between

caregiving duration (in years) and whole blood TL (98), although only 15% of participants reported serving as a caregiver during their lifetime, which may have constrained this association.

Together, these findings suggest that caregiving duration and perceived burden are more consistent predictors of TL than is caregiving status alone, although associations are generally small. Of note, the three studies (from two independent samples) that measured TL in PBMCs with either qPCR or Southern Blot assays yielded significant results; however, there were no discernible patterns in the findings based on sample size. Considerably more research is needed to better characterize whether caregiving stress is associated with TL shortening. Importantly, existing research has not tested longitudinal changes in TL over time in caregivers with high stress compared with noncaregivers. Likewise, a number of protective factors could modulate these associations, including time for leisure activities and healthy lifestyle, and further research should test these moderators.

3.3. Work-Related Stressors

Another type of adulthood exposure that has received attention is work-related stressors, as ongoing work stress is thought to contribute to worse health outcomes. The five studies that investigated work-related stressors have used either an objective measure of work schedules (e.g., full-time compared with part-time employment, number of hours worked per day or per week) or a more subjective measure of perceived work stress, strain, or exhaustion as it relates to TL. The most consistent findings have been observed in moderately sized studies of work schedules. In a sample of first-year medical residents and first-year university student controls, Ridout et al. (101) found that medical residents had greater sTL attrition over one year than controls, and among medical residents, working longer hours per week was associated with greater sTL shortening. In a population-based sample of women with a sister who had breast cancer, Parks et al. (86) found that women who were employed full time or overtime had shorter LTL than those who worked part time or were not employed. Among employed women, those who worked full time for 20 years had shorter LTL than did those who worked full time for 1–5 years, and working multiple jobs was associated with shorter LTL. In contrast, in a population-based sample of current and retired workers, Fujishiro et al. (42) found that LTL did not differ by employment status. Overall, the effects of work schedule on TL are strong, with future research needed to understand which components of work schedule are particularly detrimental (e.g., poor sleep and/or diet, reduced physical activity).

In comparison, studies of work-related stress, strain, and exhaustion have yielded mixed findings. In a large population-based sample, Ahola et al. (1) found that adults who reported severe work exhaustion (i.e., exhaustion symptoms experienced daily or weekly) had shorter LTL than did those who reported mild or no work exhaustion, a finding that could reflect a reverse causal model, because shortened TL also contributes to fatigue. In contrast, in a cohort of adult men, Osler et al. (84) found that stressful events at work were not associated with LTL, although this study utilized a checklist approach to assess events such as loss of a job and long-standing conflicts with a supervisor. In a population-based sample, Fujishiro et al. (42) found that several measures of work strain (i.e., physical activity and hazard exposure on the job, interpersonal stressors, job control and demands) were not associated with LTL; however, these measures were considered simultaneously in a single regression model, which may have confounded individual effects and limited power.

Overall, the findings on work stress suggest that working longer hours is related to shorter TL, but the intensity of work stress is inconsistently related to TL. The majority of studies focused on work-related stressors used a qPCR approach to measure LTL, with one study measuring sTL. In

addition, the findings suggest that work schedules may have a particular influence on TL among individuals who are experiencing elevated levels of other forms of stress (e.g., medical illness of a family member, medical residency, caregiving) or decreased time to perform protective health behaviors (e.g., exercise, sleep), although these mechanisms are not clear and warrant investigation in future research.

3.4. Financial Strain

There is only one published study of financial strain, or psychosocial distress related to insufficient resources, and TL. In a large cohort of adults with a lifetime diagnosis of depression and/or anxiety and healthy controls, Révész et al. (100) found that self-reported financial strain (i.e., insufficient money to buy food) in the previous year did not relate to baseline LTL or change in LTL over a six-year period; however, the financial strain measure in this study was not well characterized. Although financial strain has been included as a stressful life event in other studies, whether it has a unique influence on TL remains unclear.

3.5. Summary of Adult Stress Exposure

Overall, the literature on adult stress exposure suggests that associations with TL are observable but small, with variable findings depending on the time frame and stress measure adopted in each study. For instance, stressful life events, when episodic in nature, showed limited associations with TL. When specific events were examined, half of the studies found an association; however, when count measures of events were examined, more reliable, albeit small, associations with TL were evident. In addition, caregiving duration and perceived burden were more consistent predictors of TL than status alone, and work schedules had a particular influence on TL among individuals who were experiencing elevated levels of other forms of stress (e.g., medical illness of a family member, medical residency, caregiving). Together, these findings suggest that chronic exposure to multiple stressors may impact telomere biology through gradual degradation at the cellular and systemic levels. To better understand the cumulative impact of stress exposure on TL attrition, future research is needed that adopts a longitudinal design to comprehensively assess stress exposures and TL over the same time period.

4. ADULT STRESS RESPONSE

In contrast to the literature on adult stress exposure, other investigations have focused on individuals' psychological response to an exposure that is characterized by feelings of overwhelm and anxiety and/or the perception that one lacks personal or social resources to cope with environmental demands rather than on the stress exposure itself. This literature is composed of 11 studies that focus specifically on adult stress responses, including perceived stress (a more global measure of feeling stressed or out of control), perceived discrimination (response to unfair or prejudicial treatment), and threat appraisals (anticipatory threat in relation to a future stressor). Each of these stress responses can result in repeated or ongoing activation of the stress response system that is thought to contribute to TL attrition. Discrimination, in particular, is also thought to emotionally burden individuals, which can promote sustained vigilance to potential threat and tonic elevations in stress systems and/or exaggerated physiological stress responses. Of these studies, 55% involved sample sizes of less than 200, 27% between 200 and 1,000, and 18% had more than 1,000 participants. In addition, 55% of the studies measured LTL, 27% measured sTL, and the remaining studies involved other sample sources.

4.1. Perceived Stress

Perceived stress has been characterized in the literature as the degree to which an individual appraises their life as stressful, including feelings of being stressed, upset, or angry, and cognitions that one does not have control or that the demands of a situation outweigh one's resources (25, 38, 60). Of the 8 studies identified, the majority used the Perceived Stress Scale (PSS) (25), a well-established and validated measure that assesses global perceived stress over the previous month that is not directly related to a specific stressor. Of these, two were excluded owing to poor reliability of TL measurement (23, 118).

Although the reviewed studies utilized well-validated measures of stress, they yielded inconsistent findings. In a small sample of maternal caregivers of a chronically ill child and mothers of healthy children, Epel et al. (37) found that higher perceived stress was moderately associated with shorter PBMC TL. Puterman et al. (95) found that women with short LTL (i.e., lower tertile) reported higher perceived stress than did women with long LTL (i.e., higher tertile); however, the authors reported that this association was moderated by physical activity. Bersani et al. (6) found that, after adjusting for covariates, perceived stress was not associated with TL among combat-exposed veterans; however, given the magnitude of association, it is possible that the small sample size limited statistical power to detect a significant association. The remaining studies yielded null findings for parents with adolescent-aged children (99), women who have a sister with breast cancer (87), and caregivers for a family member with a long-term illness or disability (66).

Finally, Mathur and colleagues (76) published a systematic review and meta-analysis to determine the association between perceived stress and TL. The meta-analysis was based on 22 studies with a total of 8,724 participants; correlations were obtained from published manuscripts or communication with study authors. Although only 3 of the published studies reported a significant association between perceived stress and TL, the meta-analysis revealed a marginal zero-order correlation between perceived stress and TL and a small but significant partial correlation ($r = -0.06$) when adjusting for age.

All the studies on perceived stress used qPCR to measure TL, with indiscernible differences in findings based on sample source. Given the considerable heterogeneity in sample size and population between the reviewed studies, more research is needed to better characterize whether perceived stress is associated with TL, especially studies that investigate the influence of perceived stress to TL shortening over time.

4.2. Perceived Discrimination

Discrimination has been defined in the literature as "unfair or prejudicial treatment of different categories of people, especially on the basis of race, age, or sex" (62, p. 224). Experiences of discrimination range in magnitude from daily occurrences (e.g., being treated rudely) to major discriminatory treatment that threatens the livelihood, safety, and life opportunities of categories of people (44). There are four studies of perceived discrimination in the TL literature: Three focused on racial discrimination and one focused on age discrimination. Chae et al. (20) found that, among African American men with an antiblack racial bias, higher perceived racial discrimination was associated with shorter LTL. In addition, Lee et al. (61) found that lifetime discrimination was related to shorter sTL, and Liu et al. (67) found that perceived daily discrimination was related to shorter sTL in African American older adults. In contrast, Stephan et al. (116) found no association between age discrimination and sTL. Each of the studies used qPCR to measure TL, and findings suggest a consistent but small effect of racial discrimination on TL.

4.3. Threat Appraisals

Threat appraisals can be differentiated from measures of perceived stress because the appraisal occurs in relation to a specific situation. There is only one published study of threat appraisals in the adult stress literature, which defined threat appraisal as an anticipatory threat in relation to a future stressor. In a small sample of female caregivers for a family member with dementia who were recruited on the basis of their perceived stress level (i.e., PSS >12) and controls, O'Donovan et al. (81) found that higher anticipatory threat appraisals to an acute laboratory stressor were associated with shorter LTL. Threat appraisals represent an intriguing area for future research, as they may be capturing an underlying, trait-like or more stable response to perceived threat. Likewise, it is possible that threat appraisal may drive findings linking ELA with TL later in life, and future work should disentangle this plausible mechanism.

4.4. Summary of Adult Stress Response

Taken as a whole, associations between adult stress responsiveness and TL were more consistent for discrimination and threat appraisals than for more global measures of perceived stress. This may be because perceived stress is most commonly measured over the previous month, whereas measures of perceived discrimination and threat appraisals are thought to represent more stable stress response patterns that may be chronic in nature and therefore more caustic. Although associations were typically small, this research highlights the value of measuring psychological responsivity to stress exposure as an important element in whether stress results in cellular aging. Future research is needed that involves larger samples and populations in which more variance in stress exposure or more severe stress exposure is expected. Future directions should also begin to identify the unique mechanisms of action that the stress response system has on plausible intracellular systems that drive cellular aging, such as the impact of cell stress on mitochondrial health (89–91).

5. ADULT SOCIAL STRESS

A growing literature on adult social stress investigates a lack of social connections and/or experience of poor-quality relationships (characterized by conflict or low support) as adverse exposures in adulthood. We reviewed five distinct forms of social stress, namely social network size (number of social contacts in an individual's network), marital status (comparing married, divorced, widowed, or unmarried individuals), social support (availability of emotional, informational, and tangible support), social strain (presence of conflict, criticism, and control), and social isolation/loneliness (actual or perceived lack of social connection). Research suggests that high-quality relationships confer health benefits by providing companionship, a source of meaning and well-being, and additional resources that can buffer stress and increase health-promoting behaviors, whereas poor-quality relationships or a lack of social connection is deleterious. Each of these types of social stress can alter an individual's perception that they have the personal and social resources necessary to cope with environmental demands and may therefore drive cellular aging through stress response pathways. This literature is composed of 14 studies that focus specifically on adult social stressors, including social network size, marital status, social support, social strain, and social isolation/loneliness. Of these, approximately 36% involved sample sizes of less than 200, 36% between 200 and 1,000, and 28% had more than 1,000 participants. In addition, 86% of the studies measured LTL, and 14% measured sTL.

5.1. Social Network Size

Social network size refers to the number of social contacts individuals have in their network and represents a more objective or structural aspect of social relationships. There is only one published study of social network size and TL. In a large cohort of adults with a lifetime diagnosis of depression and/or anxiety and healthy controls, Révész et al. (100) found that the size of an individual's social network over the previous year was not associated with their baseline LTL or change in LTL over a six-year period. Because social network size has been identified as a significant predictor of increased risk for mortality (48), future research on this aspect of social stress is warranted.

5.2. Marital Status

Previous research has identified marital status as a significant predictor of morbidity and all-cause mortality (48). The majority of studies on marital status and TL have compared individuals who are married (or in a committed romantic relationship) with those who are separated, divorced, widowed, and never married. To date, four studies have investigated associations between marital status and TL, with largely consistent findings documenting an association between having a spouse or romantic partner and longer TL. The strongest evidence comes from a large cohort of adults with a lifetime diagnosis of depression and/or anxiety and controls, in which individuals who did not have a romantic partner had greater LTL attrition over a six-year period (100). In moderate to large population-based samples, Whisman et al. (126) and Mainous et al. (73) found that married individuals had longer sTL and LTL, respectively, than individuals who were separated, divorced, widowed, or never married. In addition, Yen & Lung (127) reported that Taiwanese older adults who were married had longer LTL than did those who were widowed, divorced, or single, although the small effect was reduced to marginal significance when adjusting for several covariates. Given that the magnitude of the association was similar to that reported by Whisman et al. (126), it is possible that the smaller sample size limited the statistical power to detect a significant association.

Overall, large population-based studies provide compelling evidence that marital status is related to TL, although associations are typically small. Future research would benefit from investigation of the influence of marital status on TL shortening over time and the potential psychological and behavioral mechanisms that may explain the observed associations, including the importance of a close supportive relationship and the experience of emotional connection and physical affection.

5.3. Social Support

Social support has been defined in the literature as the perception that emotional, informational, and/or tangible support is available, if needed. A sizeable literature suggests that perceived social support is associated with decreased risk for earlier morbidity and mortality (28, 29), and six studies have investigated links between perceived social support and TL. The strongest evidence of the association between social support and TL comes from larger population-based studies. For example, Carroll et al. (16) found that low perceived social support was associated with shorter LTL in older adults (65–84 years) but not younger adults (45–64 years). Similarly, Barger & Cribbet (4) found that married older adults who did not list their spouse as "the most helpful person in providing emotional support" in the past year had shorter LTL than did those who listed their spouse as most helpful. Zalli et al. (128) classified participants into groups on the basis

of PBMC TL and telomerase levels, finding that adults with short PBMC TL/high telomerase reported lower perceived social support than did those in the other groups; however, this effect was further modified by gender, with stronger effects for men than women. In contrast with these findings, Lincoln et al. (65) reported that higher perceived emotional support from extended family members was associated with shorter sTL in older adults, in analyses that also accounted for negative interactions (e.g., criticism) with family members.

Smaller cohort studies also report consistent findings. Mitchell et al. (77) reported that, among perinatal women, lower perceived support from family (but not from a romantic partner or friends) was associated with shorter PBMC TL, averaged across early, middle, and late pregnancy, and 7–11 weeks postpartum, as TL did not change during this period. In a small sample of former Israeli prisoners of war, Stein et al. (115) found that lower perceived social support assessed 18 years after repatriation was associated with shorter LTL measured 24 years later, in older adulthood, even when accounting for perceived loneliness.

Overall, these findings suggest that low perceived social support is linked with shortened TL, although this association may by moderated by sample characteristics such as participant age, biological sex, and relationship type (e.g., romantic partner, other family members). The majority of these studies used a qPCR to measure TL, with a variety of sample sources. Given that findings from these studies were small but mostly consistent, the influence of social support on TL is a promising future direction that warrants additional investigation.

5.4. Social Strain

Social strain has been characterized as the presence of conflict and other negative interactions (e.g., criticism, control) in social relationships. To date, three studies have investigated associations between strain in social relationships and TL, with mixed findings. We note that two of the studies were based on the same sample of participants.

In a moderately sized sample, Uchino and colleagues (122) found that adults who had a greater number of ambivalent social relationships (characterized by both high positivity and negativity) had shorter PBMC TL, while also accounting for the number of supportive, aversive, and indifferent (characterized by low positivity and negativity) social relationships; however, this association was moderated by participant gender, with a significant association for women but not men. In the same sample of adults, Uchino et al. (121) also reported that greater perceived social network control (attempts by social network members to get an individual to modify their health behaviors or lifestyle) was associated with shorter PBMC TL. In contrast, in a larger population-based study of older adults, Lincoln et al. (65) found that experiencing more negative interactions with extended family members (characterized by making demands, criticism, letting one down, and getting on one's nerves) was not associated with sTL when also accounting for perceived emotional support.

Each of the studies on social strain used qPCR to measure TL but differed in sample source and sample size. Together, these studies provide preliminary evidence that greater social strain is related to shorter TL, but they varied widely in their measurement of social strain. As with social support, future research would benefit from the inclusion of well-validated measures of social strain and additional consideration of participant age, biological sex, and relationship type (e.g., romantic partner, other family members) as moderators of the association between social strain and TL.

5.5. Social Isolation and Loneliness

Previous research has identified social isolation, or lack of social contact or communication, as a significant risk factor for mortality that is comparable in magnitude to smoking (47). Loneliness,

which is a related construct that involves feelings of social isolation, disconnectedness, and not belonging, has also been associated with poor health and increased risk for early mortality. To date, however, only three studies have investigated associations between loneliness and TL. In a small sample of former Israeli prisoners of war, Stein et al. (115) found that higher reported feelings of loneliness assessed 18 years after repatriation were moderately associated with shorter LTL measured 24 years later, in older adulthood, while also accounting for perceived social support. In contrast, in two large European samples of male older adults, Rius-Ottenheim et al. (103) found that loneliness was not associated with LTL or change in LTL over a seven-year period in one of the samples. In addition, in a moderately sized cohort study of older adults with depression (in which 74% had been diagnosed with a current depressive disorder) and controls, loneliness was not associated with LTL (108).

Considering the lack of findings in cohort studies with very specific populations (e.g., older adult males and individuals with depression), additional research that investigates the influence of social isolation and loneliness on TL shortening in samples that are more representative of the general population is recommended.

5.6. Summary of Adult Social Stress

A number of social stressors in adulthood, including having a small network size, lacking a committed romantic partner, having low perceived social support, experiencing social strain, and feeling lonely were all found to relate to shorter TL. The most consistent results were observed for social support, marital status, and social strain, whereas more varied findings were observed for social network and loneliness. Future research will benefit from the use of well-validated measures across studies and repeated assessments of social stress and TL. These findings highlight the need for further research that better characterizes the social environment as a source of stress and a resource to protect from stress-induced cellular aging.

6. CONCLUSIONS

This article has aimed to review and evaluate the extant literature on psychosocial stress exposures and experiences in childhood and adulthood and TL. The most consistent findings were observed across studies that investigated childhood SES, ELA (using a count measure of adverse exposures), racial discrimination, marital status, and perceived social support. In contrast, the least consistent findings were observed across studies that focused on childhood abuse (assessed retrospectively), caregiving status, and loneliness. Of note, some of the largest associations were reported between childhood SES and ELA and adult TL, and in some cases, these associations were found over and above or in the absence of associations between adult stressors and TL. The most convincing evidence comes from larger studies that adopted a longitudinal design (e.g., childhood abuse) and assessed stress exposure (e.g., stressful life events) during the same time period as the measurement of TL change. Areas of research that were underdeveloped but warrant future research include work-related stressors, threat appraisals, discrimination, family separation, social network size, social strain, and social isolation/loneliness. It is important to note the potential for publication bias against significant results in this literature; however, given that there are a number of published studies with large samples and null findings, it seems likely that unpublished studies may involve smaller samples that lack the statistical power to detect small to modest effects. Although there are differences in the literature with respect to the consistency and strength of association between specific types of stressors and TL, stress exposures and responses likely ultimately share common biological and behavioral pathways to shortened TL.

6.1. Mechanisms

The existing data on TL, as an indicator of biological age, support the premise that psychosocial stress can, in certain circumstances, influence rates of biological aging across the life span. A number of potential biological mechanisms have been proposed to explain how stress may contribute to accelerated aging by activating two sympathoadrenal-mediated pathways. First, the neuroendocrine response pattern is characterized by an increased release of norepinephrine and epinephrine, and a secondary release of cortisol, which then increases the release of energy stores (including elevating blood glucose) into circulation and activates intracellular processes that produce ATP (104). Second, the immune cells' response to adrenergic stimulation results in activation of nuclear factor kappa B (NF-κB) and secondary release of inflammatory mediators that promote proinflammatory cell activity (51). These pathways can both increase the release of reactive oxygen and nitrogen species, which results in damage to DNA, and promote cell replication. Telomeric ends of the DNA are particularly vulnerable to damage and under circumstances of high cell replication can experience rapid shortening. In complement to the adrenergic pathway, cortisol release and subsequent binding to cells downregulate telomerase enzymatic activity (24), which rebuilds lost telomeric repeats and has a concurrent impact on cellular maintenance of the telomere ends (8). The end result of these processes of DNA damage (including to mitochondrial DNA) (89), reduced telomerase activity, and TL attrition is activation of cellular senescence, a hallmark of biological aging (70). Thus, prolonged or repeated activation of these stress response pathways leads to wear and tear in the intracellular environment that is detrimental to the sustained, long-term life of the cell. This response has likely been conserved as evolutionarily adaptive because, in the face of pending threat, it is advantageous for survival (at least in the short term) to shift resources in favor of protection from invading microbes and wound repair rather than organism longevity, and acute events should have minor lasting effects. However, prolonged activation and/or repeated events can ultimately erode cell health. The effects of chronic stress are likely to be most pronounced when occurring over decades of life, which no studies to date have investigated, although Puterman and colleagues' (94) findings suggest that ELA may be the most detrimental for TL over and above the influence of adult stress exposure.

In this discussion, it is also highly relevant to recognize the role of recovery and repair mechanisms in restoring cellular health. To maintain cell health and promote longevity, the caustic cellular events that occurred as a result of stress must be restored through activation of repair mechanisms once the stressor ceases (104). Allowing time for restoration in which threats are neutralized is of great importance, given that daily stressors may continue to exact a toll if accompanied by an inability to turn off the stress response system. Thus, sleep represents a critical period of restoration and healing on a daily basis. Given that many individuals who experience stressors during waking hours continue to suffer through the night with an inability to fall asleep and stay asleep (58, 92, 102), sleep may be a particularly important window of opportunity for restoration of cellular health. Indeed, research has linked insomnia and poor sleep to TL shortening (17, 27, 93) and older epigenetic age (18), and experimental sleep deprivation has been shown to increase DNA damage (14) and inflammation (53). Sleep disturbance may therefore represent a behavioral pathway through which psychosocial stress has an impact on cellular aging. Future research is needed that carefully examines daytime stress exposure, nighttime restorative sleep, and molecular processes that lead to cellular aging. Although existing research links psychosocial stress to cellular aging, it will be important for future research to characterize the intracellular environment as it responds to prolonged or repeated stress, as well as secondary restoration responses, such as DNA repair, telomerase activity, and anti-inflammatory patterns that are promoted during sleep.

6.2. Limitations of the Measure

As researchers develop new tools to characterize cellular aging, the field of psychosocial influences on aging will also need to adopt new techniques. The measure of TL used in the majority of studies in this review is capturing an estimate of TL across a number of cell types in blood or saliva (i.e., predominantly leukocytes). This average estimate of TL may obscure changes that occur within specific immune cell compartments (e.g., T cells), as a result of cellular stress and/or replication, and inordinately represent cells in the pool that are derived from stem cell reserves, which can be replenished daily to weekly (i.e., granulocytes). In addition to the cell subset distributional changes, we do not know whether the TL estimate that is captured in blood is representative of TL change in other tissues; although correlations between blood and tissue have been noted (30, 117), similar estimates in TL across tissues likely reflect length similarities from shared stem cells in early development rather than changes in TL in tissue over the sampling time frames in adulthood. Beyond TL, other hallmarks of biological aging have been proposed (70), including the epigenetic clock (49, 63, 72) and cellular senescence (68), both of which may better capture the biological aging process than TL attrition in white blood cells. For instance, one study in this review investigated more than one marker of biological aging: TL and cellular senescence marker $p16^{INK4a}$. In a sample of middle-aged parents, Rentscher et al. (99) found that chronic stress exposure, perceived stress, and accumulated daily stress appraisals were each associated with $p16^{INK4a}$ expression but not with LTL. Future research will need to confirm this finding, as well as associations between TL and other hallmarks of aging.

6.3. Future Directions

An important direction for future research on psychosocial stress and TL will be to improve the definition and reliable assessment of stress exposures and responses and to increase the consistency of stress measurement across studies. The Stress Measurement Network is a network of expert stress researchers that was developed at the University of California, San Francisco, in 2015 to improve the measurement of psychosocial stress in research. In a recent paper, Epel and colleagues (38) outlined that the measurement of stress is complex because it is experienced at multiple levels (physiological, psychological, and social) and over different time scales (acute stress, daily events/hassles, life events, and chronic stressors). The authors explained that one of the most defining characteristics of a stressor is its duration, which in this review was rarely addressed, with the exception of research on caregiving. Given that stressors do not occur in isolation, future research will benefit from measuring the intensity and duration of multiple stressors across levels, time scales, and domains (e.g., caregiving, financial strain, etc.), which are likely to interact to influence aging and health. In addition, measuring cumulative exposures across a lifetime allows researchers to test dose–response associations between stress and rates of biological aging (38).

A second direction for future research will be to incorporate additional measures of biological aging. To date, TL has provided a useful tool to begin to test the association between psychosocial stress and biological aging; however, future psychosocial research should not be dependent on any one indicator of biological aging. Rather, the imperative to conduct convincing scientific inquiry to delineate how psychosocial factors "get under the skin" to influence aging and health requires that future investigations apply a multimodal assessment that captures dynamic cellular aging by tracking multiple hallmarks of aging (e.g., mitochondrial function, cellular senescence, the epigenetic clock) (56, 70). This approach requires a thoughtful application of biological aging theory in the context of psychosocial stress exposure, which then has the potential to identify convincing behavioral targets for intervention.

A final direction for future research is to develop and refine our causal understandings of the effects of psychosocial stress on TL, with an eye toward reducing stress in order to prevent, stabilize, and in some cases even reverse TL shortening and other biological aging processes. Most TL research is conducted using observational designs, with limited attempts to home in on causality through interventions or quasi-experimental methods (9, 112). To move the field forward, it will be necessary for TL research to attempt to causally link stressors to TL using quasi-experimental methods and potentially large-scale interventions (41, 43, 50, 88).

Fortunately, many quasi-experimental studies already exist and may be a unique opportunity to rapidly move the field forward by adding a biological sample as part of the data collection. For example, large population-based studies such as the Fragile Families and Child Wellbeing Study and the Health and Retirement Study, which have already measured TL, are well positioned to study the impact of various macro-level modifiers as exogenous shocks (e.g., policy change, natural disasters) and how this might shift TL in a population. Similarly, focused studies of specific major disasters or other exogenous events may be amenable to adding biological data collection. Documented causal pathways would then inform future interventions (55, 114).

A particularly exciting avenue in future research is to apply psychosocial interventions (in contrast to the more macro or economic ones mentioned above) to examine how targeting psychosocial and behavioral factors may help mitigate the damage incurred from exposure to psychosocial stress. In this review, we highlighted research by Brody and colleagues (5, 11), who found that a family-based group intervention for supportive parenting was associated with longer TL. A number of other interventions with demonstrated effectiveness could be applied in this context, including behavioral modification to improve sleep and manage stress (e.g., cognitive behavioral therapy for insomnia, tai chi, yoga) (10, 52) and promotion of increased physical activity and other healthy lifestyle modifications (82, 83, 97). Likewise, mindfulness meditation has been effective at lowering stress appraisal, responsivity, and neuroendocrine mediators (26, 85) and has been proposed as a means to impact telomere biology (35). In addition, some evidence indicates that group-based support and family interventions can improve mental health and perceptions of social support in caregivers and reduce loneliness in older adults (19, 28, 31, 69), yet the impacts on biological aging pathways have not yet been fully examined.

6.4. Concluding Remarks

Taken together, findings from existing studies linking a wide range of psychosocial stress exposures to shortened TL are mixed. Associations between stress and TL appear strongest when examining the impact of in utero adversity and ELA, testing more proximal indices of stressful life events, and looking at the role of close social relationships, whereas associations with self-reported perceived stress and SLEs that occurred many years prior to the TL assessment were modest and inconsistent. The most consistent links between stress and TL come from studies of ELA, suggesting that the timing of stress exposure across the life course may be particularly important, with a window of vulnerability in early life. Likewise, the type of stress may be particularly salient, with social stress in adulthood, including social strain, loneliness, and a lack of social support, yielding relatively consistent findings and pointing to the importance of high-quality social relationships for health (48, 105, 120). In addition, designs that included comprehensive characterization of participants' stress exposures and responses and assessed changes in TL over time yield stronger effects than designs with single-occasion measurement of stress and TL, providing support for the role of stress in accelerating TL attrition. However, most research to date has been cross-sectional or provided TL assessments at a single time point, limiting conclusions about causal inference. It will be important for future investigations to employ repeated assessments of stressor exposures,

to examine pathways using experimental models, and to broaden the measurement of biological aging parameters beyond a single measurement approach.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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