Telomeres and Early-Life Stress: An Overview

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The long-term sequelae of adverse early-life experiences have long been a focus in psychiatry, with a historic neurobiological emphasis on physiological systems that are demonstrably stress-responsive, such as the hypothalamic-pituitary-adrenal axis and neuroimmune function. However, there has been increasing recognition in the general medical literature that such sequelae might encompass more pervasive alterations in health status and physiology. Recent findings in telomere biology have suggested a new avenue for exploring the adverse health effects of childhood maltreatment. Telomere length in proliferative tissues declines with cell replication and the effect can be accelerated by such factors as inflammation, oxidative stress, radiation, and toxins. Reduced telomere length, as a proxy for cellular aging, has been associated with numerous chronic somatic diseases that are generally considered to be diseases of aging, such as diabetes, cancer, and heart disease. More recently, shorter telomeres have been demonstrated in several psychiatric conditions, particularly depression. Sustained psychosocial stress of a variety of types in adulthood appears to be associated with shorter telomeres. Now, emerging work suggests a robust, and perhaps dose-dependent, relationship with early-life stress. These findings present new opportunities to reconceptualize the complex relationships between experience, physical and psychiatric disease, and aging.

Key Words: Childhood adversity, childhood maltreatment, early-life stress, stress, telomerase, telomere

That early-life experiences have enduring sequelae has been a central tenet of psychiatry for over a century. Initial formulations of this idea emphasized clinical implications, particularly in classical psychoanalytic theory, and it is now well documented 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 disorders may have a more virulent course in individuals with a history of childhood maltreatment (1).

More recently, an etiological role for early-life stress has been documented for 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, perhaps multifactorial, etiology and pathophysiology. However, some investigators suggest that early environmental factors can also impact the risk for conditions generally thought to have a relatively clear pathogenesis, such as cardiovascular disease and type 2 diabetes (8). Indeed, individuals with a history of early-life stress 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 adverse childhood experiences (9).

Efforts to elucidate how early-life stress is transduced into physiological dysfunction and clinical impairment have focused on the hypothalamic-pituitary-adrenal axis (1), not surprisingly, given the historic centrality of that system in understanding the stress response. Other research has provided evidence for the role of neuroimmunological mechanisms in linking early-life stress and disease (10). Now, rapidly emerging clinical findings suggest that telomere biology might offer a new avenue for exploring the adverse health effects of childhood maltreatment. This review will examine those findings; contextualize them in light of current understanding of the relationship between telomeres, illness, and stress; and highlight key methodological issues requiring consideration as the field moves forward.

Telomeres: Basic Concepts

Telomeres (from the Greek telos [end] and meros [part]) are DNA protein complexes at the ends of chromosomes, composed of tandem TTAGGG repeats ranging from a few to 15 kilobases in length. Their critical role in maintaining chromosomal stability was first described in the 1930s by McClintock (11) and Muller (12). It is now established that telomeres shorten with each cell division (13) and that maintenance of telomere function depends on both a minimal length of TTAGGG repeats and telomere-binding proteins (14). Telomere length can be maintained by the enzyme telomerase, a ribonucleoprotein reverse transcriptase mainly expressed in stem cells, germ cells, and regenerating tissues. However, 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 serve as a kind of biological counter, ticking off the passage of time with each cell division (15). Telomere shortening is also influenced by recombination, epigenetic regulation, and genetic factors, as well as oxidative stress, and the ability of telomerase to counteract these influences is limited.

Measurement of Telomere Length

For years, the gold standard for measuring telomere length has been the Southern blot. There are significant limitations to this method: it is time consuming and labor intensive, significant amounts of genomic DNA are required, deducing telomere length from a Southern blot smear is problematic, and there are potential issues of reproducibility. Cawthon (16) developed an easier method utilizing quantitative polymerase chain reaction (PCR), which mimics DNA replication. The method developed by Cawthon (16) 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. Quantitative PCR demonstrates good correlation with results from Southern blot analyses and is now widely used. However, this method has greater measurement error than the Southern blot and can show substantial variability across laboratories (17), necessitating careful quality controls and multiple sampling to assure reliability.

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There are also methods employing hybridization coupled with cytometry (18,19), 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.* (20). Most psychiatric studies examining telomere length have used either Southern blot analyses or the Cawthon (16) quantitative PCR method. Since individual laboratories internally calibrate their measurements of telomere length, it can be difficult to compare measurements across groups.

Cross-Sectional Versus Longitudinal Approaches in Studies of Telomere Length

A major drawback to using telomere length as a clinical measure is the high variability between individuals, which is present at birth (21,22). Moreover, although telomere length is equal between the sexes at birth, shortening with age occurs more rapidly in male than female individuals, and rates may also differ between ethnic groups (23). These factors limit the power of cross-sectional studies, which utilize measurements at a single time point. Such studies require large sample sizes because of the marked variability of telomere length, as well as careful control subjects for age and sex. Aviv *et al.* (22) estimates that longitudinal studies, measuring actual telomere erosion rates within individuals over time, would require five times fewer subjects than cross-sectional studies. Longitudinal studies also better support an assertion of causality by the independent variable of interest, which is severely constrained in cross-sectional designs.

Despite these considerations, very few longitudinal telomere studies have been conducted, and their dearth is particularly evident in work involving 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 variable of interest 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.

Telomeres and Somatic Disease

Because of their prominence in aging (24), telomeres have been intensively investigated in medical conditions associated with aging. Most clinical studies have utilized telomeres derived from leukocytes, since peripheral blood is more easily obtained than most other tissues. The major determinants of aging, including cell replication, inflammation, and oxidative stress, are all demonstrable in leukocyte telomeres (15,24,25). A potential pitfall 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 (22). If such a factor is of major interest (e.g., human immunodeficiency virus), telomere length might be more appropriately ascertained in a specific subset. Similarly, since telomere length reflects the leukocyte's replicative history, any condition that increases leukocyte turnover can introduce bias. Controlling for factors that alter leukocyte turnover or subsets (e.g., acute or chronic 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 ideal for studies with children (26–28), although at present there is less experience with this tissue source.

A key finding from clinical studies is that alteration of leukocyte telomere dynamics reflects organ dysfunction elsewhere in the body (25). A prime example is cardiovascular disease, in which reduced telomere length is observed not only in leukocytes but also in myocardial and arterial wall tissue (29,30). Findings in other medical conditions, including cancers (31,32), stroke (33,34), diabetes (35–37), and autoimmune diseases (38), support the notion that reduced telomere length in leukocytes correlates with shorter telomeres in the target tissue.

A possible explanation for this observation could be that common underlying mechanisms for these diseases also manifest themselves in leukocytes. For example, oxidative stress, which is caused by age-related mitochondrial dysfunction, is involved in diabetes, cardiovascular disease, and cancer and affects tissues in general. Telomerase could also be involved, perhaps as a mediating agent. Indeed, some evidence implicates telomerase in the cell survival-promoting actions of brain-derived neurotrophic factor in early postmitotic hippocampal neurons (39), which could be relevant to the association of telomere length with stress and depression, as discussed below.

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.* (40) 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 (41,42) and hypertension (43). Reports of reduced telomere length in association with smoking (44), obesity (45), and alcohol abuse (46) 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 (15). Progeroid syndromes, characterized by clinical manifestations of accelerated aging and

Table 1. Telomeres and Psychiatric Conditions

Diagnosis	References	Total *n*	Findings
MDD	49–51, 53–58	MDD = 700 (including 204 with stable CHD) HC = 1765 (including 746 with stable CHD)	Shorter telomeres associated with MDD: 5 studies No difference in telomere length: 3 studies Increased telomerase activity with MDD: 1 study
BIP	50, 52, 58	BIP = 103 HC = 118	Shorter telomeres associated with BIP: 2 studies No difference in telomere length: 1 study
SCZ	58–60	SCZ = 145 HC = 187	Shorter telomeres associated with SCZ: 2 studies[a] No difference in telomere length: 1 study

BIP, bipolar disorder (I and II); CHD, coronary heart disease; HC, healthy control subjects; MDD, major depressive disorder; SCZ, schizophrenia.
[a]Only in treatment-resistant patients in one study.

molecular evidence of defective DNA repair, may also reflect causal involvement of telomeres (15). A preliminary report suggests an increased rate of neuropsychiatric disorders in dyskeratosis congenita (47). At this point, it would be premature to exclude an etiologic contribution of telomere dysfunction in other conditions.

Telomeres and Psychiatric Conditions

Independent of stress, most of the findings implicating telomeres in psychiatry have involved mood disorders (Table 1). In an initial epidemiological study ($n = 433$), Lung *et al.* (48) reported an association of reduced telomere length with the high-activity allele of the monoamine oxidase A promoter polymorphism, which has been linked to aggression and impulsivity; this association was later found mediated by MDD (49). Simon *et al.* (50) demonstrated shorter telomeres in patients with MDD ($n = 15$) or bipolar disorder (type I or II not stated) ($n = 29$) compared with healthy control subjects ($n = 44$) (50). This was replicated by Hartmann *et al.* (51), who found no effect of illness duration or severity or nature or intensity of treatment in a study comparing MDD patients ($n = 54$) with control subjects ($n = 20$). Elvsåshagen *et al.* (52), describing reduced telomere length in bipolar II patients ($n = 28$) compared with control subjects ($n = 28$), detected an association with lifetime number of depressive episodes but not illness duration. Wikgren *et al.* (53), reporting shorter telomeres in MDD patients ($n = 91$) versus control subjects ($n = 451$), also noted an association with hypocortisolism in both groups. Wolkowitz *et al.* (54) 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. This group also reported increased telomerase activity in drug-free MDD patients versus control subjects, with superior antidepressant responses in patients showing the greatest further increases (55). In an epidemiological study of 952 patients with coronary heart disease, Hoen *et al.* (56) found MDD associated with shorter telomeres. While these studies all utilized leukocytes, no differences from control subjects were found in telomere length in occipital cortex of patients with MDD ($n = 24$) (57) or in cerebellar gray matter of patients with MDD ($n = 15$), bipolar disorder ($n = 46$), or schizophrenia ($n = 46$) (58).

Shorter leukocyte telomeres have been reported in schizophrenia (59), treatment-resistant schizophrenia (60), obstructive sleep apnea (61), migraine (62), mild cognitive impairment (63), and Alzheimer disease (64) (one study failed to replicate the latter two findings [65]). Reduced telomere length correlated with decreased mental health in chronic heart failure (66) (but not in community-dwelling elderly men [67]), poorer cognition in community-dwelling elders (68) and healthy women (69), unspecified poor sleep quality in healthy women (70), and pessimism in postmenopausal women (71). It remains to be clarified whether the shorter telomeres observed in these heterogeneous conditions reflect a spe-

Table 2. Telomeres and Psychosocial Stress

Type of Stress	References	Total *n*	Findings
Caregiver Stress	72, 74, 78–80	Stressed = 126[a] Control subjects = 64[a]	Shorter telomeres associated with perceived stress: 1 study Shorter telomeres associated with caregiver status: 1 study Telomere length not associated with caregiver status: 1 study Reduced telomerase activity associated with perceived stress: 1 study Reduced telomerase activity associated with caregiver status: 1 study Increased telomerase activity associated with caregiver status: 1 study Shorter telomeres associated with greater salivary cortisol response to TSST: 1 study Shorter telomeres associated with higher anticipatory threat appraisal to the TSST: 1 study
TSST	73	Stressed = 62	Shorter telomeres and reduced telomerase activity associated with increased nocturnal urinary cortisol and catecholamines: 1 study
Laboratory Challenge Tasks	26	78 (children)	Shorter telomeres associated with increased heart rate and cortisol reactivity
Dietary Restraint (Preoccupation with Weight, Restricted Food Intake)	75	Stressed = 56	Shorter telomeres associated with greater dietary restraint: 1 study
Perceived Stress (PSS)	76	647	Shorter telomeres associated with perceived stress: 1 study
Interpersonal Violence	77	Stressed = 61 Control subjects = 41	Shorter telomeres associated with interpersonal violence: 1 study
Rape	81	Stressed = 64 (9 with PTSD)	Shorter telomeres associated with PTSD following rape: 1 study
Chronic Pain	82	Stressed = 18 Control subjects = 18	Shorter telomeres associated with chronic pain + high stress: 1 study
Hostility	83	434	Shorter telomeres and increased telomerase activity associated with hostility in men: 1 study
SES	27, 85	1622	Shorter telomeres associated with lower SES: 2 studies
Minority Ethnicity	23	African American = 117 Caucasian =115	Shorter telomeres associated with African American ethnicity (trend): 1 study
Educational Attainment	86, 87	5046	Shorter telomeres associated with lower educational attainment: 2 studies
Employment/Work Schedule	88	608	Shorter telomeres associated with current and long-term full-time work schedule: 1 study

PSS, Perceived Stress Scale; PTSD, posttraumatic stress disorder; SES, socioeconomic status; TSST, Trier Social Stress Test.
[a] *n*s estimated due to overlapping samples.

Table 3. Studies Examining the Relationship Between Telomere Length and Early-Life Stress

Author	Sex Distribution	Presence of ELS in Sample	Age at Telomere Measurement ($\bar{X} \pm$ SD or Range, Years)	Type of ELS and Assessment Method
Tyrka *et al.* (2010) (89)	9 M, 22 F	10/31	26.9 ± 10.1	Emotional/physical/sexual abuse, emotional/physical neglect; CTQ subscales
Glass *et al.* (2010) (90)	Not specified	20/540 (physical abuse); 34/550 (sexual abuse)	Not specified	Physical/sexual abuse; individual survey questions
Kananen *et al.* (2010) (91)	617 F (202 Anx), 357 M (119 Anx)	1.94 adverse events (Anx); .97 adverse events (control subjects)	49.7 ± 12.8 (Anx); 49.8 ± 12.6 (control subjects)	Adverse childhood social environment (financial difficulties, parental unemployment, parental physical/mental illness, familial conflict, bullying, personal illness); sum of individual survey questions
Kiecolt-Glaser *et al.* (2011) (92)	37 M, 95 F	42/132 (abuse); 74/132 (adverse event)	70.10 ± 9.41 (caregivers); 69.37 ± 10.73 (control subjects)	Emotional/physical/sexual abuse, childhood adversity (parental death, parental marital conflict, familial mental illness, familial alcohol problems, lack of close relationship with adult); CTQ; sum of individual survey questions
Surtees *et al.* (2011) (93)	0 M, 4441 F	2234/4441	62 (median)	Childhood social adversity (separation from mother for >1 year, extended hospital stays, parental unemployment, traumatic events, removal from home, divorce, parental substance use, physical abuse); HLEQ
O'Donovan *et al.* (2011) (94)	43 M (22 PTSD), 45 F (20 PTSD)	50 trauma reports (PTSD); 6 trauma reports (control subjects)	30.40 ± 6.63 (PTSD); 30.68 ± 8.19 (control subjects)	Physical neglect, physical abuse, family violence, forced sexual touch, forced sexual intercourse; sum of individual interview items on Life Stressor Checklist interview
Drury *et al.* (2011) (95)	67 M, 69 F	136/136	6–10	Time spent in institutionalized care
Entringer *et al.* (2011) (96)	21 M, 73 F	45/94	25 ± .8 (prenatal stress); 24 ± .6 (controls)	Exposure to prenatal stress during mother's pregnancy (defined as experience of negative life events, such as death/illness in family, loss of residence, etc.); interview
Shalev *et al.* (2012) (28)	120 M, 116 F	108/236	Baseline: 5; Follow-up: 10	Exposure to domestic violence between mother and her partner, frequent bullying victimization, physical maltreatment by an adult; CTS, interview

Anx, anxiety disorder (full or subthreshold); BMI, body mass index; CAPS, Clinician-Administered PTSD Scale; CES-D, Center for Epidemiologic Studies Depression Scale; CTQ, Childhood Trauma Questionnaire; CTS, Conflict Tactics Scale; ELS, early-life stress; F, female; GAD, generalized anxiety disorder; HDL, high-density lipoproteins; HLEQ, Health and Life Experiences Questionnaire; IL-6, interleukin-6; LDL, low-density lipoproteins; M, male; M-CIDI, Munich-Composite International Diagnostic Interview; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; qPCR, quantitative polymerase chain reaction; SCID, Structured Clinical Interview for DSM-IV; SES, socioeconomic status; SF-36, Short Form Health Survey.

cific or nonspecific preexisting 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.

Telomeres and Psychosocial Stress

It is established that biophysical stress and stressors (e.g., radiation, toxins) (31,32) can impact telomere dynamics. However, Epel *et al.* (72), in a study of mothers caring for either a chronically ill (n = 39) or healthy (n = 19) child, were the first to demonstrate shorter telomeres (and reduced telomerase activity) in association with psychosocial stress (Table 2). 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) (73). Subsequent studies have examined telomere length and telomerase activity in various stress-related contexts. Damjanovic *et al.* (74) reported shorter telomeres and increased telomerase activity in caregivers of Alzheimer's disease patients (n = 41) compared with control subjects (n = 41). Kiefer *et al.* (75), 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.* (76) 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.* (77) detected shorter telomeres in women with a history of intimate partner violence (n = 61) compared with control subjects (n = 41). In a study of female caregivers of dementia partners (n = 14) and control subjects (n = 9), Tomiyama *et al.* (78) found that shorter telomeres were associated with greater salivary cortisol responses to the TSST and higher overnight urinary free cortisol. In one expanded sample from this study (n = 22 caregivers, n = 22 control

Table 3. (continued)

Sample Composition and Assessment of Psychopathology	Controlled Covariates	Telomere Measurement Method	Findings
No current or past major Axis I disorder; SCID	Age, sex, oral contraceptives, smoking, BMI, race, education, SES, perceived stress	qPCR; leukocytes	Shorter telomeres associated with ELS.
Epidemiological sample; psychopathology not specified	Age, sex, BMI, smoking	Southern blot; leukocytes	Telomere length no different between subjects with and without ELS.
Anxiety disorder (full or subthreshold) versus control subjects; assessed MDD/dysthymia, alcohol use disorder; M-CIDI	Comorbid disorders, psychiatric medication, BMI, blood pressure, blood chemistries (homocysteine, triglycerides, HDL, LDL, glucose, insulin), diabetes, lifestyle factors (smoking, sleep, exercise)	qPCR; leukocytes	Shorter telomeres associated with ELS (greater number of childhood adverse events). Telomere length no different between anxiety and control groups.
Caregivers versus control subjects; assessed depressive symptoms; CES-D	Age, sex, BMI, exercise, sleep, alcohol use, caregiving status	Southern blot; leukocytes	Shorter telomeres associated with ELS (≥2 childhood adversities; abuse without other adversities not associated with telomere length). Shorter telomeres associated with increased plasma IL-6.
Epidemiological sample; assessed MDD, GAD; HLEQ, SF-36	Age, physical health score, self-reported health, social class, obesity, smoking, preexisting disease	qPCR; leukocytes	Shorter telomeres associated with ELS (greater number of childhood adverse events).
PTSD versus control subjects; assessed alcohol/substance abuse/dependence, MDD; CAPS, SCID	Age, sex, BMI, smoking, education	qPCR; leukocytes	Shorter telomeres associated with ELS (greater number of ELS types); shorter telomeres in PTSD versus control subjects (accounted for by effect of ELS).
Psychopathology not specified	Institutionalized versus foster care, ethnicity, age at telomere collection, low birth weight	qPCR; buccal cells	Shorter telomeres associated with ELS (greater time in institutionalized care).
Assessed depressive symptoms; CES-D	Age, BMI, birth weight percentile, early-life and concurrent life stress	qPCR; leukocytes	Shorter telomeres associated with ELS (prenatal stress); effect greater in females than males.
Subset of epidemiological sample; psychopathology not specified	Age, sex, BMI, SES	qPCR; buccal cells	Telomere shortening from age 5 to age 10 associated with exposure to ≥2 forms of violence.

subjects), telomerase activity was lower at baseline in caregivers but rose similarly in both groups during the TSST (79); in another expanded sample ($n = 27$ caregivers, $n = 23$ control subjects), 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 (80). Kroenke *et al.* (26) 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.* (81) 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.* (82) 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.* (83) 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.* (84) 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.

Reduced telomere length has been correlated with several sociodemographic variables thought to represent proxies for sustained psychosocial stress, including lower socioeconomic status (27,85), African American ethnicity (23), lower educational attainment (86,87), and current and long-term full-time work schedule (88).

Telomeres and Early-Life Stress

Tyrka *et al.* (89) offered the first evidence linking early-life stress with reduced telomere length, in a study of physically and psychiatrically healthy adults with ($n = 10$) or without ($n = 21$) a reported history of childhood maltreatment (Table 3). Eight other studies have since appeared examining this issue, a remarkable number given the short time interval. In response to Tyrka *et al.* (89), Glass *et al.* (90) presented data on adults from the Twins United Kingdom

cohort in which they detected no difference in telomere length between individuals who endorsed childhood sexual ($n = 34$) or physical abuse ($n = 20$) compared with those who did not ($n = 516$ and $n = 520$, respectively). However, Kananen *et al.* (91) confirmed an association of shorter telomere length with increasing number of reported childhood adverse life events in $n = 974$ adults in the Finnish Health 2000 project, even absent a relationship with current psychological distress or DSM-IV anxiety disorder diagnosis. Kiecolt-Glaser *et al.* (92) 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.* (93), studying 4441 women in the United Kingdom European Prospective Investigation into Cancer-Norfolk database, found that shorter telomeres correlated with increased reported childhood adverse experiences, although not with current social adversity or emotional health. Consistent with Malan *et al.* (81), O'Donovan *et al.* (94) observed reduced telomere length in adults with chronic PTSD ($n = 43$) versus healthy control subjects ($n = 47$); however, 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.* (95) 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. Extending the period of vulnerability, Entringer *et al.* (96) demonstrated that maternal experience of severe psychosocial stress during pregnancy was associated with shorter telomeres in young adult offspring ($n = 45$) versus control subjects ($n = 49$). In the only prospective longitudinal study thus far, involving 236 children tested at age 5 and again at age 10 years, Shalev *et al.* (28) 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 ($n = 69$). Taken together, these studies support a relationship between early-life stress and reduced telomere length and strongly suggest that this effect is dose-dependent.

Telomeres and Early-Life Stress: Mechanisms

In their review of the neurobiological interrelationship between stress, depression, and aging, Wolkowitz *et al.* (97) observe that many of the biochemical derangements in depression, and in chronic stress, result in cellular effects indistinguishable from aging. Indeed, they propose that the high comorbidity of depression with diseases of aging, such as cardiovascular disease, cerebrovascular disease, and metabolic syndrome, suggests that stress-engendered depression is itself such a disease. In this conceptualization, telomere shortening would be an expected concomitant, and/or consequence, of the hypothalamic-pituitary-adrenal 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 (78,98).

However, while examination of the biochemistry of aging and telomere dynamics (15,24,25,31,32) is beyond the present scope, there has yet to be direct demonstration of these mechanisms in affected human subjects or relevant animal models. Similarly, even as attention has turned to the role of epigenetics as a major transductive mechanism for adult sequelae of early-life stress (99,100), there are still no direct studies of telomere dynamics in this regard. Finally, as noted above, problematic lifestyle factors (e.g., smoking, obesity, alcohol abuse) are frequent sequelae of early-life stress. While most studies of telomere length and early-life stress controlled for such influences, it remains possible that these or other factors could account for the association between reduced telomere length and early-life stress.

Telomeres and Early-Life Stress: Methodological Issues

Nearly all of the clinical and epidemiological 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 (28) of the nine studies addressing the effects of early-life stress. Analogously, assessment of early-life stress can be either prospective or retrospective; all but two (28,95) of the studies in this area have been retrospective.

The limitations of cross-sectional versus longitudinal measurement of telomere length have been discussed. How early-life stress is retrospectively ascertained and assessed is highly variable across studies, but more systematic and comprehensive approaches seem more likely to compensate for the bias toward false negatives (101). Several studies have found an effect of the number of discrete childhood adversities, suggesting that early stressors may have additive effects on telomere length. Ideally, assessment tools should have demonstrable validity and reliability; short of that, ascertainment methods requiring the least amount of judgment or interpretation by the subject are preferable. Such considerations may explain why Glass *et al.* (90) failed to replicate an association between early-life stress and reduced telomere length. Timing and type of early-life stress and the impact of mitigating psychosocial or genetic factors (resilience factors) (102) could also affect findings.

Effects of Therapeutic Stress Reduction on Telomeres

Epel *et al.* (103) have proposed that therapeutic interventions designed to mitigate adverse effects of psychosocial stress (e.g., threat appraisal, rumination, negative affect, stress arousal) might promote telomere maintenance. Supporting this, vigorous exercise attenuated the correlation between perceived stress and reduced telomere length in a sample of 63 healthy women (104). In a prospective study, Jacobs *et al.* (105) showed that a 3-month intensive meditation retreat increased telomerase activity in participants ($n = 30$) compared with control subjects ($n = 30$), an effect mediated by increased perceived control and decreased neuroticism. Daubenmier *et al.* (106) found that telomerase activity increased both in overweight women receiving a 4-month mindfulness-based intervention for stress eating ($n = 47$) and in wait-list control subjects ($n = 47$), with increases correlated with decreased chronic stress, anxiety, dietary restraint, dietary fat intake, cortisol, and glucose. Lin *et al.* (107) have summarized other recent work examining effects of lifestyle interventions on telomere length and general health status.

Summary and Implications

In the 4 years since Aubert and Landsorp (15) published their review, telomere research has exploded: they identified over 5000 articles on this topic indexed in PubMed, whereas a current search yields nearly 14,000 articles. Most studies addressing the relationship between telomere length, psychosocial stress, and psychiatric illness have been published during this brief period. At present, evidence is strongest in supporting an association of reduced telomere length with psychosocial stress and depression. Given the relationship between stress and depression, this is not surprising; it remains to be established exactly when, how, and why shorter telomeres are observed in these conditions.

The more recent demonstration that reduced telomere length is associated with early-life stress poses challenges and opportunities. Should the adverse health outcomes in adults after early adversity be conceptualized as accelerated aging, following Wolkowitz *et al.* (97)? Or can these findings be better accommodated by the dysregulated homeostasis/allostatic load model (108) that currently predominates? Alternatively, perhaps reduced telomere length is not even caused by early-life stress but is rather a preexisting (risk) or acquired (disease) marker for those individuals who subsequently characterize their early-life experiences as stressful. Nor has the possibility been excluded of a spurious association between early-life stress and reduced telomere length, accounted for by other adverse health and behavioral sequelae of childhood adversity.

The role of telomerase in understanding these findings must also be considered. Since telomerase maintains telomere length, it might be expected that decreased telomerase activity would result in telomere shortening, perhaps suggesting a more proximal effect of chronic stress on this enzyme rather than on the telomere itself. However, the studies reviewed above suggest inconsistent relationships between telomere length and telomerase activity, and some authorities suggest that telomerase activity might compensatorily increase in the face of stress and/or telomere shortening. These conceptual challenges, in conjunction with the greater technical difficulty associated with the telomerase assay, limit the current utility of telomerase activity for informing our understanding of stress and telomere length.

The early findings reviewed above raise hopes that telomere length might serve as a deep biomarker of early-life stress in terms of damage done, future vulnerability, and efficacy of therapeutic interventions. But a final caveat must acknowledge that, as in most rapidly emerging areas, publication bias in favor of positive findings could be a significant factor in overstating the robustness of this association. Much of the published literature is based on studies originally designed for other purposes, with telomere findings deriving from secondary analyses using banked blood specimens. Prospective research in this area over the next several years will clarify whether telomere assessment will merely constitute a new outcome measure or serve as the basis for a new paradigm.

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