Published in final edited form as:
Soc Personal Psychol Compass. 2012 November 1; 6(11): 807–825. doi:10.1111/j.1751-9004.2012.00465.x.

An intricate dance: Life experience, multisystem resiliency, and rate of telomere decline throughout the lifespan

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Abstract

Accumulation of life stressors predicts accelerated development and progression of diseases of aging. Telomere length, the DNA-based biomarker indicating cellular aging, is a mechanism of disease development, and is shortened in a dose response fashion by duration and severity of life stressor exposures. Telomere length captures the interplay between genetics, life experiences and psychosocial and behavioral factors. Over the past several years, psychological stress resilience, healthy lifestyle factors, and social connections have been associated with longer telomere length and it appears that these factors can protect individuals from stress-induced telomere shortening. In the current review, we highlight these findings, and illustrate that combining these `multisystem resiliency' factors may strengthen our understanding of aging, as these powerful factors are often neglected in studies of aging. In naturalistic studies, the effects of chronic stress exposure on biological pathways are rarely main effects, but rather a complex interplay between adversity and resiliency factors. We suggest that chronic stress effects can be best understood by directly testing if the deleterious effects of stress on biological aging processes, in this case the cell allostasis measure of telomere shortening, are mitigated in individuals with high levels of multisystem resiliency. Without attending to such interactions, stress effects are often masked and missed. Taking account of the cluster of positive buffering factors that operate across the lifespan will take us a step further in understanding healthy aging. While these ideas are applied to the telomere length literature for illustration, the concept of multisystem resiliency might apply to aging broadly, from cellular to systemic health.

Keywords

Telomeres; Cellular Allostatis; Life Stress; Psychological Stress Resiliency; Social Connections; Healthy Lifestyle Factors; Multisystem Resiliency

INTRODUCTION

Stressors over the lifespan predict accelerated development and progression of diseases of aging, and early mortality. “Chronic stress” exposure results from different types of life experiences - notably, prenatal exposure to maternal stress and early life adversity (Shonkoff, Boyce, & McEwen, 2009), poverty, unemployment (Adler & Rehkopf, 2008; Adler & Stewart, 2010a, 2010b), caregiver burden (Gouin, Glaser, Malarkey, Beversdolf, & Kiecolt-Glaser, 2012; Kiecolt-Glaser, 2008; Vedhara, Shanks, Anderson, & Lightman, 2000; Vitaliano, Katon, & Unutzer, 2005), relationship conflict (Kiecolt-Glaser, Gouin, & Hantsoo, 2010; Kiecolt-Glaser & Newton, 2001), and discrimination (Baum, Garofalo, & Yali, 1999; Gee, Ryan, Laflamme, & Holt, 2006; Lewis et al., 2006). Some individuals are also predisposed to experience feelings of stress more often and more intensely as a result of (1) specific temperaments or personality traits (Bolger & Schilling, 1991; Bolger & Zuckerman, 1995) and (2) poor social network features that enhance perceptions of threat

and negative affect (Kiecolt-Glaser et al., 2010; Uchino, 2006; Uchino & Birmingham, 2011; Uchino, Carlisle, Birmingham, & Vaughn, 2011; Uchino, Vaughn, & Matwin, 2008).

Regardless of its source – either external repeated exposure to environmental and social stressors or individual tendencies to prolong the stress response – chronic stress across human development and its biological correlates must be examined from a lifespan perspective for several reasons. A lifespan perspective accounts for (1) sensitive developmental periods when chronic and severe acute stress have potent and irreversible neurological and peripheral biological damaging effects, perhaps shaping psychological stress reactivity (also known as biological embedding) (Ben-Shlomo & Kuh, 2002; Hertzman, 1999; Shonkoff et al., 2009), (2) the weathering of stress responsive biological systems that happens over time, presumably based on duration and severity of each individual's stress exposure (Geronimus, 1992; Geronimus, Hicken, Keene, & Bound, 2006; McEwen, 2003, 2007; Seeman et al., 2004; Seeman, Gruenewald, et al., 2010; Seeman, McEwen, Rowe, & Singer, 2001); and lastly, 3) resiliency factors that can change over the life course, altering the extent to which lifetime stress impacts current biological function (Fagundes, Bennett, Derry, & Kiecolt-Glaser, 2011), including neuroplasticity (Karatsoreos & McEwen, 2011).

In this review, we focus on a disease relevant biomarker of cell aging, telomere length, which appears to be affected by stressors across the lifespan and thus provides a valuable window into understanding a lifespan model of the accumulation of stress on aging. Short telomeres can result from prenatal adversity, early trauma, and chronic stressors (Epel, 2009a, 2009b; Epel et al., 2004; O'Donovan, Pantell, et al., 2011; Wolkowitz, Epel, & Mellon, 2008; Wolkowitz, Epel, Reus, & Mellon, 2010).

Telomeres are caps at the end of our chromosomes that protect DNA from damage and degradation, similar to the aglets, or plastic tips, at the end of the shoelace that protect the lace from fraying (Blackburn, 2005). Telomeres do not remain long forever, though, and shorten with each cell cycle, and as they reach a critical short length, the cell is no longer able to proliferate (divide). This is critical, since cells must keep dividing throughout the lifespan in order to replenish the blood and tissue. As such, the length of telomeres is now considered a marker of aging cells, and the mechanisms of short telomeres have now been shown.

We present this lifespan approach in Figure 1 and Section 2.1, after a brief overview of telomere biology in Section 1. In Section 2.2, we examine important psychosocial and behavioral factors that predict cellular aging directly, and, where data is available, explore effects on biological stress reactivity processes in the context of psychosocial and behavioral resiliency. In Section 3, we suggest that multisystem resiliency – a composite of psychological stress resilience, social connections, and healthy lifestyle factors– can promote cellular viability and longevity (and thus organismal longevity) in those with chronic stress. Our multisystem resiliency model builds on previous studies by Lachman and colleagues (Agrigoroaei, 2011; Lachman & Agrigoroaei, 2010). They have found that the combination of psychosocial and behavioral resiliency factors --social connections, physical activity and sense of control --is a moderator of socioeconomic position's effect on cognitive functioning. Other evidence to date suggests that individually, social connections, healthy lifestyle factors, primarily physical activity, and aspects of psychological stress resiliency such as adaptive emotion regulation are strong moderators of associations between chronic stress and biological outcomes, and as such, we propose that combining these factors may prove to be of greater clinical significance and utility than examining each factor alone. We conclude that with such a multisystem resiliency approach, we may better understand how

chronic stress gets under the skin to different degrees in both vulnerable and resilient individuals.

Section 1: Telomere biology in cell health and population health

Cells are constantly adapting to environmental cues and stressors, in utero through death, in attempt to remain viable. Immune cells are of particular importance to understanding the pathway through which chronic stress impacts disease outcomes, as these cells mount the essential responses to external and internal pathogens (Elgert, 2009; O'Garra & Vieira, 2004). When immune cells are `notified' that a response is to be mounted in response to some internal or external cue, they replicate in order to increase their numbers. During replication, DNA is at significant risk of damage, but several features are in place to protect it. One such feature is the telomere (Blackburn, 2000a, 2000b, 2001, 2010).

Telomeres are comprised of both DNA molecules and protective proteins that cap the ends of chromosomes, protecting DNA from degradation and damage. During cellular division, the telomeres are not completely replicated and telomeres shorten. To delay telomere shortening, a cellular enzyme called telomerase adds telomeric DNA sequences back onto the ends of telomeres during cell division. However, telomerase does not typically add back 100% of the lost telomere sequences at each division. When the telomeres become too damaged and shorten to a critical length, they send out damage signals that prevent the endangered cell from replicating. Signaling pathways trigger either (1) programmed cell death, apoptosis or (2) cellular senescence, a state characterized by arrested reproduction, loss of ability to recognize invader molecules (antigens) and continued production of pro-inflammation proteins that can lead to cardiovascular disease and Type 2 diabetes mellitus, as well as other aging related diseases (Ben-Porath & Weinberg, 2005; Blackburn, 2000b, 2010; Campisi, 2003; Campisi, Andersen, Kapahi, & Melov, 2011; Smogorzewska & de Lange, 2002; Zheng et al., 2006).

The allostatic load model conceptualizes allostasis as the dynamic physiological fluctuations in response to environmental demands. Allostatic load is the measure of this cumulative damage from excessive frequent responding (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010). Allostatic load is measured by summing measures of dysregulation across multiple physiological regulatory systems (eg, immune, metabolic, cardiovascular). Our model extrapolates from this in that we view telomere length as a model of cellular allostasis. The cell responds to multiple sources of biochemical stressors in its environment and these add up to many intracellular changes that are ultimately reflected by magnitude of telomere shortening. For example, past duration of stressor exposure (whether it be caregiving, depression, violence) is directly related to telomere length (Epel et al., 2004; Humphreys et al., 2011; Wolkowitz et al., 2011). In this way, telomere length is a sensitive cellular measure of allostatic load. In Figure 1, we track cellular allostasis throughout the lifespan.

Increasing research highlights the role that immune cell telomeres and decreased telomerase activity plays in the pathogenesis of diseases of biological aging, including, but not limited to, cardiovascular disease, type 2 diabetes mellitus, and Alzheimer's disease (Bekaert, De Meyer, & Van Oostveldt, 2005; Calado & Young, 2009; von Zglinicki & Martin-Ruiz, 2005). For example, many clinical studies evidence a link between shortened immune cell telomeres and cardiovascular diseases (CVD) (Demissie et al., 2006; Fitzpatrick et al., 2007), their risk factors, including carotid artery plaques (Benetos et al., 2004; O'Donnell et al., 2008), high blood pressure (Lung, Ku, & Kao, 2008), fasting glucose and insulin (Fitzpatrick et al., 2007), and CVD-related mortality (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003; Fitzpatrick et al., 2011). Having short telomeres predicts a

threefold risk of earlier mortality in a healthy population, larger or comparable to other well-accepted risk factors (Cawthon et al., 2003; Epel et al., 2009).

Despite the significant associations between diseases of aging with telomere biology, there remain considerable questions about the direction of causality (De Meyer, 2011). However, compelling experimental studies with a strain of mice that lack telomerase (Blasco, 1997) have laid out a new understanding of the primacy of telomerase – that telomerase deficiency and short telomeres do not simply correlate with and mark organismal aging, but in fact are one of the major highways leading to organismal aging. Telomere dysfunction mediates changes in the function and structure of the heart (Leri et al., 2003; Perez-Rivero et al., 2006; Wong et al., 2009) and in the cell's energy source, the mitochondria (Sahin et al., 2011). Recent work also demonstrates that reactivating telomerase in telomerase-ablated mice reverses neurodegeneration by restoring neural progenitors, and other cells essential for neurogenesis (Jaskelioff et al., 2011) and promotes health and longevity in mice (Bernardes de Jesus et al., 2012).

Section 2. A lifespan approach to understanding telomere decline (the model)

In Figure 1, we present our working model. This is a lifespan approach where dynamic interactions from conception through death exist between life stressors and cellular allostasis, as discussed below (Section 2.1). We examine psychological stress responsivity, social connections, and lifestyle factors that ultimately shape a multisystem vulnerability or resiliency profile that can accelerate or decelerate cellular senescence and mortality (Section 2.2). Figure 1 is derived from exceptional research in the field emphasizing developmental models of stress effects (Cohen, 2004; Kiecolt-Glaser et al., 2010; Miller, Chen, & Cole, 2009; Shonkoff et al., 2009; West, Coles, & Harris, 2010). First, *early life experiences* starting in-utero through childhood, including severe environmental stressors and parental neglect, biologically embed themselves during sensitive developmental periods through neurological and biological alterations, shaping cognitive and emotional regulation capacities toward resiliency or vulnerability.

Throughout life, stressors stimulate multiple stress reactive systems, such as the hypothalamic-pituitary-adrenal axis (HPA axis), and immune and autonomic systems in attempt to respond and adapt to stress, and these hormones and cytokines feedback to act on brain structures. With repeated and chronic exposure, stress first wears out neurocircuitry underlying the stress response, as well as peripheral stress systems (Ganzel, Morris, & Wethington, 2010). At the cellular level, there is less dendritic branching in the prefrontal cortex, which affects executive function (Karasoreos & McEwen, 2011). The historical wear and tear on the emotional circuitry can then lead to exaggerated physiological responses to current stressors, and in this recursive way continue to affect stress responses and track through life.

While stress exposures are inevitable and ubiquitous, not all individuals are at equal risk of early cellular allostatic load given the same exposures. The impact of stress depends on presence of resiliency factors. We propose that with low resiliency factors, such as heightened psychological stress sensitivity, poor social connections and unhealthy lifestyle factors, individuals are more sensitive to the effects of stressors on cellular biology, in turn accelerating cellular allostatic load, telomere shortening and systemic aging, leading to early frailty (Figure 1, left panel).

In contrast, those with higher levels of multisystem resilience develop efficient psychological and physiological coping with stress early in life, lower levels of cellular allostatic load, **including neuronal resilience to stress,** and a slower rate of aging, leading to robust health in old age (Figure 1, right panel).

In section 2.2, we describe how many individual factors can also buffer the effects of chronic stress on cellular biology, with the most evidence for social connections, psychological stress resiliency and health enhancing behaviors (i.e. healthy lifestyle factors) as moderators. Lastly, in section 3, we highlight the need to examine these resiliency factors in combination as multisystem resiliency, yet note here that there may be other equally important resiliency factors.

2.1. Life stressors and telomere decline

2.1.1. Early Life Experiences: The physiological effects of chronic stress often start in early life, from in utero stressors (i.e. exogenous toxins and elevated glucocorticoids from mothers), to adverse, traumatic events during childhood.

From a neurobiological perspective, while the neural emotion regulation pathways are still developing, early life stressors tend to have more harmful effects (Fenoglio, Brunson, & Baram, 2006; Gluckman, Hanson, Cooper, & Thornburg, 2008; Hertzman, 1999; Lupien, McEwen, Gunnar, & Heim, 2009; Shonkoff et al., 2009), in that they are linked to changes in functioning of the limbic system and even volume of certain key areas related to memory and emotion processing such as the hippocampus **and executive function** (De Bellis, Spratt, & Hooper, 2011; Jackowski et al., 2011; Karatsoreos & McEwen, 2011; McCrory, De Brito, & Viding, 2010). This is thought to magnify perception of stress and stress reactivity, thus potentially altering personality (De Bellis et al., 2011; Pine et al., 2005), and can lead to **poor control of behavior and** different profiles of dysregulation, such as a hyper- or hypo-responsive hypothalamic-pituitary-adrenal axis (Heim & Nemeroff, 2001, 2002; Heim, Shugart, Craighead, & Nemeroff, 2010).

Several studies link childhood adversity to telomere shortening in children and in adults. Children exposed to two or more traumatic stressors at age 5, such as maternal domestic violence, frequent bullying victimization and physical maltreatment by an adult, have significantly shorter telomeres at age 10 compared to children exposed to less or no violent stressors (Shalev et al., 2012). These effects seem to extend to adulthood, `casting a long shadow' (Kiecolt-Glaser et al., 2011), as adults reporting moderate to severe childhood maltreatment and stressful experiences, such as divorce and parental separation, are more likely to have significantly shorter telomeres that those reporting no maltreatment during childhood (Kananen et al., 2010; Kiecolt-Glaser et al., 2011; O'Donovan, Epel, et al., 2011; Surtees et al., 2011b; Tyrka et al., 2010).

Findings from human and animal studies also highlight that maternal stress during pregnancy can have negative effects on offspring telomere biology. Entringer and colleagues (2011) found that young adults have short telomeres if their mothers were exposed to severe negative life events while the participants were in-utero compared to a prenatally non-stressed group. In-utero effects are not limited to maternal psychological stress, however, as animal (Jennings, Ozanne, Dorling, & Hales, 1999; Tarry-Adkins et al., 2009; Tarry-Adkins, Martin-Gronert, Chen, Cripps, & Ozanne, 2008) and human (Biron-Shental et al., 2010; Entringer et al., 2011; Raqib et al., 2007) studies suggest that maternal diet, intrauterine growth restriction, and low birth weight predict shorter telomeres in various cell types in young and adult offspring. Finally, a study of embryonic exposure to the stress hormone cortisol in chickens found increased reactive oxidized species, delayed cortisol recovery in response to stress, and shorter telomere lengths in the exposed chicks, compared to non-exposed chicks (Haussmann, Longenecker, Marchetto, Juliano, & Bowden, 2011). Thus, in utero or early physiological or psychological stressors may put people on different telomere trajectories throughout life, as proposed elsewhere (Epel, 2009b).

2.1.2. Stress during Adulthood: Stressful experiences in adulthood also contribute to disease development in adulthood. In the first study linking stress to telomere length (Epel et al., 2004), telomere length and telomerase were examined in a healthy sample of premenopausal mothers of either a healthy child or a child with a chronic condition. Across all participants, current levels of perceived stress were associated with shorter telomeres, lower telomerase levels, and greater oxidative stress, demonstrating a possible acceleration towards cellular senescence in immune cells in women with higher life stress. While no significant difference in telomere length was evident between mothers of healthy and chronically ill children, within those women with children with conditions, the number of years of providing care significantly predicted shorter telomeres, lower telomerase and higher oxidative stress. Other studies have similarly shown associations between current objective and perceived stress with telomere length (Damjanovic et al., 2007; Parks et al., 2009; Puterman et al., 2010).

Additionally, past or current psychiatric disorders, including depression, posttraumatic stress disorder, and schizophrenia, are linked to short telomeres (Elvsashagen et al., 2011; Fernandez-Egea et al., 2009; Hartmann, Boehner, Groenen, & Kalb, 2010; Hoen et al., 2011; O'Donovan, Epel, et al., 2011; Simon et al., 2006; Wikgren et al., 2012; Wolkowitz et al., 2011) as is lower socioeconomic position in several studies (Batty et al., 2009; Cherkas et al., 2006; Diez-Roux et al., 2009; Shiels et al., 2011; Steptoe et al., 2011; Surtees et al., 2011a).

Section 2.2. Resiliency factors and telomere decline

2.2.1. Psychological stress resilience: Here we use the term `stress resiliency' to refer to psychological traits, appraisals, and emotion regulation processes that appear to promote healthy integrated responses to stress, rather than exaggerated over-reactions. This area has been least explored in relation to cell aging. Individuals prone to prolonged stressor reactivity and delayed recovery, such as those high in negative affectivity, pessimism, and hostility, have shorter telomeres and lower levels of telomerase (Brydon et al., 2011; Epel et al., 2006; O'Donovan et al., 2009), thus indicating that those lower in these traits may have decelerated cellular aging. Individuals respond to acute and chronic stressors with large differences in emotional and cognitive regulatory processes (Dickerson, 2008; Dickerson, Gruenewald, & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993; Lazarus, 1984; McRae, Jacobs, Ray, John, & Gross, 2012). These emotional and cognitive differences in response to chronic stress are linked to elevated cortisol and increased inflammation (Chen et al., 2006; Puterman et al., unpublished data) and to differences in activation of different neural regions (Blechert, Sheppes, Di Tella, Williams, & Gross, 2012; Goldin, McRae, Ramel, & Gross, 2008; McRae et al., 2009; Ray et al., 2005).

Recent work also indicates that chronically stressed caregivers anticipate greater threat to a standardized stressor compared to controls, and this anticipatory threat predicts shorter telomeres (O'Donovan et al., 2012). Lastly, appraisal differences such as viewing stressors as challenges, can transform the stress response toward thriving or efficient allostasis rather than toward weathering (Epel, McEwen, & Ickovics, 1998). These findings indicate that early life and adulthood stressors impact allostasis in general, including telomere maintenance, through emotion regulatory processes. Poor emotion regulation is associated with autonomic arousal, cardiovascular disease, and early mortality (Gross; Gross & John; John & Gross), and may be at the heart of personality traits such as hostility, pessimism, and negative affectivity, traits associated with short telomeres.

2.2. Social Connections—Social support is stress reducing. Perceptions of high support promote better self-regulation strategies in response to stress (Aspinwall & Taylor, 1997;

Uchino & Birmingham, 2011) and buffers acute and chronic stress effects on health and physiological markers (Cohen, 2004; Uchino, 2009; Uchino & Birmingham, 2011). It is thus not surprising that social connections have been linked to cell aging as well. New work suggests that unwed individuals (Mainous et al., 2011), those with ambivalent social ties (Uchino et al., 2012), and older people with low support (Carroll, Diez Roux, Fitzpatrick, & Seeman, 2012, March) have shorter telomeres. The extent to which social connections and perceived support can modify the impact of stress on telomere length has not been explored.

In the lifespan model, the buffering role of social connection likely starts from birth. Development of attachment style may have a long reach into future adult health. Secure attachment can promote greater self regulation ability through life, and promotes the perception of social support as an adult (Engels, Dekovic, & Meeus, 2002; Shaw, Krause, Chatters, Connell, & Ingersoll-Dayton, 2004; Uchino, 2009). Early attachment and close social connections may promote physiological resilience to cellular allostatic load (Parker, Nelson, Epel, & Siegel, 2012), and need to be more thoroughly examined as moderators of stress exposures in future studies. Recent studies suggestive of this indicate that maternal warmth buffers the relationship between parental low SES markers on adulthood metabolic syndrome (Miller et al., 2011) and inflammation (Chen, Miller, Kobor, & Cole, 2011).

2.3. Lifestyle—A large literature highlights the importance of lifestyle factors, such as physical activity, diet, sleep, smoking, and alcohol, to health and disease development. A combination of these healthy behaviors is associated with longer telomeres (Sun et al., in press). Puterman and colleagues have programmatically examined the biological benefits of maintaining a physically active lifestyle in chronically stressed individuals using an interactive model, directly testing exercise as a modifier of stress exposure-physiology relationships (Puterman, Adler, Matthews, & Epel, 2012; Puterman et al., 2010; Puterman et al., 2011).

2.3.1.a. Physical activity and fitness: improve all aspects of health A potential mechanism of fitness may be retarding cellular aging processes (He et al., 2012; Safdar et al., 2011; Werner et al., 2009; Werner et al., 2008). Self-reported physical activity (Cherkas et al., 2008; Ludlow et al., 2008; Werner et al., 2009; Zhu et al., 2011) and objective fitness markers (Krauss et al., 2011; LaRocca, Seals, & Pierce, 2010) are related to longer telomeres in healthy adolescents and adults, and in adults with coronary heart disease.

Telomerase is the major driver of lengthening telomeres and appears malleable in response to aerobic exercise training. In a study that examined telomere length and telomerase differences in athletes and sedentary non-athletes, telomerase levels were higher in athletes (Werner et al., 2009). Mouse studies evidence that increased exercise over three weeks activates telomerase in myocytes (heart muscle cells), endothelial cells (blood vessel cells), and immune cells (Werner et al., 2009; Werner et al., 2008), providing the first experimental support that aerobic exercise training alone can lead to almost immediate increases in telomerase levels.

Our group (Puterman et al., 2012; Puterman et al., 2010; Puterman et al., 2011), as well as others (Rethorst, Moynihan, Lyness, Heffner, & Chapman, 2011), have examined how physical activity modifies the associations between chronic stress and biomarkers of health. In one study, we demonstrated that exercising at levels recommended by the Center for Disease Control and Prevention moderates the association between perceived stress and telomere length. Specifically, perceived stress is associated with shorter telomere length only in inactive individuals, whereas in those active, stress is unrelated to telomere length (Puterman et al., 2010). Other studies have demonstrated the buffering potential of physical activity in psychologically distressed individuals on inflammatory proteins (Rethorst et al.,

2011), rumination-induced cortisol reactivity and recovery (Puterman et al., 2011), and fasting glucose (Puterman et al., 2012). Yet, longitudinal studies and randomized clinical trials are needed to disentangle these two related effects (exercise and stress) on biological outcomes.

2.3.2.b. Body composition: indexed by adiposity, BMI, or waist circumference ratio, has been associated with telomere length (Gardner et al., 2005; Lee, Martin, Firpo, & Demerath, 2011; Njajou et al., 2011; Valdes et al., 2005), with some exceptions (Diaz, Mainous, Player, & Everett, 2010). In coronary artery disease patients, a high waist-to-hip ratio significantly predicted telomere shortening over a five-year period (Farzaneh-Far, Lin, Epel, Lapham, et al., 2010).

Food choices and eating behavior also shape telomere maintenance. A healthy diet is associated with longer telomeres (Paul, 2011; Shiels et al., 2011), including diets lower in processed meats (Nettleton, Diez-Roux, Jenny, Fitzpatrick, & Jacobs, 2008) and polyunsaturated fats (Cassidy et al., 2010), and diets higher in dietary fiber (Cassidy et al., 2010) and dietary and supplemental vitamin intake (Paul, 2011). In the Heart and Soul Study, coronary artery disease patients with the lowest levels of baseline omega-3 fatty acids (essential fatty acids only derived from foods) had the steepest decline in telomere length over 5 years (Farzaneh-Far, Lin, Epel, Harris, et al., 2010). Excessive drive to eat and a poor brake on the drive (dietary restraint) may also matter. No studies have examined how drive to overeat is linked to telomere length. However, people who are preoccupied with trying to eat less (high restraint) have both higher cortisol and shorter telomeres (Kiefer, Lin, Blackburn, & Epel, 2008). Research describing relations between nutrition, metabolism, and telomere length is now converging, and the field must progress to studies that allow greater inference about causality, with randomized clinical trials.

2.3.3.c. Sleep and Substance Use: Whereas less work has focused on other health behaviors, lower sleep duration and quality (Liang et al., 2011; Prather et al., 2011), excessive alcohol consumption (Adams et al., 2007; Pavanello et al., 2011), and cigarette smoking (Diez-Roux et al., 2009; Surtees et al., 2011a; Valdes et al., 2005) have been linked to shorter telomeres. Understanding how these health behaviors mitigate or heighten the effects of stress on telomere biology remains unexplored.

Section 3. Next steps in understanding how life experience impacts telomere biology

3.1. Understanding resiliency as a composite of psychological stress resilience, social connections, and lifestyle—As we highlighted in this review, our work and that of others, is increasing our understanding of how psychological stress resilience, social connections, and lifestyle, in particular physical activity, may moderate relationships between stressors and biological health (E. Chen, G. E. Miller, et al., 2011; E. Chen, R. C. Strunk, et al., 2011; Miller et al., 2011; Puterman et al., 2012; Puterman et al., 2010; Puterman et al., 2011; Rethorst et al., 2011). These factors are not merely covariates or mediators of stress effects on biology, but are important to consider as modifiers of the relationship between chronic stress and health.

One point of our thesis is that combining resiliency factors (rather than examining them in isolation, as a single main effect, or a single moderator), may provide a deeper understanding of resiliency to biological weathering and accelerated cellular aging in chronically stressed individuals. And while stressors early in life may shape the expression and development of these resiliency factors, **leading to an interrelated cluster,** recent work suggests that psychosocial resources and physical activity together add up to multisystem resiliency providing increasing buffering from life stress. For example, Agrigoroaei and

Lachman (2011) demonstrated that a protective composite of control beliefs, physical activity, and social connections buffered the negative effects of low education on 10 year follow-up cognitive functioning These findings are compelling, and remain unexplored relative to biological outcomes. While examining these contributing factors separately is important as potential stress-buffers for delineating key biological mechanisms involved in stress buffering, we contend that examining *multisystem resiliency* may prove to be of greater clinical significance and utility. Theoretically and mathematically, composites of resiliency factors should be a stronger indication of personal robustness than each factor alone (Taylor & Seeman, 1999). Examining independent effects of buffering or moderating variables is important to do; but because these psychosocial resources (Gallo, 2011; Low, Matthews, Kuller, & Edmundowicz, 2011; Taylor, Kemeny, Reed, Bower, & Gruenewald, 2000) and lifestyle factors (Poortinga, 2007; Schuit, van Loon, Tijhuis, & Ocke, 2002) naturally cluster, and because we tend to examine single factors, we don't fully understand the magnitude or complexity of the interactive relationships when we neglect their combined effects.

3.2. Cell aging trajectories over time—The natural tendency of telomere length is to shorten over time (W. Chen et al., 2011). There is some evidence that short telomeres can maintain or even lengthen over time (Epel et al., 2009; Farzaneh-Far, Lin, Epel, Lapham, et al., 2010; Shalev et al., 2012; Willeit et al., 2010). Telomerase plays an essential role in lengthening, and lifestyle intervention studies suggest that on average, we can increase the total telomerase activity measured in circulating peripheral blood mononuclear cells although it is unclear whether this is per cell or due to redistribution of cells (Jacobs et al., 2011; Ornish et al., 2008). More rigorous lifestyle randomized clinical studies are necessary to truly understand the impact of lifestyle on telomere cell aging over time, and the protection lifestyle can provide chronically stressed individuals from accelerated telomere attrition over time. We also need translational studies, from clinical to basic in this case, using relevant animal models, to test causality and reveal mechanisms. In addition to clinical trials and animal research, it is important to examine TL in cohort studies longitudinally, to test some of the naturalistic trajectories and interactions with the behavioral, social, and psychological factors that appear critical to TL maintenance. Together, with these types of insights, we truly get closer to understanding the mechanisms through which chronic stress gets under the skin.

Section 4. Summary

In the current review, we propose that there is an intricate relationship between life experiences, psychosocial and behavioral factors, and telomere maintenance. Not all individuals are at equal biological risk, as clearly genetics and environments modify these associations (Shonkoff et al., 2009). We emphasize here multisystem resiliency, including psychological stress resilience, social connections, and lifestyle factors, that **cluster together and** shape the rate of biological aging when under high exposures to stress. We apply this model to the specific outcome of cell aging, using examples from this burgeoning literature, although the model may apply to other biological outcomes that reflect cumulative adversity as well. There is now a `critical mass' of such findings, which might compel other researchers to re-examine data on stress and arousal pathways, to see if relationships are present or stronger only in those with lifestyles characterized by sedentariness, who have poor social ties, and maladaptive emotion regulatory skills, or, when possible, the composite of these factors.

Examining biological risk for disease across multiple physiological systems has advanced our science in terms of understanding how experience gets under the skin to promote aging. Here we suggest that examining multisystem resiliency is an equal and necessary part of the

intricate dance between life experiences and biological aging. Early childhood adversity without protective factors such as adaptive emotion regulation, role models and social connections, or maintenance of a healthy lifestyle, might result in neural connectivity primed for stress and impulsive behavior, and accelerated immune senescence in adulthood, years earlier than expected. In contrast, early adversity might be overcome with the positive feedback loops of the buffers, obscuring the impact of biological embedding. These are empirical questions, comprising the next frontier for understanding and slowing the biology of aging.

Acknowledgments

Eli Puterman's work is supported by Award Number K99HL109247 from the National Heart, Lung, and Blood Institute. Dr. Epel is supported by the National Institute of Aging, Award number R01AG030424-01A2. Both authors are also supported by by Award Number R01HL108821-01 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We would like to thank Kirstin Aschbacher, Aoife O'Donovan, Aric Prather, and Janet Tomiyama for their significant comments on the manuscript and the editor and reviewers at Social and Personality Psychology Compass for their thorough comments that helped shape the paper considerably.

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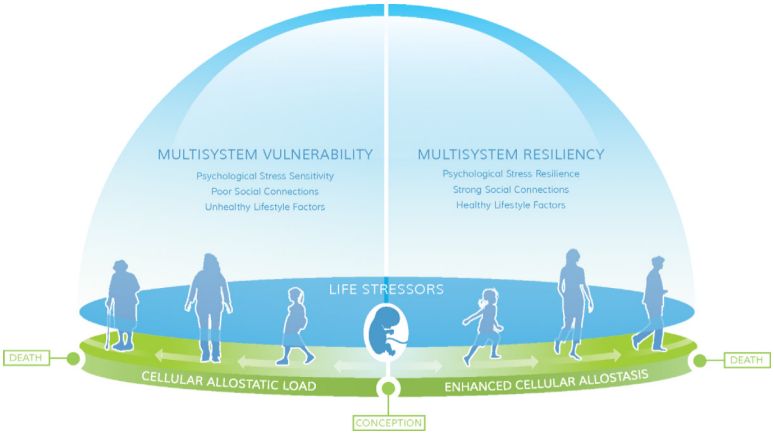

Figure 1.

Lifespan model of stress-induced cell aging as moderated by multisystem resiliency

This lifespan model suggests two divergent trajectories, for simplicity of demonstration. From conception to death, at every stage of development, we are exposed to ubiquitous stressors. The cellular impact of these stressors is partly influenced by genetics/temperament and the severity of the stressors but also by resiliency or vulnerability traits. These traits are largely a result of fetal and childhood development (and genetic dispositions) but can also develop at any time in life, and determine the extent to which cellular allostasis is impacted by subsequent stress exposures. Right panel: Strong stress resiliency traits, social connections, and adherence to healthy behaviors, often shaped by low to manageable stress exposure and secure attachment, provide a positive mutually reinforcing cluster of resiliency factors that shape enhanced cellular allostasis (efficient responding to environmental demands) and good telomere maintenance. This leads to slower organismal aging and longer health span. Left panel: In contrast, high vulnerability to stress reactivity, poor social connections, and difficulty adhering to health behaviors constitute interrelated vulnerability factors that promote cellular allostatic load early in life, and accelerated telomere shortening. This profile can start at early in life, where early exposure to severe stress, and insecure attachment, may promote neural networks primed for exaggerated vulnerability to stress reactivity, limiting development of resiliency factors. This profile of impoverished resiliency leads to rapid organismal aging and early frailty and disease.