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A Scoping Systematic Review of Social Stressors and Various Measures of Telomere Length Across the Life Course

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Abstract

Numerous studies examine the relationship between social stressors and telomere length (TL). Beyond considering methods and major findings, this scoping systematic review takes a novel approach as it groups studies according to the types of social stressor considered and by age groups. Following PRISMA guidelines, we searched PubMed, Web of Science, Embase, and Scopus. We included all English-language human subject research articles that modeled any measure of TL as a dependent variable and exposure to a social stressor as an independent variable. For the sample of 105 articles, we summarized methods and findings by type of social stressor (socioeconomic stressors, stressful life events, work-related stressors, and neighborhood stressors) and by age of the study population (infants/children, middle-aged adults, older adults, and mixed samples of middle-aged and older adults). We found more variation in TL measurement methodology in studies of infants/children and older adults than in studies focusing on middle-aged adults. The most consistent finding was a relationship between early-life stressors and shorter TL. Work and neighborhood stressors, and older populations, are currently understudied. Across all stressors, limited evidence suggests that the stress-TL relationship may be moderated by characteristics such as age, sex, and race/ethnicity. We conclude with specific suggestions for future research.

Keywords

life course; socioeconomic status; stressful life events; trauma; work; neighborhoods

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1. Introduction

The connection between health and exposure to social stressors, including chronic strains and negative events or traumas, has been well documented (Thoits, 2010). An expanding literature specifically examines the relationship between social stressors and telomere length (TL), often measured in leukocytes via quantitative polymerase chain reaction (qPCR). As a potential biomarker of weathering (Geronimus, et al., 2015), telomere shortening may be accelerated by exposure to various forms of chronic or acute stressors in the social environment. Existing systematic reviews of social stressors and TL, however, focus on a narrow range of stressors including poverty, violence, and caregiving (Oliveira, et al., 2016), post-traumatic stress disorder (PTSD; Li, et al., 2017), or childhood traumas and adverse events (Li, et al., 2017; Coimbra, et al., 2017; Ridout, et al., 2018). Given the breadth of social stressors that may be related to TL, the importance of critical periods and accumulation of exposure to stress (Thoits, 2010), the complexities of TL dynamics across the life course (Simons, 2015), and the major criticisms in the measurement of TL (Aviv, et al., 2011; Verhulst, et al., 2015; Elbers, et al., 2014; Goldman, et al., 2017), a broader map of current methods, findings, and lacunae across age groups would help to consolidate and clarify the present state of this literature.

This scoping systematic review therefore offers a novel approach to the TL and stress literature by stratifying results by age and type of stress. We address two primary aims. First, we aim to describe the varieties of social stressors considered in the TL literature and the methods used to study them across age groups. Secondly, we aim to consolidate findings across different types of social stressors by age categories, analyzing in particular the relative importance of accounting for periods within the life course. To reach these aims, we broadly searched the literature and we adopted a narrative approach to our analysis, described in the following sections.

2. Methods

To structure our scoping systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, et al., 2009), in addition to guidance on performing scoping reviews (Peters, et al., 2015; Tricco, et al., 2016).

2.1 Eligibility Criteria

We aimed to include all publications up to the date of the search (November 3, 2016) that fit the following criteria: original empirical human subject research, with full texts published in English, including any measure of TL modeled as a dependent variable and at least one measure of exposure to social stress as an independent variable. We included TL measures obtained via any methodology (e.g., qPCR, Southern Blot, FISH, etc.), from any cell source, and in any units of measurement. The social stress measure may or may not have been the primary focus of the article, provided that the paper reports statistics on the relationship between the stressor and TL. The social stress exposures could have occurred at any point in the life course, including both chronic exposures (e.g., ongoing poverty, discrimination, work-related stressors) and acute or traumatic events (e.g., death of spouse, exposure to

violence, Adverse Childhood Experiences [ACES]). We excluded studies that included either only general subjective measures of psychological stress, such as general perceived stress, or biological measures of stress, such as cortisol levels, in order to focus specifically on stressors with an explicit social exposure source.

2.2 Information Sources and Search Strategy

The first author conducted searches using PubMed, Web of Science, Embase, and Scopus. Search terms and strategies for each database were developed with assistance from library staff, and are reported in Appendix Tables A1 *and* A2. The first author also included references from all systematic reviews discovered in the search. Abstracts and references were managed, and duplicates were removed, using EndNote.

2.3 Study Selection Procedure

Abstracts and references were uploaded to Covidence (covidence.org), an online tool for managing systematic reviews. Two authors (M.W. and S.R.) independently screened all abstracts, including all studies that met the eligibility criteria. Full texts were appended to all studies that passed the first screening. The same two authors then independently reviewed all full texts against the eligibility criteria, conferring on all discrepancies and making final selection decisions together.

2.4 Data Collection Process and Data Items

Two authors (M.W. and S.R.) independently extracted data items from a randomly selected 15% of the final sample, and then resolved all discrepancies together in order to clarify data extraction criteria. After this initial development of common procedures for extracting critical information, either M.W. or S.R. extracted data for the remaining articles.

Data items are listed and defined in Appendix Table A3. In brief, we collected information about data sources and study design (dataset name, country, design), study population (inclusion and exclusion criteria, N, age, sex, race / ethnicity), the TL measure (cell type, method, lab, units of measurement, range, mean), each stressor (definition and role in the study), and results for each stressor (bivariate, multivariate with a list of covariates, and notes about potential moderation).

For each study, we utilized the Cochrane Risk of Bias assessment (Cochrane Training, 2017). Since the vast majority of our articles were cohort studies, we assessed incomplete outcome data (attrition bias), selective outcome reporting, and any other sources of bias. For each of these three categories of bias, we made notes about the study's strengths and weaknesses and supported those notes with quotations from the text. We then applied the Cochrane rating system of "high, low, or unclear" for each type of bias.

2.5 Synthesis of Results and Analysis

Given the wide variability in the measurement of both TL and social stressors in this scoping review, we planned a narrative analytic approach rather than statistical meta-analyses. Our categorizations of the literature by age and type of stress are driven by the content of the articles in our sample.

2.5.1 Stress Categories—The first author coded the stressors present in these studies into conceptually coherent groups, producing four categories: socioeconomic stressors, stressful or traumatic life events, work-related stressors, and neighborhood-level stressors. Here, we conceptualize socioeconomic stressors as the availability of resources at the individual and household levels. SES stressors that were present among the studies in this sample include the following: financial measures, such as household income or financial difficulties; measures of personal educational attainment; measures of parental income or education, as an indicator of household SES in early life; and home ownership. Stressful or traumatic life events include acute or chronic events that are commonly perceived as highly stressful. Studies in this sample had stressful life event measures that fell into the following subcategories: general counts of early life SLEs; general counts of lifetime SLEs or PTSD; caregiving as a specific SLE; and discrimination as a specific SLE. We found work-related stressors to be a third distinct category of social stressors. These work measures did not fit conceptually with the resource focus of the SES stressors, nor did they capture discrete SLEs. Rather, measures in this category included the respondents' type or class of work (occupational class), overall employment status, and stressful job characteristics. Finally, we distinguish a fourth distinctive, though small, category of social stressors measured at the neighborhood level, including neighborhood economic conditions and neighborhood characteristics of the built environment. While we consider personal and household financial measures to be SES stressors, financial or other conditions at the environmental neighborhood level may have their own independent relationship with TL.

2.5.2 Age Categories—We then sorted studies by age categories, again, based on the age ranges present in the studies. Four age groups were used based on the types of samples represented in these studies. The first group includes studies of infants and/or children, up to age 18. The second group, young and middle-aged adults, includes studies with participants who are under the age of 60. A third group includes older adults who are age 50 and over. The overlap of these two categories allowed for samples such as 30-55 year-olds to be classified as "middle-aged" while studies that included samples such as 50-65 year-olds to be classified as "older adults." The few studies that fell in the overlap of these categories were allocated to the nearest category (i.e., a study with only 50 year olds was classified as "middle-aged," and a study of 55 year olds was classified as "older adults"). A final age group included studies with broad age ranges from middle to older adulthood, both below age 50 and over age 60. Any study without clearly defined age ranges for the sample was also assigned to this broad category (e.g., no age stated, or age range described as "25 and older").

2.5.3 Analysis—First, we describe the range of studies and examine differences in the methods used by studies across age categories. Second, we switch to a stressor-focused approach, as many studies analyzed more than one stressor in a given study. Within each category of stressor, therefore, we summarize studies by age group. In the tables below, we provide the following: the number of studies (N); the proportion of those studies that acquired TL from blood using qPCR (the most common method; limitations of this method are discussed in section 4); the proportion of studies that utilized a single sex sample of all men or all women; the proportions that utilized the same datasets (e.g., if two out of 10

studies used the National Health and Nutrition Examination Survey [NHANES], three other studies among those 10 used the Health and Retirement Study [HRS], and the remaining studies used unique datasets, this is coded as "2/10; 3/10"); the proportion of the studies that included a test for moderation by sex, age, or race/ethnicity (with results summarized); the proportion employing any longitudinal methodology, including multiple measures of stressors over time, multiple measures of TL, or both; the proportion that report a significant association between the stressor and TL; a description of the direction of the association (reporting "mixed" if the direction of association is inconsistent across studies); and finally citations for all studies included in the group. For details on individual studies, see Appendix Tables A4-A16.

2.6 Follow-Up Search

Due to the fast pace of growth in TL literature, we performed a follow-up search on April 12, 2018, for new literature published since the date of the first search. The first author used PubMed and Scopus, and collected all relevant articles based on a review of abstracts. This search identified 19 recently published studies. The literature from this follow-up search is integrated throughout the discussion, after the presentation of the results of the main search below. Findings from these 19 additional studies are by and large supportive of those identified in the formal systematic review (see Appendix Table A17).

3. Results

3.1 Study Selection

From the four databases and existing systematic reviews, we identified 3181 unique abstracts (see Figure 1). Of these, we excluded 2707 for clear lack of fit with our eligibility criteria and retained 474 articles for full text assessment. The inter-rater agreement was 80% (kappa=.528) for assessment of the full text articles, and the two authors resolved all discrepancies jointly. The authors excluded 369 articles at this phase when review of the full text revealed that eligibility criteria were not fully met, leaving a final sample of 105 articles.

Two authors jointly extracted data from 17 randomly selected articles. Data extraction agreement ranged from a high of 100% agreement (including sample age, sample sex, TL extraction method, and 13 other items), to a low of 76% on study design and "other sources of bias." The authors discussed and resolved these discrepancies, developing more standardized ways of capturing these descriptive items.

3.2 Study Characteristics

3.2.1 Age Groups—Of the 105 studies, 19 utilized samples of infants or children, 23 studied young and middle-aged adults, 42 had samples that spanned all ages of adulthood, and 21 focused exclusively on older adults. For infants and children, some of the stressors considered in this paper related specifically to adult experiences are not applicable. However, among adults, studies that focus on older populations are somewhat underrepresented in the literature.

3.2.2 Methodological Approaches—The majority of articles used qPCR to determine relative TL based on blood samples (83/105 studies, or 79%). Another 13% used qPCR on saliva samples, 7% utilized Southern Blot, and one study used q-FISH. These methods do not produce equivalent results and have a variety of measurement error issues (Verhulst, et al., 2015; Elbers, et al., 2014; Goldman, et al., 2017), as will be discussed at greater length in section 4. The use of these various TL measurement methods varied across age groups. Namely, all of the studies of young and middle-aged adults (100%) measured TL using *blood cells and qPCR assays*, compared to 88% of studies of mid- and older adults, 71% of studies of older adults, and only 42% of studies of infants or children (see Figure 2). In studies of infants or children, the majority of articles (53%) measured TL from saliva or buccal cells and qPCR assays.

More studies on young and middle-aged adults utilized samples restricted to a *single sex* (44%), compared to 26% of studies of mid- and older adults, 19% of studies of older adults, and 11% of studies of infants or children. Some studies from each age group included stratification by sex or tests for effect *moderation by sex* (11% of infant/children studies, 26% of mid-aged, 2% of middle- and older, and 24% of older). Only studies of mid- and older adults and studies of older adults stratified or tested for *moderation by age* (14% and 10% respectively) or by race / ethnicity (7% and 10% respectively). All age groups included some proportion of studies that utilized some *longitudinal elements* (26% of infant/children studies, 22% of mid-aged, 10% of mid- and older, and 29% of older). Additionally, some studies within all age groups had one or more “high” potential *bias ratings* (11% of infant/children studies, 9% of mid-aged, 24% of mid- and older, and 24% of older adults).

In sum, it seems fair to say that TL measurement is more varied in studies with older adults or with infants or children, and that methodological sophistication seems not yet strongly developed in this field of research.

3.2.3 Types of Stressors—The final sample of 105 studies included a total of 220 instances where stress was measured. Finding a larger number of instances where stress was measured than the total number of studies may seem counterintuitive at first, but this occurred because many of the 105 studies investigated more than one type of stressor. As illustrated in Figure 3, out of the 220 instances in which stress was measured (100%), 99 were socioeconomic stressors (45%), 75 were stressful or traumatic life events (34%), 35 were work-related stressors (16%), and only 11 were neighborhood stressors (5%). Thus, it seems that work-related and neighborhood stressors are understudied.

Figure 4 further classifies the 220 instances in which stress was measured by type of stressor and age group. While studies that utilized both middle-aged and older adults were present across all stressor groups, studies focusing on infants or children were represented in the fewest stressor groups. Specifically, studies on infants or children only investigated parental SES, early life adversities, and neighborhood stress measures, as other socioeconomic stressors, SLEs, and work-related stressors are not applicable for the age group.

Overall, the most common finding was that associations with TL were not significant, although this varied somewhat by type of stressor. Of the studies that did report significant

associations between stressors and TL, the majority documented significant relationships in the expected directions; that is, exposure to more stress was associated with shorter TL or increases in stress were associated with accelerated decreases in TL. In contrast, very few studies documented significant relationships in the opposite direction. Results for each stressor are discussed in the following sections.

3.3 Socioeconomic Stressors

In Table 1 we describe 99 instances where studies included measures of socioeconomic stressors, out of which 41 focused on educational resources, 29 on financial resources, 25 on parental SES, and four on home ownership (see Appendix Tables A4-A7 for detailed information on each study).

3.3.1 Educational Resources—Among the 41 studies that assessed education as a measure of SES, most report null findings. Among the seven studies of *middle-aged adults* that include statistics on the relationship between education and TL, the only study to find a significant relationship in the expected direction between education and TL (with fewer educational resources associated with shorter TL) also has the oldest sample of the group (a birth cohort at age 50, Pearce, et al., 2012). Among *middle- and older-aged adults*, six studies find significant associations in the expected direction between education and TL, three find unexpected significant negative associations, and fourteen find no significant association. Several studies among each—expected significant, unexpected significant, and insignificant findings—control for other SES variables, or have a single sex sample. More of the studies with insignificant results, however, utilized samples aged 65 and younger. Two studies of mid- and older-aged adults stratified their analysis of education and TL by age groups, but with contradictory findings. Surtees and colleagues (2012) found a stronger association between education and TL for 60-69 year olds compared to those in their 40s, 50s, or 70s, while Robertson and colleagues (2012) found that education was only significantly associated with TL for a 35 year-old birth cohort, and not for cohorts aged 55 and 75. Among studies on *older adults* only, four report significant associations in the expected direction between education and TL, and seven report no association. Two out of the four studies of older adults with significant results found that race had a significant moderation by education, with stronger associations between education and TL for African Americans than for whites (Adler, et al., 2013; Sanders, et al., 2015). Race, however, was not found to have a significant moderation by education in a study of middle- and older-aged adults (Needham, et al., 2013).

In sum, while the majority of evidence suggests that there is no relationship between education and TL, some of the null findings may be due to unexplored moderators, such as age and race, or due to cohort effects.

3.3.2 Financial Resources—Measures of SES based on financial indicators are consistently not associated with TL for samples of middle-aged and middle- and older-aged adults. None of the 15 studies on *middle-aged and older adults* reported any significant associations, and only one of six studies on *middle-aged adults* reported a significant association. However, while this study by Chae and colleagues (2014) found a significant

expected association between household income to poverty ratio and TL for their sample of 30-50 year-old African American men (n=92), this same relationship in the same sample was insignificant in a subsequent study by the authors that controlled for depression and anxiety (Chae, et al., 2016).

The findings for the relationship between financial resources and TL among studies of *older adults*, however, are less consistent. Only half of the eight studies in this group found significant associations: two studies found a significant unexpected negative association between TL and wealth (Rehkopf, et al., 2013) or household income (Whisman, et al., 2016). Another study found an expected positive relationship between monthly income and TL (Yen and Lung, 2013), and the final study found that TL attrition over a six-year period was lower for those with higher incomes, as expected (Sanders, et al., 2015). Neither of the two studies that examined differences in the relationship between financial resources and TL by age found noteworthy moderation (Adler, et al., 2013; Robertson, et al., 2012).

In sum, our stratification of studies by age in this analysis suggests that the relationship between financial resources and TL might differ for middle-aged and older adults, perhaps as a result of cohort effects.

3.3.3 Parental SES—There were 25 studies assessing parental SES measures. Most (14) of these examined samples of *infants or children*, using contemporaneous measures of maternal or paternal education, household income, or both. Among these studies of infants or children, measures of parental education and measures of parental income each had some significant (n=5) and some non-significant results (n=9). When significant, the direction of the relationship was consistently as expected, indicating that higher parental SES was associated with longer TL. Of the studies that control for parental age at conception or birth (Costa, et al., 2015; Drury, et al., 2015; Drury, Mabile, et al., 2014; Drury, Shirtcliff, et al., 2014; Fillman, et al., 2016; Pawlas, et al., 2015), a correlate of TL (Factor-Litvak, et al., 2016) that may confound the relationship between parental SES and TL, all but Costa and colleagues (2015) found no relationship between parental SES and TL. However, the study by Costa and colleagues is the only study in this group rated with a high potential for bias.

Relatively fewer studies of *adults* included a measure of parental SES. These studies utilized a diverse range of respondents' retrospective reports of parental home ownership, parental occupational class, parental education, assessments of family financial difficulties, or height as a proxy for early life SES. A few studies report significant expected results, including associations between more reported years of parental home ownership and longer TL for middle-aged adults (Cohen, et al., 2013), and higher parental occupational class and longer TL for older adults (de Rooij, et al., 2015). In their study of birth cohorts, Robertson and colleagues (2012) also found an expected association for prospective measures of parental social class and parental car ownership with TL, but only for middle-aged adults and not for older adults. In a sample of middle- and older-aged adults from the Multi-Ethnic Study of Atherosclerosis, Carroll and colleagues (2013) report contradictory findings that higher paternal education was associated with shorter TL.

Overall, the evidence of association between parental SES and TL is weak and may be moderated by the age/cohort of the respondent. Significant associations between parental SES and TL are somewhat more common and are more consistently as expected among infants or children. However, this pattern could be influenced by the recall bias that is introduced in adult studies, or by the exclusion of important confounders such as parental age at conception or birth in studies of infants or children.

3.3.4 Home Ownership—Four studies reported the relationship between home ownership/rental (with home ownership understood as an indicator of greater household resources) as a measure of socioeconomic stress and TL. Only one such study had a sample of middle-aged adults, and this study found no significant association between home ownership and TL (Pathai, et al., 2013). All three studies examining middle- and older-aged adults, however, reported significant results. Two found that current home ownership was associated with longer TL as expected (Shiels, et al., 2011; Carroll, et al., 2013), while the third found that intergenerational home ownership mobility, rather than current home ownership, was associated in the expected direction with TL (Robertson, et al., 2012). Again, age and race showed moderation effects. In Robertson and colleagues' study (2012), the finding was only significant for the youngest cohort that they examined. For Carroll and colleagues (2013), home ownership was only significantly associated with TL for white and Hispanic, but not African American, respondents. In sum, home ownership shows fairly consistent association with TL, although the relationship may be moderated by age and race/ethnicity.

3.4 Stressful Life Events (SLEs)

In Table 2 we describe 75 instances where studies assessed SLEs, out of which 41 focused on early-life and 23 on lifetime stressful events or traumas, eight on caregiving for an ill child, partner, or parent, and three on discrimination (see Appendix Tables A8-A11 for detailed information on each study).

3.4.1 Early-life SLEs—Measures of early-life stressful events or traumas appeared in 41 studies. Across age groups, findings were significant nearly half of the time or more, consistently in the expected direction. Eight of the 10 studies of infants or children found the expected association between early SLEs and shorter TL. For studies of infants (Entringer, et al., 2013; Marchetto, et a., 2016), exposure to stress was measured as maternal SLEs during pregnancy, and in both cases more maternal stress was associated with shorter newborn TL. Studies of children with significant results measured stress exposure as involvement with Child Welfare or institutional care, or exposure to family instability, violence, abuse, or maternal recurrent major depression. The two non-significant studies in this younger population drew from the same study of African American teenagers, and both found that life stressors at age 17 were not associated with TL five years later (Beach, et al., 2014; Brody, et al., 2015).

Many of the studies of early SLEs and TL in adult populations utilized established retrospective scales to measure traumas or adverse events, such as the Childhood Trauma Questionnaire (e.g., Kiecolt-Glaser, et al., 2011; Kuffer, et al., 2016; Levandowski, et al.,

2016; Malan-Muller, et al., 2013; Tyrka, et al., 2010). A few studies focused on specific categories of exposure (e.g., violence exposure, Jodczyk, et al., 2014; sexual abuse, Cai, et al., 2015), or specific events (e.g., separation from parents during WWII, Savolainen, et al., 2014; exposure to famine during the Leningrad siege, Rotar, et al., 2015). Slightly more than half of the studies of adults reported significant associations between early SLEs and TL (4/10 studies of middle-aged adults, 9/14 studies of middle- and older-aged adults, and 4/7 studies of older adults), all in the expected direction with more early SLEs associated with shorter TL in later life. The overall findings appear unrelated to whether studies used comprehensive measures or specific measures of early stress exposure. Similarly the results appear unrelated to whether the studies adjusted for common health covariates (BMI, smoking, or disease indicators), or for lifetime exposure to traumas.

Only a few studies tested for moderation by age or sex. In two studies that found the expected association between more early SLEs and shorter TL, age did not significantly moderate the effect (Schaakxs, et al., 2016; Surtees, et al., 2011). Some authors found no significant differences in the association by sex (Entringer, et al., 2011; Verhoeven, et al., 2015), while others found that different types of early SLEs were associated with TL for each sex (Drury, et al., 2012; Enokido, et al., 2014) or that the association with an SLE index disappeared for males when stratified by sex (Drury, Mabile, et al., 2014).

In all, there is substantial evidence that more SLEs in childhood are associated with shorter TL in childhood, and fairly substantial evidence that this association persists across the life course. Whether sex moderates this relationship, however, remains unclear.

3.4.2 Lifetime SLEs—Lifetime stressful or traumatic events were examined in 23 studies. Among eight studies of middle-aged adults, results were mixed. Most (six) of these studies examined the relationship between PTSD status for events that occurred during adulthood (e.g., combat) and TL. Three such studies found no association between PTSD status and TL, two found that those with PTSD had significantly shorter TL than controls without PTSD as expected (O'Donovan, et al., 2011; Zhang, et al., 2014), and another found that male veterans with PTSD had *longer* TL than veterans without PTSD (Boks, et al., 2015). In the later state-of-the-art study, Boks and colleagues examined veterans' telomere lengths 6 months after deployment while controlling for pre-deployment TL and the time interval between TL measurements. The authors took several precautions to enhance the TL measurements, such as positioning baseline and follow up samples on the same plates and obtaining blood cell counts. They note that the lengthening of TL among formerly deployed veterans with PTSD, though contrary to their hypothesis, could be due to stress-induced telomerase activity, but they conclude that further longitudinal study is needed and it highlights the importance of having a reference available to evaluate the meaning of a given TL measurement.

Studies of *middle- and older-aged adults* more commonly employed stressful or traumatic life events scales rather than measures of PTSD. Studies varied in the amount of lifetime considered within the SLE scales. Several considered all stressful or traumatic events over a lifetime, finding no association with TL (Hill, et al., 2016; Simon, et al., 2015), or finding a significant association in the expected direction with TL (Cai, et al., 2015—however, this

study was rated as high potential for bias). Stressful life events in the past five years were also not associated with TL (Surtees, et al., 2011). Stressful or traumatic events in the past year were negatively associated as expected with TL in two studies (Revesz, et al., 2016; Van Ockenburg, et al., 2015), but recent major losses were also significantly associated with *longer* TL in one investigation (Parks, et al., 2009). Verhoeven and colleagues (2015) compared measures of stressful life events in the past year, 1-5 years ago, and six or more years ago, finding no significant association with TL for any of them. Of the two studies investigating the relationship between PTSD and TL in mid- and older adults, one found no association (all male veterans, Jergovic, et al., 2014) while the other found the expected significant negative association (Ladwig, et al., 2013).

Among five studies of *older adults*, all five found a significant association wherein more stress or more trauma was associated with shorter TL, as expected. These studies utilized various measures of SLEs, including a major life stressors scale (Puterman, et al., 2015), the Traumatic Experiences Checklist (Savolainen, et al., 2014; Schaakxs, et al., 2016), and a scale for PTSD (Kuffer, et al., 2016). Whisman and colleagues (2016) found a significant association between martial disruption (separation or divorce) and shorter TL, but no significant associations between TL and scales of stressful or traumatic life events.

Only two studies of older adults investigated whether the relationship between SLEs and TL is moderated by sex, finding no significant differences by sex (Savolainen, et al., 2014; Whisman, et al., 2016). Looking at the results across age groups, there are more consistent findings for the expected association between SLEs and TL among older adults. However, neither of the studies that tested for moderation by age found significant differences by age (Schaakxs, et al., 2016; Surtees, et al., 2011).

In sum, results for the effect of lifetime SLEs are mixed. There seems limited evidence to suggest that the distance between the occurrence of the events and the measurement of TL, as well as the age of the respondents, may matter.

3.4.3 Caregiving—Eight studies in this review examine the specific stress of caregiving for an ill child, partner, or parent. Half of these studies find significant correlations in the expected direction between caregiving and TL, where caregivers have shorter TL than non-caregivers (Damjanovic, et al., 2007; Kiecolt-Glaser, et al., 2011), more years of caregiving are associated with shorter TL (Epel, et al., 2004), or those with more intensive caregiving duties have shorter TL than those with less burden (Litzelman, et al., 2014). Most of these studies (five) focus on older adults. However, these studies only draw from two distinct study populations and results differ by population: O'Donovan and colleagues (2009 and 2012) and Tomiyama and colleagues (2012) use cross-sectional data from women in San Francisco and find no association, while Damjanovic and colleagues (2007) and Kiecolt-Glaser and colleagues (2011) use a study of males (27%) and females (73%) in Ohio and find significant associations. Five of the eight studies utilize all-female samples, and only one of these reports a significant association between years of caregiving and TL (Epel, et al., 2004). All three of the studies with a mixed-sex sample, however, found a significant association between caregiving and TL, though none tested moderation by sex. Overall,

there is some evidence that burdens of caregiving are associated with TL, and the role of sex and other potential moderators remains unexplored.

3.4.4. Experiences of Discrimination—As of the search date, only three studies examined the association between discrimination and TL. Two of these are based on the same sample. Chae and colleagues utilized a sample of 92 30-50 year-old African American males from the Bay Area Heart Health Study to study the association between discrimination and TL. First, they found that men with stronger internalized anti-black bias and more experiences of interpersonal discrimination had shorter TL (Chae, et al., 2014). In their second study, they found that non-depressed men had a stronger negative relationship between TL and discrimination than depressed men (Chae, et al., 2016). In a sample of individuals aged 25 and older (sex and racial composition of the sample is not stated), Geronimus and colleagues (2015) found no association between experiences of unfair treatment and TL. While more research on the relationship between TL and experiences of discrimination is needed, preliminary work suggests that there may be associations that are influenced by other psychosocial factors.

3.5 Work-Related Stressors

In Table 3 we describe 35 instances where studies assessed work-related stressors, out of which 18 focused on occupational class, 12 on employment status, five on job characteristics, such as job stress, job control, and work schedule (see Appendix Tables A12-A14 for detailed information on each study).

3.5.1 Occupational Class—One commonly studied category of work-related stressors is occupational class (18 studies). Many of these studies utilize the UK six-class ranking of occupations, while others capture the concept as professional, service, or manual work. All but one of these studies (Fujishiro, et al., 2013) utilize European or Asian samples. None of the four studies of *middle-aged adults* or the five studies of *older adults* found any significant association between class of work and TL. Among the nine studies examining *middle- and older-aged samples*, three found significant associations in the expected direction between class of work and TL, with higher class associated with longer TL. Two of these studies with significant results draw from the same Twins UK Registry, finding that manual labor was associated with significantly shorter TL in a sample of women aged 18-75 (Cherkas, et al., 2006, which has some high potential for bias) and in a sample of majority women (10% men) aged 18-81 (Cherkas, et al., 2008). In the third study reporting significant results, Robertson and colleagues (2012) found that social class mobility over time was significantly associated with TL for 35-year olds but not 55- or 75-year olds, and current occupational class was not associated with TL for any age group. Robertson and colleagues were the only authors to examine occupational class mobility; others utilized classifications of current occupation. None of the studies that tested for moderation by sex found significant differences (Adams, et al., 2007; Ala-Mursula, et al., 2013; Harris, et al., 2012; Pearce, et al., 2012).

In all, these studies suggest that there is little evidence of a cross-sectional association between current occupational class and TL, although occupational class mobility warrants further study.

3.5.2 Job Characteristics—Of the five studies that examine characteristics of jobs, three specifically focus on the relationship between measures of job stress and TL. These three studies utilized *middle- and older-aged* samples, with mixed-sex samples and TL measures from blood cells and qPCR assay. Two found no significant association between TL and job stress, measured as a scale of work stress (Von Kanel, et al., 2015), or as a series of personal measures of perceived job strain, job control, and job demands and occupation-level versions of those measures from the "Occupational Information Network" (O*NET), which is sponsored by the U.S. Department of Labor (Fujishiro, et al., 2013). Examining work exhaustion, however, Ahola and colleagues (2012) found that those who reported severe work exhaustion had significantly shorter TL than those without work exhaustion.

Two other studies considered work shifts and scheduling. In their sample of women aged 35-74, Parks and colleagues (2011) found that working multiple jobs concurrently was associated with shorter TL as expected, but that night shifts and irregular hours were not. Liang and colleagues (2011) also found no significant association between night shift work and TL for women.

In sum, research to date has not found substantial support for associations between job stress or job schedule and TL, but some evidence suggests a relationship between TL and more extreme conditions such as job exhaustion or working multiple jobs concurrently.

3.5.3 Employment Status—A final work-related stressor that appears in 12 studies is employment status. This is often measured dichotomously as employed vs. unemployed (six studies), but various authors add other categories (e.g., employed, willingly unemployed, and unwillingly unemployed in Kingma, et al., 2012). In one paper, the authors measure number of days unemployed over a three-year period (Ala-Mursula, et al., 2013). Among studies of *middle-aged adults*, only this study utilizing number of unemployment days found a significant association between long-term unemployment and shorter TL, but only among males and not females (Ala-Mursula, et al., 2013). Out of seven studies of middle- and older-aged individuals, three found positive significant associations between being employed and TL. Being unemployed was associated with shorter TL in an all-male sample (Batty, et al., 2009), and in the youngest age group of a set of mixed-sex birth cohorts (35 year-olds, but not 55 or 75 year-olds; Robertson, et al., 2012). However, in the only all-female sample in this set of 12 studies, Parks and colleagues (2011) found that women working full or overtime had significantly *shorter* TL than women who worked part-time or who were unemployed. The single study of employment status and TL in *older adults* (de Rooij, et al., 2015) found no significant association. Overall, there is some limited evidence suggesting that employment status may be associated with TL, and that the relationship may vary by sex.

3.6 Neighborhood Stressors

In Table 4 we describe 11 instances where studies assessed neighborhood measures of stress, out of which six focused on the built environment and five on the economic environment (see Appendix Tables A15-A16 for detailed information on each study).

3.6.1 Economic Environment—Five studies examine measures of neighborhood economic conditions, one in children, and four in middle- and older-aged adults. In a sample of mixed-sex African American children in the US, ages 4-14, Theall and colleagues (2013) found that a Census-derived index of neighborhood economic deprivation was not significantly associated with TL, but that a high percentage of the population below the poverty line in the neighborhood was associated with shorter TL in the children. All four studies of mid- and older-aged adults find no significant association between TL and measures of area disadvantage based on either the Scottish Census (Batty, et al., 2009; Robertson, et al., 2012; Shiels, et al., 2011) or US Census (Needham, et al., 2014).

3.6.2 Built Environment—Six studies investigate other place-based stressors that are grouped together here as aspects of the built environment. Five of the six studies found significant associations between environment and TL. Theall and colleagues' study (2013) of African-American children in the US measured caregivers' assessments of neighborhood disorder, and high neighborhood disorder scale scores were associated with shorter TL in the children. In a sample of 30 to 55 year-old African Americans, shorter TL was associated with more reported neighborhood problems (including noise, traffic, trash, violence, and poor access to food, parks, sidewalks), but only for women (Gebreab, et al., 2016). In mid and older-aged adults, shorter TL was significantly associated with poor quality neighborhoods (Park, et al., 2015), high safety concern (Geronimus, et al., 2015), and low scores on an index of neighborhood environment encompassing aesthetic quality, safety, and social cohesion (Needham, et al., 2014). Yen and Lung (2013), however, found no association between TL and an index of neighborhood quality (including security, social support, services, and facilities) among 65 to 74 year-olds in Taiwan.

While more research is needed on the relationship between TL and both economic and built aspects of neighborhoods, current work strongly suggests that negative aspects of the built environment, such as high disorder and safety concerns, are associated with shorter TL.

4. Discussion

In our systematic scoping review of 105 studies that investigated the relationship between social stressors and various measures of TL, we utilized a unique approach of stratifying studies by age groups and types of stressors in order to examine the methods and results of this literature. Our primary findings follow.

4.1 Methodology of the Literature

4.1.1 Differences in TL Measurement Across Studies and Age Groups—The articles included in this review utilized a variety of cell sources and TL measurement methodologies. Only a minority of articles (7/105, 7%) employs the "gold standard"

Southern blot method. The majority (83/105, 79%) measure TL from blood samples with qPCR. While qPCR is a very common method, offering a cheaper and quicker alternative to other methods, various authors have raised a number of critical concerns about the resulting data. Namely, qPCR is known to have greater measurement error than Southern blot (Aviv, et al., 2011, Elbers, et al., 2014). A variety of factors impact qPCR's intra- and inter-assay measurement error, from pre-analytic factors such as the sample storage medium (Eastwood, et al., 2018), to the laboratories themselves (Aviv, et al., 2011) and the expertise and experience of the technicians (Behrens, et al., 2017). The cellular source and collection method also impacts measurement error (Goldman, et al., 2016). Furthermore, qPCR offers a *relative* measure of TL (the T/S ratio), as compared to the count of kilobase pairs offered by Southern Blot.

Our analysis by age groups revealed that studies of middle-aged and middle- and older-aged samples utilized much more consistent methods of measuring TL than studies of infants/children and older adults. Studies of young and middle-aged adults universally utilized blood cells, assayed by qPCR. In comparison, only 42% of studies of infants or children and 71% of older adults used these methods. Many of the studies of infants/children and older adults utilize cells obtained from saliva samples (53% of studies of infants/children, and 14% of studies of older adults). The greater variability in the methods used for the youngest and oldest populations introduces different sources of bias in studies at the extremes of the lifespan than in studies of young and middle-aged adult populations. It may be that researchers working with these populations are more likely to strategically rely upon less-invasive saliva sampling (Goldman, et al., 2017). While TL from different tissue sources are not directly comparable, rank order of TL and rates of telomere shortening are similar across some tissues (Daniali, et al., 2013). However, TL from buccal epithelial cells tend not to follow patterns typical of TL from other cells, and some methods of saliva collection (swab, mouthwash, brush) contain greater proportions of these cells than saliva collected via passive drool (Goldman, et al., 2017). As a result, some TL measures based on certain methods of saliva collection may lead to different conclusions than one would find with TL measurements from other cellular sources.

These various issues with TL measurement, therefore, make it challenging to compare across studies. Even so, many of the papers included in this review draw on sample sizes that may help to accommodate such measurement error (Verhulst, et al., 2015). Moreover, there are some consistent findings across studies and samples, reviewed below, which enhance confidence in these measurements.

4.1.2 Paucity of Research on Effect Moderation—

We also show that very few studies have investigated whether the relationship between social stressors and TL is moderated by age, sex, or race/ethnicity, or tested for cohort effects. However, findings in the limited number of studies that do include such effect moderators suggest that, for several stressors, some of these effects may be important.

4.2 Results by Stressor and Age Group

4.2.1 Socioeconomic Stressors—Authors have investigated various sources of socioeconomic stressors, including lack of educational resources, lack of financial resources, parental SES, and housing rental vs. ownership. The evidence for a significant relationship between any of the socioeconomic stressors and TL is weak, with the majority of the studies utilizing some socioeconomic measure of stress finding no significant association with TL. However, a more recent study by Mitchell and colleagues (2018) of a small group of young, perinatal women found that common indicators of lower childhood SES were associated with shorter TL. Home ownership, not commonly studied, seems to have a fairly consistent relationship with longer TL, yet lack of home ownership is likely itself a correlate or outcome of some other more fundamental cause of stress. Across socioeconomic stressors, age and race emerge as potentially important moderators—a finding consistent with work published after the search date for this review (Flannagan, et al., 2017; Schrock, et al., 2017). While financial and educational resources are fairly consistently unrelated to TL among young and middle-aged adults, they may have a more complex relationship with TL for older adults. Measures of parental SES are more commonly investigated for infants or children, and are significantly associated with TL in more than a third of such papers.

4.2.2 Stressful Life Events—Four distinct measures of SLEs appear in the literature: childhood traumas and adverse events, lifetime stressful events and traumas, caregiving, and discrimination. There is substantial support for the expected relationship between greater early-life SLEs and shorter TL among infants or children, and there is also some evidence to suggest that the relationship persists into adulthood. These conclusions are largely consistent with recently published studies (Dagan, et al., 2017; Humphreys, et al., 2016; Kim, et al., 2017; Liu, et al., 2017; Mitchell, et al., 2017; Osler, et al., 2016; Puterman, et al., 2016; Riley, et al., 2018; Vincent, et al., 2017 — *c.f.:* Oliveira, et al., 2017 and Mitchell, et al., 2018) and recent reviews (Coimbra, et al., 2017; Hanssen, et al., 2017; Li, He, et al., 2017; Li, Wang, et al., 2017; Ridout, et al., 2018). Both lifetime stressful events and caregiving are significantly associated with TL in about half of the studies that examine the relationships, and these mixed results appear in more recently published studies as well (Chang, et al., 2018; Liu, et al., 2017). For lifetime stressors, the direction of the significant results has in a few cases been contrary to expectations, with more experiences of stressful events associated with longer TL. However, both papers with these contrary findings were on single-sex samples with at least one issue that suggested a “high” potential for bias (Boks, et al., 2015; Parks, et al., 2009). Some evidence suggests that the respondents’ age and how recently the events occurred may be important factors in the strength of this association. Recently published studies also report that timing seems to matter: in one study TL is associated with very recent stressful events (Lopizzo, et al., 2017), and in others childhood events seem to drive the relationship between lifetime stressors and TL (Osler, et al., 2016; Puterman, et al., 2016). While only three studies in this sample examined the relationship between discrimination and TL, additional research that has emerged since the search date for this review further support that experiences of discrimination are associated with shorter TL as expected for African Americans in the United States (Liu & Kawachi, 2017; Lee, Kim, & Neblett Jr., 2017).

4.2.3 Work-related Stressors—

Fewer studies overall investigated work-related stressors, including occupational class, employment status, and job characteristics such as stress, control, and work schedule. There is little evidence to suggest a cross-sectional relationship between current occupational class and TL, although occupational class mobility remains understudied. Employment status also would benefit from further study, with some limited evidence suggesting that unemployment may be associated with TL, and that the association may be moderated by sex. While one more recently published study has investigated job stressors and work characteristics, with mixed results (Chmelar, et al., 2017), more research is needed on these topics as well. This review did not find any studies that assessed the relationship between TL and retirement, a major life transition and potential source of stress for older adults. However, the word “retirement” itself was not included in the original search strategy (see Appendix Tables A1-A2). A follow-up search of the four databases, conducted in September, 2017, yielded no studies that specifically study retirement status or transitions to retirement and TL.

4.2.4 Neighborhood Stressors—

Finally, few studies have considered the relationship between characteristics of neighborhoods of residence and TL. While results suggest that there is no association between measures of neighborhood economic conditions and TL, there is notable support for a relationship between characteristics of the built environment and TL in the studies included in this review and also in newly published research (Lynch, et al., 2017).

4.3 Strengths and Limitations

This systematic scoping review offers a new way of examining the TL and stress literature, stratifying results by age and type of stressor. We developed the age and stress categories in response to the sample of articles, but we acknowledge that the classifications could have been rendered in other ways that similarly maintain conceptual clarity. The different cellular sources of TL and assay methods, the different definitions and measurements of stressors, and the varying approaches to adjustment, mediation, and effect moderation, pose challenges for assessing results across the literature. Few studies were longitudinal. The widely varying sample sizes of the studies in this review also could impact the power that some studies had to detect effects. Furthermore, some aspects of the methodological approaches appear to vary by the age of the research populations. Finally, our analysis by age groups revealed several instances of apparent differences in the relationship between stressors and TL across ages, but it remains unclear whether these are life course or cohort effects.

However, the breadth of approaches that we assess is not only a limitation but also a strength of this scoping review. While other reviews have focused on specific types of stressors, we have provided a wide overview of social stressors that have been studied in relation to a variety of measures of TL. We have furthermore organized that overview by age, because of the importance that the life course plays both in the dynamics of TL and in one’s exposure to, and accumulation of, stress. We have also applied existing guidelines for constructing well-documented and reproducible scoping systematic reviews.

4.4 Implications for Future Research

The results of this scoping review have several implications for future research on social stressors and TL. Some types of stressors, such as early life stress, have been extensively studied with consistent results. However, other domains of stress that may play important roles in TL dynamics remain understudied. In particular, work-related stressors and stressors related to the built environment need further study across various populations. Among adults, older populations are relatively understudied and would benefit from additional focus.

This review also reveals that this literature would benefit from several methodological improvements. Longitudinal studies are required to assess causal relationships between social stressors and TL. The cell types included in TL assays need more accurate clarification. A number of studies state only that TL measures come from “blood” or “leukocytes.” This literature could better utilize the variety of methods for sorting cells or making *post hoc* adjustments for the variety of cells. The literature would also benefit from more consistent accounting of efforts to manage known sources of measurement error for qPCR. The majority of these studies furthermore failed to account for potentially relevant confounders of the relationship between social stressors and TL, such as exposure to air pollution.

Finally, future research should investigate potential moderation of social stressors by age, sex, and race / ethnicity, and the potential for cohort effects. A relatively small proportion of existing studies examine how the relationship between stress and TL may vary across these characteristics, yet in several instances the moderation has been significant. Careful consideration of these, and other, influential moderators may help to explain otherwise inconsistent results across studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Scoping systematic review maps the social stressors and telomere length literature
- Methods and findings are presented by age of study participants and types of stress
- TL measurement methods varied more in studies of infants/children and older adults
- Work and neighborhood stressors, and older populations, are understudied
- The stress-TL relationship may be moderated by age, sex, and race/ethnicity

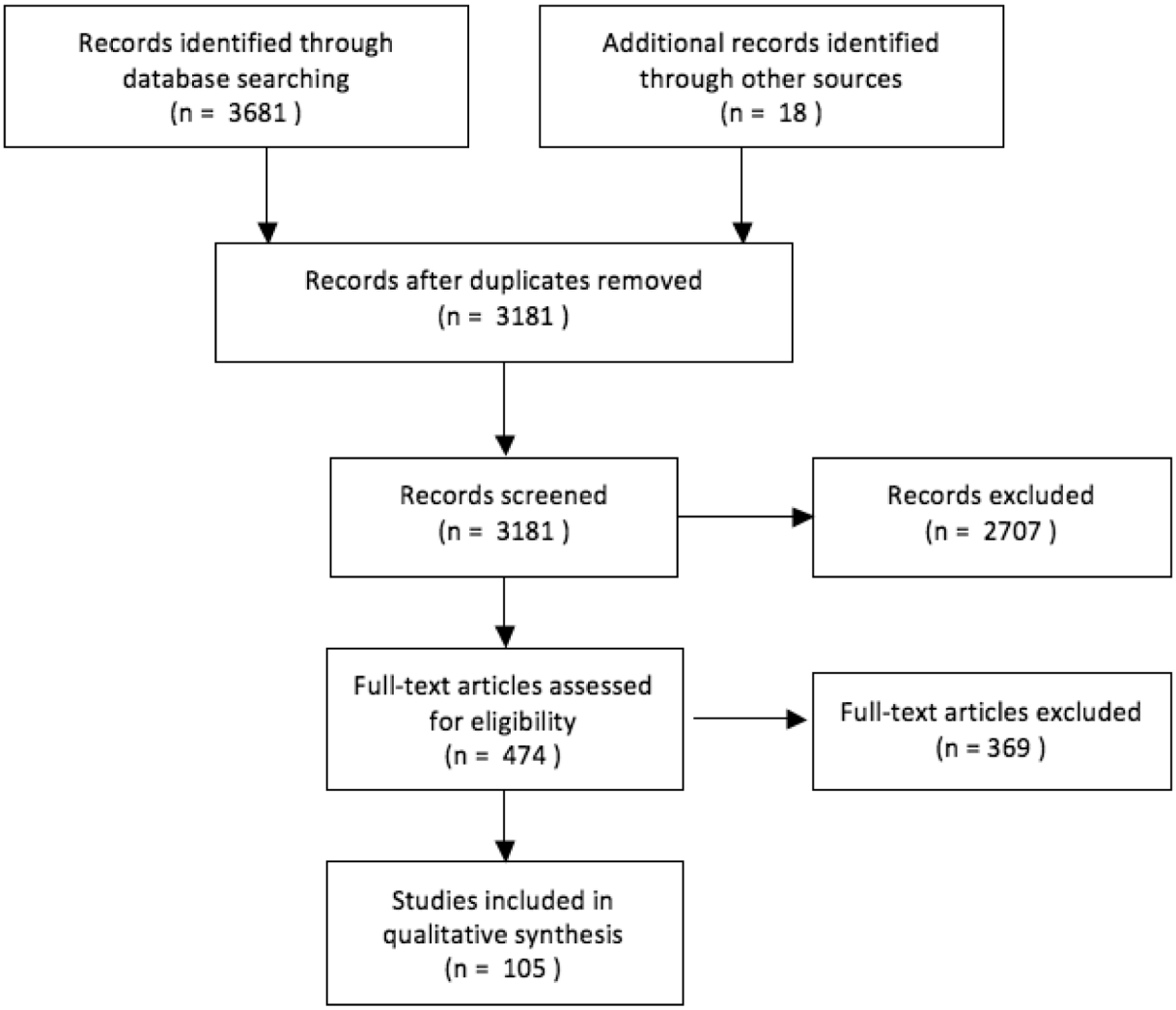

Figure 1.
PRISMA flow chart of the sample of articles.

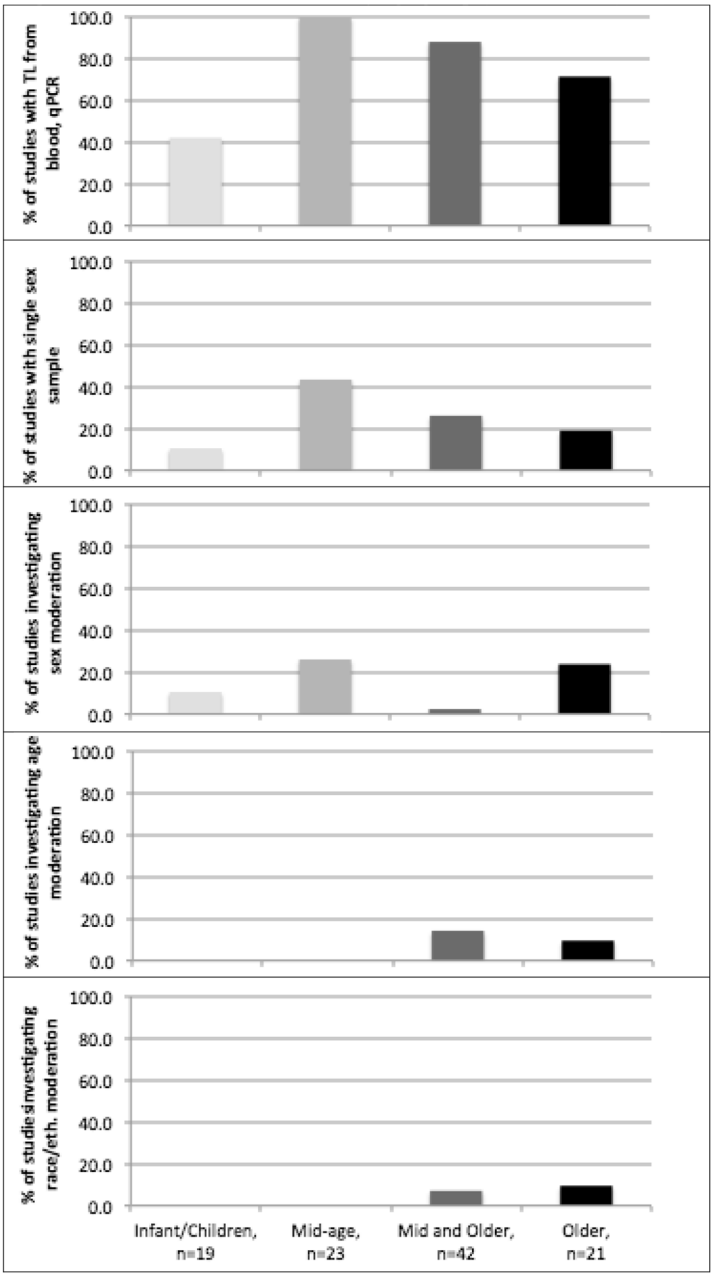

Figure 2.
Characteristics of studies, by age group (n=105 studies)

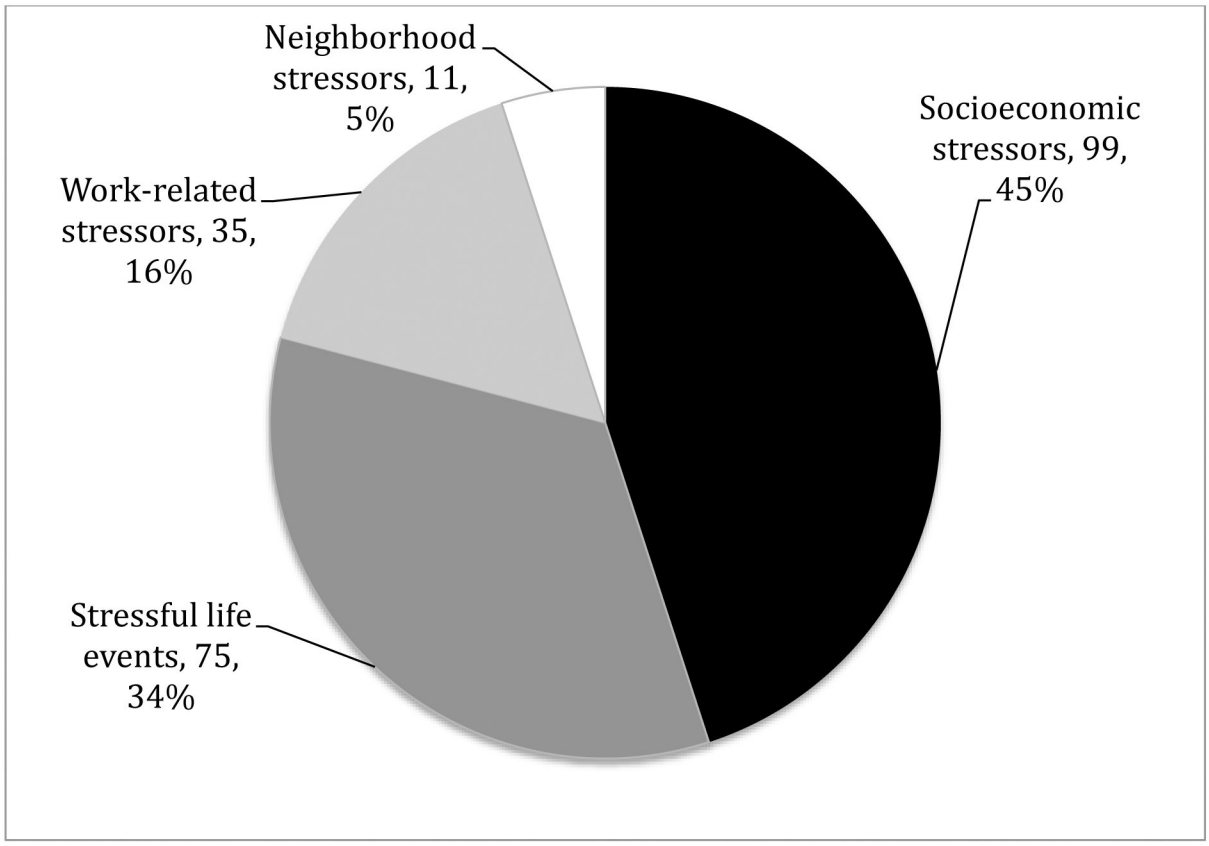

Figure 3.
Subtypes of stressors, as percentages of total instances of stress measures (n=220; most of the 105 studies included multiple stress measures).

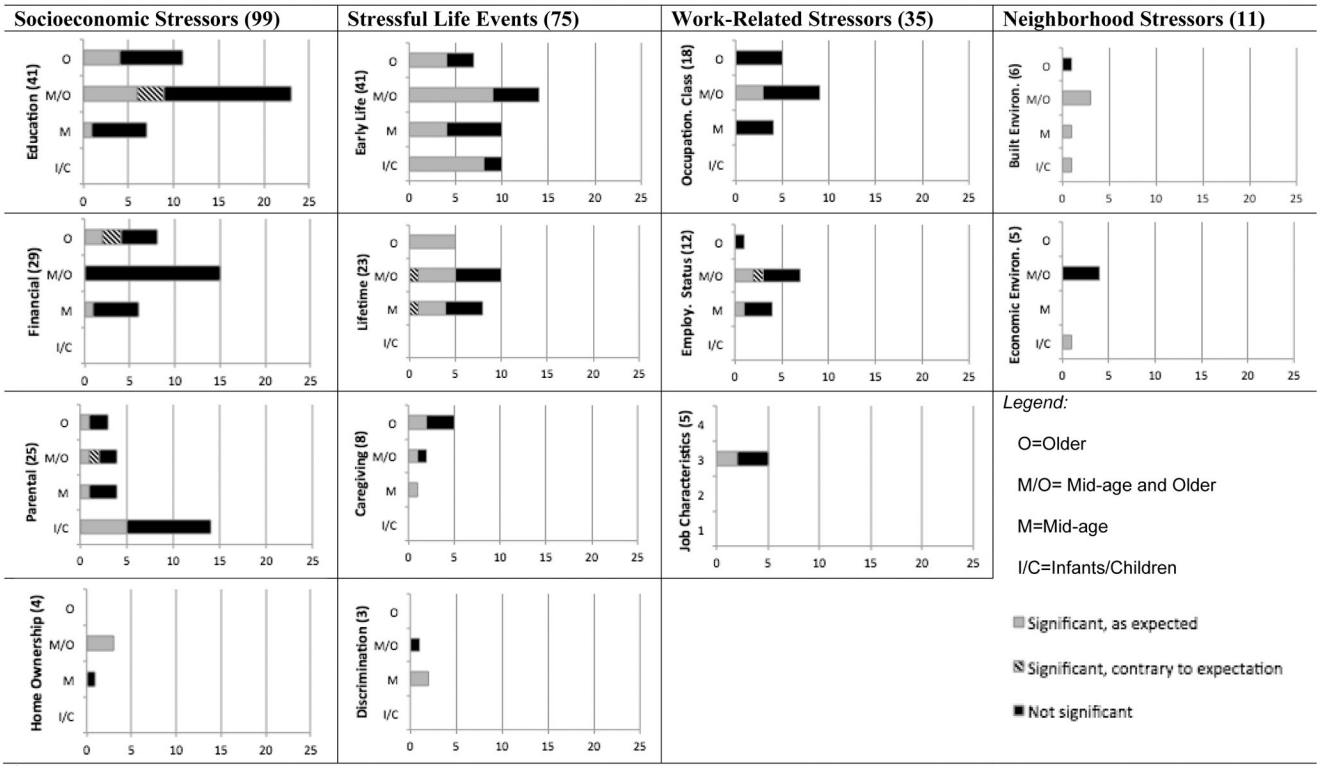

Figure 4.

Relationship between stressor and TL, by type of stressor and age group (n=220)*

* *Stress was measured 220 instances in a total of 105 studies. Within the 105 studies, many investigated more than one type of stressor.*

Table 1:

Socioeconomic Stressors (n=99)

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
	Middle aged adults	7	7/7	4/7	2/7	1/7 sex (Sig. assoc. only for males)	0/7	1/7	1 positive, as expected (for males only)	Chae et al 2014; Chae et al 2016; Loprinzi 2015; Malan et al 2011; Malan-Muller et al 2013; Pathai et al 2013; Pearce et al 2012
Educational Resources (41)										
	Middle aged and older	23	23/23	5/23	2/23; 3/23; 2/23; 3/23	1/23 race (n.s.); 2/23 age (mixed)	3/23	9/23	6 positive, as expected; 3 negative, contrary to expectation	Batty et al 2009; Carroll et al 2013; Cui et al 2013; Geronimus et al 2015; Hill et al 2016; Kananen et al 2010; Kingma et al 2012; Lee et al 2013; Leung et al 2014; Levandowski et al 2016; Litzelman et al 2014; Menke et al 2015; Needham et al 2013; Nettleton et al 2008; Park et al 2015; Parks et al 2009; Revesz et al 2016; Robertson et al 2012; Roux et al

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
										2009; Shiels et al 2011; Surtees et al 2012; Tyrka et al 2016; Van Ockenburg et al 2015
	Older adults	11	8/11	1/11	2/11; 2/11	1/11 age, sex, race (Assoc. stronger for black); 1/11 sex and race (Sig. assoc. for black males only)	2/11	4/11	4 positive, as expected	Adler et al 2013; Faul et al 2016; Harris et al 2012; Kuffer et al 2016; Puterman et al 2015; Rehkopf et al 2013; Sanders et al 2015; Steptoe et al 2011; Whisman et al 2016; Yen & Lung 2013; Zalli et al 2014
Financial Resources (29)	Middle aged adults	6	6/6	3/6	2/6	1/6 sex (n.s.)	1/6	1/6	1 positive, as expected	Adams et al 2007, Ahrens et al. 2016, Chae et al 2014, Chae et al 2016, Loprinzi 2015, Pathai et al 2013
	Middle aged and older	15	15/15	1/15	3/15; 3/15; 2/15	1/15 race (n.s.); 1/15 age (n.s.)	2/15	0/15	N/A	Carroll et al 2013; Cui et al 2013; Geronimus et al 2015; Hill et al 2016; Kingma et al 2012; Lee et al 2013; Leung et al 2014; Menke et al 2015;

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
										Needham et al 2013; Nettleton et al 2008; Park et al 2015; Revesz et al 2016; Robertson et al 2012; Roux et al 2009; Shiels et al 2011
	Older adults	8	6/8	1/8	2/8	1/8 age, sex, race (n.s.)	3/8	4/8	2 positive, as expected; 2 negative, contrary to expectation	Adler et al 2013; Faul et al 2016; Puterman et al 2015; Rehkopf et al 2013; Sanders et al 2015; Steptoe et al 2011; Whisman et al 2016; Yen & Lung 2013
Parental SES (25)										Asok et al 2013; Beach et al 2014; Brody et al 2015; Costa et al 2015; Dismukes et al 2016; Drury et al 2015; Drury, Shirtcliff et al 2014; Drury, Mabile et al 2014; Fillman et al 2016; Mitchell et al 2014; Needham et al 2012; Pawlas et al
	Infants / children	14	7/14	1/14	3/14; 2/14	0/14	2/14	5/14	5 positive, as expected	

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
										2015; Theall et al 2013; Wojcicki et al 2016
	Middle aged adults	4	4/4	0/4	2/4	1/4 sex (n.s.)	3/4	1/4	1 positive, as expected	Adams et al 2007; Cohen et al 2013; Jodczyk et al 2014; Pearce et al 2012
	Middle aged and older	4	4/4	1/4	0/4	1/4 age (Sig. assoc. only for younger)	1/4	2/4	1 positive, as expected; 1 negative, contrary to expectation	Batty et al 2009; Carroll et al 2013; Robertson et al 2012; Tyrka et al 2016
	Older adults	3	1/3	0/3	0/3	0/3	1/3	1/3	1 positive, as expected	de Rooij et al 2015; Faul et al 2016; Rehkopf et al 2013
Home Ownership (4)	Middle aged adults	1	1/1	0/1	N/A	0/1	0/1	0/1	N/A	Pathai et al 2013
	Middle aged and older	3	3/3	0/3	0/3	1/3 age (Assoc. sig. only for younger); 1/3 race (Assoc. sig. for all but black)	1/3	3/3	3 positive, as expected	Carroll et al 2013; Robertson et al 2012; Shiels et al 2011

*Longitudinal includes studies that have measures of stressors over time and TL at one time point, as well as studies that have multiple measures of both TL and stressors.

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Table 2:

Stressful Life Events and Traumas (n=75)

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
Early-life SLEs (41)	Infants/ children	10	3/10	2/10	2/10	2/10 sex (mixed)	5/10	8/10	8 negative, as expected	Asok et al 2013; Beach et al 2014; Brody et al 2015; Drury et al 2012; Drury, Mabile et al 2014; Entringer et al 2013; Gotlib et al 2015; Marchetto et al 2016; Mitchell et al 2014; Shalev et al 2013
	Middle-aged adults	10	10/10	4/10	0/10	2/10 sex (mixed)	3/10	4/10	4 negative, as expected	Bersani et al 2016; Boks et al 2015; Enokido et al 2014; Entringer et al 2011; Jodczyk et al 2014; Malan-Muller et al 2013; Mason et al 2015; O· Donovan et al 2011; Shalev et al 2014; Zhang et al 2014
	Middle-aged and older	14	11/14	4/14	3/14; 2/14	1/14 age (n.s.); 1/14 sex (n.s.)	2/14	9/14	9 negative, as expected	Cai et al 2015; Chen et al 2014; Glass et al 2010; Kanenen et al 2010; Levandowski et al 2016; Revesz et al 2016; Simon et al 2015; Surtees et al

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
										2011; Surtees et al 2012; Tyrka et al 2010; Tyrka et al 2016; Van Okenburg et al 2015; Verhoeven et al 2014; Verhoeven et al 2015
	Older adults	7	4/7	0/7	0/7	1/7 age (n.s.)	1/7	4/7	4 negative, as expected	Kiecolt-Glaser et al 2011; Kuffer et al 2016; Rotar et al 2015; Savolainen et al 2014; Schaakxs et al 2016; Whisman et al 2016; Zalli et al 2014
Lifetime SLEs (23)	Middle-aged adults	8	8/8	5/8	0/8	0/8	2/8	4/8	3 negative, as expected; 1 positive, contrary to expectation	Bersani et al 2016; Boks et al 2015; Humphreys et al 2012; Jodczyk et al 2014; Malen et al 2011; Malan-Muller et al 2013; O'Donovan et al 2011; Zhang et al 2014
	Middle-aged and older	10	8/10	2/10	2/10	1/10 age (n.s.)	2/10	5/10	4 negative, as expected; 1 positive, contrary to expectation	Cai et al 2015; Hill et al 2016; Jergovic et al 2014; Ladwig et al 2013; Parks et al 2009; Revesz et al 2016; Simon et al 2015; Surtees et al 2011; Van Okenburg et al 2015;

SLE Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
										Verhoeven et al 2015
	Older adults	5	3/5	1/5	0/5	2/5 sex (n.s.); 1/5 age (n.s.)	2/5	5/5	5 negative, as expected	Kuffer et al 2016; Puterman et al 2015; Savolainen et al 2014; Schaakxs et al 2016; Whisman et al 2016
Caregiving (8)	Middle-aged adults	1	1/1	1/1	N/A	0/1	0/1	1/1	1 negative, as expected	Epel et al 2004
	Middle-aged and older	2	2/2	1/2	0/2	0/2	0/2	1/2	1 negative, as expected	Koenig et al 2016; Litzelman et al 2014
	Older adults	5	3/5	3/5	3/5; 2/5	0/5	0/5	2/5	2 negative, as expected	Damjanovic et al 2007; Kiecolt-Glaser et al 2011; O'Donovan et al 2009; O'Donovan et al 2012; Tomiyama et al 2012
Discrimination (3)	Middle-aged adults	2	2/2	2/2	2/2	0/2	0/2	2/2	2 negative, as expected	Chae et al 2014; Chae et al 2016
	Middle-aged and older	1	1/1	0/1	N/A	0/1	0/1	0/1	N/A	Geronimus et al 2015

*Longitudinal includes studies that have measures of stressors over time and TL at one time point, as well as studies that have multiple measures of both TL and stressors.

Note: Studies with no specified age range were categorized into mid and older (three for early-life SLEs and one for lifetime SLEs).

Table 3:

Work-related Stressors (n=35)

Work Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
Occupational Class (18)	Middle-aged adults	4	4/4	0/4	2/4	3/4 sex (n.s.)	1/4	0/4	N/A	Adams et al 2007; Ala-Mursula et al 2013; Pearce et al 2012; Shalev et al 2014
	Middle-aged and older	9	7/9	4/9	2/9; 2/9	2/9 age (mixed)	1/9	3/9	3 positive, as expected	Ahola et al 2012; Cherkas et al 2006; Cherkas et al 2008; Cui et al 2013; Fujishiro et al 2013; Robertson et al 2012; Shiels et al 2011; Surtees et al 2011; Surtees et al 2012
	Older adults	5	4/5	0/5	2/5	1/5 sex (n.s.)	1/5	0/5	N/A	Bendix et al 2014; de Rooij et al 2015; Harris et al 2012; Steptoe et al 2011; Zalli et al 2014
Employment Status (12)	Middle-aged adults	4	4/4	2/4	2/4	1/4 sex (Assoc. sig. only for men)	1/4	1/4	1 positive (employed with longer TL), as expected (for males only)	Ala-Mursula et al 2013; Chae et al 2014; Chae et al 2016; Jodczyk et al 2014

Work Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
	Middle-aged and older	7	7/7	2/7	0/7	2/7 age (mixed)	2/7	3/7	2 positive, as expected; 1 negative, contrary to expectation	Batty et al 2009; Fujishiro et al 2013; Hill et al 2016; Kananen et al 2010; Kingma et al 2012; Parks et al 2011; Robertson et al 2012
	Older adults	1	0/1	0/1	N/A	0/1	0/1	0/1	N/A	de Rooij et al 2015
Job Characteristics (5)										
	Middle-aged and older	5	5/5	2/5	0/5	2/5 age (n.s.)	0/5	2/5	2 negative (more stress, shorter TL) as expected	Ahola et al 2012; Fujishiro et al 2013; Liang et al 2011; Parks et al 2011; Von Kanel et al 2015

*Longitudinal includes studies that have measures of stressors over time and TL at one time point, as well as studies that have multiple measures of both TL and stressors

Table 4:

Neighborhood Stressors (n=11)

Neighborhood Topic (N)	Age Group *Group*	*N*	TL from blood, qPCR	Single sex sample	From same study	Test moderator	Longit.*	Signif. TL Assoc.	Direction of Assoc.	Articles
Built Environment (6)	Infants / children	1	0/1	0/1	N/A	0/1	0/1	1/1	1 negative (high disorder, shorter TL), as expected	Theall et al 2013
	Middle-aged adults	1	1/1	0/1	N/A	1/1 sex (Assoc. sig. only for women)	0/1	1/1	1 negative (high problems, shorter TL), as expected (for females only)	Gebreab et al 2016
	Middle-aged and older	3	3/3	0/3	0/3	0/3	0/3	3/3	3 negative (lower quality, shorter TL), as expected	Geronimus et al 2015; Needham et al 2014; Park et al 2015
	Older adults	1	1/1	0/1	N/A	0/1	0/1	0/1	N/A	Yen & Lung 2013
Economic Environment (5)	Infants / children	1	0/1	0/1	N/A	0/1	0/1	1/1	1 negative (higher poverty, shorter TL), as expected	Theall et al 2013
	Middle-aged and older	4	4/4	1/4	0/4	2/4 age (n.s.)	0/4	0/4	N/A	Batty et al 2009; Needham et al 2014; Robertson et al 2012; Shiels et al 2011

*Longitudinal includes studies that have measures of stressors over time and TL at one time point, as well as studies that have multiple measures of both TL and stressor