Psychoneuroendocrinology 89 (2018) 161–167

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Relation of long-term patterns in caregiving activity and depressive symptoms to telomere length in older women☆

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ARTICLE INFO

Keywords:
Telomere length
Women
Depression
Caregiving
Cumulative burden
Trajectory

ABSTRACT

Background: Research links psychological stress to accelerated cellular aging. Here we examined whether long-term patterns of depression and caregiving burden, forms of chronic psychological stress, were associated with shorter telomere length, a biomarker of cellular aging.

Methods: The study included 1250 healthy older women (mean: 68.0; range: 60–81 years) in the Nurses' Health Study. Long-term patterns in depressive symptoms and caregiving activity (separated into care of children/grandchildren vs. ill or disabled family members/others) incorporated questionnaire data between 1992 and 2000; relative leukocyte telomere lengths (LTLs) were measured in 2000–2001. Least-squares means LTL z-scores were calculated across categories of depression patterns and caregiving intensity.

Results: Six empirically-derived latent classes of depressive symptom trajectories were identified: minimal-stable (63.7%), mild-worsening (3.9%), subthreshold-improving (22.8%), subthreshold-worsening (2.7%), clinical range depressive-improving (6.2%), and clinical range depressive-persistent (0.6%). After collapsing trajectory patterns into 4 groups (combining those with minimal and mild symptoms into one group and those with clinical range depressive symptoms into one group) due to very small sample sizes in some groups, we observed marginal associations ($p = 0.07$): e.g., the least-squares means LTL z-scores were lowest (−0.08; 95% CI: −0.22 to 0.06) for the clinical range depressive symptoms group and highest (0.12; 0.04–0.20) for the subthreshold-improving group (Tukey's post-hoc pairwise $p = 0.07$). With six depressive symptom trajectories, no significant associations were observed with regard to telomere lengths. There were no significant associations between caregiving intensity and LTLs.

Conclusions: There were no associations between long-term patterns of caregiving burden and telomere lengths among older women. Possible differences in telomere lengths by types of long-term depressive symptom trajectories may warrant further investigation.

1. Introduction

Psychological stress has been related to biological stress. Specifically, prior investigations have found associations between psychosocial stress and psychiatric conditions, including depression, and measures of biological aging (Shalev et al., 2013; Simon et al., 2006). Telomeres are tandem TTAGGG repeats at the ends of eukaryotic chromosomes; telomeres serve to protect chromosomal stability and naturally shorten progressively with mitosis. After telomeres reach critically short length, cells may undergo apoptosis or senescence (Bojesen, 2013) − the cellular equivalent of aging. Thus, telomere shortening may reflect cumulative exposure to damaging influences

☆ This work was supported by funding from the National Institutes of Health (UM1 CA186107, R01 CA49449, and R01MH096776).
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https://doi.org/10.1016/j.psyneuen.2018.01.005
Received 18 July 2017; Received in revised form 11 December 2017; Accepted 8 January 2018
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(e.g., inflammation, oxidative stress) and has been proposed as a hallmark of aging (Lopez-Otin et al., 2013). Although there are some individual studies suggesting that psychological stress may contribute to premature cellular aging, as measured by telomere attrition (Darrow et al., 2016; Epel et al., 2004; Lin et al., 2016; Okereke et al., 2012; Park et al., 2015; Tyrka et al., 2010), a recent meta-analysis found that increased psychological stress was associated with a small but significant decrease in telomere length cross-sectionally, but the correction for publication bias attenuated the correlation to non-significance (Mathur et al., 2016). In a recent retrospective cohort, neither early or recent psychosocial stress was associated with telomere length in older adults (Schaakxs et al., 2016). Overall, the literature is mixed.

Depression has been an increasing subject of investigation with respect to accelerated aging, and the association between depression and shorter leukocyte telomere length (LTL) has been observed in prior work; however, more studies were cross-sectional, samples were primarily clinically ascertained and featured participants with specific psychiatric disorders, and the results have been mixed (Schaakxs et al., 2015; Schutte and Malouff, 2015). In addition, fewer studies have investigated persistence of depression (such as chronicity and duration) over time in relation to telomere shortening (Edwards et al., 2016; Elvsashagen et al., 2011; Verhoeven et al., 2014; Wolkowitz et al., 2011), although chronic stress may have a larger cumulative effect compared to single time-point measures (Mathur et al., 2016). Thus, less is known about how antecedent long-term patterns of either more or less favorable trajectories of depressive symptoms relate to observed telomere lengths in later-life.

In addition, external causes such as psychosocial stress and specifically caregiving burden may contribute to a cumulative stress load (Epel et al., 2004). Family caregiving strain may increase risk of both poor mental and physical health outcomes (Chang et al., 2016a; Goren et al., 2016; Laks et al., 2016; Schulz and Beach, 1999); as more people are living longer with illness and/or disability (Colombo et al., 2011), there may be an increasing segment of the population experiencing caregiving burden − and, thus, potentially at risk for adverse biological consequences. Three studies have examined the relations between caregiving for ill/disabled family members or friends and telomere length, with mixed results (Damjanovic et al., 2007; Epel et al., 2004; Litzelman et al., 2014). Overall, these results suggest that there may not be a group difference of telomere length between caregivers and non-caregivers (Epel et al., 2004; Litzelman et al., 2014), but *cumulative* exposure of caregiving may be associated with telomere shortening (Damjanovic et al., 2007; Epel et al., 2004; Litzelman et al., 2014). Furthermore, prior work did not distinguish types of caregiving − specifically, the potential favorable influence of child-caregiving: such intergenerational interaction may be beneficial to psychological well-being or cellular aging for mid-life and older adults (Barha et al., 2016; Chang et al., 2016a; Tsai et al., 2013).

To address these limitations in the knowledge base, we aimed to evaluate two forms of long-term psychological stress with regard to telomere length in a large prospective study of older U.S. women. We hypothesized that long-term patterns of severe or worsening depressive symptoms as well as chronic psychological stress due to the burden of ill-caregiving would be positively associated with telomere shortening, whereas time spent caregiving to children or grandchildren would be inversely associated with telomere shortening.

2. Methods

2.1. Study population

The Nurses' Health Study (NHS) began in 1976 when 121,700 female nurses, aged 30–55 years and residing in the United States, completed an initial questionnaire regarding lifestyle and medical history. Participants have received questionnaires biennially since then, with > 90% follow-up in each 2-year cycle. The first blood collection was conducted in 1989–1990 among a subset of 32,825 cohort participants who also completed an accompanying supplementary questionnaire. Details of the blood collection have been described previously (Hankinson et al., 1995). Among this blood sub-cohort, a subset of 18,717 women also provided a second blood sample in 2000–2001. The current study involved a random sample of 1700 healthy participants who provided blood samples on both occasions as part of a study on depression, anxiety, and aging biology. Eligible participants had blood samples at both time points, with sufficient quantity and quality; had information on baseline anxiety in the 1988 questionnaire and depressive symptoms on the 1992, 1996, and 2000 questionnaires; were free of cardiovascular disease prior to the first blood draw; were free of cancer up to 2004 NHS questionnaire cycle (when the follow-up anxiety scale was measured); were not selected as cases or controls in prior NHS telomere studies.

2.2. Long-term pattern in depression

Information on depressive symptoms were assessed using the Mental Health Inventory-5 (MHI-5) subscale of the 36-item Short-Form Health Status Survey (Ware and Sherbourne, 1992) on the 1992, 1996, and 2000 cohort questionnaires. The MHI-5 has been validated for clinical depression (Berwick et al., 1991; Weinstein et al., 1989; Yamazaki et al., 2005), and prior NHS publications have illustrated the ability to identify important associations of depression, defined by this symptom information, with health outcomes (Pan et al., 2011; Whang et al., 2009). Eight-year patterns of depressive symptoms were assessed using latent class growth-curve analyses to estimate mean trajectories for unobserved classes, in combination with membership probability in each latent class for every individual, which is described in detail in the "Statistical analysis" section.

2.3. Long-term pattern in caregiving activity

On the 1992, 1996, and 2000 questionnaires, participants were asked about time spent (0, 1–8, 9–20, 21–35, 36–72, 73+ hours per week) providing care to children, grandchildren, a disabled or ill spouse, parent, or other person. We derived long-term patterns of caregiving intensity across 8 years from 1992 to 2000 by separating hours of caregiving to children/grandchildren from hours of caregiving to disabled or ill persons (spouse, parent, other person). For child/grandchild-caregiving, the group contrasts were: (a) no child care at all time (0 h per week in all questionnaire cycles of 1992, 1996, and 2000), (b) no/some child care combination (a mixture of 0 and 1–20 h per week on the 1992, 1996, and 2000 questionnaires), and (c) high child care (> 20 h per week) in at least 1 questionnaire cycle. For ill-caregiving, the group contrasts were: (a) no illness care at all time (0 h per week in all questionnaire cycles of 1992, 1996, and 2000), (b) no/some illness care combination (a mixture of 0 and 1–40 h per week on the 1992, 1996, and 2000 questionnaires), and (c) high illness care (> 40 h per week) in at least 1 questionnaire cycle. Because our data could not distinguish people providing no care from those who did not have specific family members to be cared for, these individuals were included in a single no care group.

2.4. Assessment of relative telomere length

The primary outcome was relative LTLs in later life, obtained during the 2000–2001 blood collection. Because of the reported "regression to the mean (RTM)" phenomenon in telomere length (Verhulst et al., 2013), we also measured baseline LTLs (in 1989–1990) to account for the RTM effect in the analyses (Hoen et al., 2011; Hoen et al., 2013). The LTLs were measured in genomic DNA extracted from peripheral blood leukocytes using a modified, high-throughput version of the quantitative real-time polymerase chain reaction-based telomere assay (Wang et al., 2008) that was run on the Applied Biosystems 7900HT

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