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Telomere length and hypothalamic—pituitary—adrenal axis response to stress in elderly adults

Katri Savolainen[a], Johan G. Eriksson[b,c,d,e], Eero Kajantie[b,f,g], Jari Lahti[a], Katri Räikkönen[a,*]

[a] *Institute of Behavioural Sciences, University of Helsinki, PO Box 9, 00014 Helsinki, Finland*
[b] *Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, PO Box 30, 00271 Helsinki, Finland*
[c] *Folkhälsan Research Centre, Haartmansgatan 8, 00290 Helsingfors, Finland*
[d] *Vasa Central Hospital, Hietalahdenkatu 2—4, 65130 Vaasa, Finland*
[e] *Department of General Practice and Primary Health Care, University of Helsinki, PO Box 20, 00014 Helsinki, Finland*
[f] *Hospital for Children and Adolescents, Helsinki University of Central Hospital, HUS, PO Box 281, 00029 Helsinki, Finland*
[g] *Department of Obstetrics and Gynecology, MRC Oulu, Oulu University Hospital and University of Oulu, OYS, PO Box 23, 90029 Oulu, Finland*

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Summary
Objective: Telomere shortening, a biomarker of cellular aging, has been associated with aging-related diseases. While psychological stress has been implicated in the process of telomere shortening, associations with activity of physiological stress systems have remained elusive. We studied whether leukocyte telomere length (LTL) is associated with hypothalamic—pituitary—adrenal (HPA) axis responses to psychosocial stress in elderly adults.
Methods: LTL, measured by qPCR method was available in 1964 women and men from the Helsinki Birth Cohort Study at a mean age of 61.5 (SD = 2.9) years. At a mean age of 63.5 (SD = 2.7) years a subsample of them took part in the Trier Social Stress Test (TSST) during which salivary cortisol ($n = 283$) and plasma cortisol and ACTH concentrations ($n = 215$) were measured.
Results: Mixed model regression analyses showed no linear or non-linear associations between LTL and HPA axis activity during TSST (p-values for LTL main effects >298; p-values for LTL × time

* Corresponding author. Tel.: +358 40 5121469; fax: +358 91 9129521.
E-mail address: katri.raikkonen@helsinki.fi (K. Räikkönen).

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interactions >096). Only one non-linear association between LTL and plasma ACTH area under the curve increment was significant after adjustments for covariates and confounders. This association did not survive correction for multiple testing.
Conclusions: Our findings suggest that LTL is not consistently associated with HPA axis activity during a standardized psychosocial stress test in elderly adults.

1. Introduction

Telomeres, repeat sequences of DNA-protein complexes (TTAGGG) located at the ends of eukaryotic chromosomes, are involved in preventing chromosome fusion and maintaining genome stability (Blackburn, 2004). When they reach a critical length they lose capping ability and the cell faces replicative senescence (Blackburn, 2004). Because age-corrected leukocyte telomere length (LTL) may reflect a cumulative measure of the history of oxidative damage and the replicative potential of the cell, it may represent a biomarker of cellular aging. Shorter LTL has been associated with aging-related physical and mental disorders (Haycock et al., 2014; Verhoeven et al., 2014), though the evidence with regard to mental disorders is not consistent (Savolainen et al., 2012). Other studies have shown that shorter LTL predicts a higher risk of mortality (Bakaysa et al., 2007; Deelen et al., 2014).

Shorter LTL has also been reported in relation to chronic psychological stress in adulthood (Epel et al., 2004), to early life stress (Tyrka et al., 2010) and to early life stress if combined with physical or emotional traumatic events across the lifespan (Savolainen et al., 2014). Shorter LTL has also been found in the newborn offspring exposed to maternal stress during pregnancy (Entringer et al., 2013). These data suggest that psychological stress may accompany the accelerated aging process. Yet, studies that have tested associations between LTL and activity of the stress-related physiological systems, particularly of hypothalamic—pituitary—adrenal (HPA) axis, are scarce. The existing studies suggest that shorter telomere length in peripheral blood mononuclear cells was associated with higher salivary cortisol responses to a modified Trier Social Stress Test (TSST) in 23 postmenopausal women (Tomiyama et al., 2012), and that shorter telomere length measured in saliva was associated with higher salivary cortisol responses to a stress task including serial subtraction and the Ewart Social Competence Interview (Ewart et al., 2002) in 97 10—14-year-old daughters of depressed and non-depressed mothers (Gotlib et al., 2014). In 78 kindergarten children buccal cell telomere length was associated with higher salivary cortisol response to tasks involving social, cognitive, sensory, and emotional elements, when this response was combined with a higher autonomic nervous system response (higher sympathetic reactivity, greater parasympathetic withdrawal) to these tasks (Kroenke et al., 2011). Shorter LTL was associated with higher overnight urinary cortisol values in 62 women aged 20 to 50 years (Epel et al., 2006) and with lower plasma cortisol values and higher percentage of cortisol suppression after a very-low-dose overnight dexamethasone suppression test in 542 men and women aged 21 to 81 years (Wikgren et al., 2012). A recent study demonstrated that in 2204 men and women aged 18 to 65 years, who were derived from a sample of which nearly 80% had current or a remitted mental disorder, LTL was not associated with salivary cortisol awakening response, evening levels or responses after a low-dose overnight dexamethasone suppression test (Révész et al., 2014). This study, however, reported that the highest tertile in salivary cortisol awakening response was associated with shorter LTL (Révész et al., 2014).

In the current study we extend the scant literature by testing the hypothesis that in a well-characterized cohort of elderly adults shorter LTL is associated with higher salivary cortisol, and plasma cortisol and ACTH responses to TSST. We also explored if the associations between LTL and cortisol and ACTH responses were non-linear, because LTL erosion may not be linear across the lifespan (Frenck et al., 1998) and because HPA axis activity may be altered in elderly individuals (Kajantie et al., 2007).

2. Methods

2.1. Participants

At a mean age of 61.5 (SD = 2.9, range = 56.7—69.8) years a subsample of the Helsinki Birth Cohort Study participants took part in a detailed clinical examination including blood sampling for telomere length measurement. Of them 144 men and 143 women ($n = 287$) took part in the TSST at a mean age of 63.5 (SD = 2.7, range = 59.8—70.9) years (Kajantie et al., 2007). Data on LTL and salivary cortisol were available on 140 men and 143 women ($n = 283$), and LTL and plasma cortisol and ACTH were available on 113 men and 102 women ($n = 215$) during the TSST. The smaller sample size for plasma cortisol and ACTH resulted from adding sampling of blood later to the study protocol. The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. All participants gave a written informed consent.

2.2. Experimental stress protocol—Trier Social Stress Test (TSST)

The Trier Social Stress Test is a well-standardized psychosocial stress test known to elicit a powerful HPA axis response (Kirschbaum et al., 1993). Briefly, subjects were given 3 min to prepare a 5-min speech. After the speech, they were asked to perform serial subtractions for another 5 min in front of a committee. We obtained saliva and blood at 18 min before the TSST stressor ended and at 0, 10, 20, 30, 45, 60, and 90 min after the end of the stressor. The