Research paper

Stress, depressive status and telomere length: Does social interaction and coping strategy play a mediating role?

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ABSTRACT

Background: Telomeres have been reported to be shorter in individuals exposed to psychosocial stress and in those with depression. Since negative environmental stress is a risk factor for depression, the present study tested whether stressors in childhood (CA) and recent adulthood (NLE) predicted telomere attrition directly and/or indirectly through individuals' depressive status 3–6 years before TL measurement; and then if social interaction and coping strategies in adulthood influenced the relationship between depressive status and TL.

Methods: Participants were 337 individuals with a recent depression diagnosis and 574 screened controls that derived from a longitudinal population-based cohort study conducted in Stockholm, Sweden. Relative TL was determined using qPCR. Relationships between the key variables stressors, depressive status, social interaction, coping strategies and TL were explored by path analysis in males and females, adjusting for age.

Results: The key variables were correlated in expected directions. In females, depressive status and age had direct negative effects on TL ($p < 0.05$) and both CA ($p = 0.025$) and NLE ($p < 0.003$) had indirect negative effects on TL. For males, the effects of stressors and depressive status on TL were mediated by social interaction ($p = 0.005$) and the coping strategy worry ($p = 0.005$). In females, no mediation effect of social interaction and coping strategy was detected.

Limitations: Only little of the TL variation was explained by the models. The environmental stress information was limited.

Conclusion: Our findings propose gender-specific paths from environmental stressors through depressive status, social interaction and coping strategy to TL.

1. Introduction

Telomeres are the protective protein-DNA complex caps located at the end of chromosomes. The telomeres are shortened during each cell division, and also through exposure to metabolic stress, inflammation and oxidative stress (Lindqvist et al., 2015). A large body of studies has demonstrated an accelerated leukocyte telomere shortening after chronic negative stress, including childhood abuse and negative life events; and the telomere erosion was suggested to be a risk marker for age-related diseases of adults who had been exposed to increased stress (Epel et al., 2004; Price et al., 2013; Puterman et al., 2014; Shalev et al., 2013). There is a well-documented association between experienced stress, both early adversities and adulthood negative life events, and internalizing disorders such as depression, as well as between age-related somatic diseases and depression (Cuijpers and Smit, 2002; Danese et al., 2009; Gao et al., 2013; Kendler et al., 1999). Based on that,

studies have tested the hypothesis that telomere attrition is a molecular signature of depression. The results of several studies supported the hypothesis, whereas other studies failed to detect an association (Schaakxs et al., 2014; Shalev et al., 2014; Wei et al., 2015a, 2015b; Verhoeven et al., 2014). Finally, meta analyses confirmed an association between shorter leukocyte telomere length (LTL) and depression although the heterogeneity between individual studies was considerable (Lin et al., 2016; Ridout et al., 2016; Schutte and Malouff, 2015). In these studies, the environmental stressors were rarely considered for the relationship between depression and telomere length. Adjusting for the negative stressors might improve the assessment of the relationship between depressive status and TL. A recent study found shorter LTL for those exposed to childhood adversity in non-depressed but not in depressed individuals. The authors proposed that this could be due to a compensatory increase of telomerase activity in the leukocytes from the individuals with depression (Chen et al., 2014). Given the small sample

size of this study (n_{total} = 40), a follow-up study was warranted.

The relationship between depressive status and LTL may be influenced also by supportive psychosocial factors. A recent study conducted in preschool children found that responsive parenting protected young children exposed to early-life stress from telomere shortening (Asok et al., 2013). Attachment with parents or caregivers is the main social contact for young children, while for adults social interactions with friends or spouses are more important and influence health (Cohen, 2004). Recent studies found that those who were unmarried or had lower social support had shorter leukocyte telomeres (Barger and Cribbet, 2016; Carroll et al., 2013; Mainous et al., 2010; Uchino et al., 2012). A meta-analysis including 148 studies confirmed that the quality and quantity of personal relationships was highly linked to morbidity and mortality across different diseases (Holt-Lunstad et al., 2010). Therefore, we hypothesized that social interaction could be a mediator in the stress-depression-telomere length relationships. In patients with cardiovascular disease multisystem resiliency factors (psychosocial and behavioral) had a moderating effect on the depression-LTL association, whereas each individual factor did not (Puterman et al., 2013).

Coping was defined by Folkman as thoughts and behaviors that the individual uses to manage internal and external demands that are appraised as stressful (Folkman, 1984). The coping strategy used depends on the individual's appraisal of the stressors as harmful, beneficial, threatening, or challenging, and thus generate different emotional responses (Folkman and Lazarus, 1990). The level of threat anticipation correlated negatively with LTL in caregivers and controls (O'Donovan et al., 2012). Therefore, we hypothesized that coping strategy could mediate the stress-depression-telomere length relationships and that social interaction could influence the individual's selection of coping strategy.

In this study we investigated the statistical relationships between a stressful experience in childhood and recent adulthood, depressive status and telomere length, and explored if social interaction and coping strategies acted as mediators. This was performed using a path analysis according to the theoretical model presented in Fig. 1.

2. Material and methods

2.1. Participants

The study subjects derived from a longitudinal population-based cohort study, PART, aimed at identifying risk and protective factors for mental health in Stockholm County, Sweden (Hällström et al., 2003). The PART study was approved by the ethical review board of Karolinska Institutet. Written informed consent was obtained from all participants and the investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Participants of PART were randomly selected 20–64 years old Swedish nationals. Self-reported questionnaire data were collected in 1998–2000 (wave 1) and participants were followed-up 3 years later (wave 2) with a similar questionnaire, the number of respondents in both waves being 8613.
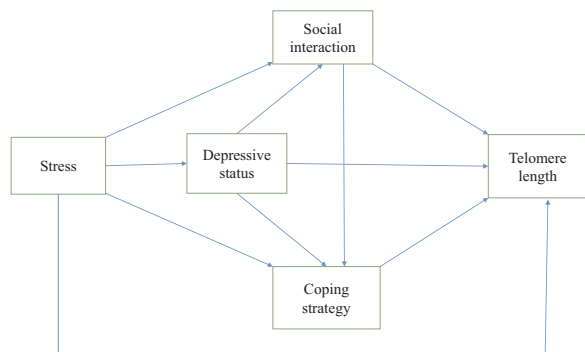

Fig. 1. The theoretical model and hypothesized relations.

The questionnaire included questions on demographic characteristics, childhood conditions, financial status, social network, negative life events, somatic health, smoking, alcohol use, usage of drugs and screening instruments for psychiatric disorders (the Major Depression Inventory (MDI)) (Wermuth, 1998), the Sheehan Patient-Rated (Panic) Anxiety Scale (Sheehan, 1983), the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989), symptoms of social phobia and agoraphobia (Marks and Mathews, 1979), eating disorders (Beglin and Fairburn, 1992), the World Health Organization Short Disability Assessment Schedule (WHO DAS-S) (Janca et al., 1996) and hazardous alcohol use according to the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 2001; Saunders et al., 1993). Detailed attrition analyses using official registries assured that the relationships between psychiatric disorders and living conditions were likely to be identified accurately (Bergman et al., 2010; Lundberg et al., 2005). A DNA collection was performed, with a nested case control design, of those participating in both wave 1 and wave 2 (Melas et al., 2010).

2.2. Definition of depression cases and controls

Depression was defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. Individuals characterized as having depression were those diagnosed with major depressive disorder, mixed anxiety depression or dysthymia, in at least one of the two waves in the PART study, using the MDI. Validation studies for the use of the MDI in making DSM-IV-based diagnoses of depression have been performed in the PART study (Forsell, 2005), and in clinical (Olsen et al., 2003b) and outpatient settings (Cuijpers et al., 2007). For the diagnosis of mixed anxiety depression, additional information was used from the Sheehan Patient-Rated (Panic) Anxiety Scale. There was no data on symptoms of mania/hypomania. Controls were individuals with no psychopathological symptom of depression, anxiety, social phobia, agoraphobia, obsessive-compulsive disorder, eating disorder, use of illicit drugs during last year, alcohol dependency or abuse or social disability due to psychological problems, in either of the two PART waves. Additionally, the controls reported that they had never received health care for a psychiatric disorder or nervousness.

Of those 8613 individuals, all those with depression in wave 1 and/ or 2, and 98% of the controls who had responded to both PART waves were asked to contribute saliva samples using a self-administered whole-saliva DNA sample collection kit (Oragene, DNA Genotek Inc., Ottawa, Canada), and the collection was done three years after PART wave 2. Finally, saliva DNA was collected from 484 (46.1%) of the depressed and 1877 (56.4%) of the non-depressed (control) individuals (Melas et al., 2010).

In the present study, only participants 60 years old or younger at the saliva sampling were included because the MDD-LTL association has repeatedly been reported to not be detectable in those older than 55–60 years old (Phillips et al., 2013; Schaakxs et al., 2014). In the controls, a subsample of n=674 was initially randomly picked and thereafter reduced to obtain an age distribution in females similar to that in males. Finally, the telomere length was tested in 337 individuals with depression and 574 controls.

2.3. Childhood adversity

Childhood adversity (CA) before the age of 18 years was assessed in wave 1 by three questions. "Did any of your parents die?" If the answer was no, then scored as 1; if yes, scored as 2. For the questions "Did your family have financial problems?" and "Did friction exist in your family?", a three-point likert scale was used from 1 (no) to 3 (2 = yes, milder or shorter periods, 3 = yes, more difficult or longer periods). The childhood adversity variable used was the sum score of these three items, thus a sum score of 3 meant no childhood adversity.