Psychoneuroendocrinology 67 (2016) 153–162

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Baseline biopsychosocial determinants of telomere length and 6-year attrition rate

Dóra Révész*,[1], Yuri Milaneschi, Erik M. Terpstra, Brenda W.J.H. Penninx

Department of Psychiatry, EMGO Institute for Health and Care Institute, VU University Medical Center, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 16 September 2015
Received in revised form 10 February 2016
Accepted 10 February 2016

Keywords:
Telomeres
Lifestyle
Metabolic syndrome
Inflammation
Autonomic nervous system
Cortisol

ABSTRACT

Background: Short leukocyte telomere length (TL) and accelerated telomere attrition have been associated with various deleterious health outcomes, although their determinants have not been explored collectively in a large-scale study.
Material and methods: Leukocyte TL was measured (baseline $N = 2936$; 6-year follow-up $N = 1860$) in participants (18–65 years) from the NESDA study. Baseline determinants of TL included sociodemographics, lifestyle, chronic diseases, psychosocial stressors, and metabolic and physiological stress markers. Multivariate linear regression models were used to examine the associations between these determinants and (1) baseline TL, and (2) 6-year TL change. Multinomial logistic regression analyses were used to examine the predictors of telomere attrition and lengthening, as compared to stable TL.
Results: Short baseline TL was associated with older age, male sex, non-European ethnicity, cigarette smoking, recent life events, and higher triglycerides, glucose and pre-ejection period ($R^2 = 11.3\%$). The 6-year telomere attrition was inversely associated with baseline TL ($R^2 = 51.6\%$); also older age, long sleep, not having a partner, high childhood trauma index, and gastrointestinal disease were associated with 6-year TL attrition (additional $R^2 = 3.7\%$). Telomere attrition seemed to have slightly more predictors than lengthening.
Conclusions: Sociodemographic, lifestyle, psychosocial stress and metabolic and physiological stress factors are cross-sectionally linked with TL. Telomere attrition over six years was strongly associated with baseline TL, suggesting an internal homeostatic influence. Modulation of the identified determinants may become target of future studies to promote telomere maintenance and healthy aging.

1. Introduction

Telomere length (TL), a proxy for cellular aging (Blackburn, 1991; Olovnikov, 1996), has been associated with aging and mortality (Rode et al., 2015). Telomeres are DNA–protein complexes that cap and protect chromosomal ends, and are maintained by telomerase, a ribonucleoprotein that synthesizes telomeric DNA repeats (Blackburn, 1991). During each somatic cell division, DNA loses telomeric repeats with an estimated shortening rate of 22–41 base pairs per year (Muezzinler et al., 2013). Cells with critically short telomeres reach replicative senescence, or apoptosis is induced in response to the accumulated DNA damage (Sahin and DePinho, 2010). Although TL in different tissues such as skeletal muscle, skin, fat and leukocytes is correlated, due to the easy availability it has mostly been investigated in leukocytes (Daniali et al., 2013).

There is a large inter-individual variation in TL, and approximately 64–70% of TL is explained by genetic factors (Hjelmborg et al., 2015; Broer et al., 2013), suggesting that genetics and early life environment are the main determinants of TL (Broer et al., 2013; Holohan et al., 2015). During the early life phases there is a faster attrition rate as compared to attrition rates seen in adults, which has a relatively small effect on overall TL (Hjelmborg et al., 2015). Consequently, 'modifiable factors' may have a smaller impact on TL in adulthood, as compared to childhood (Hjelmborg et al., 2015). Nevertheless, identification of these factors may be relevant in understanding and intervening on cellular aging-mediated health outcomes.

Cross-sectional studies suggest that behavioural and psychosocial factors play an important role in TL. Apart from chronological age, TL has been shown to be associated with sociodemographic

* Corresponding author at: P.O. Box 74077, 1070 BB Amsterdam, the Netherlands. Fax: +31 207885664.
E-mail addresses: D.Revesz@ggzingeest.nl (D. Révész), Y.Milaneschi@ggzingeest.nl (Y. Milaneschi), E.M.Terpstra@student.vu.nl (E.M. Terpstra), B.Penninx@vumc.nl (B.W.J.H. Penninx).
[1] Visiting address: A.J. Ernststraat 1187, Room M1.06, 1081 HL Amsterdam, the Netherlands.

http://dx.doi.org/10.1016/j.psyneuen.2016.02.007
0306-4530/

factors, such as ethnicity (Rewak et al., 2014), lifestyle factors, such as sleep and physical (in) activity (Puterman et al., 2014; Prather et al., 2015a), and somatic diseases like cardiovascular disease and cancer (D'Mello et al., 2014; Willeit et al., 2014). Furthermore, TL may represent a marker for the cumulative exposure to psychosocial stressors, such as psychiatric disorders, childhood trauma or adverse life events (Lindqvist et al., 2015; Shalev et al., 2013), or exposure to metabolic and physiological stressors, such as dyslipidemia and abdominal fat (Révész et al., 2014a), inflammation, a hyperactive hypothalamic-pituitary-adrenal (HPA)-axis or a dysfunctional autonomic nervous system (ANS) (Révész et al., 2014b; O'Donovan et al., 2011).

Few longitudinal studies have assessed the impact of these factors on telomere attrition over time, and findings are inconsistent. For instance, whereas most studies have found that baseline TL is the strongest predictor of telomeric attrition rate (Weischer et al., 2014; Ehrlenbach et al., 2009), some studies have also shown that accelerated attrition is predicted by black race (Rewak et al., 2014), male sex (Guzzardi et al., 2015; Huzen et al., 2014; Gardner et al., 2014), lifestyle factors such as smoking and physical activity (Puterman et al., 2014; Huzen et al., 2014), psychosocial stressors such as adverse life events (Puterman et al., 2014), chronic somatic diseases (Basu et al., 2013; Dehbi et al., 2013), and metabolic syndrome components (Huzen et al., 2014; Révész et al., 2015; Guzzardi et al., 2015). However, other studies did not find associations between telomere attrition rate and lifestyle (Toupance et al., 2015; Weischer et al., 2014; Ehrlenbach et al., 2009) or clinical factors (Toupance et al., 2015; Weischer et al., 2014).

Even though various factors have been separately associated with TL in different studies, to our knowledge, no large-scale study has combined and systematically compared the main predictors of TL and telomere attrition over time in the same research framework. The present study, a large cohort with TL measured at baseline and at a 6-year follow-up, examined a wide array of predictors categorized into domains of sociodemographics, lifestyle, psychosocial stressors, chronic diseases, metabolic and physiological stress markers. The study first aimed to identify factors that are associated (1) cross-sectionally with baseline TL, and (2) longitudinally with 6-year TL attrition rate.

2. Material and methods

2.1. Study population

Participants were from the Netherlands Study of Depression and Anxiety (NESDA), a large on-going longitudinal cohort study among 2981 adults (18–65 years), as described elsewhere (Penninx et al., 2008). Briefly, respondents were recruited between September 2004 and February 2007 from community, primary care and specialized mental health care settings, including persons with a lifetime diagnosis of a depressive and/or anxiety disorder and healthy controls. The research protocol was approved by the ethical committee of participating universities and all respondents provided written informed consent.

Baseline data collection consisted of a medical examination, a blood draw, self-report questionnaires and a detailed interview. Of the entire cohort, 2936 subjects had complete TL data at baseline, and were included in the analyses of the determinants of baseline TL. Among these, 1860 subjects had TL measured again six year later, and were included in the analyses of the determinants of telomere attrition. Compared to those with complete data at both time points ($N = 1860$), those who dropped out after baseline ($N = 1076$) had longer TL at baseline ($p = .003$), were slightly younger ($p < .001$), more often female ($p = .09$), less often of European origin ($p < .001$), had less educational years ($p < .001$), less physical activity ($p = .02$), but more sedentary hours ($p = .006$), smoked more cigarettes per day ($p < .001$), were more often non-drinker ($p < .001$), and had a slightly higher proportion of subjects with psychiatric disorders ($p < .001$).

2.2. Telomere length

Leukocyte TL was determined at baseline and six years. A more extensive description of TL assessment in our study has been reported before (Révész et al., 2014a). In short, DNA was prepared from fasting blood samples and stored in a $-20\,^{\circ}C$ freezer afterwards. Subsequently, TL was determined using quantitative polymerase chain reaction. Telomere sequence copy number in each patient's sample (T) was compared to a single-copy gene copy number (S), relative to a reference sample. We converted T/S ratios to base pairs with the following formula: base pairs $= 3274 + 2413 \times ((T/S - 0.0545)/1.16)$.

2.3. Determinants

2.3.1. Sociodemographic factors

Sociodemographic factors included sex, age, and self-reported years of attained education. Ethnicity was based on self-reported country of birth, and then categorized as European vs. other origin due to the large majority of births in the Netherlands and European countries as compared to other origins.

2.3.2. Lifestyle factors

Lifestyle factors included alcohol consumption (no drinker, mild-moderate drinker 1–14 (women)/1–21 drinks per week (men), heavy drinker >14 (women)/>21 (men) drinks per week), the number of cigarettes smoked per day, physical activity (International Physical Activity Questionnaire, expressed in metabolic equivalent (MET) hours in the past week), sedentary behaviour (working at the computer, leisure time at the computer and watching TV in hours per week). Self-reported sleep duration was categorized into short sleep (<7 h), normal sleep (7–9 h), or long sleep (>9 h).

2.3.3. Chronic diseases

Somatic diseases were determined by asking participants whether they had one of the chronic diseases, falling into these categories: (1) cardiovascular (hypertension, angina pectoris, history of cardiac disease, stroke); (2) diabetes mellitus; (3) respiratory (asthma, chronic bronchitis, pulmonary emphysema); (4) musculoskeletal (osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia); (5) gastrointestinal (ulcer, irritable bowel syndrome, Crohn's disease, colitis ulcerosa, diverticulitis, liver cirrhosis, hepatitis, constipation); (6) cancer (throat, thyroid, lymphoid, lung, esophagus, bowel, stomach, liver, uterus, cervix, ovary, bladder, testicle, prostate, skin, brain, blood); (7) neurological (migraine, epilepsy, multiple sclerosis, peripheral neuropathy, hernia); (8) endocrine (thyroid gland diseases). In order to provide an objective assessment of chronic diseases, we only deemed chronic disease to be present if participants stated that they are under treatment by a medical expert or used medication for the mentioned somatic diseases.

2.3.4. Psychosocial stress factors

Psychosocial stressors included self-reported financial difficulties (i.e. insufficient money to buy food) and marriage or partner status. Social network size was determined by the self-reported number of family members, friends and acquaintances $\geq$18 years (household members excluded), with whom the respondent reported to be in regular and important contact, and was categorized into 0–5, 6–10 and >10 persons in the network.