Journal of Psychiatric Research 46 (2012) 1346–1353

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

History of mental disorders and leukocyte telomere length in late adulthood: The Helsinki Birth Cohort Study (HBCS)

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ARTICLE INFO

Article history:
Received 9 January 2012
Received in revised form
28 June 2012
Accepted 4 July 2012

Keywords:
Leukocyte telomere length
Mental disorder
Substance use disorder
Psychotropic medication
Antidepressant medication

ABSTRACT

Shorter leukocyte telomere length (LTL) has been linked with mental disorders and with other manifestations of chronic non-communicable diseases. Mental disorders are associated with increased morbidity and premature mortality. It remains unclear if shorter LTL characterizes patients who have been diagnosed with mental disorders in the past, and who have survived till late adulthood. 1051 women and 905 men of the Helsinki Birth Cohort Study participated in this study. LTL was measured by using the real-time quantitative PCR method for subjects and patients at the mean age of 61.5 years. Patients with a mental disorder severe enough to warrant hospitalization ($n = 116$) were identified by their case records in the Finnish Hospital Discharge Register and the use of psychotropic medication by reimbursement entitlements or prescription fills ($n = 665$) data in the Finnish Social Insurance Register. Participants hospitalized for any mental or substance use disorders had longer LTL than non-hospitalized controls (p-values < 0.042). Moreover, only those any mental disorder patients who had psychotropic medication use had longer LTL than non-hospitalized controls ($p = 0.02$). Adjustment for a number of covariates did not attenuate the association. Our findings suggest that shorter LTL may not be an intrinsic feature of mental disorders. Future research is needed to elucidate if psychotropic medication is involved in leukocyte telomere length maintenance in subjects with mental disorders.

1. Introduction

Telomeres are specialized DNA-protein complexes (consisting of the DNA repeat sequence TTAGGG) that are located at the ends of eukaryotic chromosomes (Blackburn, 2000). They are involved in preventing chromosome fusion and maintaining genome stability (Blackburn, 2004). In most human cells, telomere length decreases with subsequent cell divisions (Blackburn, 2000). In the normal population, the length of leukocyte telomeres decreases with age (Frenck et al., 1998; Nordfjäll et al., 2009; Valdes et al., 2005). When the telomere reaches a critical length it loses its capping ability and the cell faces replicative senescence (Blackburn, 2004; Wong and Collins, 2003; Chan and Blackburn, 2004). Age-corrected leukocyte telomere length (LTL) can be seen to reflect both, a cumulative measure of the history of oxidative damage that the cell has undergone and its replicative potential. Therefore, LTL has been acknowledged as a biomarker of cellular ageing (von Zglinicki et al., 2000; Aviv, 2009)

Recent studies have associated longer LTL to better survival (Kimura et al., 2008; Bakaysa et al., 2007), a family history of longevity (Atzmon et al., 2010) and healthy ageing (Njajou et al., 2009). In contrast, shorter LTL has been linked with chronic inflammation (Damjanovic et al., 2007) and common age-related disorders, such as cardiovascular disease (Fitzpatrick et al., 2007), hypertension (Yang et al., 2009) and type 2 diabetes (Salpea et al., 2010; Demissie et al., 2006). Yet, there are conflicting results for

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http://dx.doi.org/10.1016/j.jpsychires.2012.07.005

which LTL does not predict all-cause mortality (Bischoff et al., 2006) or mortality from infectious diseases, cancer, or cardiac or cerebrovascular diseases among the elderly (Njajou et al., 2009; Houben et al., 2011) and among the oldest cohorts (Martin-Ruiz et al., 2005).

In addition to the association with common age-related disorders, there exists evidence that shorter LTL also associates with mental disorders, including schizophrenia (Kao et al., 2008; Yu et al., 2008), nonaffective psychoses (Fernandez-Egea et al., 2009), mood disorders (Simon et al., 2006), major depressive disorder (Hoen et al., 2011; Hartmann et al., 2010; Lung et al., 2007), alcohol abuse (Pavanello et al., 2011) and anxiety disorder among patients over 48 years of age (Kananen et al., 2010). This is not surprising given that mental disorders are shown to increase the risks of all-cause (Harris and Barraclough, 1998; Miller et al., 2006) and cardiometabolic mortality (Mitchell and Lawrence, 2011; Colton and Manderscheid, 2006; Miller et al., 2006) and morbidity (Hennekens et al., 2005; Rugulies, 2002, Vogelzangs et al., 2010; Krishnan, 2005; Spencer and Hutchison, 1999). However, the findings on LTL and mental disorders are contradictory. To the best of our knowledge only two previous studies have reported no associations for LTL with schizophrenia, with bipolar disorder (Mansour et al., 2011) or with major depressive disorder (Wolkowitz et al., 2011). The number of depressed patients in the study by Wolkowitz et al. (2011) was small ($n = 18$) for detecting significant changes in LTL but the study by Mansour et al. (2011) recruited enough psychotic disorder patients ($n > 60$) to detect differences in LTL compared to controls.

Methodological differences such as sample size, whether the cases were inpatients or outpatients, newly or previously diagnosed with mental disorder, how well the samples were characterized for other age-related disorders including cardiometabolic health or lifestyle may partly explain the conflicting findings. The populations of the previous studies have also varied in age. Some studies used younger populations (Fernandez-Egea et al., 2009; Mansour et al., 2011) and some have used wide age ranges (Hartmann et al., 2010; Wolkowitz et al., 2011). Obviously, the findings of these studies cannot be generalized to elderly populations. The age range of a cohort is particularly important for generalization since the association between age and LTL may be nonlinear (Frenck et al., 1998). Further, not all studies provided information on psychotropic medication use (Fernandez-Egea et al., 2009; Mansour et al., 2011; Pavanello et al., 2011; Lung et al., 2007; Simon et al., 2006; Yu et al., 2008).

Against this background we studied if shorter LTL associates with the history of hospitalization for a mental disorder in a well-characterized cohort of 57 to 70-year-old women and men in Finland between 2001 and 2004. Moreover, an animal study reported that antidepressants can decrease oxidative stress at the cellular level (Zafir et al., 2009). Therefore, we examined if LTL associates with indicators of antidepressant and psychotropic medication use as antidepressant or psychotropic medication reimbursement entitlements and medication purchases. We also investigated if psychotropic medication use modulated the associations of mental disorder hospitalizations and LTL. Finally, we examined if LTL shortening associates with recently reported sub-clinical symptoms of mental disorders including depression, anxiety and loss of vitality.

2. Materials and methods

2.1. Participants

The Helsinki Birth Cohort Study (HBCS) comprises 13,345 men ($n = 6975$) and women ($n = 6370$) born between 1934 and 44 in one of the two public maternity hospitals in Helsinki, who attended child welfare clinics in the city of Helsinki and who were still living in Finland in 1971 when unique personal identification numbers were assigned to all residents of Finland. Over 2001–2004 inclusive period a randomly selected sample of 2003 (69.0% of 2902 invited) subjects (men $n = 928$ and women $n = 1075$) participated in a detailed clinical examination including blood sampling for LTL measurement. Of these participants, LTL data were available for 1964 participants (men $n = 912$ and women $n = 1052$) with a mean age of 61.5 (SD = 2.9, Range = 56.7–69.8) years. Detailed descriptions of the cohort can be found elsewhere (Osmond et al., 2007; Eriksson et al., 2001). The HBCS was approved by the Ethics Committee of the National Public Health Institute. All study participants gave their written informed consent.

2.2. Telomere length measurements

Relative telomere length from peripheral blood DNA was determined by a quantitative real-time PCR-based method (Cawthon, 2002), as described in detail by Eerola et al. (2010), with the following modifications. Based on O'Callaghan's method (2008), a synthetic oligomer (Sigma) dilution series, hgb-120-mer and tel14x (0.0002; 0.002; 0.02; 0.2; 1.0; 3.0 and 6.0 pg) were included on every plate to create reaction specific standard curves. Plasmid DNA (pcDNA3.1) was added to each standard to maintain a constant 10 ng of total DNA concentration per reaction. Quality control (QC) was carried out with the Bio-Rad CFX Manager software v.1.6. At this point, triplicates with amplification curve standard deviations above 0.5 at the threshold level were omitted ($N = 38$). One subject had missing blood sample data and was therefore excluded. The final number of T/S measurements that passed QC and whose relative telomere data available was $N = 1964$. All plates included four genomic DNA control samples for the plate effect calibration and for monitoring the repeat measures correlation coefficient of variation (CV). The quantities of the control samples were used for calculating CV values as the ratio of the standard deviation to the mean, which gave means of 21.0% for the telomere reaction, 6.0% for the β-haemoglobin reaction, and 24.8% for their ratio (T/S). The plate effect was taken into account by normalizing the telomere signal and reference gene signal to the corresponding mean of 4 control samples that were analyzed for every qPCR plate before taking the T/S ratio. Three outlier samples of T/S ratio were removed before statistical analyzes commenced.

2.3. Mental disorders

Mental disorders severe enough to warrant hospitalization were identified from the Finnish Hospital Discharge Register (HDR). The HDR covers all inpatient episodes of residents in Finland in the general and psychiatric hospitals from 1969 onwards. Mental disorders were coded by the International Classification of Diseases (ICD) system. ICD-8 was used for the 1969–1986 inclusive period, ICD-9, according to the Diagnostic and Statistical Manual of Mental Disorders, Third Revision (DSM-III-R), for the years 1987–1995 inclusive and ICD-10 from the year 1996 onwards. Both the primary and subsidiary hospitalization diagnoses were used, except in the case of acute substance-intoxication (ICD-9: 305 and ICD-10: F1x.0). In such cases only primary diagnoses were used because intoxication is a frequent subsidiary diagnosis in Finnish medical practice and does not automatically indicate a substance use disorder *per se*. Mental disorders were categorized according to the ICD codes into the following groups: Any mental disorder, Substance use disorder, (Non-affective) Psychotic disorders, Mood disorders, Anxiety disorders and Personality disorders. For more details see Räikkönen et al. (2011). The number of specific mental disorder diagnoses does not equate to any mental disorder, because