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Leucocyte telomere length is no molecular marker of physical frailty in late-life depression

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ABSTRACT

Background: Although average life-expectancy is still increasing worldwide, ageing processes markedly differ between individuals, which has stimulated the search for biomarkers of biological ageing.
Objectives: Firstly, to explore the cross-sectional and longitudinal association between leucocyte telomere length (LTL) as molecular marker of ageing and the physical frailty phenotype (PFP) as a clinical marker of ageing and secondly, to examine whether these associations are moderated by the presence of a depressive disorder, as depression can be considered a condition of accelerated ageing.
Methods: Among 378 depressed older patients (according to DSM-IV criteria) and 132 non-depressed older persons participating in the Netherlands Study of Depression in Older persons, we have assessed the physical frailty phenotype and LTL. The PFP was defined according to Fried's criteria and its components were reassessed at two-year follow-up.
Results: LTL was neither associated with the PFP at baseline by Spearman rank correlation tests, nor did it predict change in frailty parameters over a two-year follow-up using regression analyses adjusted for potential confounders.
Conclusion: LTL is not associated with frailty; neither in non-depressed nor in depressed older persons. As LTL and physical frailty appear to represent different aspects of ageing, they may complement each other in future studies.

1. Introduction

Humans are inevitably exposed to ageing processes, but the rate of ageing markedly differs between individuals. One of the most challenging aspects of geriatric medicine is to explain the heterogeneity in biological ageing among individuals of the same chronological age. To this end, several markers of biological ageing have been proposed, including molecular markers as well as clinical phenotypes.

In this study we will explore to what extent leucocyte telomere length, a frequently used molecular marker of ageing, is associated with a clinically defined phenotype of biological ageing.

Telomere length is widely considered as a marker of cellular ageing, as shortened telomeres in white blood cells are predictive of increased mortality rates (Cawthon et al., 2003; Honig et al., 2006) and increased incidence of various age-related diseases (Collado et al., 2007; Willeit et al., 2010). With each cell division some telomeric DNA is lost and when a critical minimal length is reached the cell enters senescence or apoptosis (Collado et al., 2007; Willeit et al., 2010). Next to replication, endogenous factors may also cause telomere shortening including inflammation, metabolic dysregulation and oxidative stress (Teyssier et al., 2012; Garcia-Rizo et al., 2013), mechanisms that becomes more prominent with chronological ageing.

Frailty is conceptualized as a state of increased risk of adverse health outcomes, such as falls, reduced mobility, reduced independence, hospitalization, disability and death (Fried et al., 2001). Physical frailty can thus be considered as a clinical phenotype of biological ageing as it predicts age-related adverse health outcomes including death independent of age-related disease pathologies and

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chronological age (e.g. Fried et al., 2001; Kojima et al., 2018). The explanation of the increased health risks is sought in a reduction of the reserve capacity of various physiological systems. Frailty is characterized by diminished strength, endurance, and reduced physiological function (Morley et al., 2013) and is prevalent when the reserve capacity has decreased to a critically low point, where even small disturbances can lead to a series of complications.

Four population-based studies found that, neither in Caucasian older persons nor in Asian older persons, LTL is cross-sectionally associated with physical frailty (Woo et al., 2008; Collerton et al., 2012; Yu et al., 2015.; Breitling et al., 2016). Moreover, LTL neither predicted incident frailty at five year follow-up in the Asian cohort (Yu et al., 2015). These findings are consistent across the different frailty models chosen in these studies, i.e. the Fried Frailty Phenotype (Yu et al., 2015; Collerton et al., 2012) and the Frailty index according to the deficit model of Rockwood (Woo et al., 2008; Collerton et al., 2012; Breitling et al., 2016). These studies, however, did not take the presence of depression into account. In the past decade, major depressive disorder has been postulated as a condition associated with accelerated ageing. At a cellular level, associations have been found between LTL and major depressive disorder (e.g. Epel et al., 2004; Garcia-Rizo et al., 2013; Damjanovic et al., 2007; Kananen et al., 2010; Tyrka et al., 2010; Verhoeven et al., 2014; Lin et al., 2016). However these findings could not be replicated in the Netherlands Study of Depression in Older persons (NESDO) by our group (Schaakxs et al., 2015). This has among others been explained by the fact that late-life depression has a more heterogeneous nature as compared to depression earlier in life, which may mask (small) effects pertaining to specific subgroups. On the other hand, the phenotypic expression of biological ageing, i.e. physical frailty, has been consistently associated with late-life depression. In the NESDO study, we found that physical frailty phenotype is more prevalent in depressed compared to non-depressed older persons (Collard et al., 2014). Since depressive disorder and physical frailty partly overlap, especially among more severely depressed individuals (Mezuk et al., 2012), depression should be taken into account when examining the association between LTL and physical frailty.

The objective of the present paper is firstly to explore the cross-sectional association between the physical frailty phenotype and LTL, secondly to examine whether this association is moderated by depression, and thirdly, whether LTL at baseline is associated with a change in frailty (parameters) over time. Knowledge on the relationship between these different markers of ageing facilitate the interpretation of studies on the determinants of (healthy) ageing, like stress, hormones, nutrition, smoking, and exercise that uses such parameters as (intermediate) endpoints.

2. Methods

2.1. Study sample

The present study was embedded within a prospective cohort study: the Netherlands Study of Depression in Older people (NESDO) [Comijs et al., 2011; Comijs et al., 2015]. NESDO has included 378 depressed subjects with a 6-month major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%), of which 26.5% have two depressive disorders, next to a comparison group of 132 non-depressed older persons. Recruitment of depressed older persons was from both mental health care institutes (86.2%) and general practices (13.8%) in order to include persons with late-life depression in various developmental and severity stages. The non-depressed comparison group (no lifetime history of depression) was recruited within the participating general practices.

Depressive disorders were established using the Composite International Diagnostic Interview (CIDI version 2.1) according to the criteria of DSM-IV-TR. Depressed patients with a diagnosis of dementia according to a clinician, a Mini Mental State Examination-score (MMSE, Folstein et al., 1975) under 18, an organic or psychotic disorder and those not mastering the Dutch language were excluded (Comijs et al., 2011). Exclusion criteria for the non-depressed comparison group were a lifetime diagnosis of depression (based on the CIDI), a diagnosis of dementia, and insufficient mastery of the Dutch language.

At baseline, data were gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. Interviews were performed by trained research assistants and audiotaped regularly to control for quality. If necessary, participants were visited at home.

Measures subject to change were evaluated again at two-year follow-up. At two-year follow-up, a total of 93/378 (24.6%) of the depressed patients and a total of 16/132 (12.1%) of the non-depressed comparison group dropped out.

The study protocol of NESDO was approved by the ethical review boards of the five participating mental health centres and all participants have provided written informed consent (Comijs et al., 2015).

2.2. Measures

2.2.1. Telomere length

Leukocyte TL was determined by Telomere Diagnostics, Inc. (TDx, Menlo Park, CA, USA) using fasting blood samples collected between 8:30 and 9:30 AM. Peripheral blood mononuclear cells from all samples were isolated from whole blood using density-gradient centrifugation (with Ficoll-Paque PLUS) and stored at −80 °C freezers. Quantitative polymerase chain reaction (qPCR) was used to compare the telomere sequence copy number (T) in each patient's sample to a single-copy gene copy number (S), relative to a reference sample (100 male donors). Each sample was run in triplicate. The intra-assay coefficient of variation (CV) was 5.1% and the inter-assay CV was 4.6%. The resulting T/S ratio was proportional to mean TL. The T/S ratio was converted to basepairs (bp) by the following formula: $bp = 3274 + 2413 \times ((T/S - 0.0545)/1.16)$ (Schaakxs et al., 2015; for more specific details, see supplementary data by Verhoeven et al., 2014).

2.2.2. Physical frailty phenotype

The physical frailty phenotype was assessed according to the criteria of Fried and colleagues (Fried et al., 2001), i.e. the presence of ≥3 out of 5 dichotomous criteria: exhaustion, unintended weight loss, inactivity, slowness (gait speed), and weakness. In line with previous studies of our group (Collard et al., 2014; Arts et al., 2016) these criteria were operationalized as follows.

- Exhaustion: a score of 3 or 4 out of 4 points on one or both of the Inventory of Depressive Symptoms (IDS-SR) questions about energy level and leaden paralysis/physical energy (Rush et al., 1986).
- Unintended weight loss: positive answer to the CIDI question about unintended weight loss (≥1 kg/week, for ≥2 consecutive weeks), or a body mass index (BMI) < 18.5 kg/m^2.
- Inactivity: no daily activities such as walking or gardening, and the performance of sports less than once a week, assessed with the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003)
- Slowness (gait speed): time on a six-meter walking test ≥8 s for men ≥ 173 cm or women ≥ 159 cm, or ≥9 s for men < 173 cm and women < 159 cm.
- Weakness: low handgrip strength, measured by two squeezes with the dominant hand in a dynamometer. Cut-off values depends on body mass index and varies between 29–32 kg for men and 17–21 kg for women.

In addition to the operationalisation of Fried and colleagues, we also examined the individual frailty components. In these analyses, all components were used as dimensional measures. With respect to weight loss, we simply used weight (measured in kg), with respect to