Physical frailty in late-life depression: evidence for a depression-frailty subtype?

Arts, Matheus

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Chapter III

Telomere length and physical frailty in late-life depression

MHL Arts, RM Collard, HC Comijs, L de Jonge, P Naarding, B Penninx, Kok RM, RC Oude Voshaar

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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 aspect of ageing, they may complement each other in future studies.

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 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 (Collerton et al., 2012; Yu et al., 2015) 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; Damjanovic et al., 2007; Kananen et al., 2010; Tyrka et al., 2010; Garcia-Rizo et al., 2013; 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 amongst 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 ag*e*ing 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.

Methods

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).

Measures

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+2413x((T/S-0.0545)/1.16) (Schaakxs et al., 2015; for more specific details, see supplementary data by Verhoeven et al., 2014).

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 seconds for men ≥ 173 cm or women ≥ 159 cm, or ≥ 9 seconds 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 exhaustion the sum score of the two IDS-SR items, and with respect to physical activities MET-minutes based on the IPAQ (Craig et al., 2003).

Depression - Diagnoses of major depression and dysthymia were assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization version 2.1; lifetime version) according to DSM-IV-TR criteria. The CIDI is a structured clinical interview and has high validity for depressive and anxiety disorders (Wittchen et al., 1991). Questions were added to determine the DSM-IV TR research diagnosis of current minor depression. Severity of depression was measured by the 30-item self-rating Inventory of Depressive Symptomatology (IDS-SR) (Rush et al., 1986). The

IDS sum score ranged from 0 to 84 (continuous variable). The clinical interpretation of the IDS sum score is as follows: 0-13= normal, 14-25= mild depression, 26-38= moderate depression, 39-48= severe depression and 49-84= very severe depression (Rush et al., 2008).

Covariates - We considered the presence of a depressive disorder as well as variables that have been associated with LTL in previous studies, i.e. age, sex, years of education, smoking status, alcohol use, physical activity, body mass index, and chronic somatic diseases as potential confounders (Schaakxs et al., 2015).
During the baseline interview, participants' age, sex, and years of education was collected. The life-time burden of smoking was operationalized as cigarette years, i.e. the average number of cigarettes smoked per day multiplied by the number of years of smoking. Alcohol use was assessed with a self-reported questionnaire, the Alcohol Use Disorder Identification Test (AUDIT), of which the sum score was used in the analyses (Babor et al., 1989). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) and expressed in Metabolic Equivalent Total (MET)-minutes per week (ratio of energy expenditure during activity compared with rest, times the number of minutes performing the activity) (Ainsworth et al., 2011), and Body Mass Index (BMI, weight/length^2). The number of chronic somatic diseases (i.e. lung disease, cardiac diseases, liver disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus, thyroid disease, malignant neoplasms, and osteoarthritis) (Kriegman et al., 1996) was assessed by a self-report questionnaire (www.CBS.nl).

Statistical analysis - Baseline characteristics of frail and non-frail depressed patients were compared by chi-square tests in case of categorical variables and in case of continuous measures by t-test (normal distribution) or Mann-Whitney U test (skewed distribution).

For the first objective, the associations between indices of physical frailty and LTL at baseline were assessed with bivariate linear regression analyses with LTL as the dependent variable. To delineate the effect of chronological age as covariate, separate multivariate models will be presented with and without chronological age. For the second objective, we examined whether differential results were found in depressed and non-depressed persons by testing the interaction between each frailty indices and depression status. In case of significant findings, results will be presented separately for depressed and non-depressed persons. In these cross-sectional analyses LTL will be used as the dependent variable in order to examine the association with different characteristics of frailty and the interaction between frailty indices and depression. Of the dimensional frailty components, only slowness (gait speed) was not normally distributed, but a normal distribution was achieved after log-transformation.

For the third objective, we compared the LTL between persons non-frail at baseline and follow-up (robust), frail at baseline and follow-up (persistently frail) and two dynamic groups, i.e. incident frailty (non-frail at baseline, frail at follow-up) and remitted frailty (frail at baseline, non-frail at follow-up). In these longitudinal analyses, LTL is included as the independent variable and frailty as the dependent variable. Group differences were examined by MANOVA, adjusted for different sets of covariates. In addition, the impact of baseline LTL on change of the individual components of frailty (as continuous variables) were examined by linear regression analyses. In these analyses the dimensional measures of each frailty component were examined. The frailty component at follow-up was included as the dependent variable and LTL as the independent variable, adjusted for the baseline frailty component under study. The interaction between LTL and presence of depressive disorder was also tested in these latter models, to examine whether the LTL-frailty association differed between depressed and non-depressed persons.

All analyses were conducted in IBS SPSS Statistics, version 24. A p-value of less than .05 was considered statistically significant.

Results

Of the 510 study participants, LTL was missing for 14 persons, whereas the physical frailty phenotype was missing for another 15 patients, leaving 481 study participants at baseline. The 29 subjects excluded due to missing data with respect to either LTL or frailty, were less educated (9.6 (SD=3.4) versus 11.0 (SD=3.6) years, t=-2.1, df=508, p=.039) and had a higher level of depressive symptoms (31.4 (SD=15.7) versus 24.0 (SD=15.1), t=2.4, df=500, p=.016) compared to included patients, but did not significantly differ with respect to the other characteristics mentioned in table 1.

As shown in table 1, frail persons were significantly older, more often female, less educated, consumed less alcohol, had a higher number of chronic somatic diseases and were more often depressed. The LTL was significantly shorter among frail persons compared to non-frail persons at baseline (4968 (SD=332) versus 5065 (SD=401), t=2.34, df=479, p=.020).

Table 1 Baseline characteristics of non-frail and frail study participants

		Non-frail patients (n=367)	Frail patients (n=114)	Statistics
Demographics				
• Age (years)	mean (SD)	69.6 (6.9)	73.7 (8.0)	<.001
• Female gender	n (%)	228 (62.1)	83 (72.8)	.037
• Education (years)	mean (SD)	11.5 (3.6)	9.6 (3.2)	<.001
Lifestyle characteristics				
• Smoking (cigarette years)	mean (SD)	283 (376)	307 (442)	.573
• Alcohol use (AUDIT)	mean (SD)	3.2 (3.6)	1.8 (2.4)	<.001
Health parameters				
• Chronic diseases (number)	mean (SD)	1.7 (1.2)	2.4 (1.6)	<.001
• Depressive symptom severity (IDS)	mean (SD)	20.5 (13.5)	35.6 (14.2)	<.001
• Depressive disorder	n (%)	250 (68.1)	103 (90.4)	<.001

Table 2 Association of LTL and physical frailty and its individual components by linear regression

	Model 1*			Model 2*			Model 3*			Model 4*		
	B (SE)	β	p	B (SE)	β	p	B (SE)	β	p	B (SE)	β	p
Frailty frailty index												
• Frailty present (yes/no)	-96.8 (41.4)	-0.11	.020	-44.0 (41.3)	-0.05	.288	-98.5 (44.5)	-0.11	.027	-48.7 (43.8)	-0.05	.267
• Sum of components	-44.7 (13.6)	-0.15	.001	-26.8 (13.7)	-0.09	.050	-48.9 (15.1)	-0.16	.001	-29.7 (15.0)	-0.10	.048
Individual components (continous):												
• Exhaustion	4.52 (9.80)	0.02	.644	-14.2 (2.3)	0.03	.459	15.2 (12.6)	0.07	.226	15.2 (12.1)	0.07	.207
• Weight	-0.61 (1.19)	-0.02	.609	-2.08 (1.17)	-0.08	.077	0.88 (1.33)	0.03	.509	-0.94 (1.31)	-0.04	.472
• Physical activity level	0.01 (0.01)	0.06	.176	<0.01 (0.01)	0.01	.882	0.01 (0.01)	0.06	.226	<0.01 (0.01)	<0.01	.999
• Slowness (log gait speed)	-137.5 (42.5)	-0.15	.001	-38.5 (46.0)	-0.04	.404	-164.3 (48.4)	-0.17	.001	-54.7 (51.3)	-0.06	.287
• Weakness (handgrip strength)	2.24 (1.51)	0.07	.139	-0.40 (1.53)	-0.01	.797	6.30 (1.96)	0.19	.001	2.73 (2.00)	0.08	.173

* Bivariate

** Adjusted for chronological age only

*** Adjusted for gender, level of education, presence of depressive disorder, number of chronic diseases under treatment including hypertension, smoking (cigarette years), and use of alcohol (AUDIT), except age.

**** Adjusted for age, gender, level of education, presence of depressive disorder, number of chronic diseases under treatment including hypertension, smoking (cigarette years), and use of alcohol (AUDIT).

Table 2 presents the results of the association between frailty and LTL. Chronological age was associated with LTL (r=-0.25, p<.001), the presence of frailty (r=0.23, p<.001) and the number of frailty components met (r=0.25, p<.001). When adjusted for all covariates except age, both the presence of the Fried Frailty Phenotype as well as the number of frailty components met were associated with LTL.

Analysis of the individual frailty components, showed that the associations with LTL were primarily driven by gait speed and handgrip strength. Nonetheless, all associations became non-significant when adjusted for chronological age. With regard to study objective 2, none of the frailty measures in table 2 significantly interacted with the presence of a depressive disorder in explaining variance in LTL (all p-values of these interaction terms were >0.36).At follow-up, data were available for 363 persons (75.5%). Of the 291 non-frail persons at baseline, 27 (9.3%) became frail at follow-up. Of the 72 frail persons at baseline, 35 (48.6%) remained frail at follow-up.

Table 3 shows that LTL did not differ across these four groups in both the unadjusted and adjusted analyses.

Table 3 Comparison of the mean (standard error) LTL between robust, incident frail, remitted frail and persistently frail patients over a two-year follow-up

	Robust (n=258)	Incident frailty (n=27)	Remitted frailty (n=36)	Persistent frailty (n=34)	Statistics
Model 1	5068 (24)	5066 (74)	5007 (63)	4965 (65)	F=0.94, df=3,359, p=.424
Model 2	5051 (23)	5108 (72)	5014 (61)	5057 (66)	F=0.32, df=3,358, p=.809
Model 3	5066 (24)	5067 (74)	5000 (65)	4958 (67)	F=0.92, df=3,346, p=.432
Model 4	5047 (23)	5118 (72)	5007 (62)	5050 (67)	F=0.47, df=3,345, p=.706

* Bivariate

** Adjusted for chronological age only

*** Adjusted for gender, level of education, presence of depressive disorder, number of chronic diseases under treatment including hypertension, smoking (cigarette years), and use of alcohol (AUDIT), except age.

**** Adjusted for age, gender, level of education, presence of depressive disorder, number of chronic diseases under treatment including hypertension, smoking (cigarette years), and use of alcohol (AUDIT).

Furthermore, linear regression analyses showed that LTL was not associated with change in any of the individual components: exhaustion (B=0.06 [SE=0.09], β=0.04, p=.500); weight (B=-0.44 [SE=0.33], β=-0.03, p=.176), inactivity (B=157 [SE=157], β=0.06, p=.318), slowness (gait speed) (B=0.02 [SE=0.02], β=0.05, p=.350), and weakness (handgrip strength) (B=0.02 [SE=0.37], β<0.01, p=.962). Adding different sets of covariates did not change these results. Neither did we find any significant interaction of LTL with the presence of a depressive disorder on the change of any frailty component.

Discussion

Main findings - Both leucocyte telomere length (LTL) and physical frailty had a weak, but significant association with chronological age. Although this weak association contributes to the validation of both markers as biomarkers of ageing, the weak univariate association between physical frailty and LTL was halved by adding chronological age to the model. The presence of frailty (yes/no) was not associated anymore with LTL, whereas the number of frailty components remained statistically significant (when not accounting for multiple testing), but both variables explained only 1% variance of each other. This suggests that both markers identify different ageing mechanisms. These findings were independent of the presence of depressive disorder, thereby corroborating earlier findings in population based samples (Woo et al., 2008; Collerton et al., 2012; Yu et al., 2015; Breitling et al., 2016).

Association of LTL with frailty - Although molecular studies on ageing generally accept LTL as a marker of ageing (e.g. Manoliu et al., 2018), from a clinical oriented perspective different frailty phenotypes, among which the Fried frailty phenotype, are proposed as indicators of biological ageing. Previous studies showed that LTL is associated with age-related physiological disturbances, somatic diseases and even mortality (Yu et al., 2015; Breitling et al., 2016). In our sample of depressed older patients, however, LTL was not associated with changes in physical frailty

parameters over time. The weak cross-sectional association we found between LTL and physical frailty unadjusted for chronological age was driven by gait speed and handgrip strength. Shorter LTL was associated with a slower gait speed and a lower handgrip strength, the performance-based elements of the physical frailty phenotype (Arts et al., 2015). These components do not overlap with the criteria of late-life depression, whereas the other criteria (weight loss, exhaustion and low physical activity) may do so. This finding is therefore fully in line with our previous finding that LTL is not associated with late-life depression (Schaakxs et al., 2015).

A potential explanation for our results can be sought in recent insights into the dynamics of both telomere-length as well as physical frailty. Telomere length is highly dynamic, as telomeres shorten during meiosis, whereas telomerase, a ribonuclear protein-enzyme complex, facilitates telomere lengthening. Recent studies have shown that telomere maintenance (and dynamics) are under genetic controls (e.g. Blackburn et al., 2015). Likewise, modern insights also consider physical frailty as a dynamic state that is reversible (Morley et al., 2013). As frailty is determined by multiple underlying mechanisms (nutritional status, vitamin D, inflammation, physical activity, as well as genetic control), the dynamics of frailty and telomere length do not necessarily synchronise thereby contributing to the relatively low correlation coefficient found in our study.

Association of LTL with (late-life) depression - Accumulating evidence is found that depressive disorder is associated with accelerated cellular and physiological ageing, with an increased occurrence of age-related diseases, comorbidity and mortality (Licinio and Wong, 1999; Brown et al., 2004; Wolkowitz et al., 2010; Manoliu et al., 2018). Many studies argue that accelerated biological ageing in depression occurs at the level of LTL. However, telomere-shortening as one of the underlying mechanisms is indeterminate as evidenced by a number of conflicting studies, with negative results more often found in studies with older patients (e.g. Schaakxs et al.,

2015). To explain these conflicting results, the association between LTL and depression has been hypothesized to depend on the severity of the depressive symptoms (Needham et al., 2015) and duration of the depression (Lung et al., 2007; Hartmann et al., 2010; Wolkowitz et al., 2010; Wikgren et al., 2012). For example, among young adults with past-year major depressive disorder, shorter LTL was only associated among those receiving psychotropic medication but not among those suffering from less severe depression not needing antidepressants (Needham et al., 2015). Furthermore, chronic courses of depression are indeed inversely related to telomere length consistently (Lung et al., 2007; Hartmann et al., 2010). For example, among currently depressed adults (up to 69 years), LTL did not differ between depressed patients and controls, whereas lifetime depression exposure was inversely correlated with LTL shortening (Wolkowitz et al., 2011). This may point to the role of accumulated exposure to oxidative stress and inflammation in long-term depression (Wolkowitz et al., 2011).

Severity and duration of a depressive disorder, however, do not explain why inconsistent results are more often found among studies with older depressed patients. A recent longitudinal study examined the association between telomere length and depression or depressive symptoms across three age cohorts (37 years, 57 years, and 76 years) and they reported an association between depressive symptoms and reduced LTL, but only in the younger age cohort (Philips et al., 2013). More recently, we also found no difference in LTL between a clinical sample of depressed older patients compared to non-depressed subjects (Schaakxs et al., 2015), whereas others found that among community-dwelling older males, LTL was neither cross-sectionally nor longitudinally associated with measures of mental well-being (Rius-Ottenheim et al., 2012). We therefore hypothesized that the chronological age of the participants is an important source for variation in the association between depression and LTL.

One potential source of confounding that may increase with age is the presence of chronic somatic diseases, as in population-based studies or psychiatric cohort studies the severity and chronicity of somatic conditions are usually not taken into account. Interestingly, among 952 older patients with stable coronary heart disease of which 206 had a comorbid major depressive disorder, depression was associated with reduced LTL (Hoen et al., 2011). As Wolkowitz and colleagues stated that the biological age of depressed adults is at least 10 years older compared to their chronological age (Wolkowitz et al., 2010), frailty might also be such a confounding factor. Previously, we have shown the relevance of the physical frailty phenotype among depressed older persons (Collard et al., 2015; Collard et al., 2017). Nonetheless, when taking frailty into account, we still did not demonstrate any association between LTL and depression in our sample.

Methodological considerations - For proper interpretation, some methodological issues need to addressed. Strength of this study is the comprehensive assessment of the depression characteristics and confounding factors. As our sample consists primarily of depressed older patients, our results show that previously reported population-based findings (also no associations found between LTL and frailty) can be extrapolated to a depressed older sample. In this regard, the small sample size of our non-depressed comparison group is not a major issue (as results can be considered to be driven by the depressed group).

However, some limitations should also be acknowledged. First of all, our sample size is relatively small. Nonetheless, compared to previous population-based studies, the number of frail persons is comparable (Yu et al., 2015; Breitling et al., 2016). Although only 29 patients (5.6%) had missing data on either LTL or frailty at baseline, these patients might have been biologically older (being less educated and more depressed) biasing our sample minimally towards a healthier group. A second issue might be the difficulty to disentangle frailty and late-life depression. However, by

including follow-up data, we were able to exclude persons with a so-called dynamic frailty status. However, the LTL did also not differ between persistently non-frail and persistently frail persons. Thirdly, a main limitation using follow-up results might be that the most frail persons may die or dropout (survival bias). On the other hand, as both ageing markers predicts physical deterioration and mortality, it is difficult to estimate to what extent, if any, the association between both markers would be affected. Moreover, a duration of follow-up of two years is relatively small. Finally, as LTL was only available at baseline, we can not answer whether frailty predicts changes in LTL over time.

Final conclusion - In conclusion, we could not demonstrate any association between physical frailty and LTL over and above chronological age. Therefore, our results show that LTL and the physical frailty phenotype are different markers of the ageing process and may be complementary in studies of accelerated ageing in (late-life) depression.

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