Chapter VIII

Frailty predicts mortality in late-life depression

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Abstract

Objectives - Frailty is a clinical phenotype of biological aging that predicts negative health outcomes including mortality. Late-life depression is also associated with increased mortality rates, but partly overlaps with frailty. Therefore, we examined whether frailty predicts mortality among depressed older patients.

Methods - Among 378 older patients (≥60 years) with a depressive disorder (DSM-IV criteria) we examined whether frailty predicts time-to-death during a six-year follow-up using Cox-regression analyses adjusted for relevant confounders. Frailty was defined according to Fried's criteria (muscle weakness, slowness, exhaustion, low activity level, unintended weight loss). Similarly, we examined the predictive value of aging-related biomarkers, i.e. three inflammatory markers, vitamin D level, and leucocyte telomere length, and whether these biomarkers were explanatory factors in the association between frailty and mortality.

Results - During follow-up, 27/103 (26.2%) frail depressed patients died compared to 35/275 (12.7%) non-frail depressed patients (p<.001). Adjusted for confounders, the number of frailty components was associated with an increased mortality rate (HR=1.38 [95%CI: 1.06–1.78], p=.015). Higher levels of hsCRP (HR=1.41 [95%CI :1.08–1.83], p=.011) and lipocalin-2 (HR=1.30 [95%CI: 1.00–1.68], p=.048) predicted death, whereas higher levels of vitamin D (HR=0.60 [95%CI: 0.43–0.85], p=.004) were protective for death. All aging related biomarkers partly explained the association between frailty and mortality.

Conclusion - In late-life depression, frailty is a valid concept to identify older patients at risk of adverse negative health outcomes. Therefore, among frail-depressed patients, treatment models that include frailty-specific interventions might reduce mortality rates.

Introduction

Physical frailty is a clinical state in which there is an increase in an individual's susceptibility for developing vulnerability, dependency and death when exposed to a stressor (Morley et al., 2013). Although physical frailty is characterized by diminished strength, endurance, and reduced physiological function, operationalizations still partly overlap with the criteria of a depressive disorder (Lohman et al., 2013). This has even led to exclusion of depressed patients from frailty research, as done in the hallmark study of the Fried Frailty Phenotype (Fried et al., 2001). This decision seems to be justified by latent class analyses (LCA) on the Fried frailty criteria and DSM-IV depression criteria among community-dwelling older people (Mezuk et al., 2012). In this study, LCA had identified two groups of persons based on frailty criteria and three groups based on depression, which substantially overlap (with a kappa of 0.66). Moreover, all persons classified as severely depressed were also classified as being frail (Mezuk et al., 2012). Nonetheless, in the Netherlands Study of Depression in Older persons (NESDO), we showed that only 27.2% of the patients suffering from a DSM-IV defined depressive disorder were physically frail (Collard et al., 2014). Furthermore, a meta-analysis on the association between depression and frailty estimated that 40.4% of depressed persons were frail and that 38.6% of frail persons were depressed, with the sparse longitudinal studies showing a bidirectional association between depression and frailty (Soysal et al., 2017).

Several papers have reported increased mortality rates in late-life depression, although many studies can be considered to be of low quality (Cuijpers et al., 2014; Miloyan et al., 2017). Studies limited to depressive disorders according to DSM criteria, however, still showed a pooled hazard ratio for mortality of 1.2 [95%CI:0.8–1.6]. The authors emphasize the need to study which characteristics in particular modify the relationship between depression and mortality (Miloyan et al., 2017). Frailty might be an explanation for this increased mortality rate (Almeida et al.,

2015). Nonetheless, depressive disorder itself is increasingly recognized as a disorder of accelerated aging based on its association with many physiological and cellular markers of aging, like low-grade inflammation, shortening of telomere length, and lower vitamin D levels (Verhoeven et al., 2014). In the NESDO-study, however, we did not find consistent associations between late-life depression and low-graded inflammatory markers (Rozing et al., 2019) or leucocyte telomere length (Révész et al., 2014), whereas lower vitamin D levels were only cross-sectionally but not prospectively associated with late-life depression (Oude Voshaar et al., 2014; van den Berg et al., 2016). Consistent with the literature on frailty, we found that within NESDO, physical frailty was associated with low-graded inflammation (Arts et al., 2015), a shorter leucocyte telomere length (Arts et al., 2018), and lower vitamin D levels (van den Berg et al., 2018). Therefore, frailty could be a modulator factor to adverse outcomes like death among depressed older adults.

The present study examines the predictive value of the physical frailty phenotype on mortality among clinically depressed older patients. Physiological and cellular biomarkers of aging and frailty will be examined as potentially explanatory mechanisms of the hypothesized association between frailty and mortality. We hypothesize that all physiological and cellular biomarkers of aging will predict mortality in our cohort and thus at least partly explain the effect of frailty on mortality.

Methods

Study population - The present study was embedded within the Netherlands Study of Depression in Older persons (NESDO) and include 378 depressed subjects aged ≥60 years who meet the criteria for a DSM-IV depressive disorder using the Composite International Diagnostic Interview (CIDI version 2.1) (Comijs et al., 2011). Of these 378 patients, 95% had a past 6-month major depressive disorder, 26.5% a past 6-month dysthymia, and 5.6% a past-month minor depression (numbers do not

add up to 100% as 26.5% have two depressive disorders). Exclusion criteria were a diagnosis of dementia, a Mini Mental State Examination-score (MMSE) under 18, an organic or psychotic disorder and insufficient mastery of the Dutch language.

All participants underwent a baseline examination at one of the five research locations or at the homes of the participants. When necessary, the assessment was spread over two appointments.

The overall aim of NESDO is to examine the course and consequences of depressive disorders in older persons. Therefore, all baseline characteristics amenable to change were also administered at two- and six-year follow-up. Every six months, up to six years, postal questionnaires were sent to monitor depressive symptom severity (amongst other measures). During all follow-up measures, the postal and site-visits, and reasons for dropout, including mortality were registered (Jeuring et al., 2018).

The ethical review boards of all participating study centers have approved the NESDO -study protocol and all participants have provided written informed consent (for details, see Comijs et al., 2011; Jeuring et al., 2018).

Physical frailty phenotype - The physical frailty phenotype was assessed according to Fried's criteria (Fried et al., 2001). Patients were classified as frail when at least three out of the five criteria were present, including weight loss, weakness, exhaustion, slowness and low physical activity. The operationalization of these criteria has been described before (Collard et al., 2014) and is summarized below:

- *Unintentional weight loss* was defined as either unwanted weight loss of a minimum of one kilogram a week during two or more consecutive weeks or a body mass index (BMI) <18.5 kg/m^2.
- *Weakness* was based on the maximum handgrip strength of their dominant hand (in kg) and assessed with a handgrip dynamometer. The best out of two squeezes was stratified by gender and BMI quartiles according to Fried and

colleagues (Fried et al., 2001). Participants unable to perform the test were also considered weak.

- *Exhaustion* was determined by two questions from the Center for Epidemiologic Studies-Depression scale (CES-D), identical to other studies (Fried et al., 2001): "I felt that everything I did was an effort" and "I could not get going." Participants answering "3 or more days a week" to either of these two items were categorized as positive.
- *Slowness* was measured by a six meter walking test, using sex and length stratified cut-offs as extrapolated from Fried and colleagues (Fried et al., 2001): 9 seconds for men ≤173 centimeters (cm) and women ≤159 cm tall; 8 seconds for men >173 cm and women >159 cm).
- *Low physical activity level* was defined as no daily activities such as walking and gardening and no sports activity less than once weekly, as assessed with the short form of the International physical Activities Questionnaire (IPAQ) (Craig et al., 2003).

Aging and frailty biomarkers - Fasting blood samples were obtained in the morning around 8 am and kept at −80°C for subsequent analyses of biomarkers.

Low-graded inflammation - We assessed plasma levels of C-reactive protein (CRP), Interleukin-6 (IL-6) and Neutrophil Gelatinase Associated Lipocalin-2 (NGAL-2). High-sensitivity plasma levels of CRP were measured in duplicate by an immunoturbidimetric assay (Tina-quant CRPHS, Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay coefficients of variation were 2% and 2%, respectively. Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact™ ELISA, Sanquin, Amsterdam, the Netherlands). Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Finally, the plasma NGAL-2 levels (ng/ml) were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) (Naudé et

al., 2013). The intra- and inter-assay coefficients of variation were 2% and 5%, respectively.

Vitamin D - Serum 25-(OH) vitamin D levels were measured at baseline using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously (Oude Voshaar et al., 2014).

Leucocyte Telomere Length (LTL) – LTL was determined by Telomere Diagnostics, Inc. (TDx, Menlo Park, CA, USA). 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. 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 base pairs (bp) by the following formula: bp=3274+2413x((T/S-0.0545)/1.16) (for details, see Schaakxs et al., 2015).

Covariates - As covariates we included the most important determinants of death, i.e. demographic data (age, sex, and years of education), lifestyle characteristics, and somatic disease burden.

Lifestyle characteristics included smoking (yes/no) and number of alcoholic drinks based on the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 1989).

The somatic disease burden was quantified as the number of chronic somatic diseases under treatment as well as the number of prescribed medications. The total number of self-reported chronic diseases was determined by well-validated algorithms (Kriegsman et al., 1996), and included lung disease, cardiovascular disease, diabetes, osteoarthritis or rheumatic disease, cancer, ulcer, intestinal problems, liver disease, epilepsy, and thyroid gland disease. To calculate the number of medications, all drugs with a unique Anatomical Therapeutical Chemical Classification System (ATC) code at a three-digit level were counted. Dermatological preparations, medications without an ATC code, medications used less than half of

the week (except drugs for which non-daily use is common, i.e. bisphosphonates, methotrexate), and for use 'if necessary' were excluded. Data on drug use were collected at the interviews (and checked by medication containers).

In addition, analyses were also adjusted for depressive symptom severity because depression itself has been associated with death. Depressive symptom severity was measured by the well-validated 30- item self-rating Inventory of Depressive Symptomatology (IDS) (Rush et al., 1986).

Finally, models including vitamin D levels were additionally adjusted for the astronomical season of blood withdrawal (winter: 21 November–20 February; spring: 21 February–20 May; summer: 21 May–20 August; autumn: 21 August–20 November).

Data analysis - Baseline characteristics are presented stratified for frail and non-frail depressed patients and tested by Student's t-tests for (normally distributed) continuous variables and chi-square tests for categorical variables.

Cox's regression (proportional hazard analysis) models were used to investigate the effect of frailty upon time to attrition due to death adjusted for all covariates described above. Survival time ranged from baseline till either death (outcome) or censored at time of study dropout or end of the follow-up (at six years). The presence of frailty (yes/no) and the number of frailty components present (range 0-5) were the primary variables of interest. In order to explore the impact of frailty in more depth, we also examined the impact of specific frailty components, i.e. 1) the impact of each of the five Fried's frailty criteria (yes/no), 2) gait speed and hand grip strength as continuous, unidimensional proxies for frailty, and finally 3) two frailty dimensions based on the principal components analysis (PCA) with direct oblimin rotation on the five components of the Fried Frailty Phenotype as described before (van den Berg et al., 2016). The Cox-proportional hazard assumption was checked

by visual inspection of the survival curves for patients with and without meeting the frailty criteria.

Thereafter, we examined whether the three inflammatory markers, vitamin D level, and leucocyte telomere length (independently) predicted mortality using separate Cox-regression models with time to death as the dependent variable (similarly built and checked as the frailty models). Analyses of vitamin D levels, however, were additionally adjusted for season of blood withdrawal. In order to be able to compare the effect size of the different underlying mechanisms, we calculated Z-scores of each variable. Before calculating Z-scores, gait-speed, handgrip strength, hsCRP and IL-6 were log-transformed in order to achieve a normal distribution. For NAGL-2, three outliers were trimmed at 3 times the standard deviation in order to achieve a normal distribution.

Finally, significant inflammatory markers, vitamin D levels, and/or LTL length were added to the final models with frailty as the primary predictor in order to examine whether the strength of the hypothesized association between frailty and mortality was significantly reduced. As a rule of thumb, these variables may be a relevant explanatory factor when the strength between frailty and mortality (B value of the Cox-regression) is reduced by 10% or more. The delta (Δ)B is calculated as the B in the original multivariate Cox-regression model minus the B of frailty when the physiological or cellular marker under study is added divided by the original B and multiplied by 100.

All p-values less than .05 will be considered statistically significant. Analyses will be conducted in SPSS version 25.

Results

Sample - The baseline characteristics of the study sample (n=378) are presented in table 1, stratified by the presence of frailty. Compared to non-frail patients, frail patients were significantly older, less educated, more severely depressed, drank less

alcohol and had more chronic somatic diseases. Both groups did not differ with respect to sex and smoking status.

Table 1 Baseline characteristics, stratified by frailty status

Characteristics		Non-frail depressed patients (n=275)	Frail depressed patients (n=103)	Statistics
Socio-demographics				
• Age (years)	mean (SD)	69.6 (6.9)	73.7 (7.9)	t=-5.0, df=376, p<.001
• Female sex	n (%)	179 (65.1)	71 (68.9)	Chi^2=0.5, df=1, p=.482
• Level of education (years)	mean (SD)	10.7 (3.5)	9.7 (3.2)	t=2.7, df=376, p=.008
Lifestyle characteristics				
• Alcohol use (number of drinks/day)	median (IQR)	0.06 (1.18)	0.03 (0.53)	Z=-2.33, p=.020
• Smoking (yes)	n (%)	75 (27.4)	25 (24.8)	Chi^2=0.3, df=1, p=.611
Psychopathology				
• Depressive symptom severity	mean (SD)	27.5 (12.3)	37.2 (12.4)	t=-6.8, df=371, p<.001
Physical functioning				
• Number of chronic diseases	median (IQR)	2.0 (2.0)	2.0 (2.0)	Z=-2.2, p=.026
• Number of prescribed medications	mean (SD)	4.4 (2.8)	5.5 (3.0)	t=-3.4, df=373, p=.001
Markers of biological aging				
• hsCRP (mg/l)	median (IQR)	1.74 (3.17)	2.17 (3.52)	Z=-1.04, p=.297
• IL6 (pg/l)	median (IQR)	0.49 (1.09)	0.55 (2.26)	Z=-1.46, p=.145
• Lipocalin-2 (ng/l)	mean (SD)	59.9 (21.8)	67.9 (26.1)	t=-3.0, df=367, p=.003
• 25-OH vitamin D (nmol/l)	mean (SD)	54.6 (23.9)	41.7 (24.1)	t=4.2, df=365, p<.001
• Leucocyte telomere length (bp)	mean (SD)	5048 (400)	4990 (392)	t=1.2, df=366, p=.218

Abbreviations: SD, standard deviation; IQR, interquartile range; bp, basepairs.

Frailty and mortality - During the 6-year follow-up, a total of 27/103 (26.2%) frail depressed patients died compared to 35/275 (12.7%) non-frail depressed patients (Chi^2=9.94, df=1, p=.002). Adjusted for covariates, the HR of frailty was 2.43 [95% CI:1.33–4.43], p=.004.

Table 2 presents the association of the different frailty measures with mortality. As shown, all associations between frailty components and mortality point to the same direction, although only the components weight loss and performance based physical frailty reached statistical significance.

Table 2 Association of the different frailty measures with 6-year mortality by separate multivariate statistics (Cox-regression) among depressed patients

Predictors	Unadjusted HR	[95% CI]	p-value	Fully adjusted* HR	[95% CI]	p-value
Fried Frailty Index						
• Frailty, dichotomous	2.14	[1.26 – 3.63]	.005	2.43	[1.33 – 4.43]	.004
• Frailty, number of components	1.29	[1.05 – 1.58]	.014	1.38	[1.06 – 1.78]	.015
Presence of FFI components (yes)						
• Exhaustion	1.27	[0.76 – 2.12]	.368	1.16	[0.66 – 2.02]	.614
• Weight loss	1.74	[1.04 – 2.92]	.035	1.98	[1.15 – 3.41]	.013
• Low physical activity level	1.16	[0.69 – 1.95]	.579	1.11	[0.65 – 1.89]	.710
• Low gait speed	1.50	[0.87 – 2.60]	.145	1.39	[0.74 – 2.61	.310
• Low handgrip strength	1.49	[0.86 – 2.63]	.149	1.35	[0.75 – 2.44]	.314
Frailty proxies, (uni)dimensional						
• Gait speed, log(s)	3.61	[0.92 – 14.1]	.065	3.16	[0.57 – 17.4]	.187
• Handgrip strength, log(kg)	0.93	[0.25 – 3.50]	.911	0.23	[0.04 – 1.26]	.090
Frailty dimensions (PCA)						
• Performance based FFI**	1.30	[1.03 – 1.66]	.029	1.34	[1.00 – 1.80]	.050
• Vitality based FFI**	1.18	[0.92 – 1.52]	.181	1.29	[0.99 – 1.66]	.055

* Adjusted for age, sex, years of education, alcohol use (drinks per day), current smoking (yes/no), depressive symptom severity (IDS sumscore), number of chronic somatic diseases, and number of prescribed medications.

** Performance based FFI was based on three components, i.e. gait speed, handgrip strength and low physical activity, whereas vitality based FFI was based on weight loss and exhaustion. Abbreviations: HR, hazard rate; CI, confidence interval; FFI, Fried Frailty Index; s, seconds; kg, kilogram.

Impact of aging and frailty biomarkers - Except for the level of IL-6, all biomarkers were significantly associated with the mortality rate, although the impact of LTL lost statistical significance in the fully adjusted model. Higher hsCRP and NGAL-2 levels were risk factors for death, whereas higher vitamin D levels and LTL were protective (see table 3).

Adding the biomarkers to the main frailty (presence/absence) model neither changed the hazard rate nor the significance level of the individual physiological and cellular markers. Moreover, none of these markers reduced the association between frailty and mortality by more than 10% (table 3). These findings were confirmed when repeating the analyses with frailty based on the sum score, with one exception, namely that the impact of frailty on death was reduced 13.7% after adding vitamin D level to the model (while frailty also remained significant: $HR_{\text{frailty sum score}}$=1.34 [95% CI:1.03–1.74], p=.032).

Table 3 Separate bi- and multivariate Cox-regression to examine the independent effect of physiological and cellular markers of biological aging*

	Unadjusted analyses			Adjusted analyses** (frailty not included in model)			ΔB of frailty	
Predictors	HR	[95% CI]	p-value	HR	[95% CI]	p-value	Dichotomous	Sum score
Inflammatory markers								
• hsCRP	1.47	[1.14-1.89]	.003	1.41	[1.08-1.83]	.011	+ 2.7 %	- 6.8 %
• Interleukin-6	1.22	[0.94-1.59]	.140	1.12	[0.85-1.48]	.425	+ 0.2 %	- 1.2 %
• Lipocalin-2	1.44	[1.15-1.81]	.002	1.30	[1.00-1.68]	.048	+ 3.0 %	- 2.1 %

	Unadjusted analyses			Adjusted analyses** (frailty not included in model)			ΔB of frailty	
Predictors	HR	[95% CI]	p-value	HR	[95% CI]	p-value	Dichotomous	Sum score
*Vitamin D****								
• 25-OH vitamin D	0.58	[0.42-0.81]	.001	0.60	[0.43-0.85]	.004	- 9.3 %	- 13.7 %
Telomere length								
• Leucocyte telomere length	0.66	[0.49-0.90]	.008	0.73	[0.52-1.03]	.072	+ 0.8 %	- 1.3 %

* All characteristics are expressed as Z-score, to be able to compare the HR of the individual makers.
** Adjusted for age, sex, years of education, alcohol use (drinks per day), current smoking (yes/no), depressive symptom severity (IDS sumscore), number of chronic somatic diseases, and number of prescribed medications.
*** All analysis additionally adjusted for astronomical season.
Abbreviations: HR, Hazard ration; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; ΔB, change in the B of frailty (either dichotomous (yes/no) or sum score of components) after the predictor under study is added to the final multivariate model.

When adding all biomarkers simultaneously to the model, the HR of the presence of frailty hardly changed (ΔB of 6.2%) and the hazard rate remained significant (HR=2.36 [95% CI:1.26–4.43], p=.007). Nonetheless, the hazard rate of the sum score decreased substantially (ΔB=24.5%) and became insignificant (HR=1.29 [95% CI:0.98–1.68], p=.065).

Discussion

In line with a recent meta-analysis on the relationship between frailty and mortality (Vermeiren et al., 2016; Kojima et al., 2018), we showed that physical frailty in late-life depression also predicts mortality over a 6-year follow-up, even when adjusted for depression severity. Therefore, the concept of frailty remains valid in the presence of depression. The impact of frailty on mortality in late-life depression could not be explained by one simple mechanism like low-grade inflammatory

markers, vitamin D level or leucocyte telomere length, but taken together these mechanisms partly mediated the impact of frailty on mortality (Cardoso et al., 2018). As the concept of frailty has been introduced to explain (and identify) older persons at increased risk for disability and death, associations between specific frailty models and death are the ultimate validation of those indices. Indeed, all 19 longitudinal studies included in the meta-analysis on the frailty index according to Rockwood (Rockwood et al., 2005) found a significant association between frailty and mortality (Kojima et al., 2018). The pooled hazard ratio of the Frailty Index (range 0–1) was 1.04 [95% CI:1.03–1.04] per 0.01 point increase (13 studies) or 1.28 [95% CI:1.26–1.31] per 0.1 point increase (6 studies) (Kojima et al., 2018). Comparably, many studies have shown that the Fried Frailty Phenotype is also associated with increased mortality rates (Hanlon et al., 2018), although the impact might be less in patients with neuropsychiatric diseases compared to other chronic disease clusters (Nguyen et al., 2018). This might be explained by overlapping criteria between frailty and (neuro)psychiatric disorders as well as independent associations of dementia, depression and stroke with mortality (Nguyen et al., 2018). Our finding was most robust for the original operationalization of the Fried Frailty Phenotype (especially the number of components met), showing that frailty is more than the sum of its parts. Within the NESDO-study, the mortality rate was significantly higher among depressed patients compared to the non-depressed comparison group (Jeuring et al., 2018). However, when adjusted for demographic, lifestyle and somatic comorbidity, this difference lost significance (van den Berg et al., 2018). Previous studies on the association between depression and mortality have been criticized for incomplete correction for potential confounders (Miloyan et al., 2017).

Frailty is supposed to result from many different pathophysiological mechanisms (Cardoso et al., 2018). In this study, we have examined whether three of these potential mechanisms may explain the increased mortality rate associated with frailty, i.e. immunosenescence, vitamin D deficiency and shortened LTL.

Of the three inflammatory markers, increased hsCRP and NGAL-2 levels were independent predictors of mortality in our sample. Immunosenescence manifests itself by a decline of B- and T-cell function and an impaired response to chronic antigenic stimuli (Grolleau-Julius et al., 2010). Paradoxically, it creates a condition of chronic low-level inflammation, also called "inflamm-ageing" (Grolleau-Julius et al., 2010), and characterized by elevated levels of the inflammatory cytokine interleukin 6 (IL-6) and the non-specific acute phase reactant CRP (Moshage, 1997). Both frailty and depression have been associated with higher serum levels of CRP and IL-6 (Howren et al., 2009), albeit frailty more consistently compared to depression (Soysal et al., 2016). Previously, we have shown that physical frailty is associated with low-graded inflammation in late-life depression (Arts et al., 2015).

We found that shorter LTL was associated with mortality in our sample, although, this effect was lost after correction for lifestyle and somatic disease burden. Telomere length, as a marker of cellular aging, has been associated with increased mortality rates and the onset of various age-related diseases. With each cell division some telomeric DNA is lost, leading to apoptosis when a critical length is reached. Next to replication, endogenous factors may also cause telomere shortening, including inflammation, metabolic dysregulation and oxidative stress (Garcia-Rizo et al., 2013). These mechanisms become more prominent with chronological aging. Shortened LTL is also consistently associated with depression earlier in life (Verhoeven et al., 2014), but the association seems to be lost in older age samples (Schaakxs et al., 2015). Thus far, the limited studies did report no or only a weak association between telomere length and frailty (Arts et al., 2018), which is in line with the lack of any association between LTL and mortality in our sample.

In our study, higher vitamin D levels were protective for death. One of the key features of frailty, and a potential link with vitamin D deficiency, is the loss of skeletal muscle or sarcopenia (Fried et al., 2001). In older persons, a consistent relationship between hypovitaminosis D and muscle dysfunction has been demonstrated, as well

as a positive effect of vitamin D supplementation on balance and muscle strength (Muir & Montero-Odasso, 2011). A recent dose-response meta-analysis showed an association between low-levels of vitamin D and higher risk for frailty (Ju et al., 2018). Although frailty-experts consider vitamin D supplements useful for frail persons who are vitamin D deficient (Morley et al., 2013), intervention studies into the effect of vitamin D supplementation on frailty are currently lacking (Bruyère et al., 2017). Previously, we have shown that physical frailty in late-life depression is associated with low vitamin D levels (van den Berg et al., 2018). Moreover, low vitamin D levels are consistently associated with (late-life) depression (van den Berg et al., 2018), although causality has been questioned and they are merely seen as a marker of poor health (van den Berg et al., 2016). In line with this latter assumption, we found that lower vitamin D partly mediates the association of frailty with mortality in late-life depression. This suggests that randomized controlled trials of vitamin D supplementation in late-life depression should have mortality as an end point instead of improvement of depressive symptoms.

For proper interpretation, some methodological issues need to be addressed. Strengths of this study are the relatively large sample of patients with a confirmed depressive disorder as well as the comprehensive assessment of depression characteristics and confounding factors. However, some limitations should also be acknowledged. First of all, the Fried Frailty Phenotype (Fried et al., 2001) has been criticized for taking little account on variables including cognitive and emotional domains in the older adult. However, using the Fried criteria for studying frailty in a psychiatric sample enables us to disentangle mental disorders, cognitive aging and physical frailty. Moreover, the frailty phenotype is a well validated instrument and is widely used in frailty research (Buta et al., 2016). Secondly, we did not have access to causes of death. On one hand, inclusion of only older adults who deceased from frailty-related causes in the sensitivity analyses would have led to more accuracy. On

the other hand, even if causes of death are known, it is arbitrarily which causes of death should be considered frailty-related.

Although physical frailty may partly overlap with the criteria of a depressive disorder, the Fried Frailty Phenotype remains a valid concept, as it is associated with biomarkers of aging, and predictive of mortality. Of the mechanisms explored in the present study, especially low vitamin D levels seem to explain the association between frailty and mortality. This may argue for vitamin D supplementation in late-life depression, even though vitamin D augmentation has no additive effect on the improvement of the depressive disorder. However, in light of the many mechanisms underlying frailty, we should adopt a wider range of interventions when targeting frailty in late-life depression.

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