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

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# Chapter VIII

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The impact of frailty on depressive disorder in later life: Findings from the Netherlands Study of depression in older persons

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## **Abstract**

*Background* - Physical frailty and depressive symptoms are reciprocally related in community-based studies, but its prognostic impact on depressive disorder remains unknown.

*Methods* - A cohort of 378 older persons ( $\geq 60$  years) suffering from a depressive disorder (DSM-IV criteria) was reassessed at two-year follow-up. Depressive symptom severity was assessed every six months with the Inventory of Depressive Symptomatology, including a mood, motivational, and somatic subscale. Frailty was assessed according to the physical frailty phenotype at the baseline examination.

*Results* - For each additional frailty component, the odds of non-remission was 1.24 [95% CI=1.01-1.52] ( $p=.040$ ). Linear mixed models showed that only improvement of the motivational ( $p<.001$ ) subscale and the somatic subscale ( $p=.003$ ) of the IDS over time were dependent on the frailty severity.

*Conclusions* - Physical frailty negatively impacts the course of late-life depression. Since only improvement of mood symptoms was independent of frailty severity, one may hypothesize that frailty and residual depression are easily mixed-up in psychiatric treatment.

## Introduction

Depressive disorder is a highly prevalent condition among older persons, with pooled prevalence rates of 1.8% for independently living persons aged 55 years and over (Beekman et al., 1999), and 7.2% for persons aged over 75 years irrespective of their living arrangement (Luppa et al., 2012). Depression in later life constitutes an important worldwide health issue due to its chronic course with high recurrence and relapse rates (Cole et al., 1999; Mathers & Loncar, 2006). In the Netherlands Study of Depression in Older Persons (NESDO) it was previously found that after two years, 48% suffered from a depressive disorder and that 61% had a chronic course of depression (Comijs et al., 2015). Diagnosis of depression is often complicated by the presence of somatic comorbidity, pain and frailty (Mezuk et al., 2012; Penninx et al., 2013; Hanssen et al., 2014). To optimize treatment of late-life depression, understanding the processes involved in the course of this mental illness is essential. In an overview of evidence-based practices, the most extensive research support was found for the effectiveness of pharmacological and psychosocial interventions for the treatment of late-life depression (Bartels et al., 2002). Aspects such as comorbid somatic diseases and (potentially modifiable) frailty have not been incorporated in evidence-based anti-depressant treatment strategies. An important step would be to identify risk factors that predict an unfavorable course of depression. To date, only a few studies investigated risk factors of an adverse course of late-life depression. Known risk factors are higher severity of depressive symptoms, higher number of previous episodes, later age of onset, cognitive decline and medical comorbidity (Alexopoulos et al., 1996; Alexopoulos et al., 2000). Frailty may be an additional risk factor (Feng et al., 2014; Collard et al., 2015).

Frailty is a condition of increased risk of adverse health outcomes (Fried et al., 2001). In a recent consensus meeting it has been concluded that physical frailty is an important medical syndrome with multiple causes and contributors (Morley et al., 2013). The physical frailty phenotype is defined as the presence of three or more of

the following five characteristics: weight loss, weakness, slowness, exhaustion and low activity level (Fried et al., 2001). The dimensional nature of frailty is acknowledged by including a prodromal frailty state in this definition; prefrailty, which is defined as the presence of only one or two of the characteristics. When no frailty characteristics are present an older person is classified as robust (Fried et al., 2001). Meta-analytic research has shown that approximately one out of ten persons over 65 years can be classified as physically frail (Collard et al., 2012). Remarkably, the hallmark study of Fried and colleagues (Fried et al., 2001), developing the physical frailty phenotype, excluded patients with depression and/or on antidepressant treatment. The authors wanted to preclude that persons were classified physically frail on the presence of one disorder only. Recently, we showed that more than a quarter of clinically depressed older persons fulfill criteria for physical frailty (Collard et al., 2014). As this proportion is comparable to chronic somatic diseases, it simply implies that frailty deserves a similar level of attention in geriatric psychiatry as in chronic somatic diseases.

The association between physical frailty and depressive symptoms in the population is assumed to be bidirectional (Mezuk et al., 2012; Collard et al., 2014). This leads to the question whether frailty and late-life depression are causal factors for each other, or whether they share the same underlying mechanisms that may also influence the presentation of one another. Suggestions for the latter hypothesis involve both psychosocial factors and stress-related pathophysiological dysregulations (Feng et al., 2014). On the other hand, three longitudinal studies in the general population have identified physical frailty as an independent predictor of the increase and protracted course of depressive symptoms (Feng et al., 2014; Collard et al., 2015; Makizako et al., 2015), while one study showed that depression is a predictor of incident frailty (Lakey et al., 2012). Because these studies focused on depressive symptoms instead of a depressive disorder according to DSM criteria, results may be confounded by overlap between self-report depressive symptoms

and signs of frailty. Moreover, these community-based findings cannot be extrapolated to a psychiatric population. Latent class analyses on the individual components of physical frailty and DSM-IV criteria for major depressive disorder also showed that physical frailty and major depressive disorder identify the same set of persons, especially among those suffering from severe depression (Mezuk et al., 2013). Nonetheless, these analyses also pointed to a cluster of patients suffering from either physical frailty or depression alone. This has led to the conclusion that the most appropriate model for understanding the depression – frailty association is one of comorbidity (Mezuk et al., 2013). The next step would be to assess frailty and the course of depression in a clinically depressed sample.

The first objective is to examine whether physical frailty predicts non-remission of depressive disorder over a two-year follow-up. The second objective is to examine whether physical frailty is associated with an adverse course of depressive symptoms over time.

Hypothesizing a negative effect of physical frailty on depression outcome, we expect lower remission rates at follow-up and a worse course of depressive symptoms over time among those who are physically frail.

## Methods

Study participants came from the NESDO (Comijs et al., 2011), an ongoing cohort study aimed at examining the long-term course and consequences of depressive and anxiety disorders in older persons (aged  $\geq 60$  years). Recruitment of depressed older persons took place in five regions in The Netherlands from both mental health institutes (in- and outpatients) and from primary care in order to include persons with late-life depression in various developmental and severity stages. The NESDO study has included a total of 378 depressed subjects (age range: 60 through 93 years) who suffered from a current DSM-IV diagnosis of major depressive disorder (95%), dysthymia (26.5%), or minor depression (5.6%), of which 26.5% have two types of

depressive disorders. Persons with a primary diagnosis of dementia, a Mini Mental State Examination-score (MMSE) under 18 or an organic or psychotic disorder were excluded, since the course of these persons will be largely determined by the primary disorder. Insufficient mastery of the Dutch language was another exclusion criterion. All participants were competent to consent to participation and all gave written informed consent. The ethical review boards of the participating institutes approved of this study. More detailed information about the NESDO is described elsewhere (Comijs et al., 2011; Comijs et al., 2015).

Data collection included an examination at one of the participating clinics or at the homes of the participants, including a structured diagnostic interview, physical tests (such as blood pressure and gait speed), and paper and pencil questionnaires. These assessments were conducted at baseline as well as after two years follow-up (Comijs et al., 2015). The course of late-life depression was followed up every six months by means of a postal assessment (five questionnaires were sent during the two years follow-up), including questionnaires on the severity of depressive symptoms and physical health in the past six months.

Because 93/378 (24.6%) dropped out before the two-year follow-up assessment, this study consisted of 285 eligible participants. Persons that were lost to follow-up had lower cognitive functioning (MMSE score 27.2 versus 27.9,  $p=.014$ ) and more frailty characteristics (2.2 versus 1.7,  $p=.002$ ) than the persons that did participate in the two-year follow-up. No baseline differences with regard to age, gender, educational level, severity of depression, number of diseases and use of antidepressants were found between persons that participated in follow-up and persons that did not participate in follow-up.

### *Measures*

*Depression* - The Composite International Diagnostic Interview (CIDI), version 2.1 was used in order to determine the presence of depression at baseline, as well as at

two years follow-up (WHO, 1997). The CIDI is a structured interview that assesses psychiatric disorders in adults according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). To determine the research DSM-IV diagnosis of current minor depression, questions were added to the CIDI, as in the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008). Non-remission at two-year follow-up was defined as neither major depression or dysthymia in the past six months, nor minor depression in the past month. Severity of depression was measured by the well-validated 30-item self-rating Inventory of Depressive Symptoms 30 item version (IDS) (Rush et al., 1986). In the IDS, items are scored on a four-point scale, with each item equally weighted and summed up to a total score. IDS scores range from 0-84 points, with higher scores indicating more severe depression. In older persons, the IDS has three subscales, reflecting a mood-, motivation-, and somatic dimension of depression (Hegeman et al., 2012).

*Frailty* - Physical frailty was operationalized by the following five criteria of Fried et al. (Fried et al., 2001):

- A six-meter walking test was used to assess *slowness*. For men  $\leq 173$  centimetres (cm) tall the cut off time was 9 seconds, for men  $> 173$  cm the cut off time was 8 seconds. The cut off time for this criterion for women with a height of  $\leq 159$  cm was 9 seconds, for women  $> 159$  cm the cut off time was 8 seconds (extrapolated from the data of Fried and colleagues) (Fried et al., 2001).
- The self-administered version of the International Physical Activities Questionnaire (IPAQ) (Craig et al., 2003), was used to collect *physical activity* data over the last seven days. *Low physical activity level* was defined as no daily

activities such as walking and gardening, or the performance of sports less than once weekly.

- The CIDI question about *unwanted weight loss* was used to determine the loss of a minimum of one kilogram a week, during two or more consecutive weeks. Body Mass Index (BMI) was defined as weight in kilograms divided by height in meters squared. With a BMI of  $<18.5 \text{ kg/ m}^2$  weight loss was also considered to be present. The presence of unintentional *weight loss* or low body mass index was used for the weight loss criterion.
- Two questions from the IDS (Rush et al., 1986), about energy level and leaden paralysis/physical energy were used to determine *exhaustion*. Participants confirming the presence of low energy level or leaden paralysis by answering positive on one or both of these two questions were categorized as exhausted.
- A handgrip dynamometer was used to assess muscle *weakness*. Participants were asked to perform two squeezes with the dynamometer, using the dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Cut off scores were stratified by gender and BMI quartiles according to Fried (Fried et al., 2001). Participants unable to perform the test were also considered weak.

To be consistent with the frailty literature, we used the number of criteria present (range 0 – 5) as the primary variable of interest. For clinical interpretation, a frailty score of 0 is considered robust; a score of 1 or 2 is considered prefrail whereas a score of 3 or more is considered physical frail. Since we previously showed that physical frailty in late-life depression may not be unidimensional (Arts et al., 2015), we also examined the impact of performance-based physical frailty (based on slowness, weakness, low physical activity) and vitality based physical frailty (based

on exhaustion and weight loss), as well as the impact of the individual components of frailty.

### *Covariates*

*Demographics* - Demographic data were collected during the baseline assessment (age, gender, and educational level). Global cognitive functioning was assessed by the MMSE (Folstein et al., 1975). MMSE score (range 0-30) will be used as a continuous variable, with higher scores indicating better cognitive functioning (Saunders et al., 1993).

*Multimorbidity* - Multimorbidity was assessed using a self-report questionnaire about the presence of somatic diseases (lung disease, cardiovascular disease, diabetes, arthritis, rheumatism, cancer, ulcer, intestinal disorder, liver disease, epilepsy, allergy, thyroid gland disease and (head) injury), as originally developed by Statistics Netherlands (Centraal Bureau voor de Statistiek, [www.cbs.nl](http://www.cbs.nl)). This questionnaire has high accuracy for chronic somatic disease as previously reported (Kriegsman et al., 1996). Multimorbidity was considered present when >1 somatic disease was reported.

*Health indicators* - Health indicators included smoking status, use of alcohol and the number of somatic diseases present. Smoking status was divided into two categories: non-smoker and current smoker. The Alcohol Use Disorder Identification Test (AUDIT) is designed to detect hazardous and harmful alcohol consumption (Saunders et al., 1993). AUDIT score was used as a continuous score (range 0-40).

*Antidepressants* - Antidepressant use was determined by inspection of the medication containers and classified according to the Anatomical Therapeutic Chemical (ATC) classification (WHO, 2010). The use of either selective serotonin

reuptake inhibitors (SSRIs; ATC code: N06AB), or tricyclic antidepressants (TCAs; ATC code: N06AA), or other antidepressants were dichotomized into yes/no.

*Statistical analyses* - Baseline demographics and clinical characteristics of the depressed participants were compared using one-way ANOVA's for continuous variables and  $\chi^2$  tests for categorical variables.

Logistic regression analyses were used to assess whether the different frailty indicators at baseline (predictor) were associated with non-remission of depression during follow-up (dependent variable). The frailty sum score analyses (range 0 -5) were considered the primary analyses. All analyses were performed unadjusted, and subsequently adjusted for socio-demographics (age, gender, education), health indicators (MMSE score, smoking status, alcohol use and number of somatic diseases) and use of antidepressants. Multi-collinearity of variables included in the final model was tested with correlation matrices. Only between frailty and baseline severity of depression (IDS score) borderline collinearity was detected (correlation: 0.48). No correction for baseline severity of depression was made to avoid overcorrection.

Fully adjusted linear mixed models were used to examine the association between frailty (predictor) and severity of depression (IDS total score) during five time points (dependent variable). These analyses were repeated with the three IDS subscale scores (Hegeman et al., 2012). Frailty and all covariates were entered as fixed factors. Subjects were treated as random factors. The interaction term frailty by time was added to the final model to assess whether the course of depression differed according to the level of frailty.

When estimated mean scores of depression severity and depressive subscales were calculated, frailty was used as a nominal variable with three categories (robust, prefrail and frail) for graphical purposes. In all other analyses the frailty sum score

was used as a continuous variable (primary variable) as well as the two frailty dimensions (post-hoc analyses).

All p-values were tested two-tailed and p values  $\leq .05$  were considered statistically significant. Data were analysed using Statistical Package of the Social Sciences (SPSS), version 20.0.

## Results

The mean age of the participants was 70.7 (SD=7.4) years and 66.1% was female. One participant had more than two missing items on the frailty count and was therefore considered missing. Five participants had missing data on one of the covariates and were removed from the analytical sample (n=280). Baseline characteristics of the remaining 280 participants are shown in table 1. Group differences between the frail, prefrail and robust groups were found with respect to age, cognitive functioning, alcohol use, presence of multimorbidity, severity of depression and presence of all five separate frailty components.

**Table 1** Sample characteristics of depressed patients at baseline (N=280)

Characteristics	Frail (N=74, 26.4%)	Prefrail (N=157, 56.1%)	Robust (N=49, 17.5%)	P Value <sup>a</sup>	Post-hoc analysis (p $\leq$ .05) <sup>b</sup>
• Age, mean (SD), y	73.4 (8.1)	69.6 (6.8)	69.0 (6.9)	<.001	1>2, 1>3
• Female gender, %	73.0	61.8	65.3	.249	
• Education, mean (SD), years	9.9 (3.1)	10.8 (3.6)	11.0(3.4)	.131	
• MMSE score, mean (SD)	27.4 (2.1)	28.0 (1.7)	28.1 (1.5)	.016	1<2
• Smoker, %	20.3	28.0	18.4	.250	
• Alcohol use, mean AUDIT score (SD)	1.8 (2.8)	2.6 (3.1)	4.0 (5.0)	.002	1<3, 2<3
• Multimorbidity, %	56.8	42.0	32.7	.022	1>2, 1>3
• IDS score, mean (SD)	37.5 (12.4)	29.5 (11.8)	19.3 (7.5)	<.001	1>2, 1>3, 2>3
• <i>Antidepressant use</i>				.195	
• TCA, %	17.6	19.1	14.3		
• SSRI, %	31.1	24.8	16.3		
• Other, %	32.4	26.8	28.6		
• None, %	18.9	29.2	40.8		

Characteristics	Frail (N=74, 26.4%)	Prefrail (N=157, 56.1%)	Robust (N=49, 17.5%)	P Value <sup>a</sup>	Post-hoc analysis (p≤.05) <sup>b</sup>
<i>Frailty components</i>					
• Weight loss, %	56.8	34.4	0	<.001	1>2, 1>3, 2>3
• Weakness, %	64.9	8.2	0	<.001	1>2, 1>3, 2>3
• Slowness, %	57.5	15.9	0	<.001	1>2, 1>3, 2>3
• Exhaustion, %	91.9	54.1	0	<.001	1>2, 1>3, 2>3
• Low physical activity level, %	74.3	32.0	0	<.001	1>2, 1>3, 2>3

Abbreviations: IDS, Inventory of Depressive Symptomatology; MMSE, Mini Mental State Examination; WHODAS, WHO-Disability Assessment Schedule; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup> Overall group differences. Comparison using ANOVA (continuous variables) and  $\chi^2$  statistics (categorical variables).

<sup>b</sup> Groups in post-hoc analysis noted as: 1= frail group, 2= prefrail group, 3= robust group.

*Depression diagnosis after two years* - A total of 141/280 participants achieved a full remission at the two-year follow-up. Of the 137 non-remitted patients at two-year follow-up, 43.8% suffered from double depression (major depression and dysthymia), 39.4% from major depressive disorder, 8.8% from dysthymic disorder, and 8.0% from minor depressive disorder.

Frail depressed patients achieved 2-year remission significantly less often compared to their prefrail and robust counterparts (55.4% versus 51.6% versus 30.6%,  $\chi^2=8.3$ ,  $df=2$ ,  $p=.016$ ). Adjusted for covariates, the odds ratio (OR) for non-remission was 1.24 [95% CI: 1.01-1.51] per additional frailty component ( $p=.041$ , see table 2). The performance-based dimension of frailty was associated with non-remission of depression (OR [95%CI] 1.40 [1.07, 1.85],  $p=.015$ ). The vitality-based dimension of frailty was negatively associated with non-remission of depression (OR[95%CI] 0.63 (0.49, 0.82),  $p=.001$ ).

With regard to the five frailty components, only exhaustion and low physical activity level at baseline were significantly associated with depression diagnosis after two years.

**Table 2** Logistic Regression Analysis of the Association Between Frailty and Depression Diagnosis After Two Years of Follow-up

Characteristics (N= 280)	OR (95% CI)	P Value
<i>Frailty (number of components):</i>		
• Unadjusted	1.23 (1.02, 1.49)	.028
• Adjusted <sup>a</sup>	1.24 (1.01, 1.52)	.040
<i>Frailty (three categories)<sup>a</sup></i>		
• Frailty	2.66 (1.17, 6.02)	.019
• Prefrailty	2.36 (1.16, 4.80)	.017
• Robust	Reference	
<i>Frailty dimensions<sup>a</sup></i>		
• Performance-based	1.40 (1.07, 1.85)	.016
• Vitality-based	0.63 (0.49, 0.82)	.001
<i>Individual frailty components<sup>a</sup>:</i>		
• Weight loss	0.73 (0.44, 1.23)	.239
• Weakness	1.10 (0.61, 1.99)	.762
• Slowness	1.61 (0.86, 3.03)	.137
• Exhaustion	1.97 (1.19, 3.26)	.008
• Low physical activity level	1.84 (1.10, 3.06)	.020

<sup>a</sup> Adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use, multimorbidity and use of antidepressants.

*Chronicity of depressive symptoms* - The severity of frailty at baseline was associated with higher depressive symptom scores over the whole follow-up period, also after adjusting for socio-demographics and health indicators simultaneously (table 3). When subscales of the IDS were analyzed (mood, motivation and somatic subscale), frailty was associated with higher severity over the two-year follow-up on all three subscales (table 3). Repeating the analyses with the two frailty dimensions, showed that performance-based physical frailty revealed significant results in the same direction of the overall frailty measures.

**Table 3** Linear Mixed Model Analysis of the Longitudinal Association Between Number of Frailty Components and Depressive Symptoms<sup>a</sup>, and Depressive Symptoms Subscales<sup>a</sup>

Characteristics (N=280)	Depressive Symptoms		Mood Subscale		Motivation Subscale		Somatic Subscale	
	$\beta$ (SE)	P Value	$\beta$ (SE)	P Value	$\beta$ (SE)	P Value	$\beta$ (SE)	P Value
<i>Frailty</i>								
• Unadjusted	3.51 (0.48)	<.001	1.10 (0.19)	<.001	0.61 (0.11)	<.001	1.09 (0.16)	<.001
• Adjusted <sup>b</sup>	3.34 (0.51)	<.001	1.13 (0.20)	<.001	0.63 (0.11)	<.001	0.96 (0.16)	<.001
<i>Frailty dimensions<sup>b</sup></i>								
• Performance-based <sup>b</sup>	3.57 (0.69)	<.001	1.23 (0.27)	<.001	0.65 (0.15)	<.001	1.08 (0.22)	<.001
• Vitality-based <sup>b</sup>	-2.04 (0.65)	.002	-0.78 (0.25)	.003	-0.61 (0.14)	<.001	-0.19 (0.21)	.361

<sup>a</sup> Measured every six months during two years (five time points).

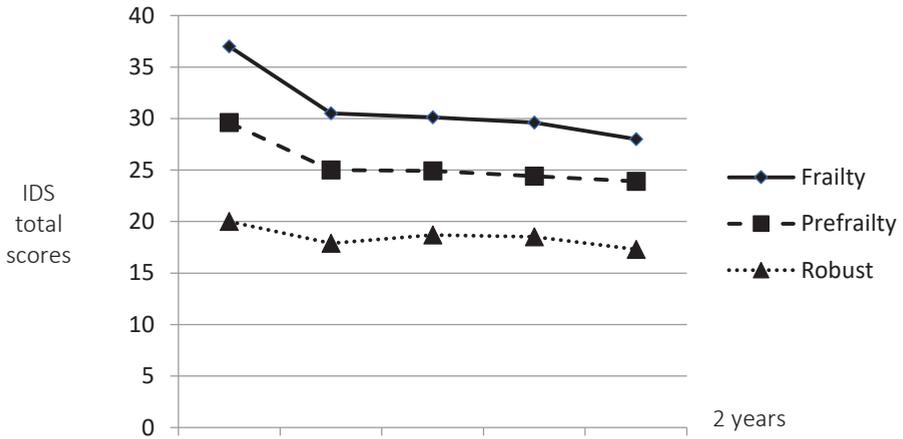
<sup>b</sup> Adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use, multimorbidity and use of antidepressants.

A significant interaction effect of frailty with time was found ( $p < .001$ ), implying that the course of depressive symptoms differs according to frailty status at baseline. Figure 1 presents the course of depressive symptoms graphically for robust (score 0), prefrail (score 1 or 2) and frail (score  $\geq 3$ ) depressed older persons. Figure 1A shows that robust persons have rather consistent depressive symptom levels over time, in contrast to prefrail and frail depressed persons who show persistent elevated levels of depressive symptoms despite higher symptom reduction over two years.

Mood symptoms of depression reduced equally over the two-year follow-up for all categories of frailty in depressed older persons (figure 1B,  $p$ -value of frailty by time interaction is .197). A higher level of frailty predicted more decline of motivational and somatic symptoms of depression (figures 1C and 1D,  $p$ -values of frailty by time interaction are  $< .001$  and .300, respectively).

**Figure 1** Course of estimated mean scores of depressive symptoms (A) and depressive symptoms subscales: mood (B), motivation (C) and somatic (D) over two years for robust (score 0), prefrail (score 1 or 2) and frail (score  $\geq 3$ ) depressed older persons (N=280)<sup>a, b</sup>

**Figure 1 A** Course of depressive symptoms

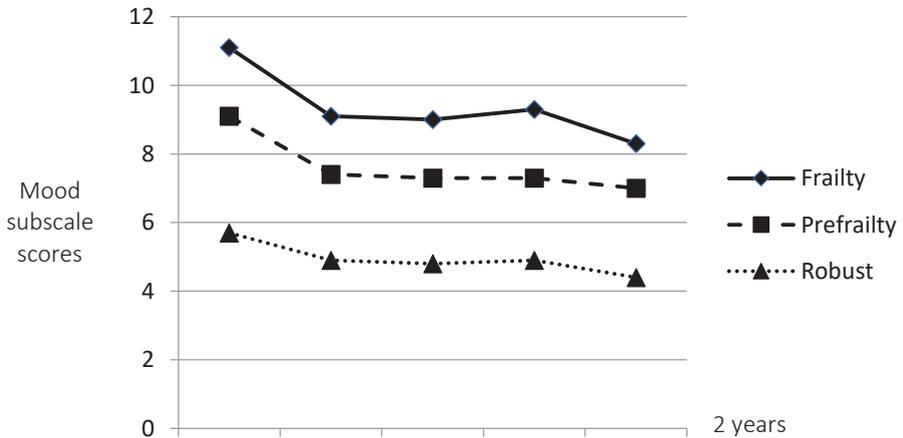


<sup>a</sup> Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use, multimorbidity and use of antidepressants.

<sup>b</sup> Interaction effect frailty\*time:  $p=.001$ .

Abbreviation: IDS, Inventory of Depressive Symptomatology

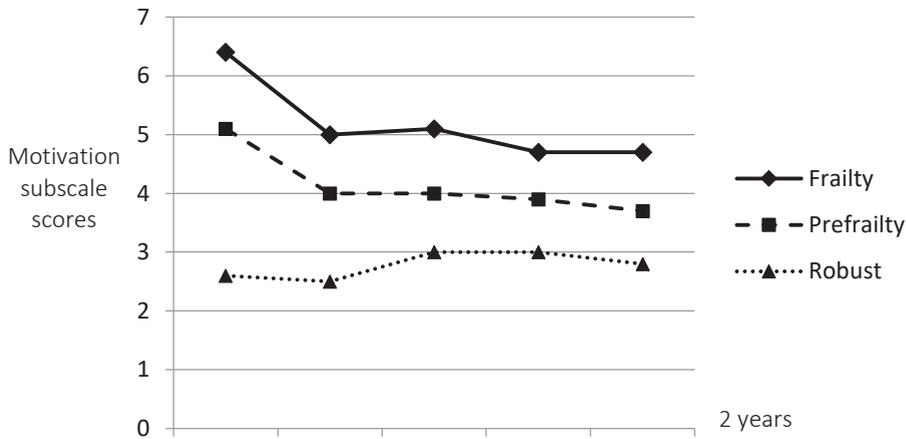
**Figure 1 B** Course of depressive symptoms subscales: mood



<sup>a</sup> Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use, multimorbidity and use of antidepressants.

<sup>b</sup> Interaction effect frailty\*time:  $p=.197$ .

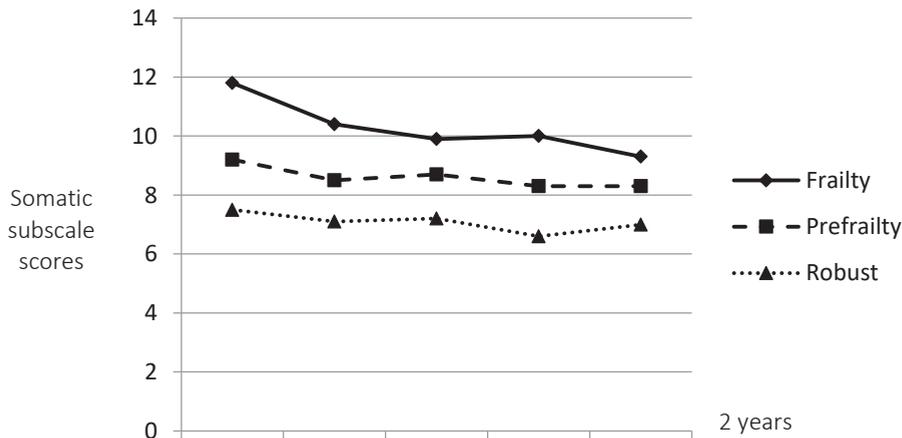
**Figure 1C** Course of depressive symptoms subscales: motivation



<sup>a</sup> Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use, multimorbidity and use of antidepressants.

<sup>b</sup> Interaction effect frailty\*time:  $p < .001$ .

**Figure 1D** Course of depressive symptoms subscales: somatic



<sup>a</sup> Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use, multimorbidity and use of antidepressants.

<sup>b</sup> Interaction effect frailty\*time:  $p = .003$ .

Of the two frailty dimensions, only performance-based dimension of frailty predicted an adverse course of depressive symptoms over two years, and a non-significant result for the vitality-based frailty dimension (data not shown).

## Discussion

*Main findings-* The present study, to our knowledge, is the first to examine the longitudinal association between physical frailty and the course of depression in a sample of clinically depressed older persons. Our results confirm that late-life depression is a highly persisting disorder with half of the patients not achieving remission at two-year follow-up. In line with our hypothesis, a higher level of physical frailty predicted non-remission of depression at two-year follow-up. Physical frailty was also associated with a higher level of depressive symptoms over time. In contrast to our hypothesis, a higher level of frailty predicted more decline in depression severity over time. This finding was driven by the motivational and somatic symptoms of depression, which may point to some overlap between both syndromes, as has been remarked before (Mezuk et al., 2013; Lohman et al., 2016). Of the individual frailty components, only the presence of exhaustion and a low physical activity level predicted non-remission of depression at two years. Since physical frailty might not be a uni-dimensional concept in a depressed population (Mezuk et al., 2013; Arts et al., 2015), we also examined the two frailty dimensions as identified previously in our population (Arts et al., 2015). Higher scores on the performance-based dimension of frailty predicted non-remission of depression, while opposite effects were found for the vitality-based dimension of frailty. This latter result puzzled us, but a possible explanation might be that the vitality-based dimension of frailty reflects a classic, uncomplicated clinical depression. This kind of depression may be more amendable by treatment than the type of depression that is complicated by underlying physical vulnerability as measured by the performance-based dimension of frailty.

The linear mixed models, however, showed that only the performance-based dimension of frailty predicted a different course of depressive symptoms over two years. This result is fully in line with the primary outcome on the main physical frailty

measure. Collectively, these results further substantiate that in a depressed population frailty is best represented by the performance-based dimension of frailty.

*Comparison with literature* - Our results are in line with findings from a recent literature review on the relation between frailty and depression, that finds that in all prospective studies, frailty is a predictor of (persistence of) depressive symptoms (Mezuk et al., 2012). However, previous studies mainly defined frailty as activities of daily living (ADL) indices or used a simplified proxy for frailty, such as gait speed. Results from that same review suggest a bidirectional relation between frailty and depression, which might imply a vicious frailty-depression circle. More recently, three longitudinal studies, not included in this review, showed that physical frailty was a predictor of incident depressive symptoms as well as a protracted course of depressive symptoms in community-dwelling older adults (Feng et al., 2014; Collard et al., 2015; Makizako et al., 2015). Our study extends these findings to a clinical population suffering from depressive disorder, emphasizing the importance of physical frailty for geriatric psychiatry.

In our clinically depressed sample, physical frailty was associated with higher depressive symptom severity over the two-year follow-up. Interestingly, motivational and somatic symptoms of depression decline faster with increasing frailty, an effect not found with respect to the mood symptoms of depression. These findings may point to an aggravation of frailty-related motivational and somatic depressive symptoms at baseline as measured by the inventory of depressive symptoms (IDS). However, despite the faster decline of motivational and somatic symptoms over time, depressed patients with physical frailty still suffered from a higher level of motivational and somatic depressive symptoms at the two-year follow-up.

In clinical practice, remaining symptoms will often be regarded as residual depressive symptoms that need further (intensifying of) psychiatric treatment.

However, our results suggest that these symptoms might also be accounted to frailty. If true, these symptoms may alert clinicians to the vulnerability of these patients, and warrant more aggressive treatment of depression in order to reduce risk of the adverse effects attributable to depression and frailty. These results imply that assessment of physical frailty at the start of and during the treatment of the depression may guide treatment choices. Persons suffering from this type of frailty-depression might be eligible for integrated care, targeting both frailty and depression.

Interventions on reducing frailty could be promising, because previous research shows that frailty is a reversible condition (Woods et al., 2005) that can be treated with assistance in daily living, vitamin D supplementation, protein enriched diet, and improving exercise frequency (Chang et al., 2010; Markle-Reid et al., 2011; Rolland et al., 2011; Theou et al., 2011; Singh et al., 2012;). Furthermore, polypharmacy is recognized as a major contributor to the pathogenesis of frailty, and evaluation of inappropriate medication use seems beneficial for frailty status, as well as health care costs (Morley et al., 2013). Growing evidence suggests the effectiveness of these interventions not only for frailty, but also for the treatment of depression (Penninx et al., 2013; Milaneschi et al., 2014). Since late-life depression and frailty frequently co-occur, these interventions may be particularly beneficial for the frailty-depressed subgroup (Mezuk et al., 2012; Penninx et al., 2013; Hanssen et al., 2014). Underlying mechanisms of the association between frailty and depression may include inflammatory processes, sarcopenia, and lifestyle factors such as smoking and lack of exercise, as these have all been associated with both frailty and depression (Cesari et al., 2004; Leng et al., 2007; Kim et al., 2011; Penninx et al., 2013; Cesari et al., 2014). Since the analyses in this study were corrected for smoking and somatic comorbidity, a possible explanation for the chronic course of depression in the case of co-existing frailty could lie in the hampering effect of frailty-induced inflammation and sarcopenia on the recovery from late-life depression. Previous

studies have shown the negative effect of inflammation and sarcopenia on the course of depression (Kim et al., 2011; Penninx et al., 2013).

*Methodological considerations* - This study has some important strengths. We prospectively examined whether frailty predicted a chronic course of depression. Furthermore, we included a sample of older persons with a DSM-IV confirmed depression diagnosis, contrary to previous studies that used self-report questionnaires as an indicator of depression status (Mezuk et al., 2013; Feng et al., 2014; Collard et al., 2015; Makizako et al., 2015). In addition to the formal depression diagnosis, this study used a well-validated measure of severity of depressive symptoms (IDS) that included symptom profiles of depression, in order to perform in-depth analysis of the associations that were found between frailty and depression diagnosis after two years.

A limitation of this study is the naturalistic aspect of the cohort, in which some differentiation was made between the types of treatment that depressed older persons received. It is not certain whether the treatment that persons received was the most appropriate treatment. Although the analyses were adjusted for antidepressant drug use, we cannot fully exclude the possibility that frail patients would have received a different kind of treatment that might have resulted in confounding by indication. This is an important topic for future research. Finally, those who dropped out had significantly higher frailty scores at baseline. This may have biased our results towards an underestimation of the association between frailty and depression at follow-up. The most important limitations, however, may be that we still cannot disentangle symptoms of frailty and symptoms depression definitively, as both constructs share overlapping diagnostic criteria and have been measured at the same time. Since the problem of overlapping criteria is especially relevant when applying a self-report depressive symptom severity scale, we did not adjust our analyses for baseline depression severity. In our sample, the frailty sum

score indeed significantly correlated with the IDS sum score ( $r=0.48$ ,  $p<.001$ ) which would inevitably lead to overcorrection. These limitations deserve more attention in clinical practice since attributing weight loss and exhaustion to frailty may result in opposite treatment choices than when the residual symptoms are attributed to depression.

*Clinical implications* - In closing, our results clearly show that depression with comorbid frailty is less likely to resolve than depression unaccompanied by frailty. Taking previous studies into account, it seems that frailty and depression are intertwined and that frailty contributes to a chronic, more severely depressed subtype. Frailty and depression might thus stimulate each other's occurrence, but once both are present, multiple interactive processes may arise, worsening the depression as well as the frailty status more and more (Barry et al., 2011; Mezuk et al., 2012; Mezuk et al., 2013). This indicates that frailty may be an important element in the treatment of late-life depression and that multi-faceted interventions are needed for this particularly vulnerable subgroup.

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