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

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# Chapter IV

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## Vitamin D deficiency and course of frailty in a depressed older population

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## **Abstract**

*Objective* - To study the association between vitamin D levels and frailty, its components and its course in a depressed sample.

*Methods* - Baseline and two-year follow-up data from the depressed sample of the Netherlands Study of Depression in Older persons (NESDO), a prospective observational cohort study, were analyzed. The 378 participants were aged 60-93, and had a diagnosis of depression according to DSM-IV criteria. Frailty was defined according to Fried's physical phenotype. 25-OH vitamin D measurement was performed by liquid chromatography – tandem mass spectrometry. Linear and logistic regression analyses were performed, adjusted for covariates.

*Results* - A cross-sectional association between higher vitamin D levels and lower prevalence of frailty was demonstrated (OR 0.64 [95%-CI 0.45 – 0.90],  $p=.010$ ). Among non-frail depressed patients, higher vitamin D levels predicted a lower incidence of frailty (OR 0.51 [95%-CI 0.26 – 1.00],  $p=.050$ ). Surprisingly, higher vitamin D levels predicted the persistence of frailty among frail depressed patients (OR 2.82 [95%-CI 1.23 – 6.49],  $p=.015$ ).

*Conclusions* - In a depressed population, higher vitamin D levels were associated with a lower prevalence and incidence of frailty. Future studies should examine whether the favorable effect of low vitamin D levels on the course of frailty can be explained by confounding or whether unknown pathophysiological mechanisms may exert protective effects.

## Introduction

With one billion vitamin D deficient people (Holick, 2007), vitamin D deficiency is a major public health problem worldwide (Palacios & Gonzalez, 2014). It is especially common among older persons, mainly due to lack of sunlight exposure, decreased synthesis of vitamin D in the skin and loss of renal function with aging (Gallagher, 2014).

The role of vitamin D in calcium and phosphate metabolism is well-known. Recently, knowledge about its extra-skeletal effects has been expanding. Vitamin D receptors are widely distributed in the body, and have been, among others, localized in the skeletal muscles (Bischoff et al., 2001) and the brain (Eyles et al., 2005). Epidemiological studies have shown associations between hypovitaminosis D and several conditions, such as depression (Anglin et al., 2013; Oude Voshaar et al., 2014) and physical frailty (Shardell et al., 2009; Chang et al., 2010; Wilhelm-Leen et al., 2010; Ensrud et al., 2011; Smit et al., 2012; Hirani et al., 2013; Pabst et al., 2015).

A key feature of frailty, and potential link with vitamin D deficiency, is sarcopenia, the loss of skeletal muscle (Fried et al., 2001). In older persons, a consistent relationship between hypovitaminosis D and muscle dysfunction has been demonstrated (Halfon et al., 2015), as well as a positive effect of vitamin D supplementation on balance and muscle strength (Muir & Montero-Odasso, 2011). While vitamin D indirectly affects muscle function by its impact on the calcium and phosphate balance, its direct effects are supposed to stimulate synthesis of proteins involved in contractility, proliferation and distribution of muscle cells (Ceglia & Harris, 2013).

Yet, frailty is more multifaceted than sarcopenia alone (Morley et al., 2013). Frailty has been defined as a medical syndrome, with multiple causes and contributors, characterized by diminished strength, endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency or death (Morley et al., 2013).

Meta-analysis of longitudinal population-based studies showed increased odds of low vitamin D levels on incident frailty (Zhou et al., 2016). Although frailty-experts consider vitamin D supplements useful for frail persons with vitamin D deficiency (Morley et al., 2013), intervention studies are currently lacking (Bruyère et al., 2017). In spite of a consistently found association between low vitamin D levels and depression (Anglin et al., 2013), the potential causal mechanism is still debated. Recently, it was demonstrated that vitamin D levels did not predict the course of depression in a sample of older persons. Instead, lower vitamin D levels were associated with mortality (Van den Berg et al., 2016). Since frailty and late-life depression have been reciprocally related in the population (Collard et al., 2015b; Lakey et al., 2012), frailty might be a somatic pathway underlying this association. The present study aims to evaluate the cross-sectional and longitudinal association of vitamin D and frailty in a cohort of depressed older persons.

### **Materials and methods**

*Sample* - Data were obtained from the Netherlands Study of Depression in Older persons (NESDO), a cohort study designed to examine the determinants, course and consequences of late-life depression (Comijs et al., 2011; Comijs et al., 2015).

In total, 378 depressed patients and 132 non-depressed controls, aged 60 to 93, were recruited from mental health institutions and general practitioners between 2007 and 2010. Depressed patients had a diagnosis of major depressive disorder (95.0%) and/or dysthymia (26.5%) in the previous six months, or minor depression (5.6%) in the last month, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) and assessed by the Composite International Diagnostic Interview (CIDI; WHO version 2.1, life time version). Controls had no lifetime diagnosis of depression. Subjects with a severe primary disorder, such as a psychotic disorder, a primary diagnosis of dementia, or suspected for dementia according to their clinician, as well as subjects with a Mini

Mental State Examination (MMSE; Folstein et al., 1975) score <18/30 or insufficient command of the Dutch language were excluded. The cut-off on the MMSE was lowered from 24 to 18 in order to be able include the more severely depressed patients with transient cognitive decline due to their depressed state. This was considered possible, as clinicians experienced in the diagnostics of dementia had to exclude all patients they suspected from an underlying dementia.

At baseline, data were gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. Measures subject to change were evaluated again at follow-up. Interviews were performed by trained research assistants and audiotaped regularly to control for quality. If necessary, participants were visited at home. The ethical review boards of the participating centers approved the study. All participants provided informed consent.

Of the 378 depressed patients, 352 with complete data on frailty and vitamin D were included in the cross-sectional analyses. Excluded persons (n=26) were lower educated (8.5 vs. 10.6 years,  $t=2.98$ ,  $df=376$ ,  $p=.003$ ), more often frail (63.6% vs. 29.0%,  $\chi^2=6.10$ ,  $df=1$ ,  $p=.014$ ) and scored higher on the Inventory of Depressive Symptomatology (IDS-SR; Rush et al., 1996): 36.7 vs. 29.7 points (interpretation: 0-13 not depressed; 14-25 mildly depressed; 26-38 moderately depressed;  $\geq 39$  severely depressed);  $t= -2.51$ ,  $df=371$ ,  $p=.012$  than participants. Since actual vitamin D levels were available, vitamin D supplementation was not taken into account in cross-sectional analyses. Nonetheless, sensitivity analyses without supplementation users (n=14) were performed.

At two-year follow-up, 285 initially-depressed patients still participated, 26 had died and 67 were lost to follow-up for other reasons. Participants with missing frailty data (n=30) or baseline vitamin D data (n=5), and users of vitamin D supplementation (n=18) were excluded, leaving a sample of 235 persons for longitudinal analyses. Compared to participants, excluded persons (n=143) were less educated (9.7 vs.

10.9 years,  $t=3.16$ ,  $df=376$ ,  $p=.002$ ), had more chronic diseases (2.8 vs. 2.4,  $t=-2.29$ ,  $df=259,2$ ,  $p=.023$ ), used less alcohol (Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1989) sum score 2.2 vs. 2.8 (range 0-40); Mann-Whitney U  $p=.021$ ), were more often smokers (32.2% vs. 23.0%;  $\chi^2=4.10$ ,  $df=1$ ,  $p=.043$ ) and more often frail at baseline (32.9% vs. 26.4%,  $\chi^2=4.21$ ,  $df=1$ ,  $p=.040$ ). For 22 of 26 deceased persons complete baseline frailty and vitamin D data were available. They were included in the sensitivity analyses and considered frail at follow-up.

### *Health outcomes*

*Vitamin D levels* - Serum 25-(OH) vitamin D<sub>3</sub> levels were measured at baseline using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously (Doorenbos et al., 2012).

Method characteristics are the following: limit of quantitation 4.0 nmol/l, intra-assay coefficient of variation <7.2% and inter-assay coefficient of variation <14.1% for three concentrations between 20 and 150 nmol/l; recovery ranges from 93 to 98% and linearity was acceptable ( $r^2 = 0.9972$ ). The accuracy of 25-(OH) vitamin D<sub>3</sub> levels was established using (the National Institute of Standards and Technology, Gaithersburg, MD, USA) reference material to establish true values for calibration standards. Calibration standards, quality control samples and patient samples were stable for 6 days at 6°C (coefficient of variation < 11%). Samples were stable for at least three freeze-thaw cycles (coefficient of variation <3%).

The optimal 25-(OH) vitamin D level is thought to be between 75 and 100 nmol/l, above which point studies found parathyroid hormone levels (inversely related to vitamin D) beginning to level off (Holick, 2007).

*Frailty* - According to Fried's physical frailty phenotype, frailty was defined as the presence of  $\geq 3$  out of 5 dichotomous criteria: exhaustion, weakness, slow walking speed, inactivity, and unintended weight loss (Fried et al., 2001). These criteria were

operationalized as follows (Collard et al., 2014).

- *Weakness*: low handgrip strength, measured by two squeezes with the dominant hand in a dynamometer. Cut-off values depended on body mass index and varied between 29-32 kg for men and 17-21 kg for women (Fried et al., 2001).
- *Unintended weight loss*: positive answer to the CIDI question about unintended weight loss ( $\geq 1$  kg/week, for  $\geq 2$  consecutive weeks), or a body mass index (BMI)  $< 18.5$  kg/m<sup>2</sup>.
- *Slowness*: time on a six-meter walking test  $\geq 8$  seconds for men  $\geq 173$  cm or women  $\geq 159$  cm height, or  $\geq 9$  seconds for men  $< 173$  cm and women  $< 159$  cm height.
- *Low physical activity*: 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)
- *Exhaustion*: a score of 3 or 4 out of 4 points on one or both of the IDS-SR (Rush et al., 1996) questions about energy level and leaden paralysis / physical energy.

The primary outcome measures were incident frailty (the presence of frailty at follow-up in a person without frailty at baseline) and persistent frailty (the presence of frailty at follow up in a person with frailty at baseline). Secondary outcome measures were the continuous dimensions underlying the individual frailty components of the Fried model, i.e. highest value for handgrip strength in kilograms (weakness), weight in kilograms (weight loss), six-meter walking time in seconds (slowness), number of Metabolic Equivalent of Task (MET)- minutes per week (Craig et al., 2003) (physical inactivity) and sum scores of the two IDS-SR (Rush et al., 1996) questions about energy level and leaden paralysis / physical energy (exhaustion).

*Covariates* - Based on their association with vitamin D level, depression or frailty, we a priori selected age, gender, years of education, astronomical season of blood withdrawal, smoking, use of alcohol, cognitive functioning, number of chronic diseases, renal function and depression symptom score as covariates (Oude Voshaar et al., 2014; Collard et al., 2015a). Use of alcohol was assessed by AUDIT sum scores (Babor et al., 1989). The number of chronic diseases was assessed by means of self-report questions, an accurate method when compared to data from general practitioners (Kriegsman et al., 1996). The MMSE was used to assess global cognitive functioning (range 0–30) (Folstein et al., 1975). Glomerular filtration rates (GFR) were estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI; Levey et al., 2009) formula to assess renal function. Severity of depressive symptomatology was assessed by IDS-SR (Rush et al., 1996) scores.

*Statistical analysis* - Vitamin D levels were standardized using Z-scores. The different groups, based on frailty status, were compared with T-tests, ANOVA and chi-square tests. Non-parametric tests were performed in case of a skewed distribution.

The cross-sectional and longitudinal association between vitamin D and frailty was analyzed using logistic regression, with the presence of frailty (yes/no) as the dependent parameter. The association between vitamin D level and the individual frailty components was analyzed by linear regression. At follow-up, frailty components were adjusted for their own baseline value, in order to assess their course. Continuous values for walking speed were log transformed to achieve a normal distribution.

Analyses were adjusted for all covariates. Missing covariates were imputed with the group mean (IDS score  $n = 2$ , AUDIT sum score  $n = 2$ , smoking status  $n = 2$ ).

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0.0.1. (IBM Corp., NY, USA). All statistical tests were two-sided, p-values at or below .050 were considered significant.

## Results

*Cross-sectional analyses* - At baseline, 102 of 352 participants (29.0%) were frail. Persons with frailty were on average older, had had less years of education, used less alcohol, had more chronic diseases, higher severity of depression, worse cognitive functioning and lower vitamin D levels than non-frail persons (see table 1). Lower vitamin D levels were associated with the presence of frailty. Regarding the individual frailty components, higher vitamin D levels were associated with more physical activity and greater grip strength (see table 2). Exclusion of users of vitamin D supplementation (n=14) neither altered the association with frailty (adjusted OR for frailty 0.64 [95%-CI 0.45 – 0.92], p=.015) nor the association with the individual frailty components (results not shown).

**Table 1** Baseline characteristics, stratified by baseline frailty status

Characteristics	Non-frail (n = 250)	Frail (n = 102)	Statistics
• Age (years); mean (sd)	69.7 (6.9)	73.2 (8.1)	T -3.83, df 163.8, p <.001
• Female sex; n (%)	159 (63.6%)	72 (70.6%)	$\chi^2$ 1.57, df 1, p .210
• Years of education; mean (sd)	10.9 (3.5)	9.7 (3.3)	T 2.98, df 350, p .003
• Currently smoking; n (%)	65 (26.0%)	24 (23.5%)	$\chi^2$ 0.166, df 1, p .683
• Alcohol usage (AUDIT sum score, 0-40); median (IQR)	2.0 (4.0)	1.0 (3.0)	Mann-Whitney U p .003
• Renal function (CKD-EPI, ml/min/1.73m <sup>2</sup> ); mean (sd)	72.6 (14.8)	69.7 (17.3)	T 1.55, df 350, p .123
• Number of chronic diseases; mean (sd)	2.3 (1.5)	3.0 (1.8)	T -3.63, df 348, p <.001
• Severity of depression (IDS-SR score, 0-84); mean (sd)	26.6 (11.9)	37.3 (12.4)	T-7.53, df 348, p <.001
• Cognitive functioning (MMSE score 0-30); median (IQR)	28.0 (2.0)	28.0 (3.0)	Mann-Whitney U p .005

Characteristics	Non-frail (n = 250)	Frail (n = 102)	Statistics
• 25-(OH) vitamin D (nmol/l); mean (sd)	<b>56.1 (22.7)</b>	<b>43.9 (21.6)</b>	<b>T -2.81, df 350, p .005</b>
• Season of blood withdrawal			
○ Winter; n(%)	41 (16.4%)	28 (27.5%)	<b><math>\chi^2</math> 9.19, df 3, p .027</b>
○ Spring; n(%)	70 (28.0%)	33 (32.4%)	$\chi^2$ 0.66, df 1, p .415
○ Summer; n(%)	76 (30.4%)	26 (25.5%)	$\chi^2$ 0.85, df 1, p .357
○ Autumn; n(%)	<b>63 (25.2%)</b>	<b>15 (14.7%)</b>	<b><math>\chi^2</math> 4.63, df 1, p .032</b>

**Bold** = statistical significance ( $p \leq .050$ )

Abbreviations: sd = standard deviation; IQR: interquartile range; df: degrees of freedom, AUDIT: Alcohol Use Disorders Identification Test; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; IDS-SR: Inventory of Depressive Symptomatology, self-report; MMSE: Mini-Mental State Examination.

**Table 2** Cross-sectional association of standardized vitamin D levels and prevalence of frailty and the individual frailty components (n = 352)

Model	Frailty (n = 352)	Individual frailty components				
		Slowness* (n = 349)	Exhaustion (n = 344)	Physical inactivity (n = 343)	Weakness (n = 352)	Weight loss (n = 352)
	OR [95%-CI]	B (se)	B (se)	B (se)	B (se)	B (se)
	p-value	p-value	p-value	p-value	p-value	p-value
25-OH vitamin D	0.53 [0.40–0.70] <b>p &lt; .001</b>	-0.07 (0.02) <b>p .002</b>	-0.18 (0.09) <b>p .047</b>	559.99 (125.21) <b>p &lt; .001</b>	2.54 (0.61) <b>p &lt; .001</b>	0.64 (0.77) p .407
25-OH vitamin D + covariates†	0.64 [0.45–0.90] <b>p .010</b>	-0.02 (0.02) p .448	-0.15 (0.10) p .126	481.88 (133.71) <b>p &lt; .001</b>	1.22 (0.51) <b>p .016</b>	0.38 (0.76) p .616

**Bold** = statistical significance ( $p \leq .050$ )

Abbreviations: OR = odds ratio, 95%-CI = 95%-confidence interval, B = Beta, se = standard error.

\* logtransformed

†Covariates in final model: sexe, age, level of education, severity of depressive symptomatology, number of chronic diseases, cognitive functioning, renal function, smoking status, use of alcohol, season of blood withdrawal.

*Longitudinal analyses* - At two-year follow-up, 173 of the 250 participants without frailty at baseline, participated again. Of those, 21 (12,1%) had become frail.

Compared to the persistently non-frail, participants with incident frailty were older (mean 74.0 (standard deviation (s.d.) 7.8) vs. 68.6 (s.d. 6.5) years,  $p=.001$ ), had more chronic diseases (mean 2.9 (s.d. 1.6) vs. 2.1 (s.d. 1.4),  $p=.011$ ) and lower scores for cognitive functioning (median 27.0 (interquartile range (IQR) 3) vs 28.0 (IQR 2),  $p=.002$ ). Remission of depression at follow-up did not differ between the persistently non-frail ( $n=86$ ; 56.6%) and the incident frail ( $n=9$ ; 42.9%,  $p=.236$ ). There were no significant differences with respect to the other variables (results not shown).

**Table 3** Association of standardized vitamin D levels and incidence of frailty and change of the individual frailty components

Model	Incident frailty (n = 173)	Incident frailty or death (n = 182)	Individual frailty components				
			Slowness* (n = 172)	Exhaustion (n = 173)	Physical inactivity (n = 173)	Weakness (n = 170)	Weight loss (n = 171)
	OR [95%-CI] p-value	OR [95%-CI] p-value	B (se) p- value	B (se) p- value	B (se) p- value	B (se) p- value	B (se) p- value
• 25-OH vitamin D	0.58 [0.33 – 1.01] p .054	0.49 [0.29 – 0.82] <b>p .006</b>	-0.04 (0.03) p .144	-0.11 (0.12) p .341	410.33 (214.64) p .058	1.15 (0.80) p .152	-0.90 (1.14) p .434
• 25-OH vitamin D+ covariates <sup>†</sup>	0.51 [0.26 – 1.00] <b>p .050</b>	0.42 [0.23 – 0.78] <b>p .006</b>	-0.02 (0.02) p .458	-0.01 (0.11) p .929	518.78 (229.34) <b>p .025</b>	0.50 (0.56) p .372	-1.14 (1.09) p .296

**Bold** = statistical significance ( $p \leq .050$ )

Abbreviations: OR = odds ratio, 95%-CI = 95%-confidence interval, B = Beta, se = standard error.

\* logtransformed

<sup>†</sup>Covariates in final model: sexe, age, level of education, severity of depressive symptomatology, number of chronic diseases, cognitive functioning, renal function, smoking status, use of alcohol, season of blood withdrawal

As shown in table 3, a significant association between higher baseline vitamin D levels and lower odds for incident frailty at two-year follow-up was found. When

deceased persons were considered incident frail as well, this association was even stronger. Regarding the individual frailty components, only the association between higher baseline vitamin D levels and more physical activity at follow-up was significant.

Of the 102 baseline-frail persons, 62 participated again at two-year follow-up. Frailty had remitted in 31 persons (50%). Participants with persistent frailty were older (mean 75.9 (s.d. 8.6) vs 70.5 years (s.d. 7.1),  $p=.009$ ) and had less renal function at baseline (mean GFR 68.1 ml/min/1.73m<sup>2</sup> (s.d. 17.4) vs 77.7 ml/min/1.73m<sup>2</sup> (s.d. 14.6),  $p=.022$ ) compared to persons with remission of frailty. Among persistently frail persons, depression had remitted less often ( $n=8$ , 25.8%) than in persons with remitted frailty ( $n=21$ ; 67.7%;  $p=.001$ ). The other variables did not differ significantly (results not shown).

In fully adjusted analyses (see table 4), higher vitamin D levels were associated with higher odds of persistent frailty at follow-up. As depression remitted significantly less often in persistently frail patients, we checked post-hoc the interaction between baseline vitamin D level and the presence of depression at two-year follow-up. This interaction term, however, was not significant.

Furthermore, the impact of vitamin D levels on persistence of frailty was neither present in the univariate analyses, nor in the sensitivity analyses. A stepwise procedure demonstrated that adjustment for use of alcohol amplified the effect of higher vitamin D levels on persistence of frailty the most. Regarding the individual frailty components, higher vitamin D levels were associated with increased exhaustion. For the other frailty components, no significant association with vitamin D levels was found.

**Table 4** Association of vitamin D levels (standardized) and persistence of frailty and change of the individual frailty components

Model	Persistent frailty (n = 62)	Persistent frailty or death (n = 75)	Individual frailty components				
			Slowness* (n = 62)	Exhaustion (n = 61)	Physical inactivity (n = 62)	Weakness (n = 62)	Weight loss (n = 60)
	OR [95%-CI] p-value	OR [95%-CI] p-value	B (se) p- value	B (se) p- value	B (se) p- value	B (se) p- value	B (se) p- value
• 25-OH vitamin D	1.73 [0.98 – 3.07] p .061	1.28 [0.77 – 2.13] p .347	-0.09 (0.07) p .188	0.51 (0.20) <b>p .014</b>	-109.63 (291.21) p .708	1.39 (1.33) p .300	1.14 (2.05) p .579
• 25-OH vitamin D+ covariates <sup>†</sup>	2.82 [1.23 – 6.49] <b>p .015</b>	1.65 [0.82 – 3.31] p .162	-0.05 (0.06) p .464	0.52 (0.24) <b>p .034</b>	-275.92 (307.91) p .375	0.29 (1.19) p .805	0.23 (2.16) p .915

**Bold** = statistical significance ( $p \leq 0.050$ )

Abbreviations: OR = odds ratio, 95%-CI = 95%-confidence interval, B = Beta, se = standard error.

\* logtransformed

<sup>†</sup> Covariates in final model: gender, age, level of education, severity of depressive symptomatology, number of chronic diseases, cognitive functioning, renal function, smoking status, use of alcohol, season of blood withdrawal

## Discussion

*Main findings* - In a cohort of depressed, older persons, lower vitamin D levels were cross-sectionally associated with greater odds of prevalent frailty, which is mainly driven by the components physical inactivity and weakness. In persons without frailty at baseline, lower vitamin D levels doubled the odds of incident frailty and were associated with a further decrease of physical activity at two-year follow-up. In the subgroup of baseline-frail participants, frailty had remitted in 31 of 62 participants (50%) two years later. Remarkably, higher vitamin D levels were associated with persistent frailty over time, irrespective of the fact that improvement of frailty was significantly associated with remission of depression.

### *Comparison to the literature*

Our cross-sectional findings are in line with previous studies, reporting associations between lowest vitamin D levels and presence of frailty according to the Fried phenotype (Fried et al., 2001; Semba et al., 2006; Chang et al., 2010; Shardell et al., 2009; Ensrud et al., 2011; Hirani et al., 2013; Tajar et al., 2013).

Regarding the individual frailty components, we found that lower vitamin D levels were associated with weakness and physical inactivity, while other studies have demonstrated associations solely with weakness (Ensrud et al., 2011) or with all frailty components except weight loss (Hirani et al., 2013; Tajar et al., 2013). Due to these inconsistencies, it is neither possible to draw conclusions about whether low vitamin D levels are related to frailty as an overall-concept (which might include more than just the sum of the individual components) nor to generalize conclusions about the driving factors of the association.

We may have found less associated frailty components than some other studies (Hirani et al., 2013; Tajar et al., 2013) due to the presence of depression in our sample. Since depression and frailty are thought to be reciprocally associated (Lakey et al., 2012; Collard et al., 2015b), frailty prevalence rates are expected to be higher within a depressed population. In our sample the frailty rate was 29.9%, whereas in community-dwelling populations this rate was 9.9% (Collard et al., 2012). Furthermore, depression has been associated with lower vitamin D levels in our population (Oude Voshaar et al., 2014), and other populations (Anglin et al., 2013). Therefore, an association between vitamin D levels and frailty (and its components) might be harder to detect in a depressed sample.

Since frailty had remitted in half of the baseline-frail participants, our longitudinal data underline that frailty is a dynamic process, as previously stated in a frailty consensus paper (Morley et al., 2013). In our depressed population, this dynamism might be partly confounded by overlap between frailty and depression (Lohman et

al., 2016). Nevertheless, the impact of vitamin D on the improvement of frailty was independent of depression status at follow-up.

In line with our finding, a recent meta-analysis of seven longitudinal studies showed a pooled odds ratio of 1.27 (95%-CI 1.17 – 1.38) for incident frailty for lowest vitamin D levels (Zhou et al., 2016). Potential mechanisms explaining this prospective association include 1) the development of sarcopenia and muscle weakness, due to regulatory effects of vitamin D on calcium and mineral homeostasis and protein signaling pathways (Bruyère et al., 2017), 2) secondary hyperparathyroidism, caused by low 1,25 OH<sub>2</sub> vitamin D and low calcium, leading to decreased bone mineralization and increased bone resorption, thus increasing fracture risk (Lips, 2006; Bruyère et al., 2017), and finally 3) the possible involvement of vitamin D deficiency in inflammation and activation of the immune system, which might play a role in the pathogenesis of auto-immune diseases and the development of frailty (Lips, 2006; Arnsion et al., 2007; Bruyère et al., 2017).

In our sample, lower vitamin D levels at baseline predicted a decrease of physical activity at follow up. In other, population-based samples, low vitamin D levels were associated with physical inactivity/low energy expenditure as well as slowness (Shardell et al., 2009; Vogt et al., 2015) or none of the individual frailty criteria (Ensrud et al., 2010).

The presence of depression might explain why the association between low vitamin D levels and decrease of physical activity stands out. Previously, low vitamin D levels were suggested to be a marker of poor health in our sample (Van den Berg et al., 2016). Since poor health might add to increasing physical inactivity over time, and depression itself can also cause physical inactivity (Hiles et al., 2017), this might have amplified the association in our sample.

In line with our unexpected finding of an association between lower vitamin D levels and remission of frailty, the population-based InChianti study (Shardell et al., 2012) also reported baseline frail participants with low vitamin D levels to be more likely

to transit to pre-frailty (the presence of only 1 or 2 frailty criteria) at follow up. Despite this replication, our finding might still be considered a chance finding, due to the small sample of baseline frail persons (n=62). Confounding by indication (vitamin D supplementation in frail persons) is less likely, since we excluded persons using supplementation at follow-up. Intermittent supplementation during the follow-up period is unlikely to result in the strong effects we found.

Another possibility is residual confounding, since a reciprocal association between frailty and depression exists (Lakey et al., 2012; Collard et al., 2015b;). Symptoms of depression might lead to a false-positive diagnosis of frailty, as the operational criteria of depression and frailty identify overlapping subpopulations (Mezuk et al., 2012; Mezuk et al., 2013). However, this does not fit with our finding that the effect of vitamin D levels on frailty is not moderated by an effect of vitamin D on remission of depression.

At last, a more plausible explanation might be that inactive behavior due to depression might lead to lower vitamin D levels. Upon remission of depression, frailty status also improves (partly due to overlap/confounding with depression, partly true improvement), while vitamin D levels can stay behind. In our baseline-frail subgroup, depression had remitted significantly more often in participants with remitted frailty at follow up, than in the persistently frail.

Nonetheless, taken into account that hitherto two studies reported this unexpected effect, it still might reflect yet unknown pathophysiological pathways that remain to be elucidated.

*Limitations* - First, a dichotomous outcome measure for frailty has been used, and pre-frailty was not taken into account. Second, we did not have access to causes of death. Being able to include only people who died from frailty-related causes in the sensitivity analyses would have led to more accuracy. Now sensitivity analyses are likely an overestimation, and primary analyses an underestimation of the effect.

Last, vitamin D levels were measured at baseline only. However, vitamin D levels seem to be relatively consistent over time (Jorde et al., 2010).

*Conclusion / clinical implications* - In our depressed population, like in community-based populations, lower vitamin D levels were associated with greater prevalence and incidence of frailty. Future studies should examine whether the favorable effect of low vitamin D levels on the course of frailty can simply be explained by confounding or whether unknown pathophysiological mechanisms may exert protective effects. This is highly relevant, as vitamin D supplementation is generally seen as a potential treatment strategy for frailty as well as late-life depression.

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# Part II

## Associations between physical frailty and common (neuro)psychiatric symptoms

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### Chapter 5

#### Physical frailty and cognitive functioning in depressed older adults: Findings from the NESDO study

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### Chapter 6

#### Frailty and somatic comorbidity in older patients with medically unexplained symptoms

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