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Vitamin D deficiency, depression course and mortality: Longitudinal results from the Netherlands Study on Depression in Older persons (NESDO)

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ARTICLE INFO

ABSTRACT

Objective: To study the effect of vitamin D levels on depression course and remission status after two years, as well as attrition and mortality, in an older cohort.
Methods: This study was part of the Netherlands Study on Depression in Older persons (NESDO), a prospective cohort study. 367 depressed older persons (≥60 years) were included. Baseline vitamin D status, reasons for loss to follow up, clinical depression diagnosis at two-year follow up, and six-monthly symptom scores were obtained. Data were analyzed by logistic regression and random coefficient models and adjusted for confounders of vitamin D status.
Results: Vitamin D had no effect on the course of depression or remission, except for a trend towards lower remission rates in the severely deficient subgroup (25-(OH) vitamin D < 25 nmol/l). Patients who died during follow up had significantly lower 25-(OH) vitamin D and 1,25-(OH)$_2$ vitamin D levels than patients with continued participation.
Conclusions: For the total sample we found no effect of vitamin D levels on the course of depression or remission rates. However, we did find an effect of lower vitamin D levels on mortality. This strengthens the interpretation of vitamin D deficiency being a marker for poor somatic health status. The trend towards lower remission rates in the severely deficient subgroup raises the question whether this group could benefit from supplementation. Randomized controlled trials are necessary to study this.

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Introduction

Vitamin D deficiency is a major public health problem worldwide [1], particularly in older people [2]. Increased prevalence of vitamin D deficiency with age is explained by dietary deficiencies, decreased production of vitamin D in the skin, decreased conversion of calcidiol (25-(OH) vitamin D) to calcitriol (1,25-(OH)$_2$ vitamin D) in the kidney and lack of sunlight exposure in older people [3]. Besides its effect on calcium metabolism and bone health, vitamin D deficiency has been linked to various diseases [4,5] and proposed to be a universal risk factor for multiple multifactorial diseases [6]. Vitamin D directly affects gene regulation, thereby influencing cell proliferation, vascular calcifications and inflammatory responses, as well as indirectly affects the renin–angiotensin–aldosterone system [6]. In

older populations vitamin D deficiency has also been associated with frailty and mortality [7–9]. Increased mortality rates may be explained by the association of vitamin D deficiency with several somatic diseases, particularly cardiovascular disease [10].

A meta-analysis of cross-sectional, population-based studies yielded a pooled odds ratio of 1.31 (95%-confidence interval (95%-CI) 1.00–1.71; p = .05) for association between low vitamin D levels and depression [11]. Furthermore, both younger and older patients suffering from depressive disorder had lower vitamin D levels compared to controls [12,13].

Current hypotheses about the pathophysiological mechanisms in the association between vitamin D and depression include a role for vitamin D in the regulation of neurotransmitters dopamine, noradrenaline and acetylcholine, as well as an effect on neurotrophic factors [14]. Moreover, vitamin D receptors are found in the prefrontal cortex and parts of the limbic system [15]. These brain areas have been implicated in the pathophysiology of depression [16]. Vitamin D might also reduce concentrations of inflammatory markers associated with depression

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[17]. A reverse causative mechanism might be that depression leads to decreased sun exposure, poorer dietary intake and more smoking, thereby causing vitamin D deficiency [18].

Longitudinal studies, however, are less consistent and mainly focused on vitamin D as a risk factor for the incidence of depression. Meta-analysis of three cohort studies in middle-aged to older populations [19–21] yielded a significant hazard ratio of depressive symptoms for the lowest vs. the highest vitamin D levels (2.21 (95%-CI 1.40–3.49; p < .001) [11]. Thereafter, in an older cohort no effect of vitamin D levels on the incidence of depressive symptoms was found [22]. To our knowledge, only one study has examined the effect of vitamin D status on course of depression [12]. In this sample of depressed younger adults higher vitamin D levels were associated with better depression outcomes [12]. In a meta-analysis of randomized controlled trials, vitamin D supplementation did not lead to a reduction of depressive symptoms. However, few participants were (clinically) depressed or vitamin D deficient [23].

Furthermore, nearly all studies have measured 25-(OH) vitamin D levels, while 25-(OH) vitamin D has to be converted in the kidney to the biologically active form, $1,25\text{-(OH)}_2$ vitamin D. In previous cross-sectional analyses, our group found that $1,25\text{-(OH)}_2$ vitamin D was lowered in depression as well [13].

The primary objective of the present study is to examine whether 25-(OH) vitamin D and $1,25\text{-(OH)}_2$ vitamin D levels also predict remission of late-life depression at two-year follow-up, as well as its course. The second objective, essential in an older age sample, is to study the effect of vitamin D on attrition and mortality.

Methods

Sample

The present study was part of the Netherlands Study of Depression in Older persons (NESDO), an on-going cohort study designed to examine the determinants, course and consequences of late-life depression (for details, see [24]).

The cohort consisted of 378 depressed patients and 132 non-depressed comparison subjects aged 60 to 93, recruited between 2007 and 2010 from mental health institutions and general practitioners. Data was gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. At two-year follow up all measures open to change were evaluated again. Attrition and its reasons were recorded [25]. Interviews were performed by trained research assistants and were audio taped regularly to control for quality.

Exclusion criteria were a (suspected) diagnosis of dementia, a Mini Mental State Examination (MMSE) [26] score < 18/30 and insufficient command of the Dutch language. The ethical review boards of the five participating centers approved the study. All participants received oral and written information and provided their informed consent.

For the present study, we selected the patient group. Eleven patients were excluded due to missing vitamin D levels, leaving a study sample of 367 depressed persons at baseline.

Depression

At baseline and two-year follow-up, past-six months diagnoses of depression and dysthymia according to the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV-TR)-criteria [27] were assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version), a structured clinical interview [28,29]. Additional questions were added to diagnose current minor depression according to the research criteria of the DSM-IV-TR [24].

The severity of depressive symptoms was assessed every six months with the Inventory of Depressive Symptoms — Self Report (IDS-SR) [30]. For 28 symptoms, severity and frequency were rated on a scale from 0 to 3, adding up to total scores ranging from 0 to 84, higher scores indicating more severe depression. Three subscale scores were derived, reflecting a mood (9 items), motivational (5 items) and somatic (8 items) dimension [31].

Laboratory testing

Vitamin D levels were assessed at baseline. Serum 25-(OH) vitamin D levels were measured using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously [32]. Serum $1,25\text{-(OH)}_2$ vitamin D levels were determined by radioimmunoassay.

The optimal 25-(OH) vitamin D level has been estimated to be between 50 and 100 nmol/l, since serum levels below 75 nmol/l induce parathyroid hormone (PTH) secretion [33]. Serum 25-(OH) vitamin D levels are often categorized as severely deficient (<10 nmol/l), deficient (10–25 nmol/l), insufficient (25–50 nmol/l), hypovitaminosis D (50–75 nmol/l), and sufficient (≥75 nmol/l) [34,35]. A recent study reported a reference interval for $1,25\text{-(OH)}_2$ vitamin D between 59 and 159 pmol/l [36].

Covariates

Based on the literature [37,38], we a priori selected three sets of covariates.

The first set consisted of demographic characteristics (age, gender and years of education) and 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).

The second set included the lifestyle factors smoking (yes/no), use of alcohol and physical activity. We included the Alcohol Use Disorders Identification Test (AUDIT) [39] sum score as a proxy for (subclinical) alcohol dependence severity. To measure physical activity, the number of Metabolic Equivalent of Task (MET)-minutes per week was obtained using the eight-item International Physical Activities Questionnaire (IPAQ) [40].

Parameters of somatic functioning formed the third set of confounders: waist circumference (centimeters), serum levels of PTH (obtained as described earlier [13]) and glomerular filtration rates (GFR), estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[41] The number of chronic diseases was assessed by means of self-report questions. This has been proven to be an accurate method when compared to data from general practitioners [42]. The MMSE was used to assess global cognitive functioning (range 0–30), higher scores indicating better cognitive functioning [26].

All covariates were assessed at baseline. Vitamin D supplementation, assessed at baseline and two-year follow-up, was not taken into account, as dosages were low and we were interested in the actual vitamin D levels. Nonetheless, a sensitivity analysis, excluding all patients with vitamin D supplementation will be performed.

Statistical analysis

All analyses were performed separately for 25-(OH) and $1,25\text{-(OH)}_2$ vitamin D. Vitamin D levels were standardized using Z-scores. All statistical tests were two-sided, p-values below .05 were considered significant. To meet the test assumptions, 5 positive outliers for $1,25\text{-(OH)}_2$ vitamin D levels, 6 positive outliers for PTH levels and 5 positive outliers for MET-minutes/week were trimmed at the level of the mean plus 3 standard deviations. AUDIT sum scores were log transformed.

Vitamin D levels and covariates at baseline were compared by participation status at two-year follow-up, i.e. 'participation', 'death' or

'attrition', using χ^2 tests for categorical variables and one-way analysis of variance for continuous variables.

Odds ratios for the prediction of two years participation status by 25-(OH) vitamin D and 1,25-(OH)$_2$ vitamin D levels were calculated by means of multinomial logistic regression. Because of limited numbers in the 'death' and 'attrition' outcome categories, controlling for covariates was first restricted to season of blood withdrawal in block 1. Then, in block 2, all other covariates were evaluated for inclusion in the analysis using backward elimination. Finally, vitamin D was added in block 3. Effect sizes of 25-(OH) and 1,25-(OH)$_2$ vitamin D were estimated with pseudo R^2 according to Nagelkerke.

Subsequently, the association between vitamin D levels and depression diagnosis at two-year follow up was analyzed using binary logistic regression, adjusted for all covariates. Since in our baseline paper only tricyclic antidepressant (TCA) usage (among all depression characteristics tested) was related to 1,25-(OH)$_2$ vitamin D levels [13], interaction terms for vitamin D and use of a TCA were tested.

Lastly, random coefficient models, a specific type of linear mixed models, were fitted to analyze the effect of 25-(OH) and 1,25-(OH)$_2$ vitamin D levels on the repeated measurements of IDS-SR (sub)scale scores. To correct for the correlation in data caused by the repeated measurement design, 'patient ID' was added as a random factor and random intercept and random slope were tested for improvement of the model fit. 'Vitamin D' and 'time' were added as fixed factors. The 'vitamin D' × 'time' interaction was added to the model to test the effect of vitamin D levels on the course of IDS-SR scores over time. Subsequently, all covariates were added to the model as fixed factors.

In order to preclude contamination of results by vitamin D supplementation, sensitivity analyses were conducted excluding all patients using vitamin D supplementation (n = 30/367; 8.2%).

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 22.0.0.1 (IBM Corp., NY, USA).

Results

Study sample and attrition

At baseline (n = 367) diagnoses were major depressive disorder (94.8%), dysthymia (25.9%) and minor depression (5.4%). Percentages do not add up to 100% due to double diagnoses. Mean serum levels were 52.66 nmol/l (s.d. 23.25) for 25-(OH) and 138.20 nmol/l (s.d. 49.27) for 1,25-(OH)$_2$ vitamin D. Pearson's rho for the correlation between 25-(OH) and 1,25-(OH)$_2$ vitamin D was 0.56 (p < .001).

At two-year follow up, 280 patients (76.3%) were still participating: 24 persons had died and 63 were lost to follow up (due to physical illness, n = 11; mental illness, n = 33; loss of contact/lack of interest, n = 19). In Table 1 the characteristics of the study population categorized by two-year participation status are presented. Deceased patients had decreased renal function, were more often smokers, and less physically active compared to patients still participating after two years.

Compared to patients still participating at two-year follow up, deceased patients had significantly lower levels of 25-(OH) vitamin D (F = 13.88, df = 1, p < .001) as well as 1,25-(OH)$_2$ vitamin D (F = 16.57, df = 1, p = .001), whereas those lost to follow-up only had lower 1,25-(OH)$_2$ vitamin D (F = 6.16, df = 1, p = .014).

Table 2 shows the results of multinomial logistic regression of two-year participation status by vitamin D level. In the fully adjusted models, patients with higher 25-(OH) and 1,25-(OH)$_2$ vitamin D had a significantly lower probability of being in the deceased group than in the group still participating (Nagelkerke's R^2: 0.198 for 1,25-(OH)$_2$; 0.179 for 25-(OH) vitamin D).

Table 1
Baseline characteristics of depressed patients stratified by two-year participation status.

Characteristic	Two-year participation status			Statistic		
	Participation (n = 280)	Attrition (n = 63)	Death (n = 24)			
Demographic features						
Male sex, n (%)	96 (34.3)	16 (25.4)	12 (50.0)	χ^2 = 4.83	df 2	p = .089
Age, mean (s.d.)	70.6 (7.5)	70.2 (6.9)	72.5 (7.3)	F = 0.89	df 2	p = .410
Educational level (years), mean (s.d.)	10.6 (3.4)	10.1 (3.4)	10.1 (3.6)	F = 0.69	df 2	p = .502
Season of blood withdrawal						
Winter, n (%)	51 (18.2)	11 (17.5)	10 (41.7)	χ^2 = 10.26	df 6	p = .114
Spring, n (%)	84 (30.0)	18 (28.6)	4 (16.7)			
Summer, n (%)	87 (31.1)	16 (25.4)	6 (25.0)			
Autumn, n (%)	58 (20.7)	18 (28.6)	4 (16.7)			
Lifestyle factors						
Smoking status						
Smoker, n (%)	67 (23.9)	18 (28.6)	11 (45.8)	χ^2 = 6.35	df 2	**p = .042**
Alcohol use						
AUDIT score (0–40), mean (s.d.)[a]	2.7 (3.5)	2.2 (3.1)	2.5 (4.4)	F = 1.34	df 2	p = .262
Physical activity						
MET-minutes/week, mean (s.d.)[b]	2570.6 (2375.5)	2025.6 (2309.8)	969.5 (1423.7)	F = 5.91	df 2	p = .003
Waist circumference (cm), mean (s.d.)	92.7 (12.6)	95.5 (13.0)	97.7 (13.9)	F = 2.67	df 2	p = .071
Physical health						
Number of chronic diseases, mean (s.d.)	2.5 (1.6)	2.6 (1.7)	2.9 (1.8)	F = 1.07	df 2	p = .346
Cognitive functioning						
MMSE score (0–30), mean (s.d.)	27.9 (1.8)	27.3 (2.7)	27.3 (1.9)	F = 3.16	df 2	p = .044
Renal function						
eGFR, ml/min/1.73 m^2, mean (s.d.)	72.6 (15.6)	71.2 (14.8)	65.2 (17.7)	F = 2.61	df 2	p = .075
Serum parathormone (nmol/l), mean (s.d.)[b]	7.3 (3.3)	6.5 (2.6)	8.7 (4.2)	F = 3.83	df 2	p = .023
Serum 25-hydroxy vitamin D (nmol/l), mean (s.d.)	54.4 (23.6)	51.0 (21.8)	36.2 (16.1)	F = 7.27	df 2	**p = .001**
Serum 1,25-dihydroxy vitamin D (pmol/l), mean (s.d.)[b]	142.9 (46.8)	127.0 (42.3)	102.9 (37.7)	F = 10.57	df 2	**p < .001**

Abbreviations: AUDIT, alcohol use disorders identification test; MET, metabolic equivalent of task, MMSE, mini mental state examination; and eGFR, estimated glomerular filtration rate.
Bold = p < 0.05
[a] As covariate log-transformation performed, AUDIT sum score of 24 out of the 367 participants (6.5%) was ≥8, indicating harmful alcohol use or alcohol dependence.
[b] Positive outliers trimmed to mean + 3 s.d.

Table 2
Prediction of death and attrition at two-year follow up by standardized vitamin D levels.

|		OR	(95%-Confidence interval)	p-Value
25-(OH) vitamin D				
Unadjusted	Participation	1.00		
	Attrition	0.86	(0.64–1.14)	.287
	Death	0.32	(0.17–0.60)	**<.001**
Adjusted for season	Participation	1.00		
	Attrition	0.84	(0.62–1.14)	.264
	Death	0.33	(0.17–0.64)	**.001**
Adjusted for season + other covariates[a]	Participation	1.00		
	Attrition	0.83	(0.60–1.14)	.244
	Death	0.41	(0.20–0.84)	**.014**
1,25-(OH)$_2$ vitamin D				
Unadjusted	Participation	1.00		
	Attrition	0.67	(0.48–0.92)	**.015**
	Death	0.29	(0.16–0.54)	**<.001**
Adjusted for season	Participation	1.00		
	Attrition	0.67	(0.48–0.93)	**.018**
	Death	0.31	(0.17–0.58)	**<.001**
Adjusted for season + other covariates[b]	Participation	1.00		
	Attrition	0.69	(0.49–0.97)	**.031**
	Death	0.31	(0.15–0.61)	**.001**

Participation = reference category.
Bold = p < 0.05
[a] Gender, parathyroid hormone level, physical activity and smoking status.
[b] Gender, parathyroid hormone level and smoking status.

Two-year outcome of depression

At two-year follow up (n = 280) diagnoses were major depression (40%), dysthymia (25.4%) and minor depression (3.9%). Using binary logistic regression we found no effect of 25-(OH) vitamin D (OR 0.87; 95%-CI: 0.69–1.10; p = .256) or 1,25-(OH)$_2$ vitamin D (OR 0.82; 95%-CI: 0.64–1.04; p = .095) on depression status at two-year follow up. After adjustment for all covariates, odds ratios were 0.92 (95%-CI: 0.69–1.22; p = .553) for 25-(OH) vitamin D and 0.90 (95%-CI: 0.66–1.21; p = .471) for 1,25-(OH)$_2$ vitamin D. No interactions between both forms of vitamin D and use of a TCA on depression outcome were found (p = .998 and p = .996, respectively).

Fig. 1 presents the remission rates (i.e. not having a depression diagnosis at two-year follow-up) for the different categories of 25-(OH) vitamin D. Since Fig. 1 suggests that only vitamin D deficiency (serum levels <25 nmol/l; n = 36) might be relevant, we conducted post-hoc logistic regression analyses. Vitamin D deficiency (yes/no)
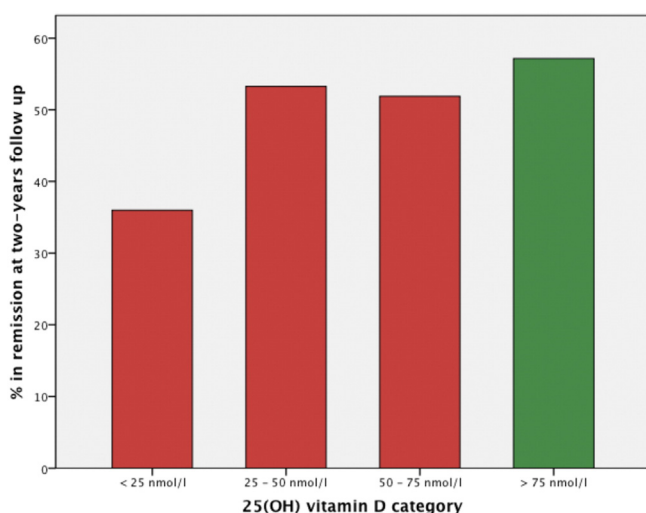
Fig. 1. Remission rates according to 25-(OH) vitamin D category.

had an odds ratio of 2.03 (unadjusted analysis; 95%-CI 0.87–4.77, p = .103) and 2.19 (after adjustment for all covariates; 95%-CI 0.82–5.89, p = .115) for the prediction of non-remission.

Two-year course of depressive symptoms

In all random coefficient models (Table 3), models with random slope and random intercept provided the best fit. For both variants of vitamin D and all IDS-SR (sub)scale scores, the interaction of vitamin D with time did not add significantly to the models, hence there is no effect of vitamin D on the course of IDS-SR scores over time.

If added as fixed factor in unadjusted analyses, higher 25-(OH) vitamin D levels yielded significantly lower total IDS-SR scores and somatic subscale scores. These effects disappeared after adjustment for covariates. Post-hoc analyses (not presented) showed that confounding was explained by lifestyle factors (smoking status, waist circumference, physical activity, and alcohol use). What remained after adjustment for all covariates are significant reductions on all IDS-SR (sub)scale scores with subsequent 6-month assessments.

Post-hoc tests of vitamin D deficiency (25-(OH) vitamin D < 25 nmol/l; yes/no) as determinant of depression course yielded significantly higher total and somatic IDS-SR scores in case of vitamin D deficiency and diminishing scores on all IDS-SR (sub)scales over time, also after adjustment for all covariates. The effects of vitamin D deficiency on the course of the IDS scores remained non-significant.

Sensitivity analyses

None of the results changed after excluding the patients using vitamin D supplementation (data not shown).

Discussion

Main findings

In a large sample of clinically depressed older people, we neither found an effect of serum 25-(OH) vitamin D or 1,25-(OH)$_2$ vitamin D levels on two-year depression status, nor on the course of depressive symptoms over time. In the subgroup with severe vitamin D deficiency (25-(OH) vitamin D < 25 nmol/l, n = 36) a trend towards lower remission rates was seen.

Interestingly, patients who died during follow up had significantly lower baseline levels of 25-(OH) and 1,25-(OH)$_2$ vitamin D than patients still participating, and significantly lower 1,25-(OH)$_2$ vitamin D levels than those lost to follow up. Since 1,25-(OH)$_2$ vitamin D levels might be normal or raised due to secondary hyperparathyroidism in 25-(OH) vitamin D deficiency, low 1,25-(OH)$_2$ levels probably reflect a more severe deficiency state.

Vitamin D and depression

As far as we know, this is the first prospective study investigating the effect of vitamin D levels on the course of depression in a clinically depressed, older population.

Previous longitudinal research in older populations focused on the incidence of depressive symptoms with respect to vitamin D status and yielded inconsistent results [19–22]. On the one hand, the absence of an association might be explained by low incidences of depression and vitamin D deficiency in two population-based cohorts [21,22]. On the other hand, the positive finding of low vitamin D predicting the onset of depression in the population-based sample of the InChianti study [19] might have been confounded by the chosen cut-off score, as depression was defined as a Center for Epidemiologic Studies Depression scale (CES-D) score ≥ 16. Consequently, compared to our population where major depressive disorder is the most prevalent diagnosis, more people with mild depressive symptoms might have been

Table 3

Effects of vitamin D, time and interaction of vitamin D with time on repeated inventory of depressive symptomatology (IDS) scores[a].

		Vitamin D		Time		Interaction vitamin D–time	
		B (s.e.)	p-Value	B (s.e.)	p-Value	B (s.e.)	p-Value
25-(OH) vitamin D[b]							
Unadjusted	Total IDS score	−1.17 (0.59)	**.048**	−1.27 (0.17)	**<.001**	0.17 (0.17)	.311
	Mood subscale	−0.30 (0.23)	.204	−0.46 (0.07)	**<.001**	0.05 (0.07)	.417
	Motivational subscale	−0.12 (0.13)	.359	−0.24 (0.04)	**<.001**	0.02 (0.04)	.560
	Somatic subscale	−0.47 (0.19)	**.013**	−0.30 (0.05)	**<.001**	0.04 (0.05)	.486
Adjusted[c]	Total IDS score	−0.32 (0.64)	.624	−1.19 (0.17)	**<.001**	0.11 (0.17)	.503
	Mood subscale	−0.03 (0.26)	.909	−0.43 (0.07)	**<.001**	0.04 (0.07)	.602
	Motivational subscale	0.08 (0.15)	.602	−0.22 (0.04)	**<.001**	0.02 (0.04)	.632
	Somatic subscale	−0.18 (0.20)	.383	−0.26 (0.05)	**<.001**	0.01 (0.05)	.792
1,25-(OH)$_2$ vitamin D[b]							
Unadjusted	Total IDS score	−1.02 (0.59)	.086	−1.28 (0.17)	**<.001**	0.06 (0.17)	.705
	Mood subscale	−0.33 (0.23)	.157	−0.46 (0.07)	**<.001**	0.02 (0.07)	.722
	Motivational subscale	−0.19 (0.13)	.148	−0.24 (0.04)	**<.001**	0.01 (0.04)	.801
	Somatic subscale	−0.20 (0.19)	.285	−0.30 (0.05)	**<.001**	−0.01 (0.05)	.807
Adjusted[c]	Total IDS score	−0.31 (0.67)	.640	−1.19 (0.17)	**<.001**	−0.02 (0.17)	.920
	Mood subscale	−0.09 (0.27)	.724	−0.43 (0.07)	**<.001**	−0.01 (0.07)	.880
	Motivational subscale	−0.00 (0.15)	.981	−0.22 (0.04)	**<.001**	0.00 (0.04)	.911
	Somatic subscale	−0.01 (0.21)	.944	−0.26 (0.05)	**<.001**	−0.04 (0.05)	.450
25-(OH) vitamin D deficiency (<25 nmol/l)							
Unadjusted	Total IDS score	4.13 (1.98)	**.037**	−1.28 (0.17)	**<.001**	−0.91 (0.57)	.112
	Mood subscale	1.24 (0.77)	.108	−0.46 (0.07)	**<.001**	−0.20 (0.23)	.376
	Motivational subscale	0.11 (0.45)	.809	−0.24 (0.04)	**<.001**	−0.17 (0.15)	.238
	Somatic subscale	1.91 (0.63)	**.003**	−0.30 (0.05)	**<.001**	−0.29 (0.18)	.116
Adjusted[c]	Total IDS score	4.15 (2.02)	**.041**	−1.21 (0.17)	**<.001**	−0.64 (0.58)	.265
	Mood subscale	1.29 (0.79)	.103	−0.44 (0.07)	**<.001**	−0.09 (0.23)	.686
	Motivational subscale	0.06 (0.46)	.903	−0.23 (0.04)	**<.001**	−0.12 (0.15)	.424
	Somatic subscale	2.01 (0.65)	**.002**	−0.27 (0.05)	**<.001**	−0.24 (0.19)	.192

Bold = p < 0.05

[a] For all analyses, random intercept plus random slope was best fitting model.

[b] Standardized vitamin D scores were used in the analyses.

[c] Adjusted for age, gender, educational level, season of blood withdrawal, smoking, use of alcohol, waist circumference, physical activity, cognitive functioning, serum parathyroid hormone level, renal function and number of chronic diseases.

included. Furthermore, with a lower cut-off score, depression scores might have been inflated due to symptoms of somatic origin [43,44].

To our knowledge, only one study has examined vitamin D levels as predictor for the onset of major depressive disorder according to DSM criteria in a middle-aged to older population [20]. This study was based on the medical records of patients with cardiovascular events in whom vitamin D levels were assessed in the clinical process. Confounding by indication, therefore, cannot be ruled out.

Acknowledging these inconsistencies and methodological issues of incidence studies, we may still expect an effect of vitamin D on the course of depression in light of the cross-sectional association between depression diagnoses and vitamin D status in our NESDO population [13], as well as its impact on course in younger adults [12]. So how can we explain our negative finding?

Firstly, an older population is more heterogeneous than a younger population. Consequently, due to the presence of multiple potential determinants of the course of depression, a small effect of vitamin D on depression might be masked by increased variability of other determinants in older patients compared to younger ones.

Secondly, in the larger Netherlands Study of Depression and Anxiety (NESDA) study (n = 922) [12], vitamin D affected the presence of depression diagnoses at follow up only for the vitamin D deficient group (<25 nmol/l). We found a similar trend towards a lower remission rate for the same group. However, due to the small number of severely vitamin D deficient patients in NESDO (n = 36) these analyses are underpowered. Moreover, the association of vitamin D deficiency and remission may partly be explained by depression severity, since severe vitamin D deficiency is associated with a higher depression severity (Table 3) and depression severity is a negative predictor for remission [45]. Taken together, the results of the NESDA and NESDO studies might be indicative for an association between vitamin D and depression, but only for the lowest vitamin D levels. This supports the

hypothesis that the brain is relatively protected from vitamin D deficiency compared to other organs [5].

Biologically active 1,25-(OH)$_2$ vitamin D

1,25-(OH)$_2$ vitamin D is not routinely measured. Its assessment is recommended in disorders of vitamin D or phosphate metabolism, as 1,25-(OH)$_2$ vitamin D levels may not adequately reflect vitamin D reserves and are thought to be frequently normal or elevated due to elevated serum PTH levels in vitamin D deficiency [46].

We found that lower 1,25-(OH)$_2$ vitamin D levels, just as 25-(OH) vitamin D levels, were associated with mortality. This might indicate that compensatory mechanisms do not always lead to elevated 1,25-(OH)$_2$ vitamin D levels in case of vitamin D deficiency. Furthermore, since cross-sectional results from NESDO demonstrated an even larger effect size for 1,25-(OH)$_2$ vitamin D than for 25-(OH) vitamin D on depression [13], it is possible that low 1,25-(OH)$_2$ vitamin D levels reflect a more severe vitamin D deficiency state than low 25-(OH) vitamin D levels.

Vitamin D, morbidity and mortality

The association between lower vitamin D levels and mortality is in line with a large meta-analysis demonstrating higher risks for all-cause and cardiovascular mortality for persons with 25-(OH) vitamin D levels in the lowest quintile [47]. Another meta-analysis of 14 studies showed a 29% decrease in all-cause mortality for the highest compared to the lowest quantiles of 25-(OH) vitamin D [48].

Since 25-(OH) vitamin D levels in these studies are strongly influenced by age, gender, season, education, obesity, physical activity and smoking, it is suggested that vitamin D deficiency is a marker for poor health status rather than a cause of mortality [47]. In line with this interpretation, we also observed that the effect of 25-(OH) vitamin D on total

and somatic IDS subscale scores disappears after correction for lifestyle factors reflecting physical fitness (smoking status, waist circumference, physical activity and use of alcohol). However, if only true vitamin D deficiency (25-(OH) vitamin D < 25 nmol/l) is taken into account, the effect on total and somatic IDS-SR subscale scores remains significant after correction for all covariates. This might be due to symptoms of somatic diseases resembling depressive symptoms, thereby influencing scores on depression symptom scales.

Methodological considerations

Strengths of our study are the large cohort of patients with clinical depression according to DSM-IV criteria, analyzing the categorical as well as dimensional perspective, and finally assessing both 25-(OH) vitamin D levels and 1,25-(OH)$_2$ vitamin D levels.

There are also some limitations. Firstly, our study is underpowered to detect effects in small subgroups, notably the vitamin D deficient group (<25 nmol/l). Since the mortality rate for our study is 6.5% at two years follow up, this might influence the detection of an effect of vitamin D on depression. Repeating all analyses using a worst-case scenario (all deceased patients still depressed at follow-up or last observation (IDS-SR) carried forward) did still reveal no effect of vitamin D on depression course.

Secondly, we did not obtain vitamin D levels at two-year follow-up and do not know whether vitamin D status is subject to change in our population. Some participants were on vitamin D supplementation, probably due to vitamin D-related conditions like osteoporosis. However, a sensitivity analysis excluding all patients on vitamin D supplementation at baseline or at two-year follow up did not reveal a significant effect of vitamin D levels on remission status at two-year follow up, just like the primary analysis.

Finally, we do not know the causes of death and thus whether this is due to potentially vitamin D- related causes.

Conclusions

A causal role for vitamin D in the pathophysiology of late-life depression seems unlikely. Nonetheless, we should be cautious, as we found a trend towards a less favorable course of depression in the subgroup with true vitamin D deficiency (25-(OH) vitamin D < 25 nmol/l), consistent with findings in younger age groups. Of even more interest, however, is the finding that lower vitamin D levels predicted mortality among depressed older persons. This supports previous observations of vitamin D deficiency as a marker for poor health status, while our results also point to overlap between somatic symptoms and symptoms of depression.

This might implicate that in case of depression, vitamin D deficiency is clinically relevant. Randomized controlled trials are needed to examine high-dose vitamin supplementation in depressed (older) patients with vitamin D levels under 25 nmol/l.

Acknowledgments and disclosures

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