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A prospective study into change of vitamin D levels, depression and frailty among depressed older persons

Karen S. van den Berg[1,2] | Johanna M. Hegeman[1] | Rob H. S. van den Brink[2] | Didi Rhebergen[3] | Richard C. Oude Voshaar[2] | Radboud M. Marijnissen[2]

[1]Department of Psychiatry, St Antonius Hospital, Nieuwegein/Utrecht, The Netherlands

[2]Department of Psychiatry, University Centre of Psychiatry, University Medical Centre Groningen, Groningen, The Netherlands

[3]Department of Psychiatry, VU University Medical Centre/GGZ InGeest, Amsterdam, The Netherlands

Correspondence
Karen S. van den Berg, Department of Psychiatry, St Antonius Hospital, postal box 2500, 3430 EM Nieuwegein, The Netherlands.
Email: k.van.den.berg@antoniusziekenhuis.nl

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Abstract

Objectives: While vitamin D is involved in frailty as well as depression, hardly any study has examined the course of vitamin D levels prospectively. The objective of this study is to examine whether a change of vitamin D in depressed older adults is associated with either depression course, course of frailty, or both.

Methods: The study population consisted of 232 of 378 older adults (60–93 years) with a DSM-IV defined depressive disorder participating in the Netherlands Study of Depression in Older persons, a prospective clinical cohort study. Baseline and 2-year follow-up data on depressive disorder (DSM-IV diagnosis), symptom severity (inventory of depressive symptoms), frailty phenotype (and its individual components) and vitamin D levels were obtained. Linear mixed models were used to study the association of change in vitamin D levels with depression course, course of frailty, and the combination.

Results: Vitamin D levels decreased from baseline to follow-up, independent from depression course. An increase in frailty was associated with a significantly sharper decrease of vitamin D levels over time. Post hoc analyses showed that this association with frailty might be driven by an increase of exhaustion over time and counteracted by an increase in walking speed.

Conclusions: Our findings generate the hypothesis that vitamin D supplementation in late-life depression may improve frailty, which may partly explain inconsistent findings of randomised controlled trials evaluating the effect of vitamin D for depression. We advocate to consider frailty (components) as an outcome in future supplementation trials in late-life depression.

KEYWORDS
depression, frailty, longitudinal associations, old age, vitamin D

Key Points

- Change in serum vitamin D is related to the course of frailty, and not independently to depression course

- Future vitamin D supplementation trials in depression should consider frailty (components) as an outcome

1 | INTRODUCTION

About half of the older persons has a vitamin D deficiency.[1] In addition to negative effects on bone health, low vitamin D levels are associated with higher prevalence of multi-morbidity.[2] Associations of vitamin D with several age-related conditions as well as the presence of nuclear vitamin D receptors in various organ systems has stimulated vitamin D research in geriatric medicine. Nonetheless, causality between vitamin D deficiency and many health conditions, in particular depressive disorder and frailty, remains elusive.

Meta-analyses of observational studies have identified cross-sectional as well as longitudinal associations of low vitamin D levels with depressive symptoms.[3–5] A causal effect is biologically plausible, as nuclear vitamin D receptors have been found in brain regions involved in depression.[6] Furthermore, vitamin D is involved in the regulation of growth factors, monoamine neurotransmitters and neuroinflammation.[7,8] Nonetheless, reverse causation cannot be excluded since depression-related behaviour easily results in less sun exposure.[9] Moreover, meta-analyses of vitamin D supplementation trials among depressed persons did not show an overall reduction of depressive symptoms.[10–12] Apart from this, the largest vitamin D supplementation trial among 18,353 persons did not reveal any effect on the prevention of depression over a 5-year follow-up.[13]

Meta-analysis also demonstrated an inverse association between frailty and vitamin D levels.[14] Again, a causal effect is biologically plausible as nuclear and non-nuclear vitamin D receptors are involved in calcium/phosphate homeostasis in muscle cells, as well as muscle cell differentiation and proliferation.[15] Low vitamin D levels have been consistently associated with declined muscle function.[16] A meta-analysis of randomised controlled trials into the effect of vitamin D supplementation among persons older than 60 years demonstrated a beneficial effect on muscle strength and balance.[17] Although sarcopenia is a core concept underlying frailty[18,19] the evidence to improve frailty by vitamin D supplementation is still insufficient.[20]

Since depression and frailty are bi-directionally associated,[21] the association between vitamin D deficiency and depression might be confounded by frailty. Furthermore, prospective studies into the association of vitamin D and depression almost without exception lack follow-up assessment of vitamin D levels. Therefore, the present study examines whether change of vitamin D levels over 2 years in older persons with a depressive disorder is related to course of depression and/or course of frailty. We hypothesise that vitamin D levels will improve over time in case of remission of the depression and further deteriorate in case of non-remission. In addition, we hypothesise that vitamin D levels over time are inversely associated with frailty over time.

2 | METHODS

2.1 | Study sample

The present study is part of the Netherlands Study of Depression in Older persons (NESDO), a multicentre prospective cohort study, designed to examine the determinants, course and consequences of late-life depression.[22,23] Between 2007 and 2010, 378 depressed persons were recruited from both mental health institutions and general practices, and 132 non-depressed comparisons were recruited from general practices. Participants were aged 60–93.

In the present study, only depressed persons were included. Depressed persons had a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR[24]) diagnosis of major depressive disorder (95.0%) and/or dysthymia (26.5%) in the previous 6 months, or minor depression (5.3%) in the last month. Reasons for exclusion from NESDO were a primary diagnosis of psychotic or bipolar disorder, or (suspicion of) dementia, a Mini-Mental State Examination[25] score <18/30, and insufficient command of the Dutch language. For the present study, we additionally excluded patients using vitamin D supplementation.

Participants were assessed at baseline and 2-year follow-up. Data were obtained about mental health outcomes, demographic characteristics as well as psychosocial, biological, cognitive and genetic determinants. Trained research assistants conducted the interviews.

The ethical review boards of the participating centres approved the study. All participants provided written informed consent. Data are available on request from the authors.

2.2 | Measures

2.2.1 | Vitamin D

Vitamin D levels were similarly assessed at baseline and 2-year follow up. Serum 25-(OH) vitamin D levels were measured using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously.[26] The limit of quantitation was 4.0 nmol/L and the intra-assay coefficient of variation was less than 7.2%.

2.2.2 | Depression

Depression was diagnosed at baseline and 2-year follow-up by the Composite International Diagnostic Interview (CIDI; WHO version 2.1, lifetime version). Depressed persons who no longer fulfilled the DSM criteria for any depressive disorder at follow-up were classified

as remitters. The severity of depression was assessed with the 30-item self-report version of the Inventory of Depressive Symptoms (IDS-SR[27]) at baseline and 2-year follow-up.

2.2.3 | Frailty

Frailty was assessed according to the frailty phenotype[18] and a severity score (0–5) was assigned, based on the number of criteria met[28]: *weakness:* maximum handgrip strength (as measured by two squeezes with the dominant hand in a dynamometer) below a cut-off stratified by sex and body mass index (BMI)[18]; *slowness:* time on a 6-m walking test ≥8 s for men ≥173 cm or women ≥159 cm tall, or ≥9 s for men <173 cm and women <159 cm tall; *exhaustion:* a score of ≥3 out of 4 points on one or both of the IDS questions about energy level and leaden paralysis/physical energy; *low physical activity:* no daily activities such as walking or gardening, and the performance of sports less than once a week, as assessed with the International Physical Activity Questionnaire (IPAQ[29]); and *unintended weight loss:* a positive answer to the CIDI question about unintended weight loss (≥1 kg/week, for 2 or more consecutive weeks) or a BMI < 18.5 kg/m^2.

Post hoc, we examined the change in the individual frailty components over time, namely maximum grip strength (in kg), time on the 6-m walking test (in s), sum score of the two exhaustion questions from the IDS (range: 2–8), Metabolic Equivalent (MET)—min per week (i.e., energy requirements of the physical activities performed, expressed as multiples of the resting metabolic rate) calculated from the IPAQ, and weight (in kg).

2.2.4 | Covariates

Based on their association with vitamin D level and depression,[30] the following covariates were selected: astronomical season of blood withdrawal at baseline and follow-up (winter: 21 November–20 February; spring: 21 February–20 May; summer: 21 May–20 August; autumn: 21 August–20 November), as well as baseline assessments of age, sex, years of education, smoking, physical activity, renal function, waist circumference in centimetres and number of chronic diseases. The level of physical activity was classified as either sufficient or insufficient according to the WHO as based on the validated norm scores of the IPAQ.[29,31] Glomerular filtration rates were estimated by the Chronic Kidney Disease Epidemiologic Collaboration[32] formula to assess renal function. The number of chronic diseases was assessed by means of self-report, as previously validated.[33]

2.2.5 | Statistical analysis

Baseline characteristics were compared by χ^2 tests, *t*-tests for independent samples, and non-parametric tests for (1) study participants versus dropouts and (2) included participants stratified by depression status at follow-up. *p*-Values less than 0.05 were considered significant.

Random coefficient mixed-effect models were used to study the associations between change in vitamin D levels on the one hand and depression course and course of frailty on the other. The dependent variable in these analyses was vitamin D level, corrected for season of blood withdrawal, as assessed at baseline and 2-year follow-up. To determine the best-fitting model, models with random coefficients for intercept and/or slope per subject were compared using the likelihood ratio test. For all analyses, a random intercept model was the best fitting model.

In separate analyses, the association of change in vitamin D with the following independent variables was examined: depression course, as assessed by (1) remission (yes/no), and (2) change in IDS score over the follow-up period; and course of frailty as assessed by (3) change in frailty score, and by (4) change in each individual frailty component score. Presence of an association was tested by the interaction of the independent variable with the variable 'time', which indicated assessment of vitamin D level at baseline or follow-up. This interaction shows whether the change in vitamin level from baseline to follow-up is associated with the independent variable and will be indicated in short as 'the interaction between change in vitamin D level and the independent variable'.

All independent variables were coded so that a positive regression coefficient (i.e., the estimate of the effect studied) indicates that an increase in health (e.g., remission of depression or reduction of frailty) is related to an increase in vitamin D level.

In a final analysis, the strongest associations of change in vitamin D level with depression course (either analysis 1 or 2 above) and course of frailty (analysis 3 or 4) were compared and checked for mutual independence by including both interactions in the model. For this selection, effect sizes (ES) of the strength of an association were computed, by dividing the regression coefficient for the above interaction by the standard deviation of the outcome variable (i.e., vitamin D level for all analyses) at baseline and multiplying it with the standard deviation at baseline of the independent variable (for continuous variables) or 1 (for categorical variables).

Analyses were performed using IBM SPSS statistics version 24 and were adjusted for all covariates.

3 | RESULTS

3.1 | Study sample

Of the 378 depressed persons included in NESDO, 232 (61.4%) participated in the present study (dropout at follow-up: $n = 93$; vitamin D level missing at baseline or follow-up: $n = 29$; vitamin D supplementation: $n = 24$). At baseline, excluded persons were more frequently frail than participants (37% vs. 26%; $\chi^2 = 5.28$, $df = 1$, $p = 0.022$) and had a lower vitamin D level (49.5 [22.4] vs. 54.5 [23.6] nmol/L; $t = 1.97$, $df = 365$, $p = 0.050$), but did not differ with respect to age, sex or depressive symptom severity.

The characteristics of the study sample ($n = 232$), stratified by depression status at follow-up, are presented in Table 1.

TABLE 1 Characteristics of the study sample, stratified by depression status at 2-year follow-up

Characteristic	Non-remitted depression N = 112	Remitted depression N = 120	Statistic
Age (year)—mean (*SD*)	70.8 (7.8)	69.9 (7.1)	$t = 0.86$, $df = 230$, $p = 0.390$
Sex (male)—*n* (%)	42 (37.5%)	43 (35.8%)	$\chi^2 = 0.07$, $df = 1$, $p = 0.792$
Education (years)—mean (*SD*)	10.7 (3.7)	10.8 (3.3)	$t = 0.11$, $df = 230$, $p = 0.910$
Number of chronic diseases—mean (*SD*)	2.4 (1.6)	1.7 (1.1)	$t = 3.87$, $df = 230$, $p < 0.001$[a]
Sufficient physical activity (IPAQ-based)—*n* (%)	80 (71.4%)	88 (73.3%)	$\chi^2 = 0.78$, $df = 1$, $p = 0.377$
Currently smoking—*n* (%)	30 (26.8%)	25 (20.8%)	$\chi^2 = 1.06$, $df = 1$, $p = 0.303$
Waist circumference (cm)—mean (*SD*)	94.8 (13.7)	90.8 (11.2)	$t = 2.42$, $df = 230$, $p = 0.016$[a]
Renal function (CKD-EPI [ml/min/1.73 m^2])—mean (*SD*)	70.8 (17.3)	74.8 (14.4)	$t = 1.91$, $df = 230$, $p = 0.057$
IDS[c] score (0–84)—mean (*SD*)	33.6 (12.2)	25.6 (11.9)	$t = 5.04$, $df = 228$, $p < 0.001$[a]
Frailty present—*n* (%)	31 (27.7%)	26 (21.7%)	$\chi^2 = 1.44$, $df = 1$, $p = 0.230$
Frailty score (0–5)—mean (*SD*)	1.9 (1.3)	1.5 (1.3)	$t = 2.16$, $df = 210$, $p = 0.032$[a]
Frailty components			
• Grip strength (kg)—mean (*SD*)	28.6 (11.3)	29.4 (12.4)	$t = -0.51$, $df = 230$, $p = 0.661$
• 6-m walking time (s)—mean (*SD*)[b]	7.8 (4.0)	6.8 (3.7)	$U = 5439.0$, $p = 0.019$[a]
• Exhaustion (score 2–8)—mean (*SD*)	4.9 (1.6)	4.4 (1.6)	$t = 2.52$, $df = 223$, $p = 0.012$[a]
• MET-min/week—mean (*SD*)	2480.2 (2260.1)	2751.5 (2375.5)	$t = 0.88$, $df = 223$, $p = 0.381$
• Weight (kg)—mean (*SD*)	76.1 (15.3)	72.5 (13.9)	$t = 1.89$, $df = 230$, $p = 0.061$
Season of blood withdrawal—*n* (%)			
• Winter	18 (16.1%)	23 (19.2%)	$\chi^2 = 1.12$, $df = 3$, $p = 0.772$
• Spring	35 (31.3%)	31 (25.8%)	
• Summer	36 (32.1%)	38 (31.7%)	
• Autumn	23 (20.5%)	28 (23.3%)	
25-OH vitamin D (nmol/L)			
• Baseline	54.1 (24.1)	54.9 (23.1)	$t = -0.26$, $df = 230$, $p = 0.797$
• 2-year follow-up	50.4 (23.0)	46.8 (19.7)	$t = 1.23$, $df = 230$, $p = 0.207$

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IDS, Inventory of Depressive Symptomatology; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalent Time.

[a]Statistically significant ($p < 0.050$).

[b]Skewed distribution; Mann–Whitney *U*-test performed, corrected for tied ranks.

3.2 | Change of vitamin D over time

In the remitted subgroup, vitamin D levels decreased more over the 2 years follow-up period (t for paired observations 4.83, $p = <0.001$) than in the non-remitted subgroup ($t = 1.82$, $p = 0.071$). However, linear mixed models showed that—also after controlling for covariates—change in vitamin D did not depend on depression status at follow-up (see Table 2). Nonetheless, an increase in vitamin D was associated with a decrease of the IDS score. Each point reduction on the IDS was related to a vitamin D level increase of 0.22 nmol/L ($SE = 0.11$; $p = 0.049$; ES is 0.12).

The interaction between course of frailty and change in vitamin D level are presented in Table 3. As shown, an increase in vitamin D levels proved to be related to a decrease in continuous frailty score: each frailty criterion less was related to a vitamin D increase of 3.04 ($SE = 1.14$) nmol/L (ES = 0.17, $p = 0.008$). Post hoc analyses suggested that an increase of vitamin D over time was in particular associated with decreasing scores on exhaustion and an increasing 6-m walking time (i.e., a slower gait speed), although results were not statistically significant (exhaustion: ES = 0.10, $p = 0.054$; walking time: ES = −0.11, $p = 0.066$).

3.3 | Combined analyses on frailty and depression

In the final analysis (see Table 4), we examined the association of vitamin D with either change in depression (IDS score) or frailty

TABLE 2 Interaction between change in vitamin D and depression course

Interaction with	F	p	Course type	Estimate (standard error)	Effect size (95%-confidence interval)
Disease model:					
Depression status at follow-up[a]	3.16	0.077	Remission	−4.61 (2.60)	−0.20 (−0.41; 0.02)
			Non-remission (=reference)	0	
Dimensional depression model:					
Change in IDS score	3.90	0.049[b]	Each point less on IDS	0.22 (0.11)	0.12 (0.00; 0.24)

Abbreviation: IDS, Inventory of Depressive Symptoms.

[a]Adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow-up), smoking, physical activity, number of chronic diseases, and waist circumference.

[b]Statistically significant ($p < .050$).

TABLE 3 Interaction between change in vitamin D and course of frailty

Interaction with	F	p	Course type	Estimate (standard error)	Effect size (95-% Confidence interval)
Severity of frailty:					
• Change in frailty score[a]	7.08	0.008[b]	Each frailty criterion less	3.04 (1.14)	0.17 (0.04; 0.29)
Frailty components:					
• Change in grip strength[a]	0.07	0.799	Each additional kg grip strength	0.04 (0.16)	0.02 (−0.13; 0.18)
• Change in 6-m walking time[a,c]	3.41	0.066	Each second walking time less	−0.67 (0.36)	−0.11 (−0.23; 0.01)
• Change in exhaustion[a]	3.75	0.054	Each point less on exhaustion questions	1.54 (0.80)	0.10 (−0.00; 0.21)
• Change in MET-min[d]	0.19	0.668	Each additional 1000 MET-min	0.21 (0.48)	0.02 (−0.07; 0.11)
• Change in weight[a]	1.44	0.232	Each additional kg	0.32 (0.26)	0.20 (−0.12; 0.52)

Abbreviation: MET, Metabolic Equivalent Time.

[a]Adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow up), smoking, physical activity, number of chronic diseases, and waist circumference.

[b]Statistically significant ($p < .050$).

[c]Δ 6-m walking time is normally distributed.

[d]Adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow up), smoking, number of chronic diseases, and waist circumference.

(number of components) when controlled for each other. This analysis showed that an increase in vitamin D level over a 2-year follow-up remained significantly associated with improved frailty scores when adjusted for the change in depression (ES is 0.13; $p = 0.042$), whereas no independent association with the change in depression was found.

4 | DISCUSSION

4.1 | Main findings

In our large sample of depressed older persons, vitamin D levels decreased over a 2-year follow-up. Increasing vitamin D levels were associated with improvement of depressive symptom severity as well as frailty. Nonetheless, analysing the association between vitamin D with depressive symptom severity and frailty simultaneously revealed only an independent effect with frailty. Post hoc analyses showed that the association of increasing vitamin D levels with decreasing frailty over time may be driven by the frailty component of exhaustion and counteracted by the frailty component of walking speed.

4.2 | Vitamin D and depression

Although meta-analyses of longitudinal studies demonstrated that baseline vitamin D level is related to depression course,[3,4] in other studies only cross-sectional associations have been found, which could be due to residual confounding or reverse causality.[9,34] The only prospective study up till now with multiple vitamin D

TABLE 4 Combined interactions of depression course and course of frailty with change in vitamin D

Interaction with	F	p	Course type	Estimate (standard error)	Effect size (95% confidence interval)
Change in frailty score[a]	4.19	0.042[b]	Each frailty criterion less	2.47 (1.21)	0.14 (0.01; 0.27)
Change in IDS score[a]	2.02	0.157	Each point less on IDS	0.18 (0.13)	0.10 (−0.04; 0.23)

Abbreviation: IDS, Inventory of Depressive Symptoms.

[a]Adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow-up), smoking, physical activity, number of chronic diseases, and waist circumference.

[b]Statistically significant ($p < 0.050$).

assessments as in our study, demonstrated an association between increasing vitamin D levels and decreasing depressive symptom scores, but only in the youngest cohort (55–65 years) with vitamin D levels less than 58.6 nmol/L and not in persons older than 65 years.[35]

Since we did not find an independent association of depression course with change in vitamin D, our results do not support a causal relationship in any direction between a clinical depression diagnosis and vitamin D deficiency.

We found a significant association between increasing IDS scores and decreasing vitamin D levels, which lost significance after addition of the association with frailty to the model. This is an important finding, since in the majority of studies included in meta-analyses into the association between vitamin D and depression[3,4] depression was defined as a score above a cut-off on a depressive symptom scale and none of the included studies adjusted for physical frailty. Due to overlapping criteria, self-reported depressive symptom scales may easily be confounded by the severity of physical frailty.[36–38]

4.3 | Vitamin D and frailty

In line with our results, significant associations between low vitamin D levels and frailty were demonstrated in a prospective study[39] and a meta-analysis of cross-sectional studies.[40] Previously, an association between lower baseline vitamin D levels and prevalence and incidence of frailty was demonstrated among depressed older persons.[41] Since sarcopenia is considered a main feature of frailty,[19] vitamin D deficiency might contribute to frailty by decreasing muscle function. In case of deficiency, the direct and indirect molecular effects of vitamin D on the muscle cell decline, as well as its anti-inflammatory properties, which may contribute to the prevention of frailty. Furthermore, hyperparathyroidism may arise, leading to loss of muscle function.[42] On the other hand, frailty may, similar to depression, contribute to low vitamin D levels by reduction of sunlight exposure due to decreased outdoor activities.

The finding that (remission of) depressive disorder was not associated with change in vitamin D levels and the association between changes in depressive symptoms and vitamin D levels disappeared after correction for frailty, may point to confounding of self-report depressive symptom severity by frailty. Frailty and depression are closely associated, with meta-analyses classifying 40.4% of depressed patients as being frail and 38.6% of frail persons as being depressed.[21] Furthermore, frailty and depression have overlapping diagnostic criteria, such as exhaustion, weight loss, reduced activity and psychomotor slowness. Our findings lead to the hypothesis that, in light of this high level of comorbidity and overlapping diagnostic criteria,[36–38] confounding by frailty of studies into the association between depression and vitamin D is indeed likely. This hypothesis fits with the results of an Australian cohort study showing a crude mortality hazard of 4.3 for depression among males older than 75 years, which dropped to 1.8 after additional correction for frailty.[43]

Subsequent analyses showed that the longitudinal association between vitamin D and frailty might be driven by subjective feelings of exhaustion. Signs of exhaustion may clinically easily be mixed up with symptoms of depression. Although exhaustion was measured by two items from the IDS questionnaire, it is known that self-report items of exhaustion are strongly associated with performance on a physical graded exercise test[44] and predictive of cardiovascular disease.[45] This means that in a depressed older population, feelings of exhaustion might be a better indicator of physical health than of depression.

Interestingly, the frailty component slowness showed a trend in the opposite direction ($p = 0.066$), but this effect was apparently not strong enough to nullify the association between vitamin D and frailty severity.

4.4 | Limitations

Compared to other studies, we found a strong decrease in vitamin D (−6.0 nmol/L) in 2 years. In most population-based studies, vitamin D levels were relatively stable during follow-up.[46–49] In the subgroup older than 65 years of the Longitudinal Aging Study Amsterdam vitamin D levels decreased on average 6.9 nmol/L in 13 years.[35] An explanation for our comparable decrease in a shorter time might be that normal behavioural changes with ageing that add to lower vitamin D levels, such as less dietary intake of vitamin D and less time spent outdoors,[50] might have been amplified in our depressed population. Another explanation is our exclusion of participants on vitamin D supplementation, since in other studies supplementation is considered an important contributing factor to increasing vitamin D levels.[46,48] Nevertheless, systematic bias cannot be fully excluded. The baseline vitamin D assessments were performed shortly after blood collection, whereas follow-up vitamin D assessments were done after a storage period of at least 6 years. However, even when

duration of storage would have affected the absolute values at follow-up, this would not have biased the association with change in depression or frailty. Finally, our follow-up period of 2 years was relatively short, compared to other studies on tracking of vitamin D levels. Since remission of depression was based on the 6 months before follow-up, the period for recovering vitamin D levels might have been too short in some patients. This is especially relevant as it is not clear how long it takes for vitamin D levels to restore after resumption of outdoor activities.

4.5 | Conclusions and implications

Among depressed older patients, an increase of vitamin D levels over the course of 2 years was not associated with a change in depression, while it was associated with improving frailty scores. Interestingly, frailty and depression are often intertwined, and exhaustion may be a feature of both conditions. Since exhaustion is a probable driving factor in the association between increasing vitamin D levels and improving frailty scores, it may be more related to physical health than to depression. Based on our results, we hypothesise that this might have added to inconclusive findings on the relationship between depression and vitamin D in previous studies. Future supplementation trials should consider inclusion of frailty and exhaustion as outcomes, besides depression parameters.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

ORCID

Karen S. van den Berg https://orcid.org/0000-0001-6085-9552
Richard C. Oude Voshaar https://orcid.org/0000-0003-1501-4774

REFERENCES

1. van Schoor NM, Lips P. Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab*. 2011;25(4):671-680.
2. Meems LM, de Borst MH, Postma DS, et al. Low levels of vitamin D are associated with multimorbidity: results from the LifeLines Cohort Study. *Ann Med*. 2015;47(6):474-481.
3. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *Br J Psychiatry*. 2013 Feb;202:100-107.
4. Ju SY, Lee YJ, Jeong SN. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. *J Nutr Health Aging*. 2013;17(5):447-455.
5. Li H, Sun D, Wang A, et al. Serum 25-hydroxyvitamin D levels and depression in older adults: a dose-response meta-analysis of prospective cohort studies. *Am J Geriatr Psychiatry*. 2019 Nov;27(11):1192-1202. https://doi.org/10.1016/j.jagp.2019.05.022
6. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat*. 2005;29(1):21-30.
7. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol*. 2013 Jan;34(1):47-64.
8. Berridge MJ. Vitamin D and depression: cellular and regulatory mechanisms. *Pharmacol Rev*. 2017;69(2):80-92.
9. Jovanova O, Aarts N, Noordam R, Zillikens MC, Hofman A, Tiemeier H. Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression. *Acta Psychiatr Scand*. 2017;135(3):185-194.
10. Gowda U, Mutowo MP, Smith BJ, Wluka AE, Renzaho AM. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. *Nutrition*. 2015;31(3):421-429.
11. Li G, Mbuagbaw L, Samaan Z, et al. Efficacy of vitamin D supplementation in depression in adults: a systematic review. *J Clin Endocrinol Metab*. 2014;99(3):757-767.
12. Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med*. 2014;76(3):190-196.
13. Okereke OI, Reynolds CF , 3rd, Mischoulon D, et al. Effect of long-term vitamin D3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. *J Am Med Assoc*. 2020;324(5):471-480.
14. Ju SY, Lee JY, Kim DH. Low 25-hydroxyvitamin D levels and the risk of frailty syndrome: a systematic review and dose-response meta-analysis. *BMC Geriatr*. 2018;18(1):206. https://doi.org/10.1186/s12877-018-0904-2
15. Remelli F, Vitali A, Zurlo A, Volpato S. Vitamin D deficiency and sarcopenia in older persons. *Nutrients*. 2019;11(12):2681. https://doi.org/10.3390/nu11122861
16. Halfon M, Phan O, Teta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. *BioMed Res Int*. 2015;2015:953241.
17. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2011;59(12):2291-2300. https://doi.org/10.1111/j.1532-5415.2011.03733.x
18. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156.
19. Morley JE. Frailty and sarcopenia in elderly. *Wien Klin Wochenschr*. 2016;128(suppl 7):439-445.
20. Dent E, Morley JE, Cruz-Jentoft AJ, et al. Physical frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. *J Nutr Health Aging*. 2019;23(9):771-787.
21. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: a systematic review and meta-analysis. *Ageing Res Rev*. 2017;36:78-87.
22. Comijs HC, van Marwijk HW, van der Mast RC, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4:524.
23. Comijs HC, Nieuwesteeg J, Kok R, et al. The two-year course of late-life depression; results from The Netherlands study of depression in older persons. *BMC Psychiatry*. 2015;15:20.

24. American Psychiatric Association. *Diagnostic and Statistics Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Publishing; 2000.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
26. Doorenbos CR, de Cuba MM, Vogt L, et al. Antiproteinuric treatment reduces urinary loss of vitamin D-binding protein but does not affect vitamin D status in patients with chronic kidney disease. *J Steroid Biochem Mol Biol*. 2012;128:56-61.
27. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477-486.
28. Collard RM, Comijs HC, Naarding P, Oude Voshaar RC. Physical frailty: vulnerability of patients suffering from late-life depression. *Aging Ment Health*. 2014;18(5):570-578.
29. Craig CL, Marshall AL, Sjostrom M, et al. International Physical Activity Questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395.
30. Oude Voshaar RC, Derks WJ, Comijs HC, Schoevers RA, de Borst MH, Marijnissen RM. Antidepressants differentially related to 1,25-$(OH)_2$ vitamin D_3 and 25-(OH) vitamin D_3 in late-life depression. *Transl Psychiatry*. 2014 Apr 15;4:e383.
31. Wassink-Vossen S, Collard RM, Penninx BW, Hiles SA, Oude Voshaar RC, Naarding P. The reciprocal relationship between physical activity and depression: does age matter? *Eur Psychiatry*. 2018;51:9-15. https://doi.org/10.1016/j.eurpsy.2017.12.029
32. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
33. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49(12):1407-1417.
34. Libuda L, Laabs BH, Ludwig C, et al. Vitamin D and the risk of depression: a causal relationship? Findings from a Mendelian randomization study. *Nutrients*. 2019;11(5):1085. https://doi.org/10.3390/nu11051085
35. Elstgeest LEM, de Koning EJ, Brouwer IA, van Schoor NM, Penninx BWJH, Visser M. Change in serum 25-hydroxyvitamin D and parallel change in depressive symptoms in Dutch older adults. *Eur J Endocrinol*. 2018;179(4):239-249. https://doi.org/10.1530/EJE-18-0187
36. Mezuk B, Lohman M, Dumenci L, et al. Are depression and frailty overlapping syndromes in mid- and late-life? A latent variable analysis. *Am J Geriatr Psychiatry*. 2013;21:560-569.
37. Lohman M, Dumenci L, Mezuk B. Depression and frailty in late life: evidence for a common vulnerability. *J Gerontol B Psychol Sci Soc Sci*. 2016;71:630-640.
38. Lohman M, Dumenci L, Mezuk B. Gender differences in the construct overlap of frailty and depression: evidence from the Health and Retirement Study. *J Am Geriatr Soc*. 2014;62:500-505.
39. Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. *J Clin Endocrinol Metab*. 2013;98(9):3821-3828.
40. Zhou J, Huang P, Liu P, et al. Association of vitamin D deficiency and frailty: a systematic review and meta-analysis. *Maturitas*. 2016;94:70-76.
41. van den Berg KS, Arts MHL, Collard RM, et al. Vitamin D deficiency and course of frailty in a depressed older population. *Aging Ment Health*. 2020;24(1):49-55.
42. Bruyere O, Cavalier E, Buckinx F, Reginster JY. Relevance of vitamin D in the pathogenesis and therapy of frailty. *Curr Opin Clin Nutr Metab Care*. 2017;20(1):26-29.
43. Almeida OP, Hankey GJ, Yeap BB, et al. Depression, frailty, and all-cause mortality: a cohort study of men older than 75 years. *J Am Med Dir Assoc*. 2015;16:296-300.
44. Kop WJ, Appels APWM, Mendes de Leon CF, Bär FW. The relationship between severity of coronary artery disease and vital exhaustion. *J Psychosom Res*. 1996;40:397-405.
45. Kop WJ, Appels APWM, Mendes de Leon CF, de Swart HB, Bär FW. Vital exhaustion predicts new cardiac events after successful coronary angioplasty. *Psychosom Med*. 1994;56:281-287.
46. Berger C, Greene-Finestone LS, Langsetmo L, et al. Temporal trends and determinants of longitudinal change in 25-hydroxyvitamin D and parathyroid hormone levels. *J Bone Min Res*. 2012;27(6):1381-1389.
47. Jorde R, Sneve M, Hutchinson M, Emaus N, Figenschau Y, Grimnes G. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. *Am J Epidemiol*. 2010;171(8):903-908.
48. McKibben RA, Zhao D, Lutsey PL, et al. Factors associated with change in 25-hydroxyvitamin D levels over longitudinal follow-up in the ARIC study. *J Clin Endocrinol Metab*. 2016;101(1):33-43.
49. van Schoor NM, Knol DL, Deeg DJ, Peters FP, Heijboer AC, Lips P. Longitudinal changes and seasonal variations in serum 25-hydroxyvitamin D levels in different age groups: results of the Longitudinal Aging Study Amsterdam. *Osteoporos Int*. 2014;25(5):1483-1491.
50. de Jongh RT, van Schoor NM, Lips P. Changes in vitamin D endocrinology during aging in adults. *Mol Cell Endocrinol*. 2017;453:144-150.

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