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Vitamin D Status and Depressive Symptoms in Older Adults: A Role for Physical Functioning?

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Objectives: *Depressive symptoms and low vitamin D status are common in older persons and may be associated, but findings are inconsistent. This study investigated whether 25-hydroxyvitamin D (25(OH)D) concentrations are associated with depressive symptoms in older adults, both cross-sectionally and longitudinally. We also examined whether physical functioning could explain this relationship, to gain a better understanding of the underlying mechanisms.* **Methods:** *Data from two independent prospective cohorts of the Longitudinal Aging Study Amsterdam were used: an older cohort (≥65 years, n = 1282, assessed from 1995–2002) and a younger-old cohort (55–65 years, n = 737, assessed from 2002–2009).* **Measurements:** *Depressive symptoms were measured at baseline and after 3 and 6 years with the Center of Epidemiological Studies Depression Scale. Cross-sectional and longitudinal linear regression techniques were used to examine the relationship between 25(OH)D and depressive symptoms. The mediating role of physical functioning was examined in the longitudinal models.* **Results:** *Cross-sectionally, associations were not significant after adjustment for confounders. Longitudinally, women in the older cohort with baseline 25(OH)D concentrations up to 75 nmol/L experienced 175 to 24% more depressive symptoms in the following 6 years, compared with women with 25(OH)D concentrations >75 nmol/L. Reduced physical performance partially mediated this relationship. In men and in the younger-old cohort, no significant associations were observed.* **Conclusions:** *Older women showed an inverse relationship between 25(OH)D and depressive symptoms over time, which may partially be explained by declining physical functioning. Replication of these findings by future studies is needed.* (Am J Geriatr Psychiatry 2018; 26:1131–1143)

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Article Highlights

- This study examined the association between vitamin D status and depressive symptoms.
- Physical functioning was explored as a possible mediator in this relationship.
- Two large cohorts of older persons were analyzed cross-sectionally and longitudinally.
- Older women with low vitamin D status reported more depressive symptoms over time.
- Decreased physical functioning may partially explain this association.

Worldwide, depression is a leading cause of disability, resulting in significant individual and societal burden.[1] In addition, low 25-hydroxyvitamin D (25(OH)D) concentrations are common, especially among older persons.[2,3] Meta-analyses have shown an inverse association between 25(OH)D concentrations and depressive symptoms, but findings are inconsistent and longitudinal studies are scarce.[4,5]

A large Italian population-based cohort of older adults found that persons with low baseline 25(OH)D had more depressive symptoms after 3 and 6 years compared with persons with higher baseline 25(OH)D.[6] Chan et al. found an inverse cross-sectional, but no prospective, association between 25(OH)D and depressive symptoms in older persons,[7] whereas Williams et al. observed the opposite pattern.[8] Furthermore, older adults with low 25(OH)D had an almost threefold risk of major depressive disorder (MDD) after one year compared with persons with normal 25(OH)D concentrations, in a population with cardiovascular disease.[9]

Biologically, a link between vitamin D status and depressive symptoms is plausible, through protective functions of vitamin D metabolites in the brain[10–12] and the presence of the vitamin D receptor in depression-related brain areas such as the hippocampus.[13] To better understand the mechanisms underlying the presumed association between 25(OH)D and depression, a mediating role of physical functioning in this relationship can also be considered. Physical functioning is associated with both 25(OH)D and depression: Low 25(OH)D concentrations were associated with lower and declining physical performance,[14,15] and bidirectional cross-sectional and prospective relationships between physical functioning and depression have been observed.[16–20]

The present cohort study investigated whether 25(OH)D concentrations are associated with the severity (cross-sectionally) and the course and onset (longitudinally) of depressive symptoms in older adults. In secondary analyses, this study investigated whether physical functioning explains the association between 25(OH)D and depressive symptoms. Data from two independent cohorts of the Longitudinal Aging Study Amsterdam (LASA) were used.[21] Part of this data set was also used in a cross-sectional study by Hoogendijk et al.,[2] on which the present study elaborates. Hoogendijk et al. observed that depressive symptoms (as determinant) were associated with lower 25(OH)D in one LASA cohort. The present study additionally investigated a second LASA cohort and examined longitudinal associations. By studying two independent cohorts, we aimed to provide more insight into the relationship between 25(OH)D and depressive symptoms across a wide age range.

METHODS

Design and Study Sample

LASA is an ongoing population-based prospective cohort study that investigates the predictors, consequences, and time course of physical, cognitive, emotional, and social functioning in multiple cohorts of older adults.[21] Participants were recruited from municipality registries in three regions in the Netherlands, together constituting a representative sample of the Dutch older population. Every 3 years, LASA participants are invited for interviews and questionnaires. Interviews are conducted at the participants' homes by trained interviewers.

Data from two LASA cohorts were used. In 1992, 3,107 participants aged 55 to 85 years were included in the first LASA cohort ("older cohort"). As 25(OH)D

was first assessed in 1995–1996, we took this second measurement cycle as baseline for this cohort. Participants of 65 years and older who agreed to have an additional medical interview (n = 1,509) were asked to donate a blood sample. Serum 25(OH)D levels were available from 1,320 participants.

The second LASA cohort commenced in 2002–2003 with 1,002 participants aged 55 to 65 years ("younger-old cohort"). Of the 919 participants who agreed to the medical interview, 739 participants had data on 25(OH)D.

Follow-up time for the present study was 6 years. Follow-up data were collected at the subsequent two measurement cycles: in 1998–1999 and 2001–2002 (older cohort), and in 2005–2006 and 2008–2–09 (younger-old cohort).

All participants gave written informed consent prior to the start of the study. The LASA study was approved by the medical ethics committee of the VU University Medical Center. Detailed information about LASA and its participants can be found elsewhere.[21]

Measurements

Depressive Symptoms

The Center for Epidemiological Studies Depression Scale (CES-D)[22] was assessed at baseline and 3 and 6 years in both cohorts. The CES-D is a widely used screening instrument that contains 20 items about depressive symptoms as experienced in the previous week. Scores range from 0 to 60, with higher scores indicating more depressive symptoms. A score of 16 or more is indicative for clinically relevant depressive symptoms. The CES-D displays high reliability[23] and good criterion validity[24] in several older populations.

Blood Sampling and Measurement of 25(OH)D

Morning blood samples for the assessment of serum 25(OH)D (in nmol/L) were obtained in 1995–1996 (older cohort) and 2002–2003 (younger-old cohort). Participants were allowed to have a light breakfast without dairy products. Samples were centrifuged and stored at –20°C until 25(OH)D determination in 1997–1998 (older cohort) and 2010–2011 (younger-old cohort). The analyses were carried out by the VU University Medical Center Endocrine Laboratory. A competitive protein-binding assay (Nichols Diagnostics, Capistrano, CA; interassay coefficient of variation [CV]: 10%) was used for the sample determinations in the older cohort, whereas a radioimmunoassay (Diasorin, Stillwater, MN; interassay CV: 10%) was used for the younger-old cohort. For the statistical analyses of the present study, 25(OH)D was divided into four categories using commonly used cutoff values: less than 30 nmol/L (deficiency), 30 to 50 nmol/L (insufficiency), 50 to 75 nmol/L, and greater than 75 nmol/L.[25,26]

Potential Effect Modifier and Confounders

Sex was examined as a potential effect modifier, as previous studies observed different associations between 25(OH)D and depressive symptoms in men and women.[6,9] Education level (years), smoking habits (never, former, current smoker), alcohol consumption (grams/week, 10 g per consumption), presence of the most prevalent somatic chronic diseases among Dutch older adults (asthma/chronic obstructive pulmonary disease, cardiac disease [myocardial infarction, coronary artery disease, heart failure, disease of the cardiac valves, arrhythmia], peripheral arterial disease, diabetes mellitus, cerebrovascular accident/stroke, osteoarthritis/rheumatoid arthritis, cancer, hypertension, and other diseases that are present for at least 3 months) and general cognitive functioning (Mini-Mental State Examination)[27] were obtained during the interviews and questionnaires. To control for seasonal variations in 25(OH)D concentrations,[28] the blood collection dates were dichotomized into winter (October–March) and summer (April–September). Body mass index was calculated by dividing measured body weight (in kilograms) by measured body height (in meters) squared. Information on physical activity in the previous 2 weeks (walking, cycling, sports, heavy household activities, in minutes/day, plus the question whether these activities were representative compared to the previous year) was taken from the LASA Physical Activity Questionnaire (LAPAQ).[29]

Potential Mediating Variables

To cover a broad domain of physical functioning, both objective performance tests and self-reported functional limitations were examined for their possible mediating role in the association between 25(OH)D and depressive symptoms. A modified version of the Short

Physical Performance Battery (SPPB)[15,30] was used to assess physical performance. The SPPB includes three tests: walking speed (walking 3 meters, turning around and walking back 3 meters as fast as possible), chair stands (standing up from a chair without using hands five times consecutively, as fast as possible) and standing balance (standing with one foot directly in front of the other for up to 10 seconds). In the older cohort, the total score of the SPPB ranged from 0 to 12. As the balance test was not administered to the younger-old cohort at baseline, the SPPB score for this cohort was composed of the walking speed and chair stands scores only, resulting in a score range of 0 to 8. Higher scores indicate better physical performance.

Functional limitations were measured with six questions assessing common daily activities: climbing stairs, cutting toenails, walking 5 minutes without resting, rising from a chair, (un)dressing, and using own/public transportation.[31] The participants indicated whether they had difficulty performing these activities (score range: 0–6). Higher scores indicate more functional limitations.

Statistical Analyses

As the two cohorts differed in age range, assessment period, and 25(OH)D assay, analyses were conducted separately for both cohorts. All analyses were conducted with SPSS version 22 (SPSS Inc., Chicago, IL), except for the mediation analyses, which were conducted with Mplus (version 7.2) and R statistical software (version 3.2.5). A double-sided p value of less than 0.05 was considered statistically significant. Baseline descriptive statistics were calculated and presented as n / % for categorical variables or as median / interquartile range for skewed continuous variables. Cross-sectional and longitudinal non-response analyses comparing included and excluded participants were conducted with Pearson χ^2 tests for categorical variables or with non-parametric Mann-Whitney tests for skewed continuous variables.

As the distribution of the CES-D scores was skewed to the right, these scores were log-transformed using the formula ln(1 + CES-D score). The four 25(OH)D categories were entered as three dummy variables in the regression analyses, with the >75 nmol/L group as reference category. To test the association of 25(OH)D with depressive symptoms, we first looked at the overall, three degrees of freedom (df) tests of the 25(OH)D dummies. If this test was statistically significant, we subsequently looked at the associations of the separate dummy variables with depressive symptoms. The Bs, standard errors (SEs), and confidence intervals (CIs) of the regression analyses were transformed back to obtain interpretable ratios (e^B = ratio). These ratios reflect the percentage of change in the outcome per one unit change in the determinant. As these ratios and resulting percentages were calculated from a log-transformed scale, note that they do not correspond to the same change in CES-D across all CES-D scores: higher scores change more than lower scores. For instance, with a ratio of 1.23 and corresponding percentage change of 23%, a CES-D score of 20 changes 4.6 points (23% of 20), whereas a CES-D score of 10 changes 2.3 points (23% of 10).

Cross-Sectional Analyses

Multiple linear regression analyses with the 25(OH)D categories as determinants and the CES-D score as outcome were conducted. To assess effect modification, sex and interaction terms of the 25(OH)D categories with sex (25(OH)D dummies × gender) were added to the unadjusted model. If an interaction term had a p value of less than 0.05, stratified analyses for men and women were conducted. If no effect modification was present, sex was added as a confounder to the analyses. Adjustments for demographic variables (age, sex, education level, season of blood collection) were made in Model 1; additional adjustments for lifestyle/health confounders (smoking, alcohol consumption, body mass index, number of chronic diseases, physical activity, and cognitive functioning) were made in Model 2.

Longitudinal Analyses

To study the course of depressive symptoms over time, linear mixed-models analyses were conducted with the 25(OH)D categories at baseline as determinants, the CES-D scores after 3 years and 6 years as outcome, and the baseline CES-D score as covariate. These analyses included participants who had baseline 25(OH)D and CES-D data and at least one follow-up CES-D measurement. A random intercept was added to the longitudinal CES-D variable to control for dependency of individual measures over time. A time-interaction term was added to the models to

examine possible differences in the association between 3 and 6 years of follow-up.

To study whether 25(OH)D predicts the onset of clinically relevant depressive symptoms over time, logistic regression analyses were conducted in a subgroup of participants without depressive symptoms at baseline (CES-D < 16) and at least one follow-up measurement. The outcome was defined as presence of clinically relevant depressive symptoms (CES-D ≥ 16) in the 6-year follow-up period. Models and effect modification procedures were similar to the cross-sectional analyses.

Finally, the possible mediating effect of physical performance and functional limitations in the relationship between 25(OH)D and depressive symptoms was examined in secondary analyses. To account for the temporal, stepwise character of this hypothesized relationship, two longitudinal mediation models were fitted in which physical performance and functional limitations after 3 years of follow-up were considered as the mediator variables. Using structural equation modeling, the effect of 25(OH)D on physical functioning and the effect of physical functioning on depressive symptoms (adjusted for 25(OH)D) were simultaneously modeled. Mediation was examined only in analyses that showed a statistically significant relationship between 25(OH)D and depressive symptoms. With these mediation analyses, the total effect of 25(OH)D on depressive symptoms was separated into direct and indirect effects. The direct effect represents the effect of 25(OH)D on depressive symptoms, adjusted for physical functioning, whereas the indirect effect represents the multiplied effects of 25(OH)D on physical functioning and physical functioning on depressive symptoms, adjusted for 25(OH)D. This indirect effect can be seen as the mediating effect of physical functioning in the association of 25(OH)D with depressive symptoms.[32] Because of the usually skewed distribution of indirect effects, we used 95% Monte Carlo simulated confidence intervals (20,000 replications).[33] The mediation analyses were performed separately for physical performance and functional limitations and were conducted in the adjusted models (Model 2).

Pooled Analyses

In additional secondary analyses, both cohorts were pooled to increase the n and to investigate the consistency of the findings. Because the cohorts used different 25(OH)D assays, the 25(OH)D values of the older cohort (Nichols assay) were calibrated towards the values of the younger-old cohort (Diasorin assay), using the formula Diasorin = 3.7778 + 0.8889 × Nichols.[28] The cross-sectional and longitudinal regression analyses were repeated in the pooled dataset, with cohort as additional confounder.

RESULTS

Of 1,320 participants with a 25(OH)D measurement in the older cohort, 38 participants were excluded because of missing CES-D scores, leaving 1,282 participants available for analysis. In this cohort, 217 participants (16.9%) had vitamin D deficiency (25(OH)D < 30 nmol/L) and 400 participants (31.2%) had insufficient 25(OH)D concentrations (30–50 nmol/L). Clinically relevant depressive symptoms (CES-D ≥ 16) were present in 193 participants (15.1%) at baseline, in 202 of 1,071 participants (18.9%) at 3 years and in 169 of 853 participants (19.8%) at 6 years of follow-up. Non-response analyses comparing analyzed participants (n = 1282) with initially eligible participants who were excluded from the cross-sectional analyses (n = 227) showed that non-respondents were older (U = 104,475.5, $p < 0.001$), less educated (U = 130,516.0, $p = 0.02$), smoked more ($\chi^2_{(2)} = 8.9$, $p = 0.01$), drank less alcohol (U = 121,669.5, $p < 0.001$), had more depressive symptoms (U = 96,413.0, $p = 0.01$), were less physically active (U = 74,118.0, $p < 0.001$), had worse cognitive functioning (U = 95,058.0, $p < 0.001$) and physical performance (U = 72,670.5, $p < 0.001$), and more functional limitations (U = 87,667.5, $p \leq 0.001$), compared with included participants. Non-response analyses comparing participants who were excluded from the longitudinal analyses (n = 207) with included participants (n = 1075) showed similar results as above. Furthermore, excluded participants were more often male ($\chi^2_{(1)} = 34.6$, $p < 0.001$) and had more chronic diseases (U = 538,854.0, $p = 0.01$).

Of the 739 participants with a 25(OH)D measurement in the younger-old cohort, two participants were excluded from analysis for very high 25(OH)D concentration (182 nmol/L) or a missing CES-D score. Of the resulting 737 participants, 56 participants had vitamin D deficiency (7.6%) and 243 participants had insufficient vitamin D status (33.0%). Clinically

relevant depressive symptoms were present in 100 participants (13.6%) at baseline, in 95 of 703 participants (13.5%) after 3 years, and in 69 of 648 participants (10.6%) after 6 years. Cross-sectional non-response analyses in this cohort revealed that non-respondents (N = 182) smoked more ($\chi^2_{(2)} = 14, 5$; p = 0.001) compared with included participants (N = 737). Longitudinal non-response analyses showed that excluded participants (N = 33) had more depressive symptoms (U = 39,562.0, p = 0.04), were more often smokers ($\chi^2_{(2)} = 11, 3$; p = 0.004), and had more functional limitations (U = 33,340.0, p < 0.001) compared with included participants (N = 704). Table 1 displays baseline characteristics of both cohorts.

Cross-Sectional Analyses

Table 2 presents the results of the baseline regression analyses. Sex was not an effect modifier in either cohorts (cohort 1: $t_{(1274)} = -1.08$ to -1.64, p = 0.10 to 0.28; cohort 2: $t_{(729)} = -0.48$ to -1.17, p = 0.24 to 0.63). In the older cohort, participants with 25(OH)D less than 50 nmol/L had significantly more depressive symptoms compared with participants with 25(OH)D greater than 75 nmol/L (<30 nmol/L: ratio = 1.25, 95% CI: 1.0–1.5; 30–50 nmol/L: ratio = 1.17, 95% CI: 1.0–1.4). This association was attenuated after adjustment for lifestyle/health variables, however. Similarly, in the younger-old cohort, no statistically significant cross-sectional relationship between 25(OH)D and depressive symptoms was seen in the adjusted model.

Longitudinal Analyses

In the older cohort, the interaction of sex with the third 25(OH)D dummy had a p value of 0.052 ($t_{(1011)} = 1.95$). As this value was very close to our preset 0.05 cutoff, we decided to stratify the mixed-models analyses for men and women, so we would not miss any potentially relevant effects (Table 3). No significant associations were observed in men, whereas women in baseline 25(OH)D categories below 75 nmol/L experienced more depressive symptoms after 3 and 6 years compared with women with 25(OH)D of greater than 75 nmol/L (adjusted model: < 30 nmol/L: ratio = 1.23, 95% CI: 1.02–1.49; 30–50 nmol/L: ratio = 1.17, 95% CI: 1.00–1.37; 50–75 nmol/L: ratio = 1.24, 95% CI: 1.06–1.45). Corresponding to these ratios, participants with 25(OH)D concentrations below 30 nmol/L had a 23% higher CES-D score over 6 years than persons with 25(OH)D greater than 75 nmol/L. Similarly, participants with 25(OH)D concentrations of 30–50 nmol/L had a 17% higher CES-D score over 6 years, and persons with 25(OH)D concentrations of 50–75 nmol/L had a 24% higher CES-D score over 6 years compared with persons with 25(OH)D levels greater than 75 nmol/L. It should be noted that the overall test of the 25(OH)D categories for the adjusted model had a p value of 0.051 ($F_{(3,553)} = 2.60$), but we still interpreted the associations of the separate dummy variables as this value was so close to the cutoff. This slightly higher p value was caused by the association of the second dummy (30–50 nmol/L) being less strong than the other two dummies.

In the younger-old cohort, sex was not an effect modifier ($t_{(686\ to\ 691)} = -0.53$ to 0.25), p = 0.60 to 0.89). After adjustment for lifestyle/health confounders, a significant relationship between baseline 25(OH)D and depressive symptoms over time was no longer observed (Table 3).

Time interaction terms were not significant in either cohort (cohort 1: $t_{(941\ to\ 1010)} = -0.85$ to 0.65), p = 0.40 to 0.85; cohort 2: $t_{(670\ to\ 673)} = -0.30$ to 0.49), p = 0.63 to 0.77), indicating that the effect of 25(OH)D on the course of depressive symptoms did not differ between 3 and 6 years of follow-up.

In the logistic regression analysis of the older cohort, sex was an effect modifier for the first and third 25(OH)D dummy (Wald(1) = 3.96, p = 0.047 and Wald(1) = 6.83, p = 0.009, respectively). Hence, the analyses were stratified for men and women. In the stratified analyses, however, the overall tests for the association of the 25(OH)D dummies with the onset of depressive symptoms were not statistically significant for both men and women (Wald(3) = 5.59, p = 0.13 and Wald(3) = 4.78, p = 0.19, respectively), so analyses for the separate 25(OH)D dummy variables were not performed. Because of the small number of cases in the stratified analyses, however, the reliability of these results is uncertain. Similarly, in the younger-old cohort, no associations between 25(OH)D and the onset of depressive symptoms were observed (Wald(3) = 0.57, p = 0.90).

Mediation of Physical Functioning

The mediation analyses for physical performance and functional limitations were performed for the longitudinal mixed-models analysis of the older women, as

TABLE 1. Baseline Characteristics of the Two LASA Cohorts

	Older Cohort (N = 1282)				Younger-old Cohort (N = 737)			
Serum 25(OH)D	<30 nmol/L (N = 217)	30–50 nmol/L (N = 400)	50–75 nmol/L (N = 434)	>75 nmol/L (N = 231)	<30 nmol/L (N = 56)	30–50 nmol/L (N = 243)	50–75 nmol/L (N = 310)	>75 nmol/L (N = 128)
Depressive symptoms								
CES-D score	9 [4–15]	7 [3–13]	5 [2–10]	4 [2–9]	10 [3–16]	6 [3–12]	5 [2–10]	6 [2–9]
CES-D ≥ 16	46 (21.2)	70 (17.5)	52 (12.0)	25 (10.8)	15 (26.8)	38 (15.6)	32 (10.3)	15 (11.7)
Women	135 (62.2)	240 (60.0)	201 (46.3)	83 (35.9)	28 (50.0)	135 (55.6)	158 (51.0)	78 (60.9)
Age, years	80.9 [75.5–84.5]	76.3 [70.9–82.1]	72.8 [68.8–78.5]	70.7 [67.6–75.8]	61.7 [58.0–63.2]	59.7 [56.9–62.6]	60.4 [57.5–62.6]	59.5 [56.6–62.0]
Education, years	9 [6–11]	9 [6–11]	9 [6–11]	9 [6–11]	11 [7–15]	10 [9–12]	10 [9–11]	10 [9–11]
Season of blood collection								
Winter	147 (67.7)	226 (56.8)	215 (49.7)	108 (46.8)	42 (75.0)	182 (74.9)	213 (68.7)	86 (67.2)
Summer	70 (32.3)	172 (43.2)	218 (50.3)	123 (53.2)	14 (25.0)	61 (25.1)	97 (31.3)	42 (32.8)
Smoking								
Current	45 (20.7)	75 (18.8)	68 (15.7)	42 (18.2)	22 (39.3)	85 (35.0)	72 (23.2)	23 (18.0)
Former	75 (34.6)	167 (41.8)	231 (53.2)	121 (52.4)	21 (37.5)	108 (44.4)	161 (51.9)	67 (52.3)
Never	97 (44.7)	158 (39.5)	135 (31.1)	68 (29.4)	13 (23.2)	50 (20.6)	77 (24.8)	38 (29.7)
Alcohol consumption (g/wk)	10 [0–70]	20 [0–70]	30 [5–120]	60 [10–210]	60 [5–210]	70 [20–200]	70 [30–210]	70 [45–210]
Body mass index (kg/m^2)	26.8 [23.5–29.6]	27.3 [24.7–30.0]	26.5 [24.3–29.2]	25.6 [23.4–28.2]	26.5 [24.1–29.1]	27.6 [24.5–30.3]	26.6 [24.2–29.1]	26.4 [24.6–29.0]
Number of chronic diseases	2 [1–3]	2 [1–3]	2 [1–2]	1 [1–2]	2 [1–3]	1 [0–2]	1 [0–2]	1 [0–2]
Cognitive functioning (MMSE)	27 [24–28]	28 [26–29]	28 [26–29]	28 [27–29]	28 [26–29]	28 [27–29]	28 [27–29]	28 [27–29]
Physical activity (min/day)	21.4 [5.4–54.3]	38.6 [15.0–65.4]	56.8 [30.0–99.6]	61.5 [28.8–102.1]	48.0 [16.4–86.6]	66.4 [35.4–109.3]	72.9 [42.5–129.5]	62.9 [37.9–110.0]
Physical performance [a]	6 [2–8]	7 [5–9]	9 [7–10]	9 [8–11]	6 [4–7]	6 [5–7]	6 [5–7]	6 [5–8]
Functional limitations	2 [0–4]	1 [0–3]	0 [0–2]	0 [0–1]	0 [0–2]	0 [0–1]	0 [0–0]	0 [0–1]

Notes: Values are displayed as N (%) for categorical variables or as median [interquartile range] for skewed continuous variables. 25(OH)D: 25-hydroxyvitamin D; CES-D: Center for Epidemiological Studies Depression Scale; MMSE: Mini-Mental State Examination.

[a]The physical performance score ranges from 0–12 in the older cohort and from 0–8 in the younger-old cohort.

TABLE 2. Cross-sectional Associations Between 25(OH)D and Depressive Symptoms in the Two LASA Cohorts

	Older Cohort							Younger-old Cohort						
	Model 1					Model 2		Model 1					Model 2	
	F (df1, df2)	p	Ratio[a] (SE)	t (df)	p	F (df1, df2)	p	F (df1, df2)	p	Ratio[a] (SE)	t (df)	p	F (df1, df2)	p
Overall test of 25(OH)D categories[b]	3.91 (3, 1270)	0.009				2.16 (3, 1238)	0.091	3.40 (3, 729)	0.017				1.35 (3, 710)	0.26
<30 nmol/L			1.25 (1.10)	2.41 (1270)	0.016					1.38 (1.16)	2.21 (729)	0.028		
30–50 nmol/L			1.17 (1.08)	1.99 (1270)	0.047					1.20 (1.10)	1.87 (729)	.0062		
50–75 nmol/L			0.99 (1.08)	−0.10 (1270)	0.92					1.01 (1.10)	0.07 (729)	0.94		
>75 nmol/L				Ref							Ref			

Notes: Analyzed with multiple linear regression analysis. Model 1: adjusted for age, sex, education, and season. Model 2: additionally adjusted for smoking, alcohol use, body mass index, chronic diseases, cognitive functioning, and physical activity. 25(OH)D: 25-hydroxyvitamin D; CES-D: Center for Epidemiological Studies Depression Scale.

[a]As the outcome variable was ln(1 + CESD), Bs and SEs were transformed back to normal scale to obtain interpretable ratios.

[b]The individual 25(OH)D categories were tested only if the overall test of the categories was statistically significant.

TABLE 3. Longitudinal Associations Between 25(OH)D and Depressive Symptoms in the Older LASA Cohort; Stratified for Sex. Longitudinal Associations Between 25(OH)D and Depressive Symptoms in the Younger-old LASA Cohort

A.

	Women							Men					
	Model 1					Model 2		Model 1			Model 2		
	F (df1, df2)	p	Ratio[a] (SE)	t (df)	p	F (df1, df2)	p	Ratio[a] (SE)	t (df)	p	F (df1, df2)	p	F (df1, df2)	p
Overall test of 25(OH)D categories[b]	3.35 (3, 567)	0.019				2.60 (3, 553)	0.051				0.77 (3, 480)	0.97	0.12 (3, 464)	0.95
<30 nmol/L			1.30 (1.10)	2.69 (569)	0.007			1.23 (1.10)	2.13 (553)	0.034				
30–50 nmol/L			1.23 (1.08)	2.61 (545)	0.009			1.17 (1.08)	1.92 (532)	0.055				
50–75 nmol/L			1.26 (1.08)	2.92 (544)	0.004			1.24 (1.08)	2.70 (530)	0.007				
>75 nmol/L				Ref				Ref						

B.

	Model 1					Model 2	
	F (df1, df2)	p	Ratio[a] (SE)	t (df)	p	F (df1, df2)	p
Overall test of 25(OH)D categories[b]	3.62 (3, 686)	0.013				1.91 (3, 670)	0.13
<30 nmol/L			1.31 (1.12)	2.46 (687)	0.014		
30–50 nmol/L			0.99 (1.07)	−0.18 (688)	0.86		
50–75 nmol/L			0.94 (1.07)	−0.85 (689)	0.40		
>75 nmol/L				Ref			

Notes: Analyzed with linear mixed-models analysis, with the CES-D score after 3 and 6 years as outcome and baseline CES-D as covariate. Model 1: adjusted for age, sex, education, and season. Model 2: additionally adjusted for smoking, alcohol use, body mass index, chronic diseases, cognitive functioning, and physical activity. 25(OH)D: 25-hydroxyvitamin D; CES-D: Center for Epidemiological Studies Depression Scale.

[a]As the outcome variable was ln(1 + CESD), Bs and SEs were transformed back to normal scale to obtain interpretable ratios.

[b]The individual 25(OH)D categories were tested only if the overall test of the categories was statistically significant.

TABLE 4. Mediation Effects of Physical Functioning (After 3 Years) in the Longitudinal Association Between Baseline 25(OH)D and Depressive Symptoms Over 6 Years in Women of the Older LASA Cohort

	Physical Performance			Functional Limitations		
Serum 25(OH)D	Indirect Effect [a]	95% CI [b]	% Mediation[c]	Indirect Effect[a]	95% CI[b]	% Mediation[c]
<30 nmol/L	1.03	0.99–1.07	12.4	1.04	0.99–1.09	16.7
30–50 nmol/L	1.03*	1.00–1.07	20.6	1.02	0.99–1.06	13.3
50–75 nmol/L	1.01	0.98–1.04	3.3	1.02	0.98–1.05	7.4
>75 nmol/L		Ref			Ref	

Notes: As the outcome variable was ln(1 + CESD), the Bs and confidence intervals of the indirect effects were transformed back to normal scale to obtain interpretable ratios. Mediation analyses were performed in the adjusted Model 2. 25(OH)D: 25-hydroxyvitamin D; CI: confidence interval.

[a]The indirect effect is the mediating effect of physical functioning on the association between 25(OH)D and depressive symptoms. It represents the multiplied effects of 25(OH)D on physical functioning and physical functioning on depressive symptoms, adjusted for 25(OH)D.

[b]Bootstrapped confidence intervals with Monte Carlo simulation.

[c]Percentage mediation calculated by (indirect effect / total effect) × 100. Total effects are displayed in Table 3.

*Statistically significant indirect effect using the bootstrapped confidence interval.

this analysis was statistically significant (Table 4). The indirect effect (mediation effect) of physical performance was statistically significant for the 30–50 nmol/L 25(OH)D category, compared with the reference category of greater than 75 nmol/L (ratio of indirect effect: 1.03, bootstrapped 95% CI: 1.0–1.1). The corresponding percentage mediation of 20.6% suggests that physical performance after 3 years partially mediates the longitudinal association between 25(OH)D and depressive symptoms. The indirect effects of the other 25(H)D categories of physical performance and the indirect effects of functional limitations were not statistically significant, but the substantial mediation percentages of the less than 30 and 30–50 nmol/L categories suggest that physical functioning may have a modest mediating role in the relationship between 25(OH)D and depressive symptoms.

Pooled Analyses

The cross-sectional and longitudinal regression analyses were repeated in the pooled data set. Cross-sectionally, participants in 25(OH)D categories up to 50 nmol/L experienced significantly more depressive symptoms than participants with 25(OH)D greater than 75 nmol/L in the adjusted model (<30 nmol/L: ratio = 1.20, 95% CI: 1.03–1.40; 30–50 nmol/L: ratio = 1.16, 95% CI: 1.03–1.30; Supplemental Table S1). Corresponding to these ratios, participants with 25(OH)D less than 30 nmol/L had a 20% higher CES-D score than persons with 25(OH)D greater than 75 nmol/L. Similarly, participants with 25(OH)D concentrations of 30–50 nmol/L had a 16% higher CES-D score compared with persons with 25(OH)D greater than 75 nmol/L. The longitudinal pooled analyses revealed no significant associations between 25(OH)D and depressive symptoms in the adjusted models (Supplemental Table S2). Because of multiple cohort differences, these results should be interpreted with caution.

Sensitivity Analysis

As an additional sensitivity analysis, we examined whether the results would be different if we excluded participants who indicated that their physical activity pattern (confounder, LAPAQ) of the previous weeks was not representative of the previous year. We repeated the tests for interaction of sex and the cross-sectional and longitudinal regression analyses without these participants (–28.2% and –31.4% in the older and younger-old cohort, respectively) and the results were very similar to the original analyses and the conclusions did not change (results not shown but available from the author on request).

DISCUSSION

This study investigated the baseline and prospective 6-year association between 25(OH)D concentrations and depressive symptoms in two large population-based cohorts of older adults. Cross-sectionally, this association was not significant after adjustment for confounders, although the longitudinal analyses revealed a difference between men and women in the older

cohort (≥65 years at baseline): Women with 25(OH)D concentrations <75 nmol/L at baseline experienced 17% to 24% more depressive symptoms in the following 6 years than women with 25(OH)D > 75 nmol/L. Low physical performance partially mediated this relationship. No such associations were observed in men or in the younger-old cohort (55–65 years old at baseline). According to Geerlings et al., a change of 5 points in the CES-D score can be regarded as a meaningful change in depressive symptoms.[34] Hence, it depends on the initial CES-D score whether change in 25(OH)D status is associated with a meaningful change in depressive symptoms over 6 years. Higher initial CES-D scores are associated with more relevant change.

The observed differences between the two cohorts could be explained by the better general health status of the younger-old cohort. These participants had higher 25(OH)D concentrations, better physical functioning, fewer chronic diseases, and were physically more active compared with the older cohort. This may have enabled the younger persons to better withstand negative effects of low 25(OH)D on mood. On the other hand, the smaller sample size of the younger-old cohort may have limited the power of our analyses.

To increase power and to investigate the consistency of the results, both cohorts were pooled in secondary analyses. Cross-sectionally, these analyses demonstrated significantly more depressive symptoms in persons with lower 25(OH)D concentrations (up to 20%), confirming the consistency of the associations in both cohorts. In the longitudinal pooled analyses, however, the associations were not statistically significant. By comparing the longitudinal analyses of the separate and pooled cohorts, the associations of the separate cohorts seemed to cancel each other out in the pooled analyses, especially in the 30–50 and 50–75 nmol/L categories (data not shown but available from author on request). This may be explained by considerable cohort differences regarding health status and assessment periods. Because of cohort differences, the results of the pooled analyses should be interpreted with caution.

In the older cohort, a longitudinal association between baseline 25(OH)D and the course of depressive symptoms was observed in women only. This sex difference could be attributable to the generally lower 25(OH)D concentrations in women compared with men (25(OH)D < 50 nmol/L in 56.9% of women and 38.9% of men). Milaneschi et al. found a similar sex difference in the InCHIANTI study.[6] In contrast, no interaction with sex was observed in the Health ABC study.[8]

We hypothesized that low vitamin D status would reduce physical functioning, which in turn would increase depressive symptoms.[14,15,18–20] Indeed, we observed partial mediation of the association of 25(OH)D with depressive symptoms by physical performance in secondary analyses. This provides evidence for a potential mediating role of physical functioning in the relationship between low 25(OH)D and increasing depressive symptoms. To the best of our knowledge, this explanatory role has not previously been investigated prospectively. At most, these variables were treated as confounders in former studies.[6–9,35] The influence of physical functioning may in fact be an important reason why we did not observe significant associations in men and in the younger-old participants. Men in the older cohort had better physical performance than women ($U = 174{,}121.0$, $p < 0.001$). Similarly, participants in the younger-old cohort generally had higher physical function scores compared with the older cohort (see Table 1). It can be speculated that having adequate physical functioning may act as a "buffer" to safeguard older persons from the negative impact of low 25(OH)D on their mood. It should be noted that this mediating role of physical functioning is still exploratory and should be confirmed by other studies.

Hoogendijk et al. partly used the same data as the present study and did find a significant cross-sectional association between depression status and 25(OH)D concentrations.[2] This disparity can be explained by their use of different confounders and different operationalization of depression. Hoogendijk et al. categorized depression status into no depression (CES-D < 16), minor depression (CES-D ≥ 16) and major depressive disorder (MDD) (diagnosis after psychiatric interview) and analyzed it as determinant instead of an outcome. We chose not to use the MDD variable as outcome, because the number of participants with MDD is very limited within the LASA study, which would substantially reduce the power of our analyses.

The present study combines several strengths. The use of data from two large, population-based, independent cohorts with a long follow-up increases the value and generalizability of our results. In addition, we studied the influence of 25(OH)D on the severity,

course, and onset of depressive symptoms using both cross-sectional and longitudinal analysis techniques, adjusted for relevant confounders. By studying 25(OH)D at baseline, physical functioning after 3 years, and depressive symptoms over 6 years, we explored the potential mediating role of physical functioning longitudinally. This method takes into account the temporal character of the underlying mechanism. To the best of our knowledge, this is the first study that explored physical functioning as a possible mediating factor in the relationship between vitamin D status and depressive symptoms.

This study also has some limitations. Serum 25(OH)D was only measured at baseline, although it was shown that 25(OH)D concentrations are relatively stable over time.[28,36] Furthermore, as depressive symptoms were measured only once every 3 years, we did not have information about intermediate time points. Because of the fluctuating nature of depression, we may have missed episodes of depressive symptoms. Unfortunately, some potential confounders were not measured in the LASA measurement cycles that we used. Because of this, we were unable to adjust for variables such as diet and vitamin D supplement use, possibly resulting in residual confounding. Furthermore, over 99% of LASA participants are Caucasian,[28] which may have limited the generalizability of our findings to other ethnicities, as evidence suggests that polymorphisms of the vitamin D binding protein and hence bioavailability of vitamin D may differ between ethnicities[37] (but see Nielson et al.[38]). The non-response analyses showed that included participants were healthier than excluded persons, which may limit generalizability. In addition, the physical activity measure (LAPAQ) only provides information about activities in the previous 2 weeks, and no information about the longer-term habitual activity pattern of the participants. Therefore, we conducted a sensitivity analysis without participants who indicated that their activities were not representative for the previous year. Results of these analyses were similar to the regular analyses. Although this suggests that lack of information on past-year physical activity does not influence the conclusions, it cannot be ruled out that longer-term habitual physical activity may still be a potential confounding factor.

It should also be noted that we decided to interpret the associations of the separate 25(OH)D dummy variables for the women of the older cohort, although the test for the overall effect had a p value of 0.051, which was just above the cutoff of 0.05. This p value was slightly higher because the association of the second dummy (30–50 nmol/L) was less strong compared with the other two dummies. In this case, the potential clinical relevance of the findings made us decide to interpret the separate dummy associations after all. Replication of our findings by future research is therefore especially important in this case. Finally, cohort differences, such as different time periods and 25(OH)D assays, may have compromised the comparability of the two cohorts.

In conclusion, this study showed that older women with 25(OH)D concentrations below 75 nmol/L at baseline experienced 17% to 24% more depressive symptoms over 6 years compared with women with 25(OH)D concentrations greater than 75 nmol/L. This relationship may be partially explained by reduced physical functioning. To the best of our knowledge, this longitudinal mediating role of physical functioning has not been studied before. Our results suggest that having 25(OH)D concentrations greater than 75 nmol/L and adequate physical functioning is especially important for the mental health of older women. Randomized controlled trials investigating both vitamin D supplementation and behavioral interventions to improve physical functioning should examine the causality of these associations further, which may aid treatment or prevention strategies for depression.

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APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2018.03.004.

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